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SUPERINTENDENCIA

Delegatura de propiedad Industrial
División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21 **EXPEDIENTE No**

03-39926

54 **TÍTULO** MODOS DE TRATAR CONDIÇÕES ASSOCIADAS COM
QUINA P3B Y COMPUESTOS DE PIZROSTRIAZINO
ÚTILES COMO INHIBIDORES DE QUINASA

51 **CLASIFICACIÓN INTERNACIONAL** AGIK 31/53

71 **SOLICITANTE** PARSONS MYCOS SOLIDS COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE
AMERICA

74 **APODERADO** RAMIRO GONZALEZ DIAZ

22 **BOGOTÁ, D C.,**

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

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Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
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, 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. 16-58 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>170.322 TP 1003</u>
4 INVENTOR (ES) (72)	Nombre: Katerina Leftheris, Joel Barish, John Hynes, Stephen T. Wroblewski Dirección: 92 Richmond Drive, Skillman, NJ 08558, US; 38 Dorchester Lane, Richboro, PA 18954, US; 95 Dispatch Drive, Washington Crossing, PA 18977, US; 1507 South Branch Drive, Whitehouse Station, NJ 08889, Estados Unidos de América (Respectivam.) Nacionalidad o Domicilio: Estados Unidos de América		
5 PCT (86)			
Solicitud Internacional No. <u>PCT/US01/49982</u>		Fecha <u>07-11-2001</u>	
Publicación Internacional No. <u>WO 02/40486 A2</u>		Fecha <u>23-05-2002</u>	
Título (54): <u>MÉTODOS DE TRATAR CONDICIONES ASOCIADAS CON QUINASA p38 Y COMPUESTOS DE PIRROLOTRIAZINA ÚTILES COMO INHIBIDORES DE QUINASA</u>			
7 Clasificación Internacional (51) <u>C07D 487/04 A61K 31/53</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	US	17-11-2000	60/249.877
	US	07-08-2001	60/310.561
9 Comprobante de pago No. <u>03-26.880</u> Fecha <u>12-05-2003</u>			

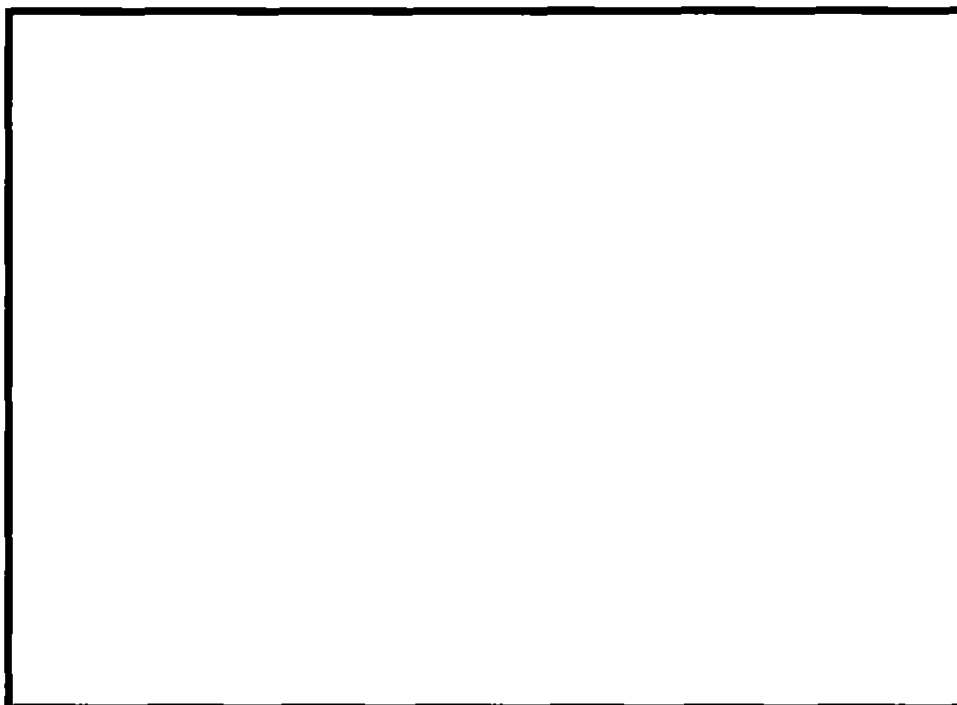
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$400.000
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 19358
- ☐ Documento de cesión del Inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

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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***** 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	5323804	15/04/2003	27,780,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL :	\$ 400,000.00

SOM: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

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PATENTE ☒ X 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 METODOS DE TRATAR CONDICIONES ASOCIADAS CON QUINASA p38 Y COMPUESTOS DE PIRRO-
LOTIAZINA ... CLASIFICACION _____

EXPEDIENTE No. _____ FECHA DE SOLICITUD _____ ROLLO MICROFILM _____

CERTIFICADO No. _____ FECHA DE CONCESION _____ VIGENCIA DESDE _____ HASTA _____

PRORROGA _____ CAMBIO DE NOMBRE _____

TRASPASO A _____

INVENTOR (ES) KATERINA LEFOTHERIS, JOEL BARRISH, JOHN HYNES, STEPHEN T. WROBLESKI

OTROS _____

OFICINA DE COMUNICACIONES

(19) World Intellectual Property Organization
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PCT

(10) International Publication Number
WO 02/40486 A2(51) International Patent Classification⁷: C07D 487/04,
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253:00, 209:00) (C07D 519/00, 487:00, 487:00) (C07D
519/00, 487:00, 471:00)WROBLESKI, Stephen, T. [US/US]; 1507 South Branch
Drive; Whitehouse Station, NJ 08889 (US).

(21) International Application Number: PCT/US01/49982

(74) Agents: WINSLOW, Anastasia et al.; Bristol-Myers
Squibb Company, P.O. Box 4000, Lawrenceville-Princeton
Road, Princeton, NJ 08543-4000 (US).(22) International Filing Date:
7 November 2001 (07.11.2001)(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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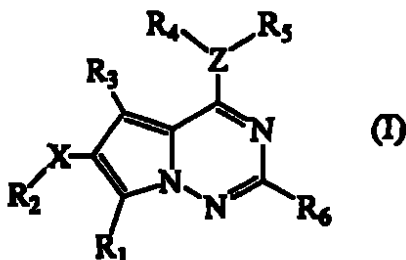
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60/249,877 17 November 2000 (17.11.2000) US
60/310,561 7 August 2001 (07.08.2001) US(84) Designated States (*regional*): ARIPO patent (GH, GM,
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BI, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).(71) Applicant (*for all designated States except US*): BRIS-
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95 Dispatch Drive, Washington Crossing, PA 18977 (US).

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upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(54) Title: METHODS OF TREATING p38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS
USEFUL AS KINASE INHIBITORS(57) Abstract: Methods of treating one or more conditions associated
with p38 kinase activity are disclosed comprising administering to a pa-
tient in need thereof at least one compound having the formula (I); or a
pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein R₁
is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, or NH₂,
preferably methyl, and X, R₁ through R₄, and Z are as described in the
specification. Advantageously the groups ZR₃ taken together comprise
an NH-substituted aryl.

METHODS OF TREATING p38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS**Related Inventions**

- 5 This application 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, both of which are incorporated herein by reference.

Field of the Invention

- 10 This invention relates to methods of treating conditions associated with p38 α and β kinases and to pyrrolotriazine compounds, more particularly, to pyrrolotriazine carboxamide and benzamide compounds useful for treating p38 kinase-associated conditions.

Background of the Invention

- 15 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
20 *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.*,
25 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
30 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 , p38 β , p38 γ , and p38 δ . The α and β isoforms are expressed in inflammatory cells and are key mediators of TNF- α production. Inhibiting the p38 α and β enzymes in cells results in reduced levels of TNF- α expression. Also, administering p38 α 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 methods of treating conditions associated with p38 kinase activity comprising administering to a patient in need thereof certain pyrrolotriazine compounds. The invention further provides select pyrrolotriazine compounds, including 5-methyl and 5-trifluoromethyl pyrrolotriazine-6-carboxamide compounds useful as kinase inhibitors, particularly kinases p38 α 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. Pyrrolotriazine compounds substituted with an acidic group reportedly having sPLA₂-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 is directed to methods of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof one or more pharmaceutically-active compounds having the Formula (I):

R_4 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

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

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

R_{20} is hydrogen, lower alkyl, or substituted alkyl, or R_{20} may be absent if the carbon atom to which it is attached together with R_4 and R_5 is part of an unsaturated bicyclic aryl or heteroaryl;

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

R_{24} is selected from halogen, trifluoromethyl, haloalkoxy, keto ($=O$), nitro, cyano,

$-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$,

$-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$,

$-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alkyl; aryl optionally

substituted with one to three R_{27} ; cycloalkyl optionally substituted with

keto ($=O$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon

atoms; and heterocyclo optionally substituted with keto ($=O$), one to three R_{27} ,

or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29}

are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl,

C_{3-7} -cycloalkyl, and C_{3-7} -heterocycle, or may be taken together to form a C_3

-heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted

with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro,

amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;

and

R_{27} is selected from alkyl, R_{30} , and C_{1-4} -alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy,

nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$,

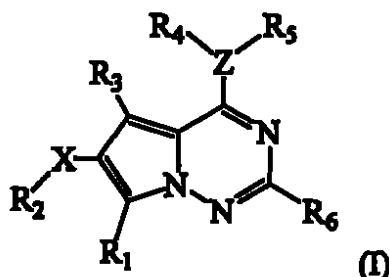
$-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$,

$-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered

carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen,

hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30}

and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl,



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

5 R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano, or NH_2 ;

X is selected from $-\text{O}-$, $-\text{OC}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{C}(=\text{O})-$, $-\text{CO}_2-$,

$-\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, $-\text{NR}_{10}\text{C}(=\text{O})\text{NR}_{11}-$, $-\text{NR}_{10}\text{CO}_2-$, $-\text{NR}_{10}\text{SO}_2-$,

$-\text{NR}_{10}\text{SO}_2\text{NR}_{11}-$, $-\text{SO}_2\text{NR}_{10}-$, $-\text{C}(=\text{O})\text{NR}_{10}-$, halogen, nitro, and cyano, or X is absent;

10 Z is selected from O, S, N, and CR_{20} , wherein when Z is CR_{20} , said carbon atom may form an optionally-substituted bicyclic aryl or heteroaryl with R_4 and R_5 ;

R_1 is hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$,

$-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{23}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{23}$, $-\text{NH}_2$, $-\text{NR}_{24}\text{R}_{23}$,

$-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{23}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{23}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{23}$,

15 $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{23}$, halogen, nitro, or cyano;

R_2 is selected from:

a) hydrogen, provided that R_2 is not hydrogen if X is $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{NR}_{10}\text{CO}_2-$, or $-\text{NR}_{10}\text{SO}_2-$;

b) alkyl, alkenyl, and alkynyl optionally substituted with up to four R_{26} ;

20 c) aryl and heteroaryl optionally substituted with up to three R_{27} ; and

d) heterocyclo and cycloalkyl optionally substituted with keto ($=\text{O}$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or

e) R_2 is absent if X is halogen, nitro, or cyano;

(i) R_4 is substituted aryl, aryl substituted with NHSO_2 alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and

25 R_5 is hydrogen, alkyl, or substituted alkyl, except when Z is O or S, R_5 is absent, or alternatively,

(ii) R_4 and R_5 taken together with Z form an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl;

30



The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms. When a subscript is used with reference to an alkyl or other group, the subscript refers to the number of carbon atoms that the group may contain. The term "C₁₋₄alkyl" includes a bond and alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group substituted by one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, e.g. SO₂NH₂, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, e.g. CONH₂, substituted carbamyl e.g. CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocyclos, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where the substituent on the alkyl is further substituted, it will be with alkyl, alkoxy, aryl, or aralkyl.

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

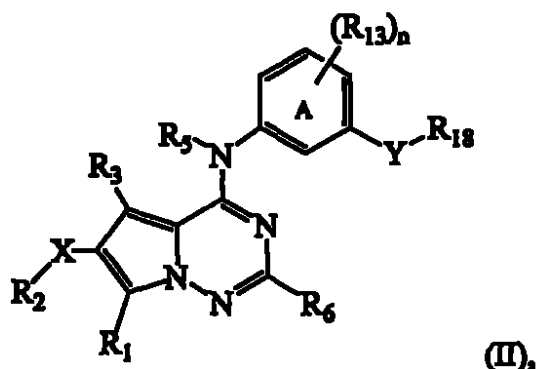
The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

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

The term "substituted aryl" refers to an aryl group substituted by one to four substituents selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono,

aralkyl, C₃₋₇cycloalkyl, and heterocycle, or may be taken together to form a C₃₋₇heterocycle.

The invention is further directed to compounds having surprisingly
 5 advantageous activity as inhibitors of p38 kinases α and β and TNF- α comprising compounds of Formula (II):



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

10 R₃ is methyl or CF₃;

R₄ is hydrogen or alkyl;

Y is -C(=O)NR₂₃-, -NR₂₃C(=O)NR₂₃-, -NR₂₃SO₂-, or -SO₂NR₂₃-;

R₁₈ and R₂₃ are selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with

one to three R₁₉, except when Y is -NR₂₃SO₂-, R₁₈ is C₁₋₄alkyl or aryl

15 optionally substituted with one to three R₁₉;

R₁₃ and R₁₉ at each occurrence are independently selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each R₁₃ and/or R₁₉ group may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl; and

20 X, R₁, R₂, and R₆ are as defined above for compounds of Formula (I).

25

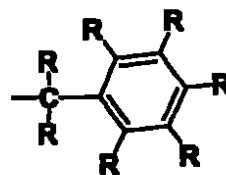
Description of the Invention

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.

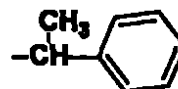
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arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy. The substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

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



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



involves the alkyl-portion being branched to define

- 15 The term "heteroaryl" refers to an aromatic group for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom and at least one carbon atom-containing ring. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms, provided
20 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
25 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.

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

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl,

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

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

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

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

15 The term "substituted alkenyl" refers to an alkenyl group substituted by one to two substituents selected from halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino, and substituted and unsubstituted heterocycles, including indolyl, imidazolyl, furyl, 20 thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

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

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

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

6/10

cycloalkyl" is substituted with one or more alkyl or substituted alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" each refer to a fully saturated or unsaturated, aromatic or nonaromatic cyclic 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 in at least one carbon atom-containing ring. Thus, the term "heterocycle" includes heteroaryl groups as described above. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, 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 heterocyclic 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 heterocycles, such as epoxides and aziridines.

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

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

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

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

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

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

15 The term "carbocyclic" means a saturated or unsaturated 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.

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

Definitions for the various other groups that are recited above in connection with substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, substituted heterocycle, substituted cycloalkyl, and so forth, are as follows: alkoxy is
 25 $-\text{OR}^a$, alkanoyl is $-\text{C}(=\text{O})\text{R}^a$, aryloxy is $-\text{OAr}$, alkanoyloxy is $-\text{OC}(=\text{O})\text{R}^a$, amino is $-\text{NH}_2$, alkylamino is $-\text{NHR}^a$, arylamino is $-\text{NHAr}$, aralkylamino is $-\text{NH-R}^b\text{-Ar}$, disubstituted amine or dialkylamino is $-\text{NR}^a\text{R}^d$, alkanoylamino is $-\text{NH-C}(=\text{O})\text{R}^a$, aroylamino is $-\text{NH-C}(=\text{O})\text{Ar}$, aralkanoylamino is $-\text{NH-C}(=\text{O})\text{R}^b\text{-Ar}$, thiol is $-\text{SH}$, alkylthio is $-\text{SR}^a$, arylthio is $-\text{SAr}$, aralkylthio is $-\text{S-R}^b\text{-Ar}$, alkylthiono is $-\text{S}(=\text{O})\text{R}^a$,
 30 arylthiono is $-\text{S}(=\text{O})\text{Ar}$, aralkylthiono is $-\text{S}(=\text{O})\text{R}^b\text{-Ar}$, alkylsulfonyl is $-\text{SO}_2\text{R}^a$, arylsulfonyl is $-\text{SO}_2\text{Ar}$, arylsulfonylamine is $-\text{NHSO}_2\text{Ar}$, alkylsulfonylamine is $-\text{NHSO}_2\text{R}^a$, aralkylsulfonyl is $-\text{SO}_2\text{R}^b\text{Ar}$, sulfonamido is $-\text{SO}_2\text{NH}_2$, nitro is $-\text{NO}_2$, carboxy is $-\text{CO}_2\text{H}$, carbamyl is $-\text{CONH}_2$, substituted carbamyl is $-\text{C}(=\text{O})\text{NHR}^a$ or

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

- 5 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.

10 Compounds of the Formula (I) 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
 15 Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Academic 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
 20 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992), each of which is incorporated herein by reference.

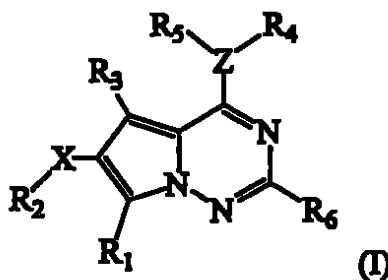
It should further be understood that solvates (*e.g.*, hydrates) of the compounds of Formula (I) are also with the scope of the present invention. Methods of solvation are generally known in the art.

25

Preferred Compounds

Preferred embodiments of the invention comprise preferred compounds of Formulae (I) and (II), and methods of treating conditions associated with p38 kinase activity comprising administering preferred compounds of Formulae (I) and (II).

30 Preferred compounds are those having Formula (I),



$-\text{C}(=\text{O})\text{NR}^*\text{R}^d$, alkoxycarbonyl is $-\text{C}(=\text{O})\text{OR}^*$, carboxyalkyl is $-\text{R}^b-\text{CO}_2\text{H}$, , sulfonic

acid is $-\text{SO}_3\text{H}$, arylsulfonylamine is $-\text{NHSO}_q\text{Ar}$, guanidino is $\begin{array}{c} \text{NH} \\ | \\ -\text{N}-\text{C}-\text{NH}_2 \\ | \\ \text{H} \end{array}$, and

ureido is $\begin{array}{c} \text{O} \\ || \\ -\text{N}-\text{C}-\text{NH}_2 \\ | \\ \text{H} \end{array}$, wherein R^* is alkyl as defined above, R^b is alkylene as defined above, R^* and R^d are selected from alkyl, aryl, and aralkyl, 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 Formula (I) 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. All references to compounds of Formula (I) herein are intended to include without limitation compounds of Formulae (Ia) to (Ii) as well as compounds of Formula (II) and (IIa)-(IIh). All references to compounds of Formula (II) are intended to include compounds of Formulae (IIa) to (IIh).

The compounds of Formula (I) may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as 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 for Formula (I) 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. For select compounds of Formula (I), mesylate and/or bisulfate salts were successfully obtained (*see, e.g.*, Example 125 herein). Both mesylate and bisulfate salts were found to be non-hygroscopic, highly water soluble, and stable in solid state.

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

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

R_3 is methyl, $-\text{CF}_3$, or $-\text{OCF}_3$,

X is selected from $-\text{C}(=\text{O})-$, $-\text{CO}_2-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, and $-\text{C}(=\text{O})\text{NR}_{10}-$, or X is

5 absent;

Z is N;

R_1 is hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$,

$-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{23}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{23}$, $-\text{NH}_2$, $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{23}$,

$-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{23}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{23}$, $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{23}$, halogen,

10 nitro, or cyano;

R_2 is hydrogen, C_{2-6} alkyl, substituted C_{1-4} alkyl, aryl, aralkyl, substituted aryl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocycle, or substituted heterocycle, or optionally-substituted cycloalkylalkyl or heterocycloalkyl;

15 R_4 is aryl or heteroaryl substituted with one R_{12} and zero to three R_{13} ;

R_5 and R_{10} independently are selected from hydrogen and lower alkyl;

R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, or halogen;

20 R_{12} is carbamyl, sulfonamido, arylsulfonylamine, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or R_{12} is alkylsulfonylamine;

R_{13} at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-\text{OR}_{14}$, $-\text{C}(=\text{O})\text{alkyl}$, $-\text{OC}(=\text{O})\text{alkyl}$, $-\text{NR}_{15}\text{R}_{16}$, $-\text{SR}_{15}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})\text{alkyl}$,

25 $-\text{S}(=\text{O})\text{aryl}$, $-\text{NHSO}_2\text{-aryl-R}_{17}$, $-\text{NHSO}_2\text{-alkyl}$, $-\text{SO}_2\text{NHR}_{17}$, $-\text{CONHR}_{17}$, and $-\text{NHC}(=\text{O})\text{NHR}_{17}$;

R_{14} is hydrogen, alkyl, or aryl;

R_{15} is hydrogen or alkyl;

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

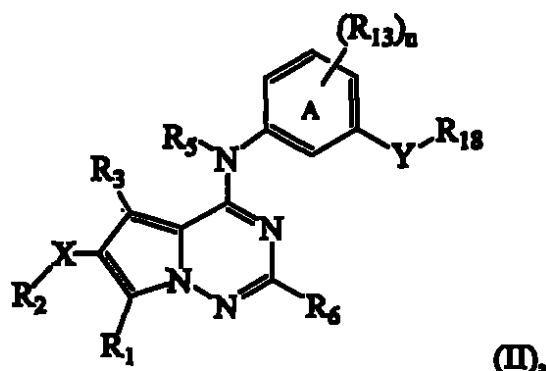
30 R_{17} is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl;

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

In compounds of Formula (I), preferably the group R_3 is methyl, trifluoromethyl, or methoxy, most preferably methyl; X is preferably $-\text{CO}_2-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, or $-\text{C}(=\text{O})\text{NR}_{10}-$, more preferably $-\text{C}(=\text{O})\text{NH}-$; Z is preferably N; R_4 is preferably substituted aryl or substituted heteroaryl, more preferably phenyl substituted with at least one of carbamyl, substituted carbamyl, arylsulfonylamido, substituted arylsulfonylamido, ureido, or substituted ureido, and optionally substituted with one or two C_{1-4} alkyl or halogen. Most preferably R_4 is phenyl substituted with at least one of $-\text{C}(=\text{O})\text{NHO}(\text{C}_{1-4}\text{alkyl})$ or $-\text{C}(=\text{O})\text{NH}(\text{optionally substituted phenyl})$, and also is optionally substituted with C_{1-4} alkyl. R_5 is preferably hydrogen or lower alkyl, more preferably hydrogen.

In preferred compounds, R_1 and R_6 may be selected from groups of substituents as defined herein; however, advantageously they are selected from hydrogen, CH_3 , $-\text{OH}$, $-\text{OCH}_3$, halogen, nitro, and cyano, and most preferably R_1 and R_6 are hydrogen. R_2 preferably is alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroaryl, or substituted heteroaryl, more preferably straight or branched C_{2-6} alkyl or optionally-substituted benzyl. The mesylate salt is the preferred form of salt.

Accordingly, preferred compounds further comprise those having the Formula (II),



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

R_3 is methyl, $-\text{CF}_3$, or $-\text{OCH}_3$;

X is $-\text{C}(=\text{O})\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, $-\text{C}(=\text{O})-$, or $-\text{CO}_2-$;

Y is $-\text{C}(=\text{O})\text{NH}-$, $-\text{NHC}(=\text{O})\text{NH}-$, or $-\text{NHSO}_2-$;

R_{10} is hydrogen or lower alkyl;

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R_{12} is selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to three R_{13} , except that when Y is $-\text{NHSO}_2-$, R_{12} is $-\text{C}_{1-4}$ alkyl, aryl or aryl substituted with R_{13} ;

5 R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-\text{OR}_{14}$, $-\text{C}(=\text{O})$ alkyl, $-\text{OC}(=\text{O})$ alkyl, $-\text{NR}_{15}\text{R}_{16}$, $-\text{SR}_{15}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})$ alkyl, $-\text{S}(=\text{O})$ aryl, $-\text{NHSO}_2$ -aryl- R_{17} , $-\text{SO}_2\text{NHR}_{17}$, $-\text{CONHR}_{17}$, and $-\text{NHC}(=\text{O})\text{NHR}_{17}$;

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

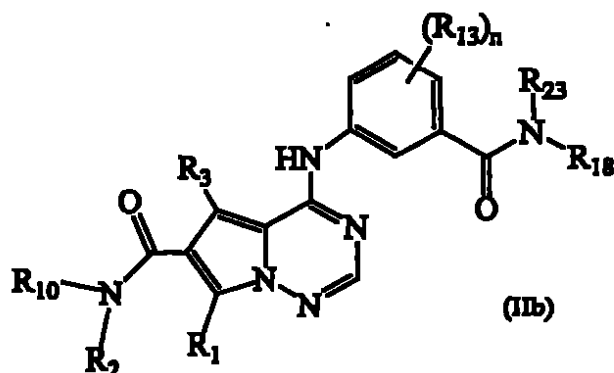
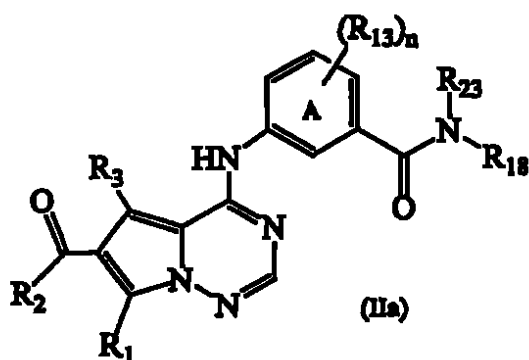
10 R_{19} at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido,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

15 n is 0, 1 or 2, and

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

More preferred are compounds having the Formula (IIa) or (IIb):

20



and pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:
 R_3 is methyl;

25 R_1 and R_{10} are hydrogen or $-\text{CH}_3$;

R_2 is selected from hydrogen; straight or branched C_{2-6} alkyl; cycloalkyl optionally substituted with keto and/or up to two R_{27} ; phenyl optionally substituted with up to two R_{27} ; heterocycle optionally substituted with keto and/or up to two R_{27} ; and C_{1-4} alkyl substituted with up to three of halogen, trifluoromethyl,

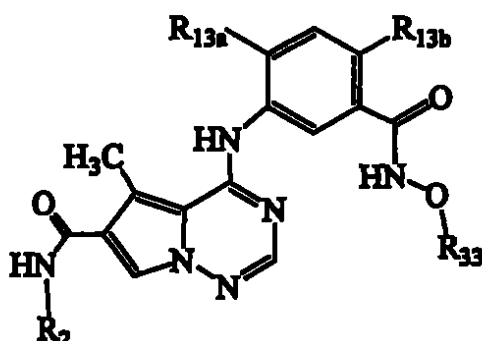
cyano, OR_{22} , $NR_{22}R_{23}$, CO_2R_{22} , aryl, heterocycle, and/or cycloalkyl, wherein the aryl, heterocycle, and/or cycloalkyl in turn are optionally substituted with up to two of halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, cyano and alkyl;

- 5 R_{18} is hydroxy, C_{1-4} alkoxy, phenyl, or phenyl substituted with one or two R_{19} ;
 R_{13} and R_{19} are selected from lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, and cyano;
 R_{27} at each occurrence is independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, hydroxy,
 10 alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy;
 R_{28} and R_{29} at each occurrence are independently selected from hydrogen, alkyl, alkenyl, phenyl, and benzyl; and
 n is 0, 1 or 2.

- 15 When R_2 is a heterocycle, advantageously it is selected from diazepinyl, morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle being optionally substituted with C_{1-4} alkyl, phenyl, and/or benzyl.

Most preferred are compounds having the formula,

20



in which R_{13a} and R_{13b} are hydrogen, CH_3 , OH , OCH_3 , CF_3 , cyano, or halogen, R_2 is C_{2-6} alkyl or optionally substituted benzyl, R_{33} is lower alkyl, and n is 0 or 1.

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Utility

- The compounds of the invention are selective inhibitors of p38 kinase activity, and in particular, isoforms p38 α and p38 β . Accordingly, compounds of formula (I) have utility in treating conditions associated with p38 kinase activity. Such
 30 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

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- 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.*, 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-38 α / β kinase," this means that either p38 α and/or p38 β kinase are inhibited. Thus, reference to an IC₅₀ value for inhibiting p-38 α / β kinase means that the compound has such effectiveness for inhibiting at least one of, or both of, p38 α and p38 β kinases.
- 10 In view of their activity as inhibitors of p-38 α / 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.
- 15 More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β -cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis, 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,
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ocular neovascularization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoplasia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin-induced platelet aggregation, endotoxemia and/or toxic shock syndrome, and conditions associated with prostaglandin endoperoxidase synthase-2.

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 and in S. Ceccarelli *et al*, "Imidazo[1,2-a]quinoxalin-4-amines: A Novel Class of Nonxanthine A₁-Adenosine Receptor Antagonists," European Journal of Medicinal Chemistry Vol. 33, (1998), at pp. 943-955; 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 azathioprine and cyclophosphamide;

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TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

5 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.

10 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, 15 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 20 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; buccally; 25 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 30 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 p38 α / β enzymes and TNF- α .

Biological Assays

Generation of p38 Kinases

cDNAs of human p38 α , β and γ isoforms 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 μ l of cell suspension was incubated with 50 μ l of test compound (4X concentration in assay medium containing 0.2% DMSO) in 96-well tissue culture plates for 5 minutes at RT. 100 μ l 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 IC₅₀ values for test compounds (concentration of compound that inhibited LPS-stimulated TNF- α production by 50%) were calculated by linear regression analysis.

5 **p38 Assay**

The assays were performed in V-bottomed 96-well plates. The final assay volume was 60 μ l prepared from three 20 μ l additions of enzyme, substrates (MBP and ATP) and test compounds in assay buffer (50 mM Tris pH 7.5, 10 mM MgCl₂, 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 μ l 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 MeltiLex 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 μ M; [γ -³³P]ATP, 3 nM;; MBP (Sigma, #M1891), 2 μ g/well; p38, 10 nM; and DMSO, 0.3%.

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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 CO₂/O₂ 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.

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Abbreviations

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

35 Ph = phenyl
Bz = benzyl

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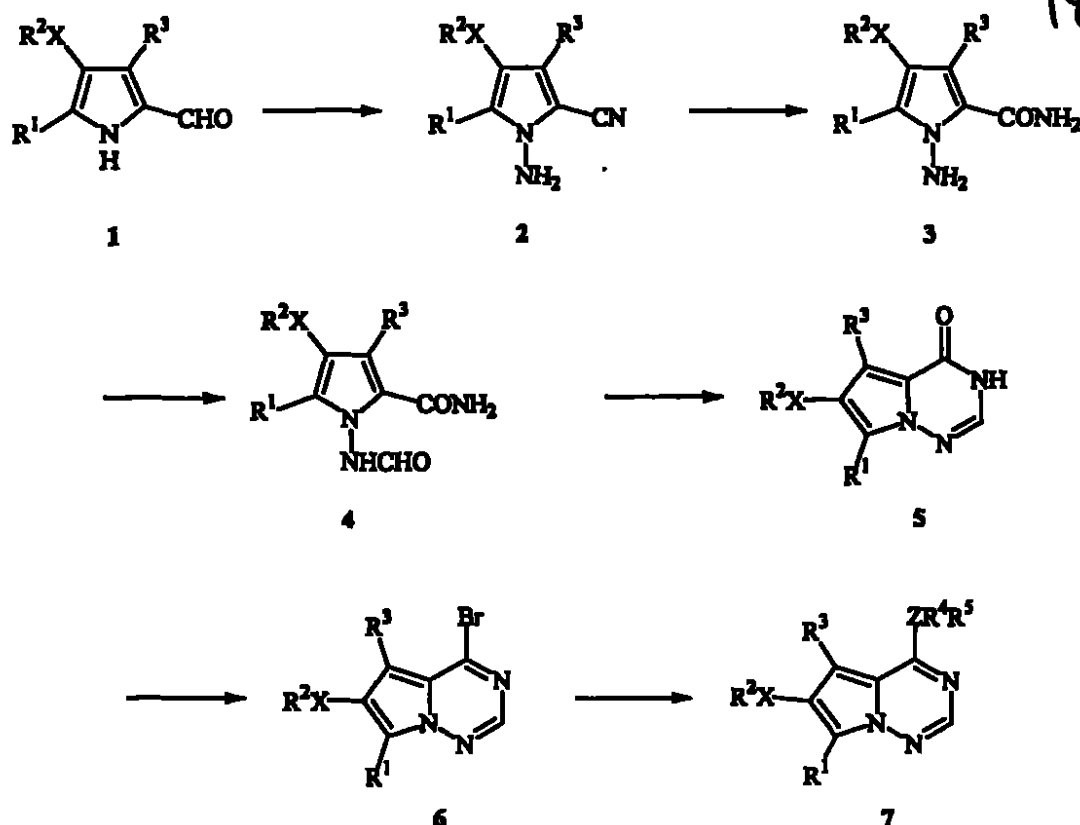
- t-Bu = tertiary butyl
Me = methyl
Et = ethyl
Pr = propyl
5 Iso-P = isopropyl
MeOH = methanol
EtOH = ethanol
EtOAc = ethyl acetate
Boc = tert-butyloxycarbonyl
10 CBZ = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
DCM = dichloromethane
DCE = 1,2-dichloroethane
DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
15 TFA = trifluoroacetic acid
THF = tetrahydrofuran
HATU = *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronim
hexafluorophosphate
KOH = potassium hydroxide
20 K_2CO_3 = potassium carbonate
 $POCl_3$ = phosphorous oxychloride
KOtBu = potassium t-butoxide
EDC or EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DIPEA = diisopropylethylamine
25 HOBt = 1-hydroxybenzotriazole hydrate
m-CPBA = m-chloroperbenzoic acid
NaH = sodium hydride
NaOH = sodium hydroxide
 $Na_2S_2O_3$ = sodium thiosulfate
30 Pd = palladium
Pd/C = palladium on carbon
min = minute(s)
L = liter
mL = milliliter
35 μ L = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
40 meq = milliequivalent
RT or rt = room temperature
ret. t. = HPLC retention time (minutes)
sat or sat'd = saturated
aq. = aqueous
45 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
50 NMR = nuclear magnetic resonance
mp = melting point

In the Examples, "HPLC Condition A" refers to YMC S5 ODS 4.6 x 50 mm Ballistic column, 4 mL/min flow rate, 4 min linear gradient elution (Start solvent %B = 0; Final solvent %B = 100), solvent A = 10% MeOH / 90% H₂O / 0.2% H₃PO₄.

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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. In the schemes, the groups R₁-R₆, R₁₀, R₁₃, R₁₈, R₂₃, X and Z are as described herein for compounds of Formula (I).

Scheme 1

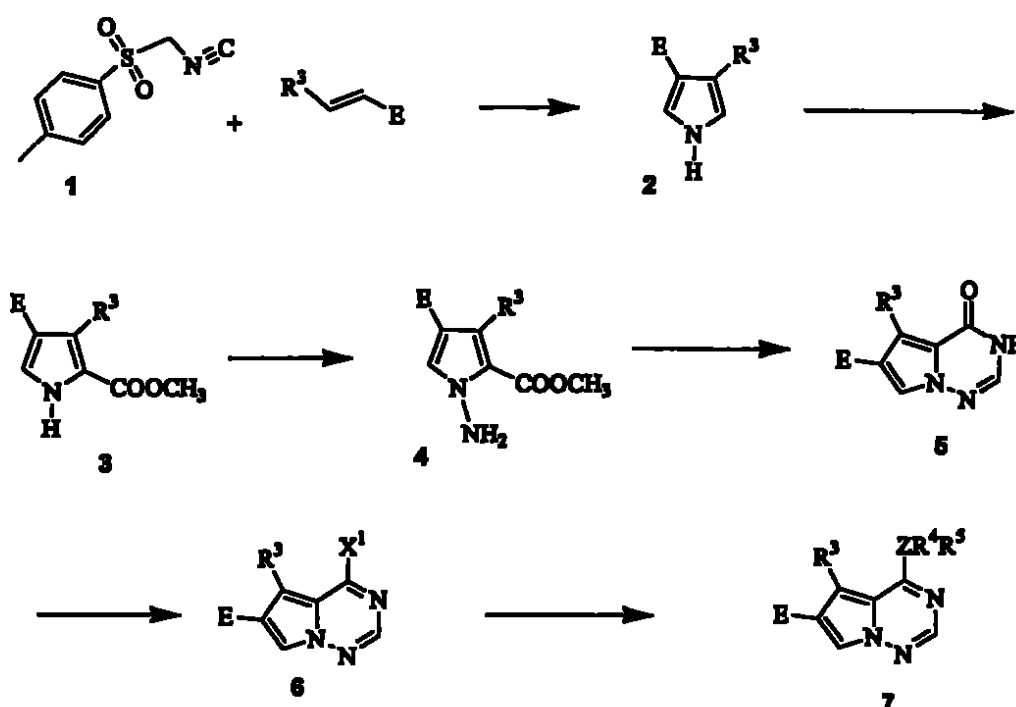
5 An optionally substituted 2-formylpyrrole (1) is reacted with an aminating reagent, such as hydroxylamine-O-sulfonic acid, in an aq. solvent at rt, followed by treatment under cooling with a base such as KOH, to form compound (2).

Compound (2) is reacted with an aq. base such as KOH at rt to form compound (3). Compound (3) is reacted with an acylating agent, such as formic acid,
 10 in an aq. solvent, to form compound (4). Compound (4) is cyclized with a base such as sodium methoxide in MeOH with heating to form compound (5). Compound (5) is halogenated, e.g., with phosphorus oxybromide at elevated temperature, to form compound (6). Compound (6) is reacted with an amine such as an aniline in an organic solvent, such as acetonitrile, to form product (7) of Scheme 1.

15 Compound (7) of Scheme 1 where R_1 = halogen can be prepared from compound (7) of Scheme 1 where R_1 = hydrogen by reaction with a halogenating agent such as bromine in a suitable solvent such as acetic acid.

Compounds (1) may be obtained from substituted pyrroles by formylation, e.g., by reaction with phosphorus oxychloride and DMF. A methylpyrrole may be
 20 obtained by reduction of a formylpyrrole, e.g., by reaction with lithium aluminum hydride.

Scheme 2



E = electron withdrawing group such as ester, nitro or ketone

X¹ = halogen

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Reacting an anion of tosylmethyl isocyanide (TosMIC) (1) with a Michael acceptor such as ethyl crotonate provides disubstituted pyrrole (2). Treatment of pyrrole (2) with an acylating agent such as trichloroacetyl chloride in the presence of a Lewis acid such as aluminum chloride at from rt to 50 °C, followed by treatment with sodium methoxide, affords trisubstituted pyrrole (3). Compound (3) can be obtained by warming an aldehyde, such as acetaldehyde, with 2 equivalents of ethyl isocyanoacetate in the presence of a base, such as DBU, in an organic solvent, such as THF. Alternatively, compound (3) can be obtained following the procedure of M. Suzuki, M. Miyoshi, and K. Matsumoto *J. Org. Chem.* 1974, 39 (1980).

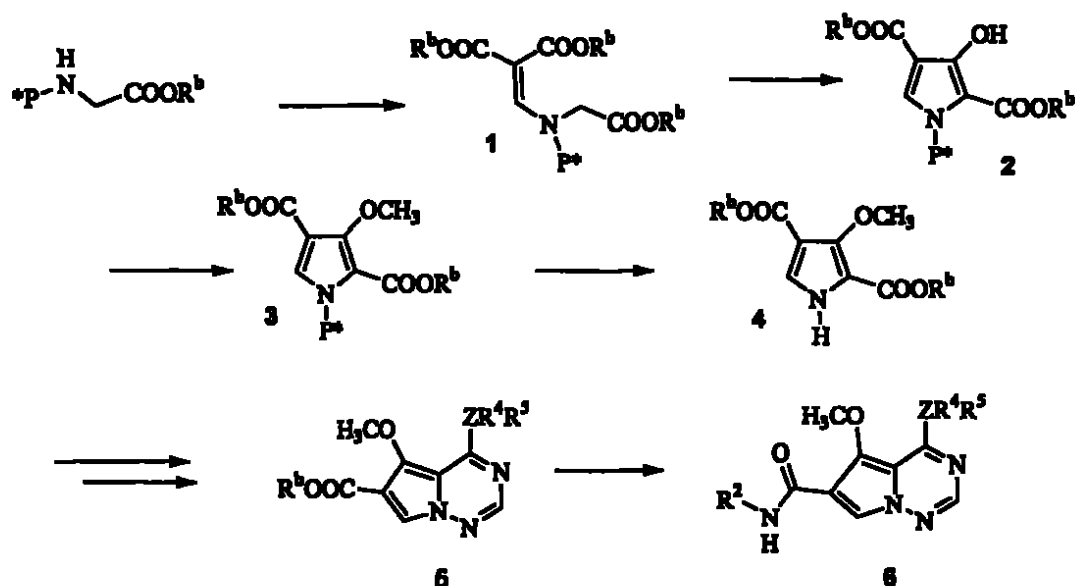
Pyrrole (3) can be aminated by an aminating reagent, such as diphenyl phosphoryl hydroxylamine, in the presence of a base, such as NaH, at rt in organic solvents, such as DMF, to form N-aminated pyrrole (4). Compound (4) is cyclized by heating at from 120 to 195 °C with formamide to afford 1,2,4-triazine (5). Treatment of compound (5) with a halogenating agent, such as phosphorous oxybromide, at from 60 to 115°C, in the presence or absence of a co-solvent such as DCE, affords compound (6).

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Compound (6) is reacted with an amine, such as an aniline in an organic solvent, such as DMF, to obtain compound (7). Alternatively, compound (7) can be obtained by treating (6) with an anion of a heterocyclic compound, such as oxindole, in an organic solvent such as THF.

- 5 An anion of TosMIC (1) can be made by treating a solution of it in DMSO with a base such as NaH at rt or a solution of it in THF with lithium hexamethyldisilazane at -78°C .

Scheme 3



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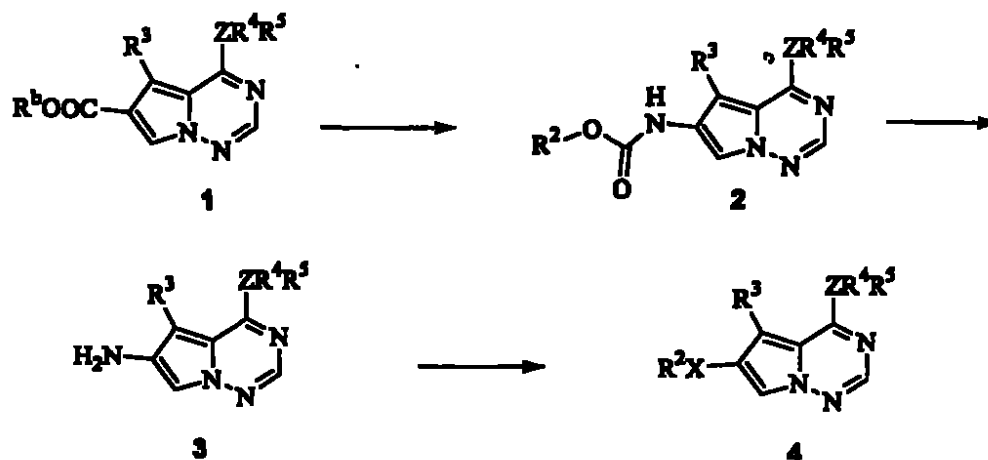
wherein P^+ = protecting group, $R^b = R^5$ described hereinbefore

- A suitably N-protected ester of glycine, such as with benzyl group, can be added to dialkyl methylene malonate at from rt to 80°C to obtain compound (1). Compound (1) is cyclized to form pyrrole (2) upon treatment with a strong base, such as lithium hexamethyldisilazane, at from -78°C to rt in an organic solvent such as THF. Pyrrole (2) is alkylated by treatment with an alkylating agent, such as iodomethane or dimethyl sulfate, in the presence of a base, such as K_2CO_3 , in an organic solvent, such as acetone or DMF to yield compound (3).

- Deprotection of compound (3) can be achieved, when optionally protected by groups such as benzyl, by hydrogenation over a catalyst, such as Pd, in the presence of ammonium formate. Compound (4) is converted to compound (5) via cyclization as described for compound (5) of Scheme 2.

Hydrolysis of the ester group in compound (5) can be achieved by treatment with a base such as aq. KOH. The resulting acid can be coupled with an amine in the presence of a coupling agent, such as DCC or PyBrop.

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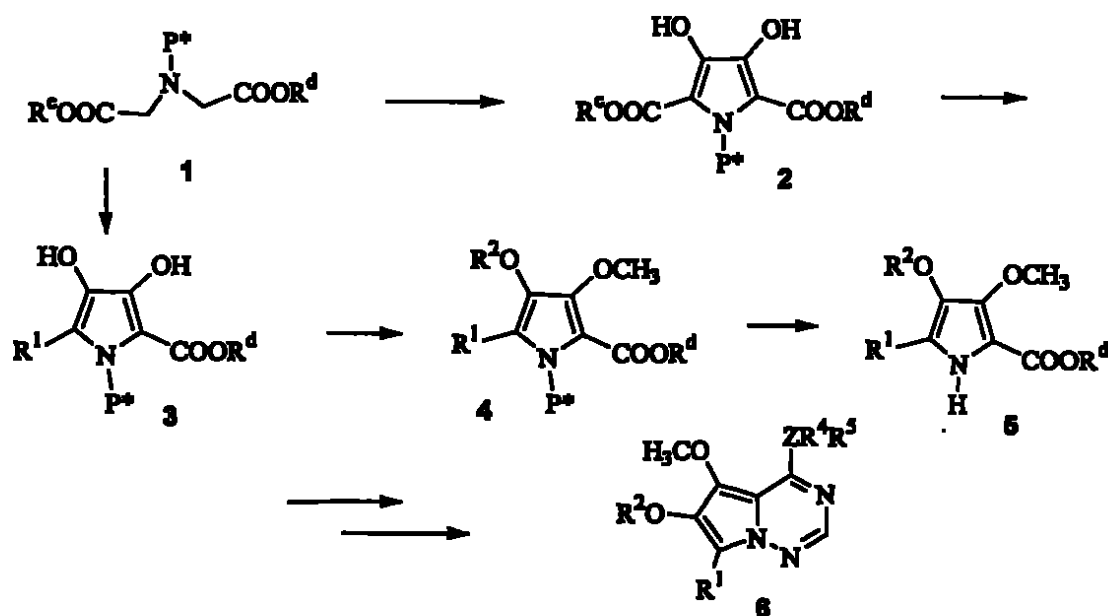
Scheme 4

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

Compound (5) from Scheme 3 can be converted to carboxylic acid (1) (wherein R₃ is methoxy or is as otherwise defined herein) by treatment with a base such as aq. KOH. This acid undergoes Curtius rearrangement by treatment with diphenyl phosphoryl azide in the presence of an alcohol, such as benzyl alcohol, in an organic solvent, such as 1,4-dioxane, to afford compound (2).

The carbamate group of compound (2) can be deprotected, when optionally protected by groups such as CBZ, by hydrogenation over a catalyst, such as Pd, to obtain compound (3). The amino group of compound (3) can be acylated to form compound (4), e.g., by treatment with a carboxylic acid in the presence of a coupling agent such as DCC, or sulfonylated, e.g., by treatment with a sulfonyl chloride. Alternatively, the amino group of compound (3) may be alkylated with alkyl halides or may undergo reductive amination with aldehydes in the presence of a reducing agent, such as sodium cyanoborohydride.

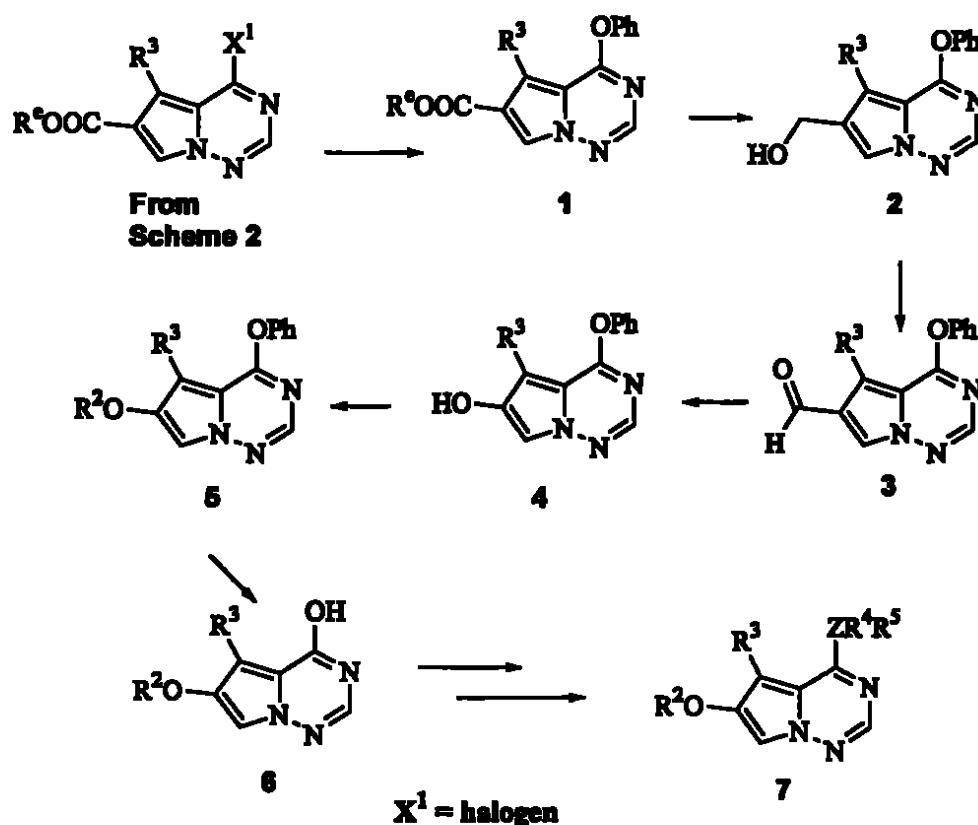
Scheme 5



wherein P^* = protecting group; $R^e, R^d = R^6$; and $R^1 = H$ or $COOR^{21}$ as described hereinbefore.

Suitably protected compound (1) (imino dicarboxylate) can be cyclized by treatment with dialkyl oxalate in the presence of a base, such as sodium methoxide, in an organic solvent, such as MeOH. Compound (2) upon selective deprotection, such as with TFA when optionally protected by tert-butyl ester, undergoes decarboxylation to afford compound (3) where $R^1 = H$. This step is omitted to form compound (3) where $R^1 = COOR^{21}$.

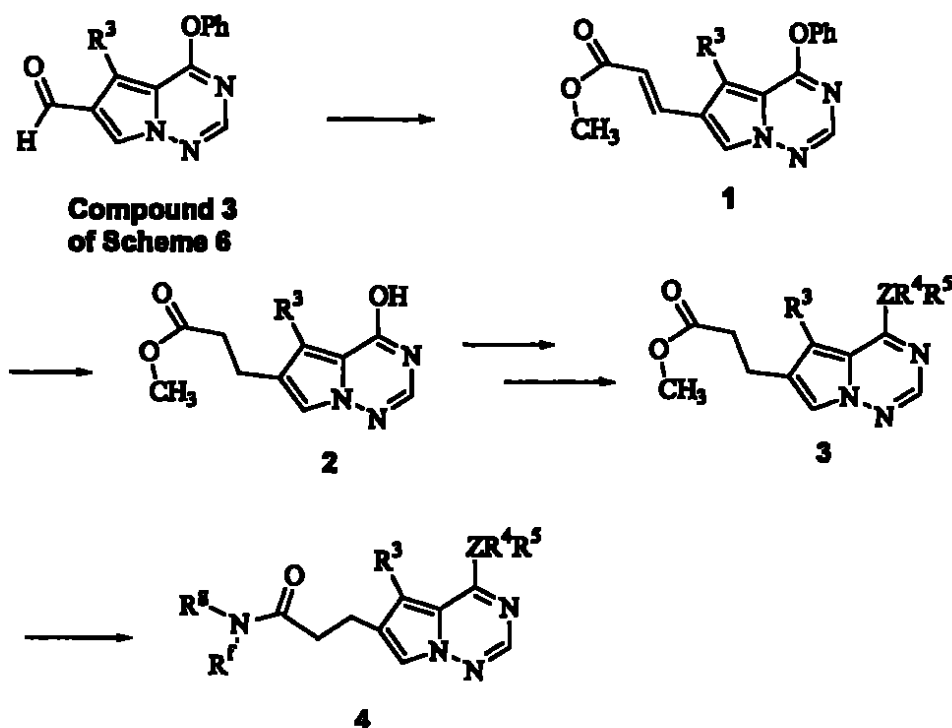
The hydroxy group of compound (3) can be etherified by reaction with an alkylating agent, such as dimethyl sulfate. Compound (4) can be deprotected by hydrogenation, when optionally protected such as with a benzyl group, to obtain compound (5). Compound (5) is then converted to compound (6) in an analogous manner to that described for compound (4) of Scheme 3 and compounds (4) through (7) of Scheme 2.

Scheme 6

- 5 Compound (6) of Scheme 2 can be etherified at the 4-position, e.g., by treatment with phenoxide anion to form compound (1). Reduction of compound (1) with a reducing agent, such as DIBAL, in an organic solvent, such as toluene, affords alcohol (2). Oxidation of the alcohol (2) can be achieved by treatment with MnO_2 at an elevated temperature in an organic solvent, such as toluene, to form (3). Treatment of compound (3) with an oxidant, such as *m*-CPBA in an organic solvent, such as DCM, followed by aq. hydrolysis with a base, such as potassium bicarbonate, affords the hydroxy compound (4).

- 10 Alkylation of the phenolic group of compound (4) with an agent, such as iodomethane, in the presence of a base, such as NaH, at from rt to 100°C, affords compound (5). Hydrolysis of compound (5) can be achieved by treatment with an acid, such as aq. HCl, at an elevated temperature to afford (6). Compound (6) can be converted to compound (7) with procedures analogous to those described in Scheme 2.

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Scheme 7

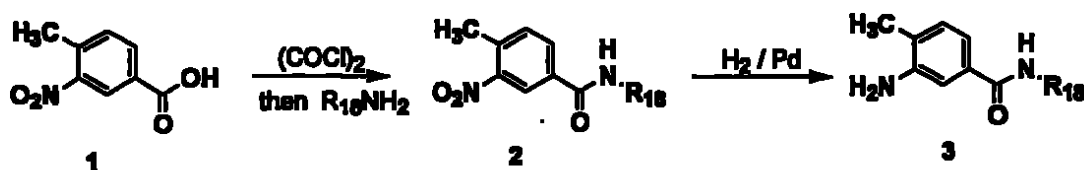
wherein R^1 , $R^2 = R^3$ as described hereinbefore

- 5 Compound (3) from Scheme 6 can undergo a Wittig reaction, *e.g.*, with phosphonates such as methyl diethylphosphonoacetate, in an organic solvent, such as DCE, in the presence of a base, such as NaH, to afford compound (1). The double bond of compound (1) can be hydrogenated by treatment with hydrogen in the presence of a catalyst, such as Pd. Compound (2) can be converted to (3) by
- 10 procedures described in Scheme 2.

Hydrolysis of the ester, as described hereinbefore, followed by coupling of the resulting acid with an amine in the presence of a coupling agent, such as DCC, affords compound (4).

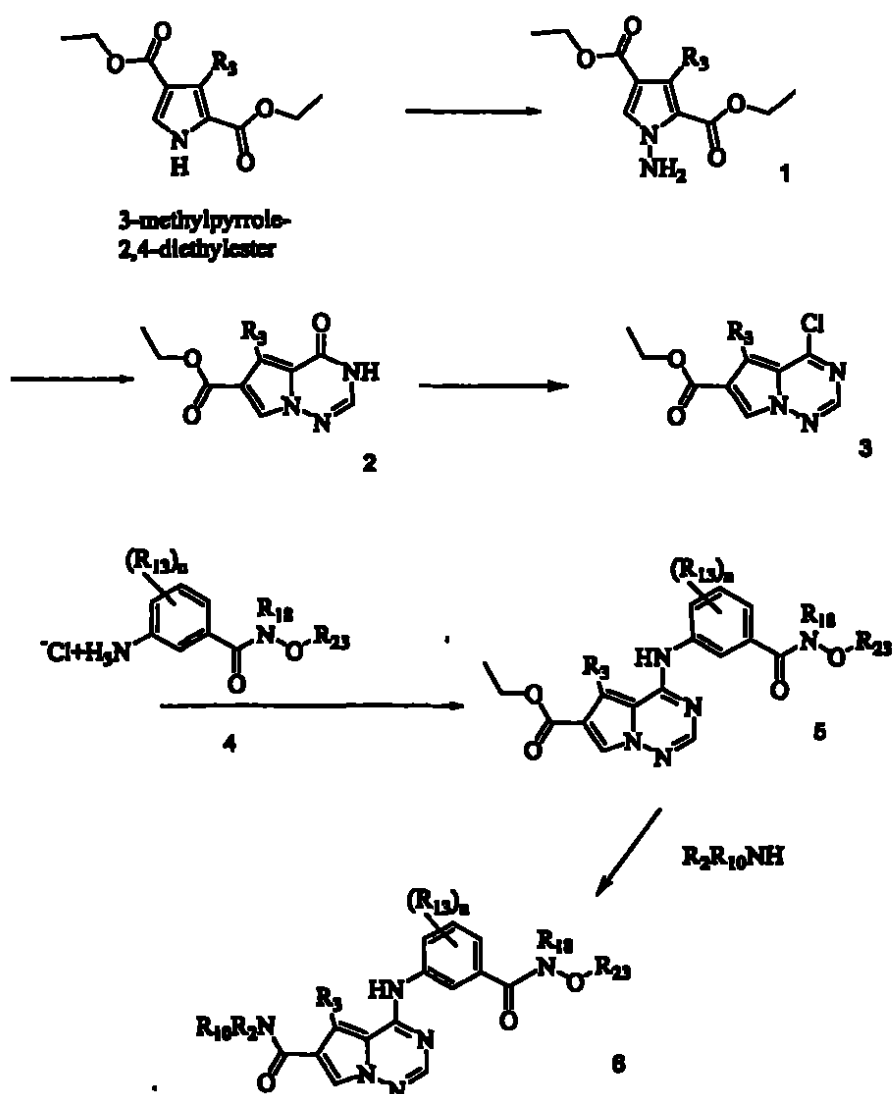
Scheme 8

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Commercially-available compound (1) can be reacted with oxalyl chloride with heating and then concentrated *in vacuo* and reacted with an amine $R_{18}NH_2$ in the presence of a base, such as 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 9 to produce compounds (6) of Scheme 9.

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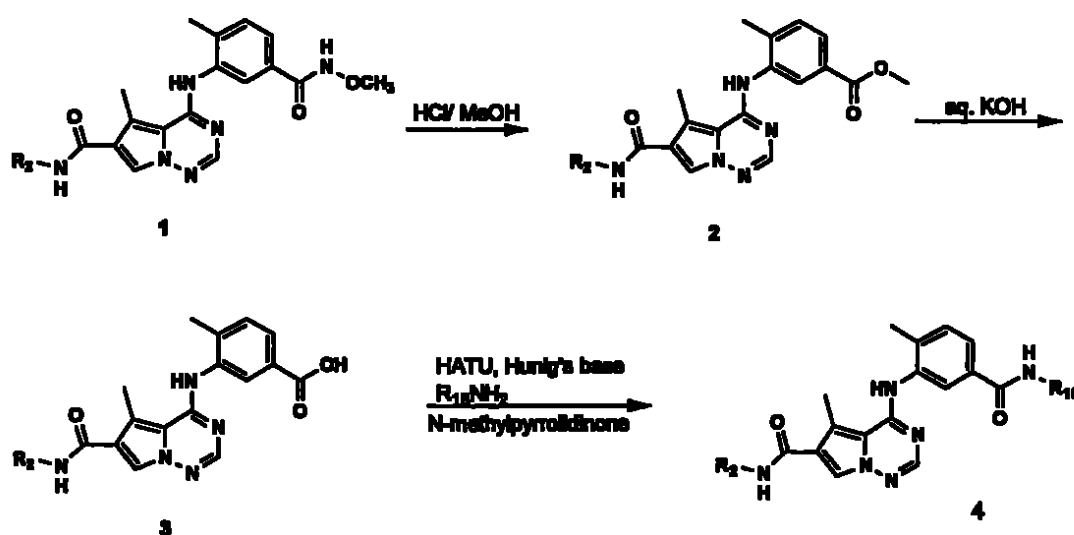
Scheme 9

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

Compound (4) can be prepared by 1) reacting commercially-available 4-amino-3-methylbenzoic acid and N-(*tert*-butoxycarbonyl)anhydride in THF to produce a BOC-protected aniline intermediate; 2) reacting the aniline intermediate with (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt, and DMF, followed by addition of methoxyamine hydrochloride and DIPEA to produce a BOC-protected N-methoxyamide intermediate; and 3) reacting that methoxyamide intermediate in a solution of HCl in dioxane to produce compound (4) as a hydrochloride salt. Alternatively, compound (4) can be prepared as shown in Scheme 8.

Scheme 10



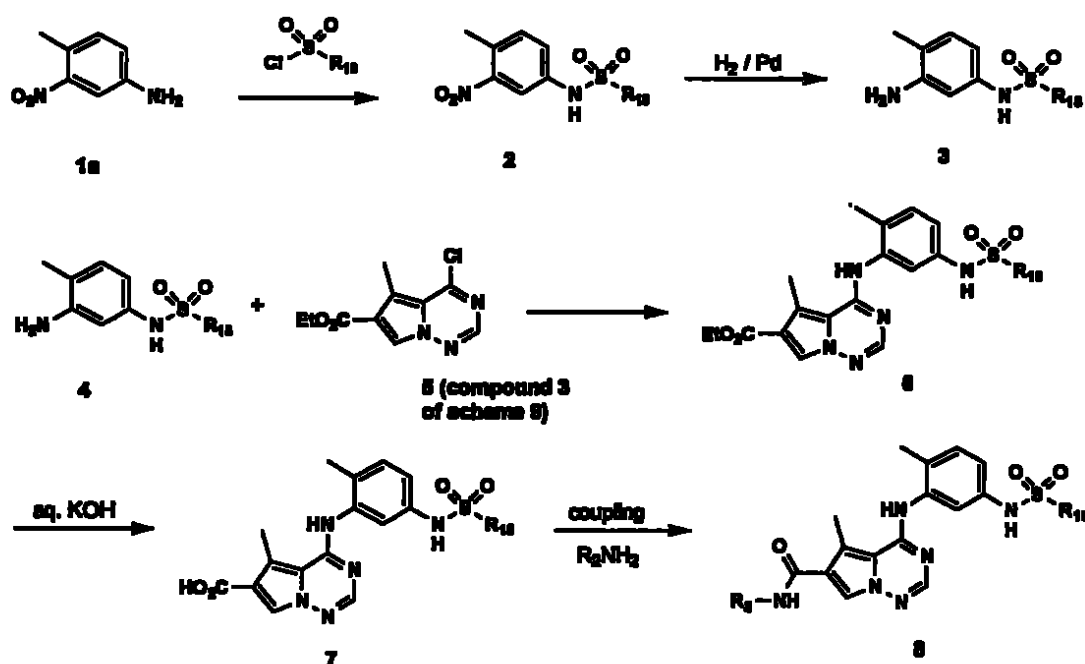
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A substituted hydroxamate (1) can be reacted with acid, such as HCl, in anhydrous MeOH, to afford compound (2). Compound (2) can be reacted with an aq. base such KOH with heating to form compound (3). Compound (3) is reacted with an amine R₁₀NH₂ in the presence of a coupling reagent, such as HATU, and a base such as diisopropylamine, in an organic solvent, such as N-

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methylpyrrolidinone to afford compounds (4). Alternatively, compounds (4) may generally be prepared as outlined in Schemes 8 and 9.

Scheme 11



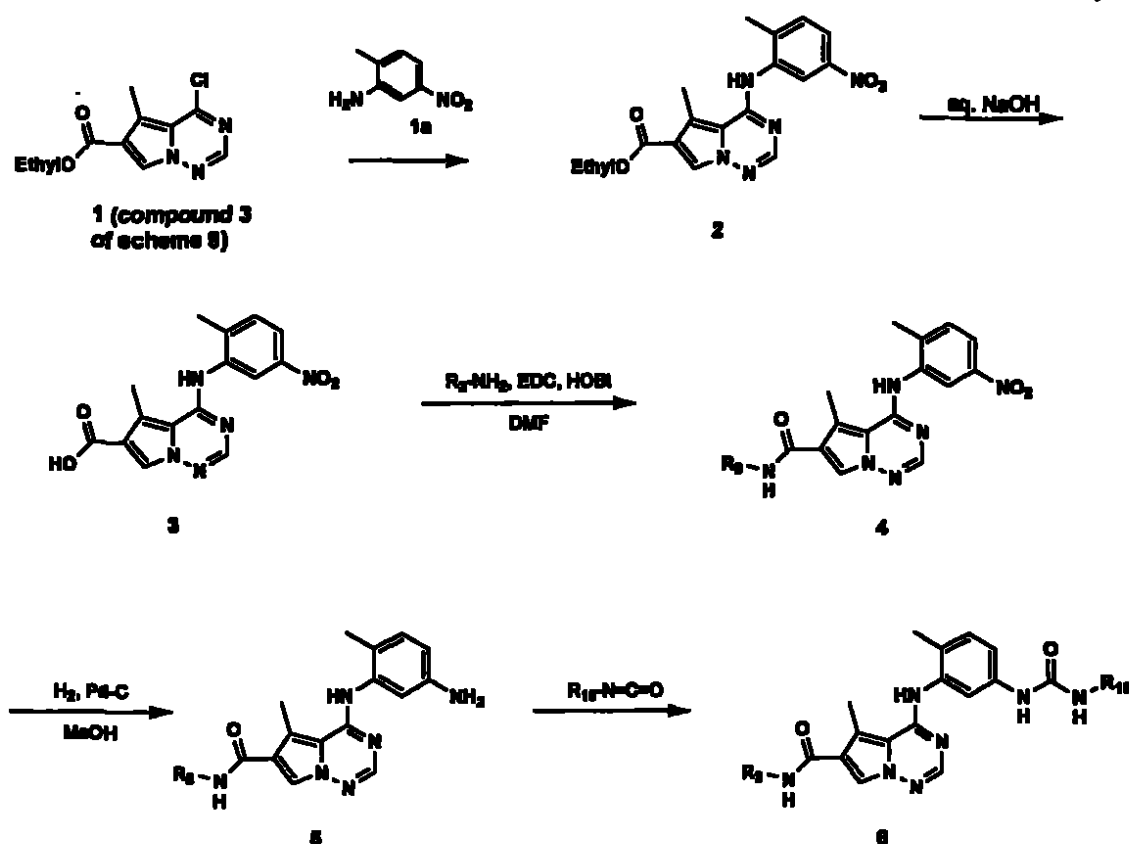
5

Commercially-available compound (1a) can be reacted with a sulfonyl chloride in the presence of a base, such as TEA, in an organic solvent, such as DCM to yield compound (2). Reaction of compound (2) with hydrogen in the presence of a catalyst, such as Pd in a solvent, such as MeOH, yields compound (3). Reaction of compound (3) with chloride (5) (compound 3 of scheme 9) in an organic solvent, such as DMF, at rt affords compound (6).

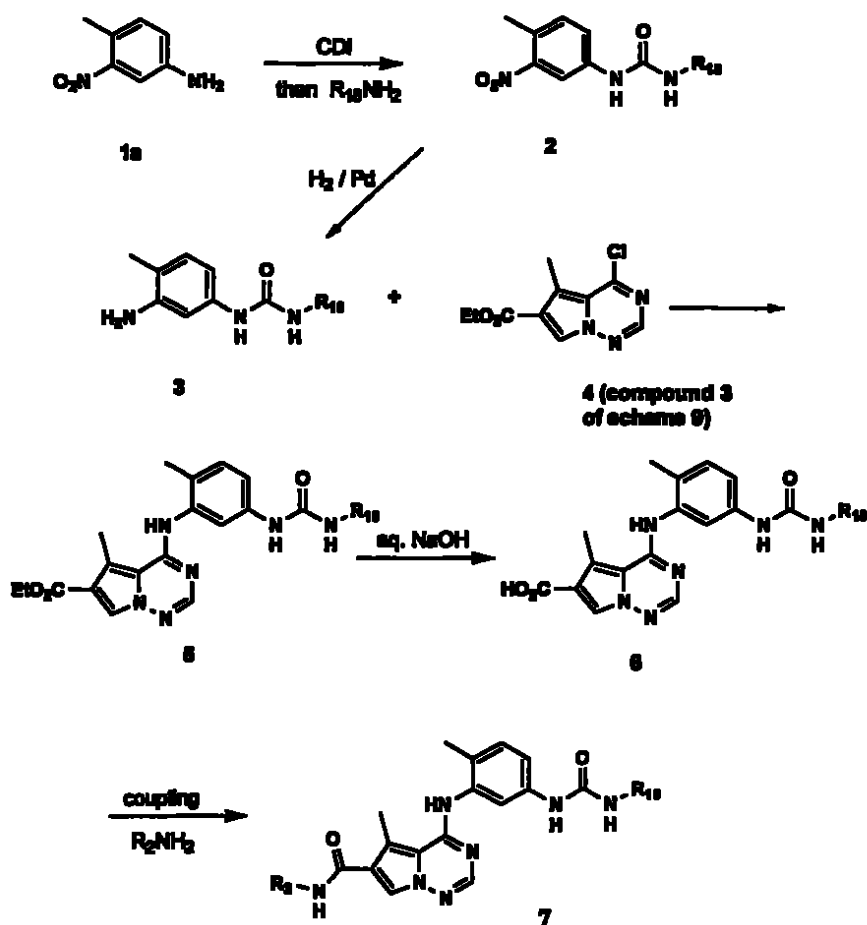
Reaction of compound (6) with aq. KOH with heating affords compound (7). Compound (7) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as EDCI, and a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (8).

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Scheme 12

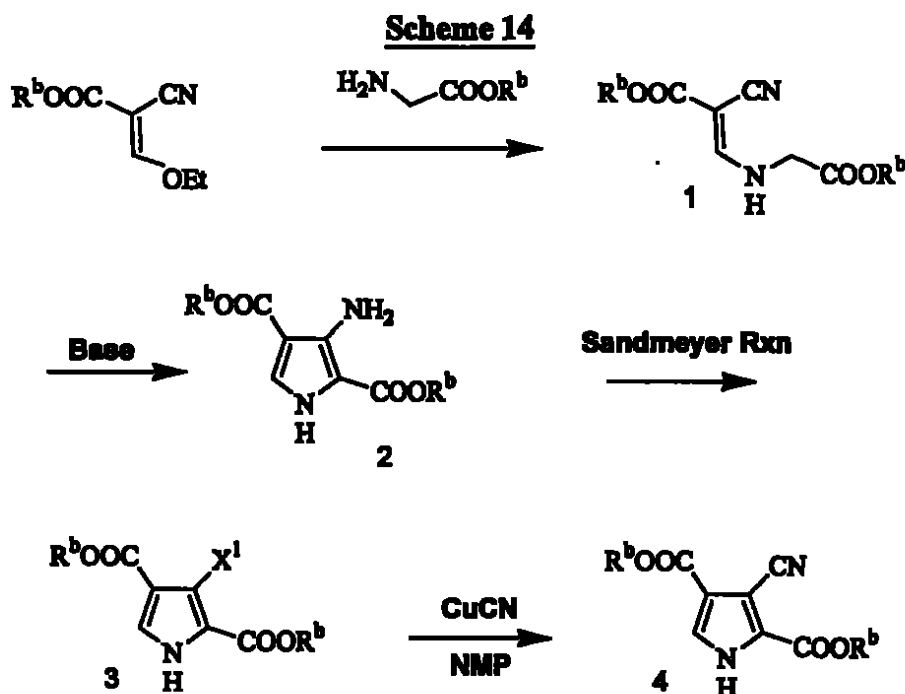


- Chloropyrrolotriazine (1) (compound 3 of Scheme 9) can be reacted with an aniline (1a) (e.g., compound 1 of Scheme 11) in anhydrous DMF at rt to afford compound (2). Reaction of compound (2) with an aq. base such as NaOH with heating affords compound (3). Compound (3) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as HOBt, with or without a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (4). Compound (4) can be reacted with hydrogen in the presence of a catalyst, such as Pd/C, in an organic solvent, such as MeOH to afford compound (5). Reaction of compound (5) with an isocyanate in an organic solvent, such as DCE affords compound (6).

Scheme 13

- Commercially-available compound (1a) (compound 1a of Schemes 11 and 12),
- 5 can be reacted with carbonyl diimidazole and with an amine $R_{18}NH_2$ in an organic solvent, such as DCE, to yield compound (8). Reaction of compound (8) with hydrogen in the presence of a catalyst, such as Pd, in an alcoholic solvent such as EtOH affords compound (9). Reaction of (9) with chloride (1) in an organic solvent, such as DMF, affords compound (10). Reaction of (10) with aq. NaOH with heating
- 10 affords product (11). Product (11) can be reacted with an amine R_2NH_2 in the presence of a coupling reagent, such as EDCI, and a base such as diisopropylamine, in an organic solvent, such as DMF to afford compound (7).

24



Glycine ethyl ester can be added to an alkyl alkoxy methylene cyanoacetate at
 5 from rt to 80°C to obtain compound (1). Compound (1) is cyclized to form pyrrole
 (2) upon treatment with a strong base, such as lithium hexamethyldisilazane, at from -
 78°C to rt in an organic solvent such as THF. Pyrrole (2) is converted to a halide
 using sodium nitrite in an organic solvent, such as DMF, and a halide source, such as
 CuBr to yield compound (3). Compound (3) can be converted to compound (4) using
 10 CuCN in an organic solvent such as NMP at elevated temperatures. Alternatively,
 compound (2) can be directly converted to compound (4) using sodium nitrite in an
 organic solvent, such as DMF, and a cyanide source such as CuCN. Compounds (3)
 and (4) can then be used as described in previous schemes (*e.g.*, as compound 3 of
 Scheme 2), to form compounds of Formula (I) wherein R₂ is halogen or cyano.

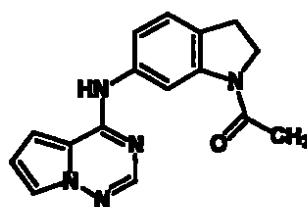
15 In addition, other compounds of formula I may be prepared using procedures
 generally known to those skilled in the art. In particular, the following examples
 provide additional methods for the preparation of the compounds of this invention.

The invention will now be further described by the following working examples,
 which are preferred embodiments of the invention. HPLC purifications were done on
 20 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

5 1-[2,3-Dihydro-6-(pyrrolo[2,1-f][1,2,4]triazin-4-ylamino)-1H-indol-1-yl]ethanone



A. 4-Bromo-pyrrolo[2,1-f][1,2,4]triazine

10 A mixture of 50 mg (0.37 mmol) of pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one [prepared as described in S.A.Patil, B.A. Otter and R.S. Klein, *J. Het. Chem.*, 31, 781-786 (1994)] and 0.5 g of phosphorus oxybromide was heated and kept at 60°C for 20 min. under argon. A clear orange melt was initially obtained which solidified to a yellow solid on continued heating. Ice was added with vigorous stirring. The mixture
15 was extracted twice with EtOAc. The combined extracts were washed with sat. NaHCO₃ and brine, dried (MgSO₄), and the solvent removed to afford 63 mg of crude Compound A as an orange oil which crystallized on standing. (M+H)⁺ = 198⁺, 200⁺.

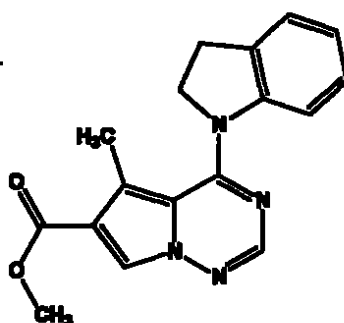
B. Example 1

A solution of 60 mg (0.3 mmol) of Compound A and 1-acetyl-6-
20 aminoindoline in 1.5 ml of acetonitrile was stirred overnight at rt under argon. A white precipitate was obtained which was removed by filtration. The filter cake was suspended in 10% isopropanol/methylene chloride for extraction. Sat'd NaHCO₃ was added and the mixture stirred until a solution was obtained. The organic layer was separated and washed with brine, dried (MgSO₄), and the solvent removed.
25 Purification by chromatography on silica gel with EtOAc yielded 4% of Example 1 as a white solid. (M+H)⁺ = 294.

Example 2

30 4-(2,3-Dihydro-1H-indol-1-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

25



A. Methylpyrrole-3-carboxylic acid methyl ester

To a 1.0 M solution of lithium hexamethyldisilazide in THF (41 mL, 41 mmol) at -78°C was added dropwise over 45 min. a solution of tosylmethyl isocyanide (8.1 g, 41 mmol) in THF. After the reaction was stirred for an additional 45 min., a solution of methyl crotonate in THF was added over 40 min. The reaction was warmed to 25°C and stirred for 5 h. The reaction was diluted with EtOAc and washed with sat. aq. NaHCO_3 . The aqueous layer was extracted three times with EtOAc, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel eluting with a gradient of 20-30% EtOAc in hexanes to provide Compound A.

B. 3-Methylpyrrole-2,4-dicarboxylic acid dimethyl ester

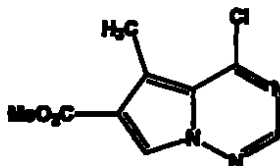
To a suspension of aluminum chloride (106.4 g, 798 mmol) in DCE (700 mL) at -40°C under nitrogen was added dropwise trichloroacetyl chloride (89 mL, 798 mmol). A solution of Compound A (37 g, 266 mmol) in DCE (200 mL) was added. The reaction mixture was gradually warmed to rt and stirred over the weekend (65 hr). A cold and pre-prepared mixture of aluminum chloride (53.2 g) and trichloroacetyl chloride (44.6 g) in DCE (450 mL) was added to the reaction mixture. After an additional 24 hr, the mixture was carefully poured into an ice-water bath (2 L) and the pH of the solution adjusted to 2.0. The organic layer was separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with 3 N HCl, brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a dark oil. This oil was dissolved in MeOH (400 mL), and the resulting solution was cooled to 0°C under nitrogen. To this solution was added sodium methoxide (25 % in MeOH) until the pH of the solution was 10. After 1 hr, the mixture was concentrated and then diluted with ice water (1 L) and the pH of the mixture was adjusted to 6. The mixture was extracted with DCM (3 x 1 L). The combined extracts were washed with NaHCO_3 , brine, dried (Na_2SO_4), and concentrated *in vacuo*. The brown solid obtained was purified by chromatography on silica gel eluting with EtOAc in hexanes to provide 44.3 g (84%) of Compound B. MS: $[\text{M}+\text{H}]^+ = 196$.

C. 1-Amino-3-methylpyrrole-2,4-dicarboxylic acid dimethyl ester

To a suspension of NaH (60% in oil, 33 mg, 0.83 mmol) in DMF (5 mL) at 0°C was added Compound B (46 g, 213 mmol) in DMF (3 mL). After 10 min. at 0°C, diphenyl phosphoryl hydroxylamine (0.19 g, 0.83 mmol) was added neat followed by DMF (3 mL). The reaction mixture was stirred for 2 hrs at 25°C and then quenched with pH 7 phosphate buffer (15 mL). The mixture was extracted with EtOAc (4 x 20 mL). The combined extracts were dried (Na₂SO₄) and after purification by chromatography on silica gel eluting with 25-30% EtOAc in hexanes, 38 g (84%) of Compound C was obtained as white solid. ESI [M+H]⁺ = 213.1.

D. 5-Methylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one-6-carboxylic acid methyl ester

Compound C (38 g, 179 mmol) was combined with formamide (400 mL) and heated to 165°C for 6 hr. The reaction was diluted with water (5 mL), extracted with EtOAc (3 x 10 mL), dried (Na₂SO₄), and concentrated. The crude material was purified by washing with ether/hexanes (7/3) to provide 33.4 g (90%) of Compound D as a white solid. ESI MS: [M-H]⁻ = 206.0

E. 4-Chloro-5-methyl-6-carbomethoxypyrrolo[2,1-f][1,2,4]triazine

20

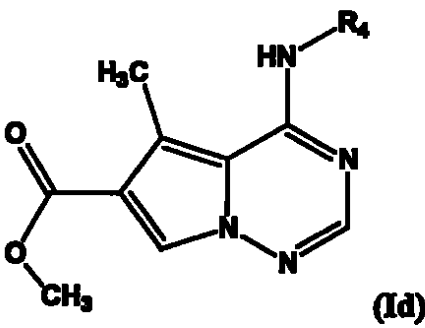
Phosphorous oxychloride (2.5 mL) was combined with Compound D (100 mg, 0.483 mmol) and heated at 100°C overnight. The melt was allowed to cool to rt and dissolved in EtOAc. The mixture was neutralized with aq. NaHCO₃ and extracted twice with EtOAc. The combined organic washes were dried (Na₂SO₄) and concentrated to provide 101 mg (93%) of Compound E. MS: (M+H)⁺ = 226.6.

F. Example 2

A mixture of Compound E (20 mg, 0.09 mmol) and indoline (21 mg, 0.177 mmol) in CH₃CN (1 mL) was shaken for 4 hrs. Then DMF (0.2 mL) was added, and the crude mixture was purified by preparative HPLC to provide 12.2 mg (45 %) of Example 2 as a white solid. [M+H]⁺ = 309.2; ¹H NMR (CDCl₃): δ 8.06 (s, 1H), 7.91 (s, 1H), 7.20 (m, 1H), 7.01 (m, 1H), 6.93-6.91 (m, 2H), 4.15 (t, J=7.8 Hz, 2H), 3.81 (s, 3H), 3.09 (t, J=7.8 Hz, 2H), 2.35 (s, 3H).

26

Examples 3-6



Compounds having the formula (Id), wherein the group R₄ has the values listed in Table 1, were prepared following the method of Example 2, using an appropriately-selected amine compound in place of indoline in step F.

TABLE 1

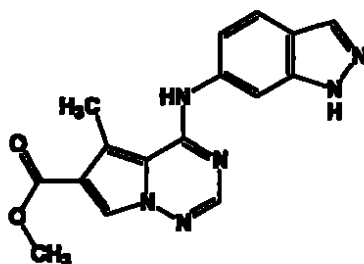
Ex	R ₄	Compound Name	Data
3		4-[[3-(Hydrazinocarbonyl)phenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 341.2; 1H NMR (d-DMSO): δ 7.79 (s, 1H), 7.58 (s, 1H), 7.11-7.05 (m, 3H), 6.72 (d, J = 8.1 Hz, 1H), 5.23 (br s, 2H), 3.76 (s, 3H), 2.67 (s, 3H)
4		4-[[3-(Acetylamino)phenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 340.2; 1H NMR (CDCl ₃): δ 7.81 (s, 1H), 7.75 (s, 1H), 7.51 (s, 1H), 7.20-7.07 (m, 3H), 3.80 (s, 3H), 2.84 (s, 3H), 1.90 (s, 3H)
5		4-[(1-Acetyl-2,3-dihydro-1H-indol-6-yl)amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 366.2; 1H NMR (CDCl ₃): δ 8.14 (d, J = 8.6 Hz, 1H), 7.95 (s, 1H), 7.82 (s, 1H), 7.51 (s, 1H), 7.12 (d, J = 8.6 Hz, 1H), 4.03 (t, J = 7.8 Hz, 2H), 3.81 (s, 3H), 3.18 (t, J = 7.8 Hz, 2H), 2.67 (s, 3H), 2.19 (s, 3H)
6		5-Methyl-4-[[2-methyl-5-[(methylsulfonyl)amino]phenyl]amino]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 390.2; 1H NMR (CDCl ₃): δ 8.04 (br s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.09-6.99 (m, 2H), 3.82 (s,

		ester	3H), 3.00 (s, 3H), 2.89 (s, 3H), 2.28 (s, 3H)
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Example 7

4-(1H-Indazol-6-ylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

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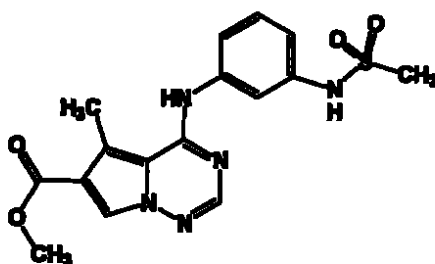


A mixture of Compound E from Example 2 (20 mg, 0.09 mmol) and 6-aminoindazole (18 mg, 0.13 mmol) in CH_3CN (1 mL) and DMSO (0.5 mL) was shaken for 4 hrs. The mixture was filtered, washed with CH_3CN , and the crude material was purified by preparative HPLC to provide Example 7 as a white solid (13 mg, 45 %). $[\text{M}+\text{H}]^+=323.1$; ^1H NMR (CDCl_3): δ 8.37 (s, 1H), 7.99 (s, 1H), 7.94 (d, $J=7.4$ Hz, 1H), 7.68 (d, $J=4.2$ Hz, 1H), 7.00 (dd, $J=7.4, 4.2$ Hz, 1H), 3.83 (s, 3H), 2.91 (s, 3H).

15

Example 8

5-Methyl-4-[[3-[(methylsulfonyl)amino]phenyl]amino]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



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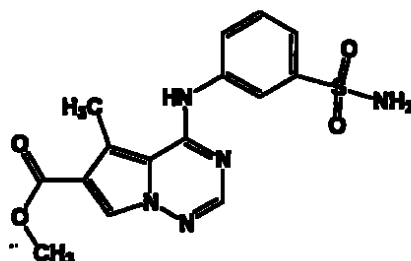
Compound E of Example 2 was dissolved in DMF (2 mL), and then 3-(methylsulfonylamino)aniline (54 mg, 0.3 mmol) was added. The reaction mixture was stirred for 4 hrs under argon at 25°C . The crude reaction mixture was purified by preparative HPLC. The material obtained appeared to be a salt of the desired compound. The material was dissolved in EtOAc and washed with sat'd NaHCO_3 . Evaporating the solvent gave 24 mg (40 %) of Example 8. MS: $[\text{M}+\text{H}]^+=376.2$; ^1H

25

NMR (*d*-DMSO): δ 8.89 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 7.38 (s, 1H), 7.34-7.32 (m, 2H), 7.01 (d, $J=8.0$ Hz, 1H), 3.81 (s, 3H), 3.02 (s, 3H), 2.82 (s, 3H).

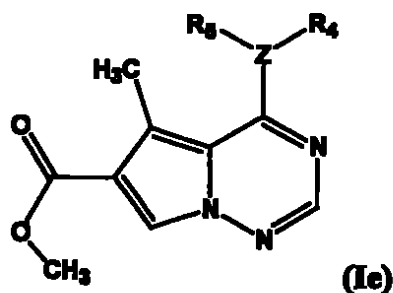
Example 9

5 4-[[3-(Aminosulfonyl)phenyl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid methyl ester



10 Compound E from Example 2 (20 mg, 0.09 mmol) was mixed with 3-aminobenzenesulfonamide (23 mg, 0.13 mmol) in DMF (1 mL) and shaken for 4 hrs. Evaporating the extracting solvent and purification by preparative HPLC gave 8.6 mg (58 %) of Example 9 as a solid. MS: $[M+H]^+ = 362$; ^1H NMR (*d*-DMSO): δ 9.08 (s, 1H), 8.18 (s, 2H), 7.98 (s, 1H), 7.91-7.89 (m, 1H), 7.62-7.58 (m, 2H), 7.42 (s, 2H),
15 3.81 (s, 3H), 2.84 (s, 3H)

Examples 10-14



20

Compounds having the formula (Ic), wherein the groups Z, R_3 , and R_4 together have the values listed in Table 2, were prepared following the method of Example 9, except instead of 3-aminobenzenesulfonamide, an appropriately-selected amino compound was used.

25

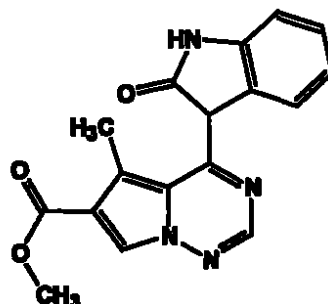
TABLE 2

Ex.	-ZR ₄ R ₅	Compound Name	Data
10		4-[[3-[(Butylamino)sulfonyl]phenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 418.2; ¹ H NMR (CDCl ₃): δ 8.07 (s, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 7.84-7.82 (m, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.49-7.45 (m, 2H), 3.82 (s, 3H), 2.93-2.89 (m, 2H), 2.81 (s, 3H), 1.44-1.18 (m, 4H), 0.84 (t, J=7.4 Hz, 3H)
11		4-[[3-(Aminosulfonyl)-4-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 376.2; ¹ H NMR (CDCl ₃): δ 8.05 (s, 1H), 7.91 (s, 1H), 6.97 (d, J=7.8 Hz, 1H), 6.31 (s, 1H), 6.23 (d, J=7.8 Hz, 1H), 4.22 (t, J=7.7 Hz, 2H), 3.84 (s, 3H), 2.84 (t, J=7.7 Hz, 2H), 2.55 (s, 3H).
12		4-[[6-(Acetylamino)-3-pyridinyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 341.2; ¹ H NMR (d-DMSO): δ 10.51 (s, 1H), 8.87 (s, 1H), 8.53 (s, 1H), 8.14-8.01 (m, 3H), 7.93 (s, 1H), 3.80 (s, 3H), 2.83 (s, 3H), 2.32 (s, 3H).
13		4-[(3,4-Dimethoxyphenyl)amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 343.2; ¹ H NMR (CDCl ₃): δ 7.91 (s, 1H), 7.85 (s, 1H), 7.21 (s, 1H), 7.00 (dd, J=8.6, 2.8 Hz, 1H), 6.82 (d, J=8.6 Hz, 1H), 3.84-3.82 (3s, 9H), 2.88 (s, 3H)
14		4-(2,3-Dihydro-3-oxo-1H-indazol-2-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 324.2; ¹ H NMR (CDCl ₃): δ 9.65 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 7.42-7.37 (m, 2H), 7.14-7.12 (m, 1H), 3.86 (s, 3H), 2.84 (s, 3H)
15		4-[5-(Aminocarbonyl)-2,3-dihydro-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 366.2; ¹ H NMR (CDCl ₃ /CD ₃ OH): δ 7.92 (s, 1H), 7.76 (s, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.25 (s, 1H), 7.05 (d, J=8.0 Hz, 1H), 3.82 (s, 3H), 2.25 (s, 3H)

7
28**Example 16**

4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

5

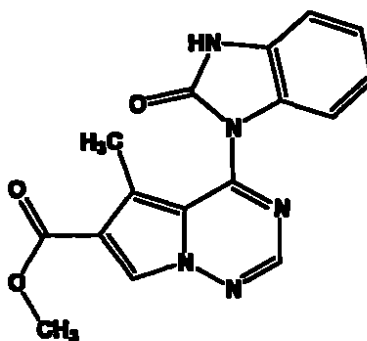


A solution of oxindole (5.32 g, 40 mmol) in THF (150 ml) and DMF (35 ml) was deoxygenated by purging with argon. This mixture was placed in an ice bath, and NaH (60% in oil, 1.7 g, 42 mmol) was added. After 30 min, 4-Chloro-5-methyl-6-carbomethoxypyrrolo[2,1-f][1,2,4]triazine (Compound E of Example 2) (3.38 g, 15 mmol) was added. After 1 hr at rt, the resulting mixture was neutralized with acetic acid. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with brine, and dried (MgSO₄). The solution was concentrated to a solid residue which was triturated with DCM and diethyl ether to afford the title compound as an orange solid (3.5 g, 72%). MS: [M+H]⁺ = 323.1; ¹H NMR (CDCl₃): δ 7.86 (s, 1H), 7.74 (s, 1H), 7.37 (s, 1H), 7.19 (d, *J*=7.6 Hz, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 7.10 (t, *J*=7.6 Hz, 1H), 7.06 (d, *J*=7.6 Hz, 1H), 3.84 (s, 3H), 2.34 (s, 3H).

20

Example 17

4-(2,3-Dihydro-3-oxo-1H-indazol-1-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



25

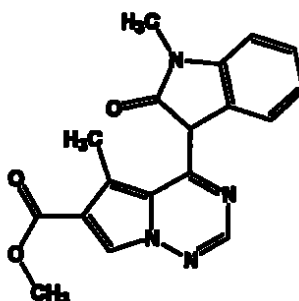
Example 17 above was prepared following the method of Example 16, except 3-indazolinone was used in place of oxindole. $[M+H]^+ = 324$; $^1\text{H NMR}$ (CDCl_3): δ 8.16 (s, 1H), 8.02-7.99 (m, 2H), 7.83-7.81 (m, 1H), 7.58-7.54 (m, 1H), 7.46 (s, 1H), 3.87 (s, 3H), 2.66 (s, 3H).

5

Example 18

4-(2,3-Dihydro-1-methyl-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

10

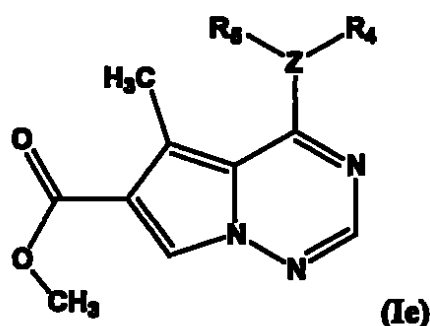


To a 0°C mixture of NaH (60%, 5 mg, 0.106 mmol) in DMF (0.5 mL) was added N-methyloxindole (22 mg, 0.15 mmol). The reaction mixture was stirred for 10 min. at 0°C . Compound E of Example 2 (22 mg, 0.10 mmol) in DMF (1 mL) was added. The reaction mixture was stirred for 45 min. at 25°C and then quenched with pH 7 phosphate buffer. The mixture was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and purified by preparative HPLC to provide Example 18 as a yellow solid. MS: $[M+H]^+ = 337.2$; $^1\text{H NMR}$ (CDCl_3): δ 7.90 (s, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 7.02 (t, $J=7.6$ Hz, 1H), 6.90 (d, $J=7.6$ Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 3.36 (s, 3H), 2.37 (s, 3H).

20

Examples 19-24

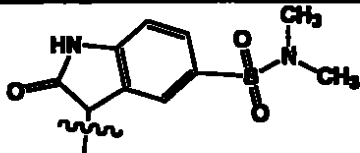
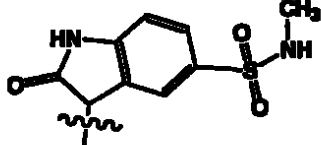
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Compounds having the formula (Ie), wherein the groups Z, R₃, and R₄ together have the values listed in Table 3, were prepared following the method of Example 18, except instead of oxindole, an appropriately-substituted oxindole was used, and for Examples 19 and 20, 2,3-dihydro-2-oxo-1H-benzimidazol (40.2 mg, 0.3 mmol) and (methylsulfonyl)amino]-2-oxo-1H-indole (90 mg, 0.4 mmol) were used, respectively, in place of oxindole. After purification by preparative HPLC, the desired material can be collected, concentrated, and neutralized with aq. NaHCO₃ or desilylated with tetrabutylammonium fluoride.

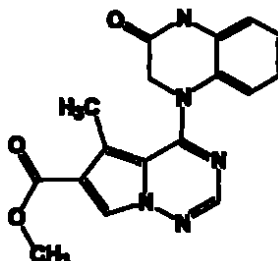
TABLE 3

Ex.	-ZR ₃ R ₄	Compound Name	Data
19		4-(2,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	¹ H NMR (CDCl ₃): δ 8.37 (s, 1H), 8.32 (s, 1H), 7.95 (br, s, 1H), 7.21-7.10 (m, 4H), 3.88 (s, 3H), 2.51 (s, 3H).
20		4-[2,3-Dihydro-5-[(methylsulfonyl)amino]-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	¹ H NMR (CD ₃ OD): δ 7.99 (s, 1H), 7.69 (s, 1H), 7.04-7.02 (m, 2H), 6.92 (d, J=8.8 Hz, 1H), 3.86 (s, 3H), 2.87 (s, 3H), 2.39 (s, 3H).
21		4-[5-(Aminosulfonyl)-2,3-dihydro-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M-H] ⁻ = 400.1; ¹ H NMR (CD ₃ OD): δ 8.05 (s, 1H), 7.83 (s, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.07 (d, J=8.3 Hz, 2H), 3.84 (s, 3H), 2.28 (s, 3H).
22		4-[2,3-Dihydro-5-[(2-hydroxyethyl)amino]sulfonyl]-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 446.2; ¹ H NMR (CDCl ₃ /CD ₃ OH): δ 7.84 (s, 1H), 7.55 (s,

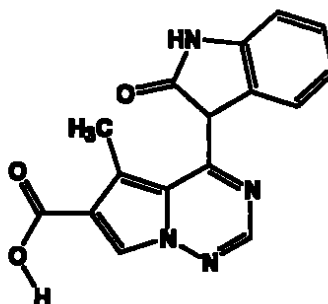
		f][1,2,4]triazine-6-carboxylic acid methyl ester	¹ H), 7.28 (d, J=8.6 Hz, 1H), 7.20 (s, 1H), 6.78 (d, J=8.6 Hz, 1H), 3.78 (s, 3H), 3.60 (t, J=7.4 Hz, 2H), 2.77 (t, J=7.4 Hz, 2H), 2.20 (s, 3H).
234		4-[5-[(Dimethylamino)sulfonyl]-2,3-dihydro-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M+H] ⁺ = 430. ¹ H NMR (CDCl ₃): δ 9.56 (s, 1H), 8.05 (s, 1H), 7.65-7.54 (m, 3H), 7.15 (d, J=8.2 Hz, 1H), 3.87 (s, 3H), 2.73 (s, 6H), 2.43 (3H, s)
24		4-[2,3-Dihydro-5-[(methylamino)sulfonyl]-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	MS: [M-H] ⁻ = 414. ¹ H NMR (CDCl ₃ /CD ₃ OH): δ 7.98 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.31 (d, J=7.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H).

Example 25

5 5-Methyl-4-(1,2,3,4-tetrahydro-3-oxo-1-quinoxaliny)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



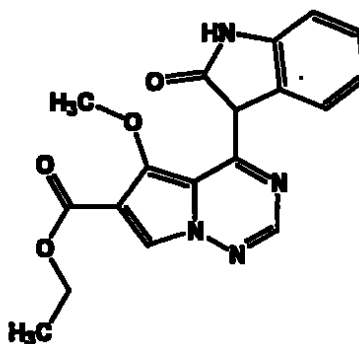
- 10 Example 2, Compound E (23 mg, 0.1 mmol) was stirred with 1,2,3,4-tetrahydroquinoxalin-2-one (44.4 mg, 0.3 mmol) in DMF (0.5 mL) for 1 hr at 50°C. Water was added, and the resulting solid material was collected, washed with water, and dried. The material was triturated with MeOH, filtered, and dried again to provide 20 mg (59%) of Example 25 as a white solid. ¹H NMR (*d*-DMSO): δ 8.30-8.25 (m, 2H), 7.12-7.03 (m, 2H), 6.83 (br s, 2H), 4.38 (s, 2H), 3.73 (s, 3H), 2.49 (s, 3H), 1.72 (s, 3H).
- 15

24
30**Example 26****4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid**

5

To a solution of Example 16 (3.3 g, 10.2 mmol) in MeOH (600 mL) was added KOH (1N aq. solution, 200 mL), and the mixture was deoxygenated by purging with argon. The reaction mixture was heated to 60°C for 20 hrs, then cooled and concentrated to about 50 mL. The residue was acidified with concentrated HCl to pH 4. The yellow solid was collected, washed with water, and dried *in vacuo* to afford the title compound (2.9 g, 92%). MS: $[M+H]^+ = 307.1$; $^1\text{H NMR}$ (CD_3OD): δ 7.94 (s, 1H), 7.71 (s, 1H), 7.18-7.10 (m, 2H), 6.94-6.86 (m, 2H), 2.45 (s, 3H).

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Example 27**4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methoxypyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester**

20

A. **[[2-Ethoxy-2-oxoethyl](phenylmethyl)amino]methylene] propanedioic acid diethyl ester**

N-benzylglycine ethyl ester (5.79 g, 30 mmol) was combined with diethyl ethoxymethylene malonate (6.48 g, 30 mmol) and stirred at 120°C for 1 hr. The crude material was used directly for the next reaction.

25

B. 1-Phenylmethyl-3-hydroxypyrrole-2,4-dicarboxylic acid diethyl ester

To a suspension of NaH (60% in oil, washed with hexanes, 500 mg, 12.5 mmol) in toluene (10 mL) was added Compound A (3.63 g, 10 mmol) in toluene (30 mL) dropwise at 50°C. After 2 hr, the mixture was poured into ice water and acidified with 1 N aq. HCl. The mixture was extracted three times with EtOAc. The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel eluting with 50% EtOAc in hexanes to provide 2.70 g (85%) of Compound B as a pink oil.

C. 1-Phenylmethyl-3-methoxypyrrole-2,4-dicarboxylic acid diethyl ester

Compound B (634 mg, 2 mmol) was stirred in acetone for 10 hrs at rt with methyl iodide (300 mg, 2.1 mmol) and K₂CO₃ (500 mg). The mixture was filtered, concentrated, and purified by chromatography on silica gel eluting with 33% EtOAc in hexanes to provide 470 mg (71%) of Compound C as a gel.

D. 3-methoxypyrrole-2,4-dicarboxylic acid diethyl ester

Compound C (27 g, 81.5 mmol) in EtOH (1 L) was mixed with Pd/C (10%, 4 g) and ammonium formate (28 g) and hydrogenated at 40 psi at 90°C for 18 hrs. The reaction mixture was cooled to rt, filtered, and concentrated. The crude material (brown oil) was purified by chromatography on silica gel eluting with 25% EtOAc in hexanes to provide 13 g (66%) of tan solid.

E. 1-Amino-3-methoxypyrrole-2,4-dicarboxylic acid diethyl ester

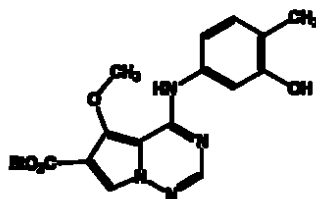
To a stirred suspension of NaH (60% in oil, 1.76 g, 70 mmol) in DMF (350 mL) under nitrogen at 0° C was added dropwise a solution of Compound D (13 g, 54 mmol) in DMF (200 mL). After 30 min, the mixture was diluted with DMF (750 mL), and then diphenyl phosphoryl hydroxylamine (15.7 g, 67.4 mmol) was added and the reaction mixture was allowed to warm to rt. After 6 hrs, the mixture was concentrated and the residue diluted with water (1 L) and extracted with EtOAc (3x1 L). The combined organic extracts were dried (MgSO₄), concentrated, and purified by chromatography on silica gel eluting with 20% EtOAc in hexanes to provide 13 g (93%) of solid.

F. 4-Hydroxy-5-methoxypyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester

Compound E (100 mg, 0.39 mmol) was combined with formamide (1 mL) and heated at 180°C for 6 hrs. The reaction mixture was cooled to rt and diluted with

water (5 mL). The solid which formed was collected, washed with water, and dried to provide 70 mg (76%) of Compound F.

G. 4-Chloro-5-methoxypyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester



5

Phosphorous oxychloride (1 mL) was combined with Compound F (23.7 mg, 0.1 mmol) and heated at reflux for 2 hrs. The melt was allowed to cool to rt and phosphorous oxychloride was removed on rotary evaporator.

10

H. Example 27

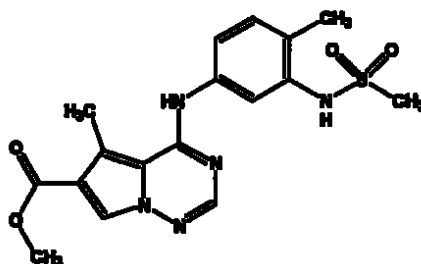
To a suspension of NaH (60%, 44 mg, 1.1 mmol) in THF (1 mL) was added oxindole (133 mg, 1 mmol). The reaction mixture was stirred for 20 min. at rt and Compound G (0.1 mmol) was added. The reaction was stirred for 2 hrs at 25°C. The crude material was purified by preparative HPLC followed by chromatography on silica gel eluting with EtOAc to provide 5.5 mg (16%) of Example 27 as a yellow solid. MS: $[M+H]^+ = 353$; ^1H NMR ($CDCl_3$): δ 8.42 (s, 0.4H), 8.10 (s, 0.6H), 7.79 (s, 1H), 7.75-6.88 (m, 4H), 4.33 (m, 2H), 3.57 (s, 3H), 1.37 (m, 3H).

15

20

Example 28

5-Methyl-4-[[4-methyl-3-[(methylsulfonyl)amino]phenyl]amino]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



25

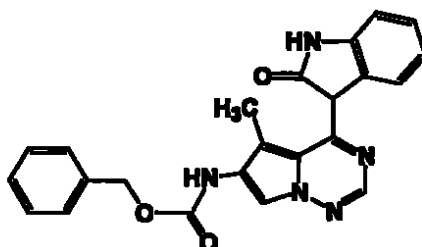
To a solution of Example 6 (16 mg, 51 μ mol) in pyridine (1 mL) at 0°C was added 4-methyl-3-[(methylsulfonyl)amino]aniline (4.4 μ L, 87 μ mol). The reaction mixture was stirred for 1 hr at 0°C and then warmed to 25°C and stirred for 4 hrs. Water (5

mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). The crude material was purified by chromatography on silica gel eluting with 2% MeOH in chloroform to provide 6.9 mg (30%) of solid. MS: $[\text{M}+\text{H}]^+ =$

5 390.2; ^1H NMR (CDCl_3): δ 7.93 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.35 (d, $J=8.2$ Hz, 1H), 7.27 (s, 1H), 7.18 (d, $J=8.2$ Hz, 1H), 6.25 (s, 1H), 3.82 (s, 3H), 3.03 (s, 3H), 2.86 (s, 3H), 2.24 (s, 3H)

Example 29

10 [4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl]carbamic acid phenylmethyl ester

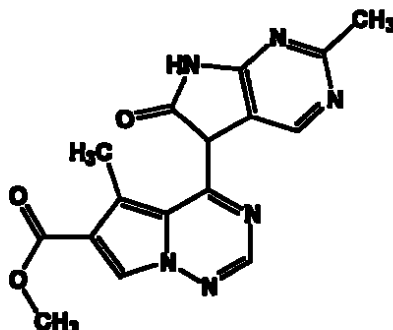


To a solution of Example 26 (29 mg, 0.09 mmol) in 1,4-dioxane (0.6 mL)
 15 under Ar with powdered 4 Å molecular sieves was added TEA (10 μL , 71 μmol),
 diphenylphosphoryl azide (15 μL , 71 μmol) and benzyl alcohol (12 μL , 0.12 mmol).
 The reaction was warmed at 50°C for 15 hrs. The mixture was concentrated *in vacuo*
 and chromatographed directly on silica gel eluting with a gradient of 2-5% MeOH in
 chloroform to provide 8 mg (50%) of an intermediate product as a white solid.
 20 Phosphorous oxybromide (5 eq.) was combined with this intermediate (16 mg, 0.054
 mmol) and heated to 60°C for 20 min. The melt was poured into ice water and
 extracted with EtOAc (4 x 5 mL). The extracts were washed with aq. NaHCO_3 , dried
 (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in a mixture of
 CH_3CN (0.5 mL) and DMF (0.1 mL), and then 5-amino-o-cresol (10 mg, 0.081 mmol)
 25 was added. The reaction mixture was stirred overnight under argon at 25°C. Solvent
 was removed *in vacuo*, and the crude material was purified by rotary chromatography
 on a 1 mm silica gel plate eluting with 2% MeOH in chloroform to afford the title
 compound as yellow oil (5 mg, 13%). MS: $[\text{M}+\text{H}]^+ = 414$; ^1H NMR (CDCl_3): δ 7.94
 (s, 1H), 7.82 (s, 1H), 7.41-7.34 (m, 5H), 7.17-7.14 (m, 1H), 7.04-7.02 (m, 1H), 6.93-
 30 6.90 (m, 2H), 6.44 (s, 1H), 5.23 (s, 2H), 2.12 (s, 3H).

32

Example 30

4-(2,3-Dihydro-6-methyl-2-oxo-1H-pyrazolo[2,3-d]pyrimidin-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



5

A. 6-Methyl-5,7-diazaoxindole

To a solution of ethyl (4-amino-2-methylpyrimidin-5-yl) acetate (WO 99/10349, 0.975 g, 5 mmol) in THF (30 ml), was slowly added potassium t-butoxide (1 M in THF, 5 mL). After one hour, the mixture was neutralized with acetic acid to pH 5. The volatiles were removed *in vacuo* and the residue purified by flash column chromatography (silica gel, 5-8 % MeOH in DCM) to afford a yellow solid (680 mg, 91%).

B. Methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

To a solution of 6-methyl-5,7-diazaoxindole (67 mg, 0.45 mmol) in DMF (2 ml) and THF (1 ml) was added NaH (60% in oil, 20 mg, 0.5 mmol). After stirring for 20 min, Compound E of Example 2 (34 mg, 0.15 mmol) was added. The mixture was stirred at rt overnight and then neutralized with acetic acid. DCM (10 ml) was added and the resulting precipitate was collected and washed with small amounts of DCM and water and then dried *in vacuo* to give the title compound as an orange solid (32 mg, 63%). MS: (M+H) = 359

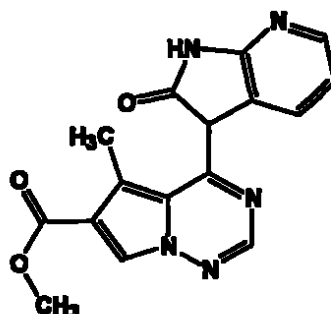
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Example 31

4-(2,3-Dihydro-2-oxo-1H-pyrazolo[2,3-b]pyridin-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

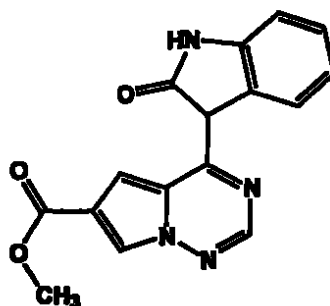
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To a solution of 7-azaoxindole (see Tetrahedron Lett., Vol. 28 (1987), at p. 4027) (60 mg, 0.45 mmol) in DMF (2 mL) and THF (1 mL) was added NaH (60% in oil, 20 mg, 0.5 mmol). After stirring for 20 min, Compound E of Example 2 (34 mg, 0.15 mmol) was added, and the mixture was stirred at rt overnight. The solution was neutralized with acetic acid, and then DCM (10 ml) was added to the mixture. The resulting solid was collected, washed with small amounts of DCM and water and dried *in vacuo* to give a yellow solid (35 mg, 72%). LC-MS: (M+H)⁺ = 324.

Example 32

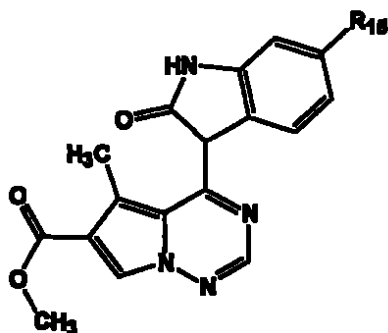
4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester



Example 2 was following using 2-methoxycarbonyl pyrrole as the starting pyrrole to afford 4-chloro-6-carbomethoxypyrrolo[2,1-f][1,2,4]triazine, which was then converted to Example 32 using the same or similar procedure of Example 31.

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33

Examples 33-36

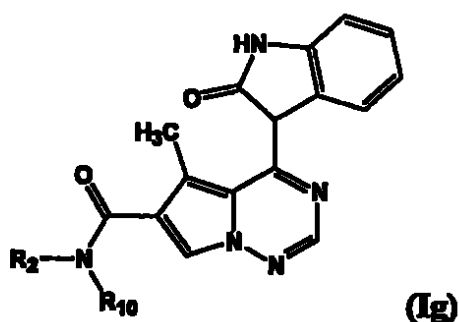


(If)

Compounds having the formula (If), wherein R_{15} has the values listed in Table 4, were prepared by following the procedure of Example 32 using appropriate reagents known in the literature (see, WO 97/42187).

TABLE 4

Ex.	R_{15}	Compound name
33	F	4-[6-Fluoro-2-hydroxy-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester
34	Br	4-[6-Bromo-2-hydroxy-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester
35	CF ₃	4-[2,3-Dihydro-2-oxo-6-(trifluoromethyl)-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester
36	SO ₂ Me	4-[2,3-Dihydro-6-(methylsulfonyl)-2-oxo-1H-indol-3-yl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester

Examples 37-49

To Example 26 (50 mg, 0.16 mmol) in DMF (1 mL) and DCM (0.5 mL) were added PyBrop (113 mg, 0.24 mmol) and DIPEA (0.08 mL, 0.5 mL). After 10 min, an appropriate amine was added. After 15 h, the reaction mixture was purified by preparative RP HPLC to provide the compounds of formula (Ig), above, wherein R₂ and R₁₀ have the values listed in Table 5.

10

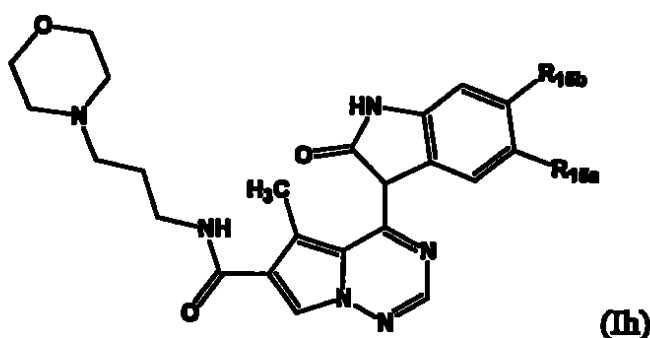
TABLE 5

EX.	R ₂	R ₁₀	Compound Name
37		CH ₃	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-N,5-dimethyl-N-[2-(1-pyrrolidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
38		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[2-(1-pyrrolidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
39		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(4-morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
40		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[2-(4-morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
41		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(4-methyl-1-piperazinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
42		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(1H-1,2,3-triazol-1-yl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

23
34

43		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(2H-1,2,3-triazol-2-yl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
44		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(1H-1,2,4-triazol-1-yl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
45		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(2-methyl-1H-imidazol-1-yl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
46		H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[4-(4-morpholinyl)butyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
47		CH ₃	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-N,5-dimethyl-N-[3-(4-morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
48	H	H	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide
49	H	CH ₃	4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

Examples 50-52



5 Compounds having formula (Ih), wherein R_{12a} and R_{12b} have the values listed in Table 6 below, were prepared by the following process, using the appropriately substituted oxindole in step C.

A. 5-Methylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one-6-carboxylic acid

To a solution of 5-Methylpyrrolo[2,1-f][1,2,4]triazin-4(3H)-one-6-carboxylic acid methyl ester (Compound D from Example 2, 1.035 g, 5.00 mmol) in a mixture of

10 acid methyl ester (Compound D from Example 2, 1.035 g, 5.00 mmol) in a mixture of

THF/MeOH/water (50 mL, 3:1:1) was added lithium hydroxide (2.062 g, 49.1 mmol). The reaction mixture was stirred at 55°C for 12 h, then cooled to 0°C and neutralized by 3N HCl. The organic solvents were removed and the aqueous solution brought to pH 4 with 1 N HCl. The resulting precipitate was filtered, rinsed with cold water, and air dried to afford Compound A as an off-white solid (0.965 g, 100%).

B. 4-Chloro-5-methyl-N-[3-(4-morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

A suspension of Compound A (2.00 g, 10.4 mmol) in phosphorous oxychloride (8 mL) was stirred at 100°C over 4 h. The solvent was removed *in vacuo* using toluene to assist in the removal. The resulting green solid was suspended in acetonitrile (20 mL) at 0°C and treated with sufficient TEA (5 mL) to bring the solution to pH 10. 4-(3-aminopropyl)morpholine (1.5 mL, 10.3 mmol) was added, and the solution was allowed to stir at rt over 1 h. The reaction mixture was poured into saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was dried (MgSO₄) and the volatiles were removed *in vacuo* to afford Compound B as a yellow solid (1.75 g, 50%).

C. Examples 50-52

To a solution of an appropriately substituted oxindole, *i.e.*, 5-fluoro oxindole for Example 50 (36 mg, 0.24 mmol) in DMF (1 mL) was added NaH (5.9 mg, 0.23 mmol). After 30 min at rt, a solution of Compound B (24 mg, 0.072 mmol) in DMF (1 mL) was added and the resulting mixture was stirred at rt over 1 h. The solvent was removed *in vacuo* and the mixture purified by RP HPLC. MeOH in the desired HPLC fractions was removed *in vacuo* and the resulting aq. solution neutralized using sat'd sodium bicarbonate solution, then extracted with EtOAc. The organic layer was dried (MgSO₄) and the volatiles were removed *in vacuo*. The solid obtained was dissolved in acetonitrile/MeOH and treated with 1 N HCl in diethyl ether. The mixture was stirred at rt over 1 h and the solvents removed *in vacuo*. The HCl salt of the title compound was obtained as an orange solid (18 mg, 51%).

TABLE 6

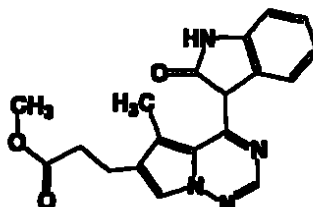
Ex.	R _{1a}	R _{1b}	Compound Name	Data
50	F	H	4-(5-Fluoro-2,3-dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(4-morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	MS: (M+H) ⁺ = 453.
51	H	F	4-(6-Fluoro-2,3-dihydro-2-oxo-1H-indol-3-yl)-5-methyl-N-[3-(4-	—

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35

			morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;	
52	-SO ₂ NH ₂	H	4-[5-(Aminosulfonyl)-2,3-dihydro-2-oxo-1H-indol-3-yl]-5-methyl-N-[3-(4-morpholinyl)propyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	—

Example 53**4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-propanoic acid methyl ester**

5

**A. 4-Phenoxy-5-methyl-6-carbomethoxypyrrolo[2,1-f][1,2,4]triazine**

10

To a solution of phenol (705 mg, 7.5 mmol) in a mixture of THF (10 mL) and DMF (10 mL) was added NaH (60% in oil, 300 mg, 7.5 mmol). After 30 min, 4-chloro-5-methyl-6-carbomethoxypyrrolo[2,1-f][1,2,4]triazine (675 mg, 3.0 mmol - Compound E from Example 2) was added. After 1 h, the solvent was removed and the residue poured into 5% aq. K₂CO₃ solution. The precipitate was collected, washed with water, and dried *in vacuo* to afford Compound A as white solid (800 mg, 94%). MS: (M+H)⁺ = 284.

15

B. 4-Phenoxy-5-methyl-6-hydroxymethylpyrrolo[2,1-f][1,2,4]triazine

To a solution of Compound A (700 mg, 2.47 mmol) in toluene (20 mL) at -60 °C, was added DIBAL (1.5 M in toluene, 6 mmol). After stirring at 0 °C for 1 h, aq. 1N HCl (30 mL) was added and the mixture stirred for 30 min. The mixture was then diluted with DCM. The organic layer was separated, dried (MgSO₄), and concentrated. The residue was purified by flash column chromatography (silica gel, 2 % MeOH in DCM) to afford Compound B as a solid (610 mg, 96%). MS: (M+H)⁺ = 256.

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C. 4-Phenoxy-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxaldehyde

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A mixture of Compound B (500 mg, 1.96 mmol) and MnO₂ (3.0 g) in toluene (30 mL) was heated at 60 °C for 1 h. After cooling to rt, the mixture was filtered through a pad of silica gel and washed with EtOAc. After concentration *in vacuo*, Compound C was obtained as a white solid (420 mg, 85%). MS: (M+H)⁺ = 254

D. 4-Phenoxy-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-propanoic acid methyl ester.

DBU (1.42 mL, 9.49 mmol) was added to a solution of Compound C (600 mg, 2.37 mmol) and methyl diethylphosphonoacetate (1.74 mL, 9.49 mmol) in DCE (20 mL). After stirring at rt overnight, the reaction mixture was diluted with DCM and washed with aq. 2% citric acid, brine, dried (MgSO_4), and concentrated. The organic extract was concentrated and the residue purified by chromatography on silica gel and elution with 20% EtOAc/DCM to afford a white solid (710 mg, 97%). MS: $(\text{M}+\text{H})^+ = 310$.

E. 4-Hydroxy-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-propanoic acid methyl ester.

Pd/C (10%, 70 mg) was added to a solution of Compound D (710 mg, 2.30 mmol) in a solvent mixture EtOAc/MeOH/THF/AcOH (100 mL/100 mL/20 mL/2 mL). The suspension was stirred under hydrogen for 2h. The reaction mixture was passed through Celite, the Celite was washed with MeOH, and the filtrate was concentrated *in vacuo* to give crude product. Trituration with hexanes afforded Compound E as a white solid (430 mg, 88%). MS: $(\text{M}+\text{H})^+ = 236$.

F. 4-Chloro-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-propanoic acid methyl ester.

A mixture of DIPEA (0.24 mL, 1.4 mmol), Compound E (220 mg, 0.94 mmol) and POCl_3 (3 mL) was heated in a sealed bottle at 80°C. After 2 h, the mixture was cooled down to rt and concentrated *in vacuo* to give a residue. The residue was partitioned between DCM and aq. NaHCO_3 solution. The DCM layer was separated, dried (MgSO_4), and concentrated *in vacuo* to give a dark green solid. Purification by chromatography on silica gel and elution with 20% EtOAc/DCM afforded Compound F as a yellow solid (220 mg, 92%). MS: $(\text{M}+\text{H})^+ = 254$.

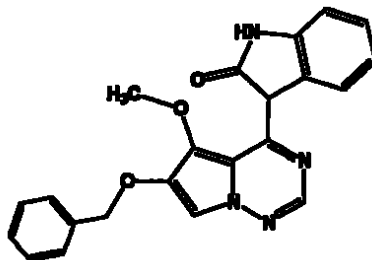
G. 4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-propanoic acid methyl ester.

NaH (60% in oil, 28 mg, 0.71 mmol) was added to a solution of oxindole (94 mg, 0.71 mmol) in DMF (2 mL) under argon. The mixture was stirred for 10 min. and Compound F (60 mg, 0.24 mmol) was added. After 1 h at RT, the reaction was quenched by the addition of acetic acid and diluted with DCM. The organic solution was washed with water, dried (MgSO_4), and concentrated *in vacuo* to give crude product. Purification by chromatography on silica gel and elution with 20% EtOAc/DCM afforded the title compound as a pure yellow solid (78 mg, 94%). MS: $(\text{M}+\text{H})^+ = 351$.

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Example 54**1,3-Dihydro-3-[5-methoxy-6-(phenylmethoxy)pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2H-indol-2-one**

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**A. 4-Hydroxy-5-methoxypyrrolo[2,1-f][1,2,4]triazine-6-methanol**

4-Hydroxy-5-methoxypyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester (Compound F of Example 27 -3.56 g, 15 mmol) was combined with lithium tri-*tert*-butoxyaluminumhydride (1 M solution in THF, 60 mL, 60 mmol) and heated at reflux overnight. The reaction mixture was allowed to cool to rt and quenched with 1 N aq. HCl. The mixture was concentrated to remove volatiles and the remaining material was combined with 100 g of silica gel and applied to a flash silica gel column which was eluted with EtOAc to provide 2.65 g (90%) of Compound A. MS: $[M+H]^+ = 196$.

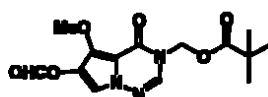
B. 2,2-Dimethylpropanoic acid [6-(hydroxymethyl)-5-methoxy-4-oxopyrrolo[2,1-f][1,2,4]triazin-3(4H)-yl]methyl ester

Compound A (195 mg, 1 mmol) was dissolved in 1.5 mL of DMF. NaH (60% in oil, 48 mg, 1.2 mmol) was added and the reaction mixture was stirred at rt for 0.5 hr. Chloromethyl pivalate (181 mg, 1.2 mmol) was added and the mixture was stirred for 1 hr. Water was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography on silica gel eluting with 33% EtOAc in hexanes to provide 260 mg (84%) of Compound B as a solid. MS: $[M+H]^+ = 310$.

C. 2,2-Dimethylpropanoic acid [6-formyl-5-methoxy-4-oxopyrrolo[2,1-f][1,2,4]triazin-3(4H)-yl]methyl ester

Compound B (740 mg, 2.39 mmol) was suspended in toluene (10 mL) with manganese dioxide (835 mg, 9.6 mmol) and heated at 100°C for 3 hr. The reaction mixture was cooled to rt, filtered, and the precipitate was washed with EtOAc. The filtrate was concentrated *in vacuo* to provide 660 mg (90%) of Compound C as a solid. MS: $[M+H]^+ = 308$.

D. 2,2-Dimethylpropanoic acid [6-formyloxy-5-methoxy-4-oxopyrrolo[2,1-f][1,2,4]triazin-3(4H)-yl]methyl ester



Compound C (660 mg, 2.15 mmol) was dissolved in CH_2Cl_2 (10 mL). M-chloroperoxybenzoic acid (57%, 745 mg, 2.46 mmol) was added with MgSO_4 (2.0 g), and the reaction mixture was stirred at rt for 5 hr. The mixture was filtered and the filtrate washed with aq. NaHCO_3 solution twice, dried (MgSO_4), and concentrated to provide 680 mg (98%) of Compound D as a solid. MS: $[\text{M}+\text{H}]^+=324$.

E. 2,2-Dimethylpropanoic acid [5-methoxy-4-oxo-6-(phenylmethoxy)pyrrolo[2,1-f][1,2,4]triazin-3(4H)-yl]methyl ester

Compound D (680 mg, 2.10 mmol, 1 eq) was dissolved in acetone (10 mL) followed by the addition of benzyl bromide (430 mg, 2.5 mmol) and K_2CO_3 (1.0 g, 7.25 mmol). The reaction mixture was stirred at 60°C for 10 hr, cooled to rt, and filtered. The filtrate was concentrated and purified by flash silica gel chromatography eluting with 25% EtOAc in hexanes to provide 485 mg (60%) of Compound E as a gel. MS: $[\text{M}+\text{H}]^+=386$;

F. 5-Methoxy-6-(phenylmethoxy)pyrrolo[2,1-f][1,2,4]triazin-4(3H)-one

Compound E (65 mg, 0.17 mmol) was stirred at rt in a mixture of MeOH (1 mL) and ammonium hydroxide (0.2 mL) for 6 hrs. The mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 , and purified by flash silica gel chromatography eluting with 33% EtOAc in hexanes to provide 45 mg (97%) of compound F as a solid. MS: $[\text{M}+\text{H}]^+=272$.

G. 4-Chloro-5-methoxy-6-(phenylmethoxy)pyrrolo[2,1-f][1,2,4]triazine

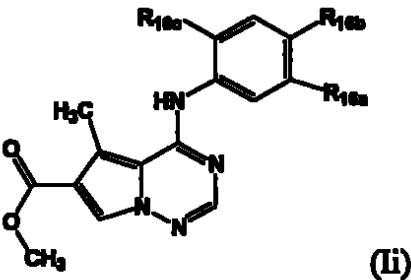
Compound F (44 mg, 0.16 mmol) was stirred with POCl_3 (0.5 mL) at 60°C for 3 hr. The mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 (2 mL), and stirred with solid NaHCO_3 for 10 min. The mixture was filtered and concentrated to provide 46 mg (99%) of Compound G as a solid. MS: $[\text{M}+\text{H}]^+=286$. (The Cl substituent may be replaced with OCH_3 upon standing in MeOH); R.T.=3.265 min (YMC S5 ODS column 4.6 x 50 mm, 10-90% aq. MeOH over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); ^1H NMR (CDCl_3): δ 8.01 (s, 1H), 7.45-7.30 (m, 6H), 5.15 (s, 2H), 4.03 (s, 3H).

2/3
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H. 1,3-Dihydro-3-[5-methoxy-6-(phenylmethoxy)pyrrolo [2,1-f][1,2,4]triazin-4-yl]-2H-indol-2-one

To a suspension of NaH (60% in oil, 19.2 mg, 0.48 mmol) in DMF (0.5 mL) was added oxindole (63.4 mg, 0.48 mmol). The reaction mixture was stirred for 1 hr at RT. Compound G (38 mg, 0.16 mmol, 1 eq) was added, and the mixture was stirred for 1 hr. The mixture was diluted with water and filtered. The resulting solid was triturated with MeOH and dried to provide 38 mg (62%) of the titled compound. MS: [M+H]⁺ = 387; ¹H NMR (d-DMSO): δ 12.83 (br s, 1H), 10.64 (br s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.50-7.31 (m, 6H), 7.02-6.94 (m, 1H), 6.89-6.82 (m, 2H), 5.10 (s, 2H), 3.55 (s, 3H).

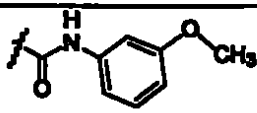
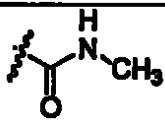
Examples 55-60



Compounds having the formula (Ii), wherein R_{16a}, R_{16b}, and R_{16c} have the values listed in Table 7, below, were prepared following the procedure described for Example 54, except using a different phenylamine.

TABLE 7

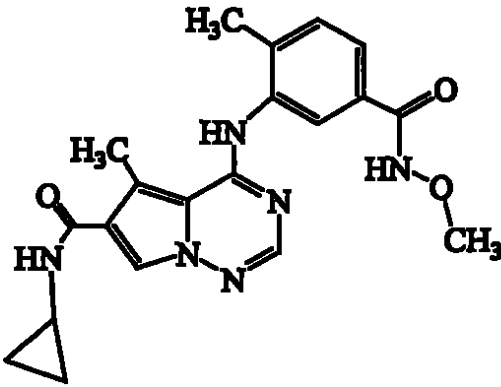
Ex	R _{16a}	R _{16b}	R _{16c}	Compound Name	Data
55	F	H	CH ₃	4-[(5-Fluoro-2-methylphenyl)amino]-5-methylpyrrolo [2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =315.2; ¹ H NMR (CDCl ₃) δ 7.97 (br s, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.13 (t, J=8.2 Hz, 1H), 6.77 (dt, J=2.7, 8.3 Hz, 1H), 3.87 (s, 3H), 2.82 (s, 3H), 2.27 (s, 3H)
56		H	CH ₃	4-[[5-[(Ethylamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo [2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =368.23; ¹ H NMR (CDCl ₃) δ 8.17 (br s, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.23 (d, J=7.7 Hz, 1H), 3.82 (s, 3H), 3.40 (m, 2H), 2.88 (s, 3H), 2.30 (s, 3H), 1.85 (m, 3H).

57	H	F	CH ₃	4-[(4-Fluoro-2-methylphenyl)amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =315.1; ¹ H NMR (CDCl ₃) δ 7.99 (s, 1H), 7.87 (s, 1H), 7.68 (br s, 1H), 6.99 (m, 2H), 3.88 (s, 3H), 2.85 (s, 3H), 2.31 (s, 3H).
58	H	F	H	4-[(4-Fluorophenyl)amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =301.1; ¹ H NMR (CDCl ₃) δ 7.94 (s, 1H), 7.85 (s, 1H), 7.54 (m, 2H), 7.05 (t, J=8.8 Hz, 2H), 3.82 (s, 3H), 2.82 (s, 3H).
59		H	CH ₃	4-[[5-[(3-Methoxyphenyl)amino]carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =446.2.
60		H	CH ₃	5-Methyl-4-[2-methyl-5-[(methylamino)carbonyl]phenoxy]pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester	[M+H] ⁺ =355.1.

Example 61

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

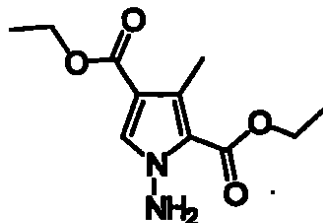
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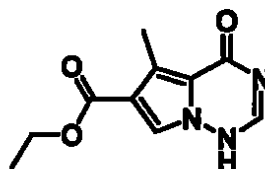
The compound of Example 61 was prepared as set forth below, using the Scheme 9 described above, wherein Compounds (A)-(E) have the structures indicated below.

5 A.



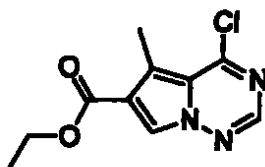
To a solution of the 3-methyl-1-pyrrole-2,4-diethyl ester (100 mg) (*J. Heterocyclic Chem* Vol. 34 (1997), at pp. 177-193; *Heterocycles*, Vol. 50 (1999), at pp. 853-866; *Synthesis* (1999), at pp. 479-482) in DMF (0.44M) was added either NaH or KOtBu (1.2 equiv) at rt. This solution was stirred for 30-45 minutes. Chloramine in ether (ca. 0.15M, 1 eq.) was added via syringe. The solution was stirred for 1.5 h or until starting material was converted to product as judged by HPLC analysis. The reaction was then quenched with aq. Na₂S₂O₃ and extracted with EtOAc or Et₂O. The organic extracts were washed with water and brine and then dried over sodium sulfate. Compound A was obtained in >90% yield. NH₄Cl in ether was prepared according to the procedure of Nunn, *J. Chem. Soc. (C)*, (1971) at p. 823.

20 B.



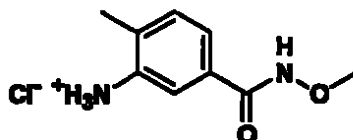
To a solution of Compound A (2 g) in formamide (8 mL) was added acetic acid (20% by weight), and the mixture was heated at 120°C for 24h. The reaction mixture was cooled and water added (32 mL) to precipitate the product. The solids were collected by filtration and washed with EtOAc to furnish Compound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

30 C.



To a solution of Compound B (10 g, 45.2 mmol) in toluene (150 mL) was added DIPEA (6.31 mL, 36.2 mmol, 0.8 equiv) and POCl₃ (5.05 mL, 54.2 mmol, 1.2 equiv) and the reaction mixture heated at 120-125 °C (oil bath temp) for 20 h. The reaction mixture was cooled and poured into ice cold sat. NaHCO₃-water-toluene (450 mL-450 mL-150 mL) and stirred rapidly to assure quenching of the excess POCl₃. The layers were separated (filtered through celite if a suspension forms) and the organic layer was washed again with sat. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford Compound C as a tan yellow solid (9.9g, 95%).

D.



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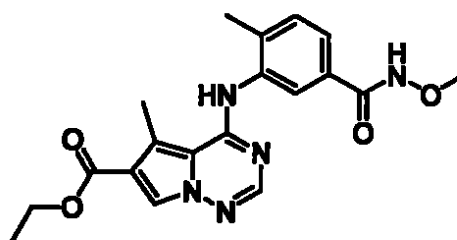
A mixture of commercially-available 4-amino-3-methylbenzoic acid (100 g, 0.66 mol) and N-(*tert*-butoxycarbonyl)anhydride (150 g, 0.68 mol) in THF (1000 mL) was slowly heated to 50°C overnight. The resulting mixture was cooled to rt and the solvent was removed on a rotary evaporator. The resulting solids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

To the above, light-pink solid was added EDCI (127 g, 0.66 mol), HOBT (90 g, 0.66 mol), and DMF (1000 mL), and the resulting mixture was stirred at rt for 30 minutes followed by addition of methoxyamine hydrochloride (55 g, 0.66 mol) in one portion. After stirring for 10 min, the mixture was cooled using an ice bath. DIPEA (250 mL, 1.4 mol) was added at such a rate so as to maintain the internal reaction temperature below 25°C. After the addition was complete, the ice bath was removed and the reaction was stirred overnight at rt. The reaction mixture was partitioned between 0.5 L of water and 1.5 L of EtOAc and the resulting layers were separated. The aqueous portion was extracted with additional EtOAc (400 mL x 3), and the combined organic extracts were washed with water (300 mL x 3), cold 0.5 N aq. HCl

(400 mL x 2), and water (500 mL). The product was then extracted with cold 0.5 N aq. NaOH (300 mL x 3) and the combined basic aqueous extracts were neutralized to pH = 8 by a slow addition of cold 0.5 N aq. HCl. The resulting solid which precipitated was collected by filtration and washed with cold water. The wet solid was decolorized in hot EtOH with active charcoal to give 106 g of white solid as the BOC-protected N-methoxyamide intermediate.

To a slurry of the above solid (91 g, 0.32 mol) in 1,4-dioxane (400 mL) at rt was added a 4M solution of HCl in dioxane (400 mL), and the resulting mixture was stirred at rt overnight. Diethyl ether (1000 mL) was added and the precipitated solid was collected by filtration and triturated with a hot EtOH/H₂O mixture (4:1 v/v). Drying the resulting solid *in vacuo* afforded 53 g of the pure hydrochloride salt (Compound D) as a white solid. ¹H NMR (d₆-DMSO): δ 9.5-9.9 (br. s, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 3.70 (s, 3H), 2.38 (s, 3H).

E.



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

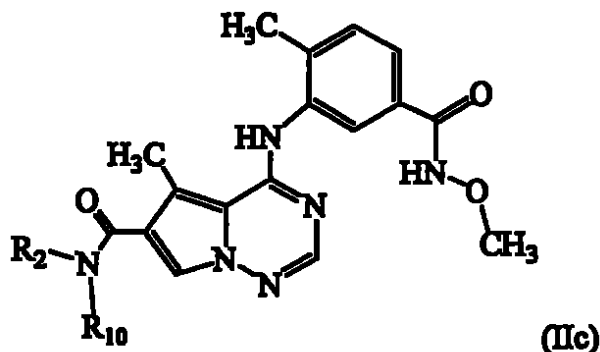
solution was cooled and placed in a cold room with stirring for 40 h. The solids were filtered and rinsed with 1/1 EtOH/Et₂O (500 mL) to give 58.5 g of Compound E as a white solid (80%).

5 F. Example 61

To a solution of ester Compound E (22.5 g, 58.7 mmol) in THF (205 mL) was added 1 N NaOH (205 mL) and the reaction mixture heated to 50 °C for 16 h. The THF was removed *in vacuo* and the mixture was acidified to pH 4-5 with 1N aq. HCl to precipitate the product. The heterogeneous mixture was stirred for 1 h, filtered and
10 washed with water (150 mL) and ether (150 mL). The collected solids were partially dried on the filter to give the crude acid intermediate as a moist white solid which was used without further purification.

To a solution of the moist acid in 300 mL of DMF was added HOBt (11.9 g, 88.0 mmol), EDCI (16.9 g, 88.0 mmol) and 1.3 equivalents (117 mmol) of
15 cyclopropyl-amine as the free base or as the hydrochloride salt. The mixture was stirred for 30 min to solubilize the solids, placed in a cold water bath, and DIPEA (20.4 mL, 117 mmol) was added slowly via syringe. The reaction mixture was allowed to stir at rt for 1 h, then poured into rapidly stirred ice water (1.2 L) to precipitate the product. After stirring for 3 h, the solids were collected by suction
20 filtration, washed with water (150 mL) and ether (2x100mL), and allowed to air dry by suction filtration to give Example 61 (92-98%) as a white solid.

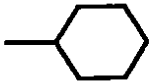
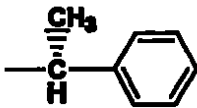
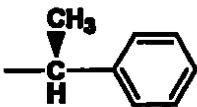
Examples 62-115

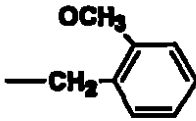
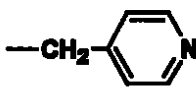
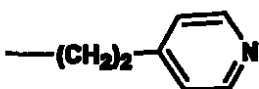
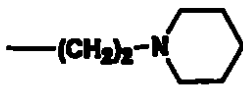
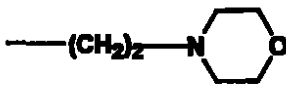
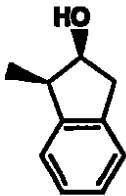
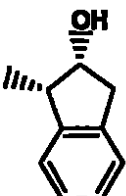
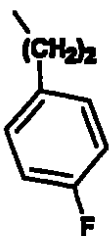


Compounds having the formula (IIc), wherein R₂ and R₁₀ have the values listed in Table 8 were prepared following the same methods set forth above in Scheme 9 and Example 61, using different amines (NR₂R₁₀) in the last step. Additionally, each compound can be recrystallized using a 7 to 1 EtOH/water mixture to afford
30 analytically pure product as a white crystalline solid.

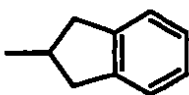
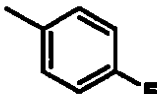
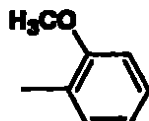
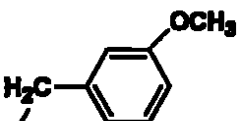
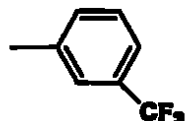
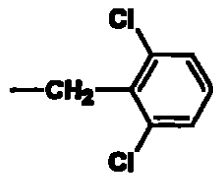
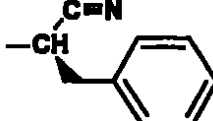
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40

TABLE 8

Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
62	$\text{---CH}_2\text{---C(CH}_3)_3$	CH ₃	N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	439.3 3.43 min
63	$\text{---CH---(CH}_3)_2$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.3 2.79 min
64	$\text{---CH}_2\text{---CH(CH}_3)_2$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylpropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.4 3.14 min
65	$\text{---CH}_2\text{---C(CH}_3)_3$	H	N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	425.3 3.35 min
66	$\text{---(CH}_2)_2\text{CH}_3$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2 2.88 min
67	$\text{---C(CH}_3)_3$	H	N-(1,1-Dimethylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.11 min
68	$\text{---(CH}_2)_2\text{---OCH}_3$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyethyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	413.2 1.99 min
69		H	N-Cyclohexyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.4 2.88 min
70		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.85 min
71		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.85 min
72	$\text{---CH}_2\text{---C}_6\text{H}_4\text{---F}$	H	N-[(4-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	463.4 2.83 min

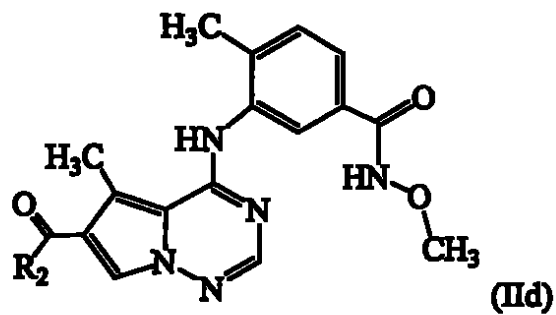
Ex.	R ₁	R ₂	Compound Name	Data MS/HPLC
73		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(2-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.4 2.83 min
74		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	446.2 1.45 min
75		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-pyridinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	460.3 1.81 min
76		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(1-piperidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	466.4 1.56 min
77		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	468.3 1.38 min
78		H	N-[(1R,2S)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.4 2.74 min
79		H	N-[(1S,2R)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.2 2.74 min
80		H	N-Cyclopropyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	395.3 2.64 min
81		H	N-Cyclopentyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	423.0 3.15 min
82		H	N-[2-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	477.3 3.53 min

Ex.	R ₁	R ₁₀	Compound Name	Data MS/HPLC
83		H	N-(Cyclohexylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.3 3.70 min
84		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(tetrahydro-2-furanyl)methyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	439.3 2.76 min
85		H	N-(2-1H-Indol-3-ylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	498.3 3.39 min
86		H	N-Butyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.16 min
87		H	N-(Cyclopropylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	409.1 2.90 min
88		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylbutyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	425.3 3.43 min
89		H	N-(2-Furanylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	435.1 2.95 min
90		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-thienylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.2 3.16 min
91		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.3 3.43 min
92		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylcyclohexyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.2 3.56 min
93		CH ₃	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2 2.59 min
94		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.1 3.01 min

Ex.	R ₂	R ₁₀	Compound Name	Data MS/HPLC
95	$-\text{CH}_2-\text{CH}_2-\text{F}$	H	N-(2-Fluoroethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	401.2 2.44 min
96		H	N-(2,3-Dihydro-1H-inden-2-yl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	471.2 3.56 min
97	$-\text{CH}_2-\text{CH}_3$	H	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	383.3 2.58 min
98	$\text{H}_2\text{C}-\text{CF}_2-\text{CF}_3$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,3,3,3-pentafluoropropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	487.2 3.40 min
99	$-(\text{CH}_2)_2-\text{N}(\text{CH}_3)_2$	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	426.5 1.38 min
100		H	N-(4-Fluorophenyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	449.2 2.92 min
101		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyphenyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	461.2 2.97 min
102		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(3-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	475.4 2.75 min
103		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	499.1 3.39 min
104		H	N-[(2,6-Dichlorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	513.1 3.10 min
105		H	N-[(1S)-1-Cyano-2-phenylethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	484.3 2.88 min

Ex.	R ₁	R ₁₀	Compound Name	Data MS/HPLC
106		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	459.3 2.91 min
107		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	446.2 1.51 min
108		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(phenylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	445.2 2.69 min
109		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-methyl-2-thiazolyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	452.3 3.50 min
110		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.20 min
111		H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2 3.20 min
112		H	N-[(3-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	463.2 2.84 min
113		H	N-[1-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	477.3 2.93 min
114		H	N-[(2,4-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	481.2 2.92 min
115		H	N-[(2,6-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	481.1 2.70 min

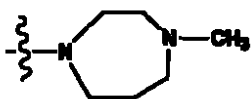
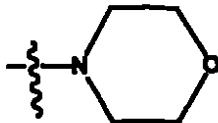
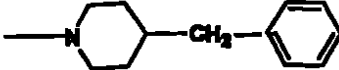
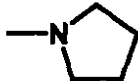
Examples 116-119

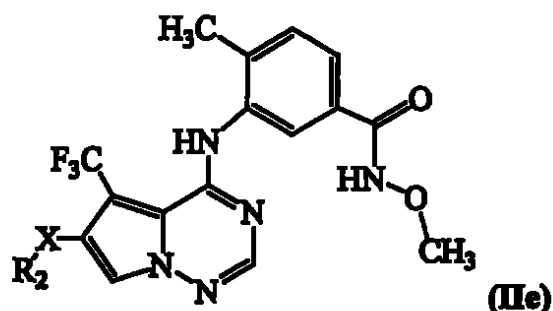


Compounds having the formula (IIId), wherein the R₂ groups have the values
5 listed in Table 9, were prepared following the same methods set forth above in
Scheme 9 and Examples 62-115.

43

TABLE 9

Ex.	R ₂	Compound Name	Data
116		3-[[6-[(Hexahydro-4-methyl-1H-1,4-diazepin-1-yl)carbonyl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-N-methoxy-4-methylbenzamide	452.1 1.63 min
117		N-Methoxy-4-methyl-3-[[5-methyl-6-(4-morpholinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	425.2 1.82 min
118		N-Methoxy-4-methyl-3-[[5-methyl-6-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	513.4 3.45 min
119		N-Methoxy-4-methyl-3-[[5-methyl-6-(1-pyrrolidinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide	409.2 2.16 min

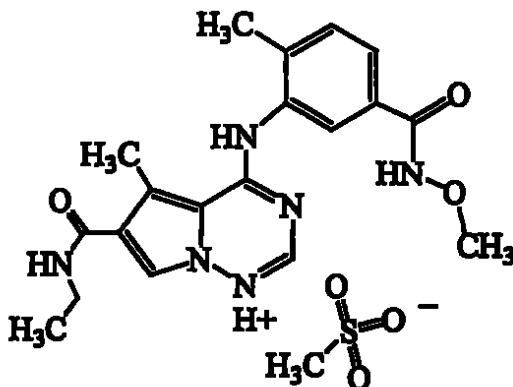
Examples 120-124

- 5 Compounds having the formula (IIe), wherein X and R₂ have the values listed in Table 10, were prepared following the same or similar procedure as in Scheme 9 and Example 61, except in the first step, commercially available 3-trifluoromethyl-1-pyrrole-2,4-diethyl ester was used instead of 3-methyl-1-pyrrole-2,4-diethyl ester.

10

TABLE 10

Ex. No.	X	R ₂	Compound Name	Data MS/HPLC
120		—CH ₂ —CH ₃	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester	438.2 3.76 min
121		—CH ₂ —CH ₃	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	437.2 2.99 min
122		—CH ₂ —CH ₂ —CH ₃	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-propyl-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	451.3 3.21 min
123		 —CH—CH ₂ —CH ₃	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(1S)-1-methylpropyl]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	465.3 3.36 min
124			4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(1S)-1-phenylethyl]-5-(trifluoromethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	513.2 1.72 min

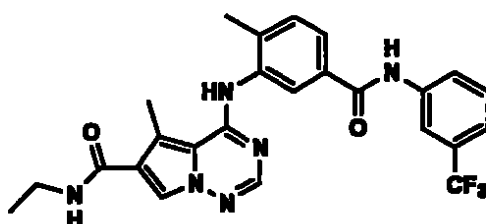
37
44**Example 125****N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide methane sulfonic acid**

5

- Example 97 as a free base was charged with acetone (10 ml/g Ex. 106), and the jacket was heated to 50-60°C. Reflux was started at 55-57°C, and the mixture was stirred for 30 min. at 50-60°C. Methanesulfonic acid (1.2 eq.) was added, and a slight exotherm was observed. The slurry was stirred at 50-60°C until DSC showed in
- 10 two consecutive samples the complete conversion of the free base (mp 220-222°C) to the mesylate salt (mp 259-261°C). The slurry was cooled to 20-25°C over about 30 min, and then stirred for at least 30 min. with the temp. kept at 20-25°C. The slurry was then filtered, washed with acetone, and dried *in vacuo* at 40-50°C to an LOD <0.5% to provide Example 125 as a white crystalline solid (yield 90-95%).
- 15 $[M+H]^+=478.4$. The above procedure may be used to prepare mesylate salts of other compounds of Formulae (I) and (II) herein.

Example 126

***N*-Ethyl-5-methyl-4-[[2-methyl-5-[[[3-(trifluoromethyl)phenyl]amino]carbonyl]phenyl]amino]pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide**

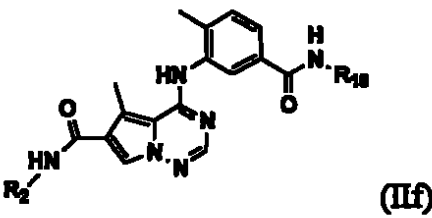


A. To a slurry of 2.0 g (4.2 mmol) of compound (1) from Scheme 10, wherein R₂ is ethyl, in 12 mL of anhydrous MeOH was added 18 mL of a 4 N solution of anhydrous HCl in dioxane at rt. The resulting clear solution was stirred at rt for 16 h and the reaction mixture was concentrated *in vacuo*. The resulting oil was dissolved in 16 mL of 1.5 N aq. KOH solution and heated to 50°C for 3 h. After cooling to rt, the mixture was diluted with 50 mL of water and 10% aq. HCl 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 compound (3) from Scheme 10. An analytical sample of this product was prepared by recrystallization from 10% aq. acetonitrile. ¹H NMR (CD₃OD): 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 (Condition A): 2.24 min.

B. A mixture of Compound A (40 mg, 0.11 mmol), HATU (65 mg, 0.17 mmol), diisopropylamine (20 μL, 0.11 mmol), and 3-trifluoromethylaniline (36 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 RP preparative HPLC to afford 41 mg (74%) of Example 126 as a light tan solid. ¹H NMR (CD₃OD w/ TFA): δ 8.28 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H), 8.11 (d, 1H), 7.84 (s, 1H), 7.71 (d, 1H), 7.58 (t, 2H), 7.47 (d, 1H), 3.44 (q, 2H), 2.94 (s, 3H), 2.47 (s, 3H), 1.26 (t, 3H). LCMS (M+H⁺) = 497.47. HPLC (Condition A) : 3.30 min.

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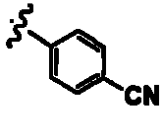
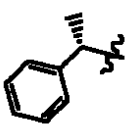
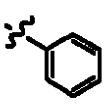
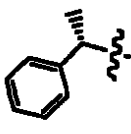
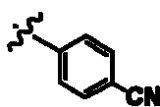
Examples 127-129



5 Compounds of Formula (IIf) were prepared as described for Example 126, except appropriate substrates and amines were selected to afford compounds where R₂ and R₁₈ have the values listed in Table 11.

TABLE 11

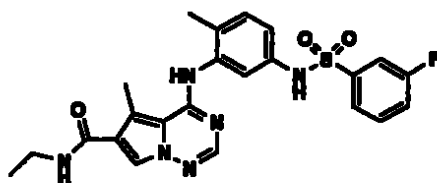
10

Ex.	R ₂	R ₁₈	Compound Name	Data
127	Et		4-[[5-[[[(4-Cyanophenyl)amino]carbonyl]-2-methylphenyl]amino]-N-ethyl-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	¹ H NMR (CD ₃ OD): δ 7.93 (br s, 1H), 7.84 - 7.86 (d, 3H), 7.74 (d, 1H), 7.62 (d, 2H), 7.58 (s, 1H), 7.40 (d, 1H), 3.30 (q, 2H), 3.21 (s, 3H), 2.76 (s, 3H), 1.14 (t, 3H). LCMS (M+H ⁺) = 454.18. HPLC (Condition A) : 2.86 min.
128			5-Methyl-4-[[2-methyl-5-[(phenylamino)carbonyl]phenyl]amino]-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	LCMS (M+H ⁺) = 505.27. HPLC (Condition A) : 3.34 min.
129			4-[[5-[[[(4-Cyanophenyl)amino]carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	LCMS (M+H ⁺) = 530.23. HPLC (Condition A) : 3.35 min.

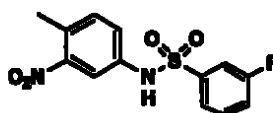
15

Example 130

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

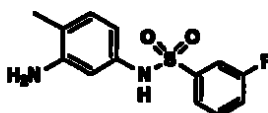


A.



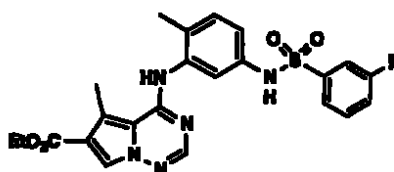
- 5 To a solution of 4-methyl-3-nitroaniline [compound (11) from Scheme 11](3.72 g, 24.5 mmol) in 150 ml of DCM at rt was added 3-fluorobenzenesulfonyl chloride (5.00 g, 25.7 mmol), followed by TEA (7.0 ml, 50.2 mmol) *via* syringe. The resulting mixture was stirred for 20 h and the solvent removed *in vacuo*. The residue was dissolved in DCM (600 ml), washed with sat'd aq. NaHCO₃, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 8.00 g of dark solid which was trituated with DCM to afford 5.46 g of yellow solid. A portion of this solid (1.63g) was dissolved in 10 ml 1N aq. NaOH and 20 ml THF, and the solution was stirred at rt for 20 h. The solvent was removed *in vacuo* and the residue acidified with 3N HCl to a pH of 2. The resulting precipitated solid was collected by filtration to afford 1.02 g (94%) of a light yellow solid as the desired Compound A. HPLC (Condition A) = 2.99 min. ¹HNMR(CDCl₃) δ 7.67 (d, 1H), 7.59 (dd, 1H), 7.49 (m, 2H), 7.32 (m, 1H), 7.28 (m, 2H), 2.54 (s, 3H).

B.



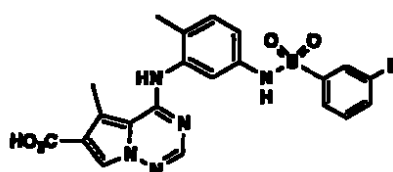
- 20 To 0.20 g (0.64 mmol) of Compound A in MeOH (10 ml) was added 10% Pd/C (20 mg) and the mixture stirred under hydrogen balloon for 6 h at rt. The solution was filtered through a pad of celite and the solvent removed *in vacuo* to give 0.18 g (100%) of Compound B as a colorless, glassy solid. HPLC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

C.

45
46

Compound B (0.18 g, 0.64 mmol) and 0.15 g (0.64 mmol) of 4-chloro-5-methylpyrrolo[1,2-a]triazine-6-ethylcarboxylate (compound 8 of Scheme 11) in anhydrous DMF was stirred at rt for 20 h. The reaction was quenched with addition of cold water and sat'd aq. NaHCO₃. The solid was collected, washed with water, and dried *in vacuo* to give 0.27 g (91%) of Compound C as a light yellow solid. HPLC (Condition A: 3.49 min. LCMS M+H⁺ (m/z) 484.

D.



10

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

15

E. Example 130

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

25

Examples 131-132

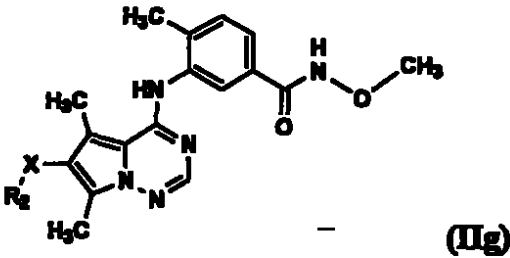
Examples 131 and 132 as shown in Table 12 were prepared from Compound D of Example 130 and an appropriate amine as described in Example 130, step E.

TABLE 12

Ex	Compound	Compound Name	Data
131		4-[[5-[[[(3-Fluorophenyl)sulfonyl]amino]-2-methylphenyl]amino]-N-[(1S)-2-methoxy-1-methylethyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	HPLC (Condition A): 2.89 min. MH ⁺ (m/z) 527.
132		4-[[5-[[[(3-Fluorophenyl)sulfonyl]amino]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	HPLC (Condition A): 3.23 min. MH ⁺ (m/z) 559.

5

Examples 133-141



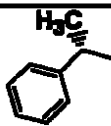
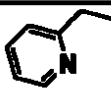
Compounds having the formula (IIg), wherein X and R₂ have the values listed in Table 13 were prepared from commercially-available diethyl-2,4-dimethylpyrrole-3,5-dicarboxylate following the same or similar procedure described above for the preparation of 5-desmethyl pyrrolotriazine.

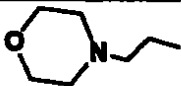
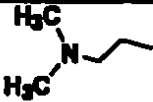
10

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TABLE 13

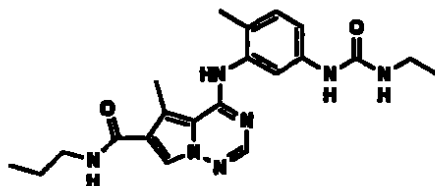
Ex	X	R ₁	Compound Name	Data
I33	-CO ₂ -	Et	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester	398.2, M+H 3.13 min, A
I34	-C(=O)NH-	Et	N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	397.2, M+H 1.70 min, A
I35	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	473.3, M+H 2.51 min, A
I36	-C(=O)NH-	-CH(CH ₃) ₂	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	411.2, M+H 1.81 min, A
I37	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(2-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	460.2, M+H 1.30 min, A
I38	-CO ₂ -	H	4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid	370.2, M+H 2.21 min, A

139	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[2-(4-morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	482.1, M+H 1.21 min, A
140	-C(=O)NH-		4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-[2-(1-piperidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	480.2, M+H 1.39 min, A
141	-C(=O)NH-		N-[2-(Dimethylamino)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	440.2, M+H 1.09 min, A

Example 142

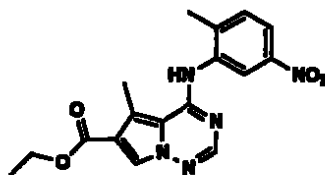
4-[[5-[(Ethylamino)carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide

5



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

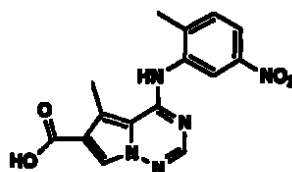
10



A suspension of chloropyrrolotriazine (compound 1 from Scheme 12) (2.03 g, 8.47 mmol) and 3-nitro-5-methyl aniline (1.41 g, 9.3 mmol) in DMF (25 mL) was stirred at rt for 24 h. Water (125 mL) was added over 30 min and the solution stirred for 1 h upon which the pH was adjusted to neutral with sat. aq. NaHCO₃. The solids

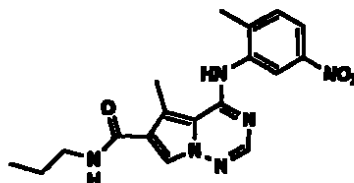
were filtered, washed with water, and dried to give compound A (2.589 g, 85% yield) as a pale tan solid. 48

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



10 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):
15 3.40 min.

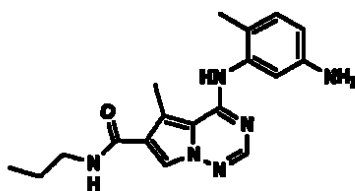
**C. 5-methyl-4-[(2-methyl-5-nitrophenyl)amino]-*N*-propylpyrrolo
 [2,1-*f*][1,2,4]triazine-6-carboxamide**



20

 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
25 was added to precipitate the product. The solids were filtered and purified via column
chromatography on silica (33% ethyl acetate/hexanes) to give compound C (0.79 g,
93% yield) as a white solid. ^1H NMR (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
30 (Condition A): 3.42 min.

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

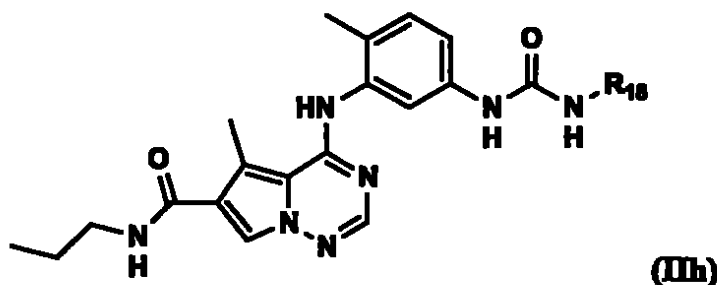


5 A solution of compound C (794 mg, 2.16 mmol) and 10% Pd/C (250 mg, wet) in MeOH (20 mL) was degassed and backfilled with hydrogen three times and stirred for 2 h. The solution was filtered and concentrated to give compound D (691 mg, 95% yield). ¹H NMR (CDCl₃): δ 7.94 (s, 1H), 7.73 (s, 1H), 7.53 (s,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

E. Example 142

To a suspension of 25.6 g (0.076 mmol) of compound D in 0.3 mL of DCE 15 was added 22 μL of ethyl isocyanate at rt. The reaction mixture was heated at 50°C for 12 h, then cooled, and isopropanol was added (1 mL). The resulting precipitated product was collected by vacuum filtration and washed with 1 mL of isopropanol and dried *in vacuo* to afford 19.6 mg (63%) of the titled compound as a pure product. ¹H 20 NMR (CD₃OD): δ 7.94 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.23 (br s, 2H), 7.44 (d, 1H), 3.23 (q, 2H), 2.84 (s, 3H), 2.24 (s, 3H), 1.66 (m, 2H), 1.16 (t, 3H), 1.02 (t, 3H). LCMS (M+H⁺) = 410.2. HPLC (Condition A): 2.82 min.

Examples 143-148

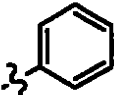
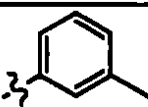
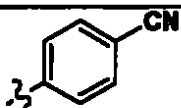
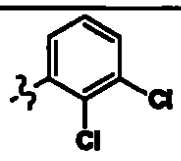
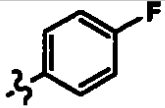
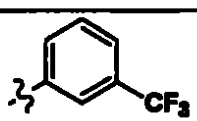


25

Compound having the formula (IIIh), wherein R₁₈ has the values listed in Table 14 were prepared following the procedure outlined for Example 142, using different isocyanates in the last step.

TABLE 14

5

Ex.	R ₁₈	Compound Name	Data MS/HPLC
143		5-Methyl-4-[[[2-methyl-5-[[[(phenylamino)carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	458.2 3.40 min
144		5-Methyl-4-[[[2-methyl-5-[[[(3-methylphenyl)amino]carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	472.5 3.60
145		4-[[5-[[[4-Cyanophenyl]amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	483.3 3.48
146		4-[[5-[[[2,3-Dichlorophenyl]amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	526.2 3.98
147		4-[[5-[[[4-Fluorophenyl]amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	476.2 3.48
148		5-Methyl-4-[[[2-methyl-5-[[[(3-(trifluoromethyl)phenyl)amino]carbonyl]amino]phenyl]amino]-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide	526.1 3.87 min

Examples 149-152

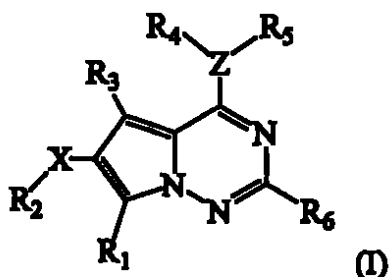
The compounds named below were prepared using methods analogous to the procedures described hereinbefore:

- 149) 1,3-Dihydro-3-[5-methoxy-6-[[4-(4-methyl-1-
5 piperazinyl)butyl]amino]pyrrolo[2,1-f][1,2,4]triazin-4-yl]-2H-indol-2-one;
150) 1,3-Dihydro-3-[5-methoxy-6-[[4-(4-morpholinyl)butyl]amino]pyrrolo[2,1-
f][1,2,4]triazin-4-yl]-2H-indol-2-one;
151) 1-[3-[4-(2,3-Dihydro-2-oxo-1H-indol-3-yl)-5-methylpyrrolo[2,1-f][1,2,4]triazin-
6-yl]-1-oxopropyl]-4-methylpiperazine; and
10 152) 2-Methyl-5-[[5-methyl-6-[3-(2H-1,2,3-triazol-2-yl)propoxy]pyrrolo[2,1-
f][1,2,4]triazin-4-yl]amino]phenol.

49
50**CLAIMS**

We claim:

1. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):



- 10 or a pharmaceutically acceptable salt, prodrug, or solvate thereof, wherein:
 R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH_2 ;
 X is selected from $-\text{O}-$, $-\text{OC}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{C}(=\text{O})-$, $-\text{CO}_2-$,
 $-\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, $-\text{NR}_{10}\text{C}(=\text{O})\text{NR}_{11}-$, $-\text{NR}_{10}\text{CO}_2-$, $-\text{NR}_{10}\text{SO}_2-$,
 $-\text{NR}_{10}\text{SO}_2\text{NR}_{11}-$, $-\text{SO}_2\text{NR}_{10}-$, $-\text{C}(=\text{O})\text{NR}_{10}-$, halogen, nitro, and cyano, or X
15 is absent;
 Z is selected from O , S , N , and CR_{20} , wherein when Z is CR_{20} , said carbon atom may form an optionally-substituted bicyclic aryl or heteroaryl with R_4 and R_5 ;
 R_1 is hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$,
 $-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{NH}_2$, $-\text{NR}_{24}\text{R}_{25}$,
20 $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{25}$,
 $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, halogen, nitro, or cyano;
 R_2 is selected from:
a) hydrogen, provided that R_2 is not hydrogen when X is $-\text{S}(=\text{O})-$, $-\text{SO}_2-$,
 $-\text{NR}_{10}\text{CO}_2-$, or $-\text{NR}_{10}\text{SO}_2-$;
25 b) alkyl, alkenyl, and alkynyl optionally substituted with up to four R_{26} or pentafluoroalkyl;
c) aryl and heteroaryl optionally substituted with up to three R_{27} ; and
d) heterocyclo and cycloalkyl optionally substituted with keto ($=\text{O}$), up to three R_{27} , and/or having a carbon-carbon bridge of 3 to 4 carbon atoms; or
30 e) R_2 is absent if X is halogen, nitro or cyano;

- (i) R_4 is substituted aryl, aryl substituted with NHSO_2 alkyl, substituted heteroaryl, or an optionally-substituted bicyclic 7-11 membered saturated or unsaturated carbocyclic or heterocyclic ring, and
 R_5 is hydrogen, alkyl, or substituted alkyl, except when Z is O or S, R_5 is absent, or alternatively,
- (ii) R_4 and R_5 taken together with Z form an optionally-substituted bicyclic 7-11 membered aryl or heteroaryl;
 R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, or halogen;
- 10 R_{10} and R_{11} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, and substituted heterocyclo;
 R_7 , R_8 , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;
- 15 R_{20} is hydrogen, lower alkyl, or substituted alkyl, or R_{20} may be absent if the carbon atom to which it is attached together with R_4 and R_5 is part of an unsaturated bicyclic aryl or heteroaryl;
 R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;
- 20 R_{26} is selected from halogen, trifluoromethyl, haloalkoxy, keto ($=\text{O}$), nitro, cyano, $-\text{SR}_{28}$, $-\text{OR}_{28}$, $-\text{NR}_{28}\text{R}_{29}$, $-\text{NR}_{28}\text{SO}_2$, $-\text{NR}_{28}\text{SO}_2\text{R}_{29}$, $-\text{SO}_2\text{R}_{28}$, $-\text{SO}_2\text{NR}_{28}\text{R}_{29}$, $-\text{CO}_2\text{R}_{28}$, $-\text{C}(=\text{O})\text{R}_{28}$, $-\text{C}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{OC}(=\text{O})\text{R}_{28}$, $-\text{OC}(=\text{O})\text{NR}_{28}\text{R}_{29}$, $-\text{NR}_{28}\text{C}(=\text{O})\text{R}_{29}$, $-\text{NR}_{28}\text{CO}_2\text{R}_{29}$, $=\text{N-OH}$, $=\text{N-O-alkyl}$; aryl optionally substituted with one to three R_{27} ; cycloalkyl optionally substituted with
- 25 keto ($=\text{O}$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocyclo optionally substituted with keto ($=\text{O}$), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycle, or may be taken together to form a C_{3-7} heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted
- 30 with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy; and
- 35 R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-\text{SR}_{30}$, $-\text{OR}_{30}$, $-\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{SO}_2$, $-\text{NR}_{30}\text{SO}_2\text{R}_{31}$, $-\text{SO}_2\text{R}_{30}$,

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$-\text{SO}_2\text{NR}_{30}\text{R}_{31}$, $-\text{CO}_2\text{R}_{30}$, $-\text{C}(=\text{O})\text{R}_{30}$, $-\text{C}(=\text{O})\text{NR}_{30}\text{R}_{31}$, $-\text{OC}(=\text{O})\text{R}_{30}$

$-\text{OC}(=\text{O})\text{NR}_{30}\text{R}_{31}$, $-\text{NR}_{30}\text{C}(=\text{O})\text{R}_{31}$, $-\text{NR}_{30}\text{CO}_2\text{R}_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} -cycloalkyl, and heterocycle, or may be taken together to form a C_{2-7} -heterocycle.

2. The method of claim 1 comprising administering to the patient at least one compound having the formula (I), or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

R_3 is methyl, $-\text{CF}_3$, or $-\text{OCH}_3$;

X is selected from $-\text{C}(=\text{O})-$, $-\text{CO}_2-$, $-\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, $-\text{NR}_{10}\text{CO}_2-$, $-\text{NR}_{10}\text{SO}_2-$, $-\text{SO}_2\text{NR}_{10}-$, and $-\text{C}(=\text{O})\text{NR}_{10}-$, or X is absent;

- 15 Z is N;

R_2 is hydrogen, C_{2-6} -alkyl, C_{1-4} -alkyl substituted with up to four R_{26} , pentafluoroalkyl, or aryl or heteroaryl optionally substituted with up to two R_{27} ;

R_4 is phenyl substituted with one R_{12} and zero to three R_{13} ;

R_5 and R_{10} independently are selected from hydrogen and lower alkyl;

- 20 R_{12} is carbamyl, sulfonamido, arylsulfonamide, or ureido, each of which is optionally substituted with up to two of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or alkylsulfonamide;

R_{13} at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-\text{OR}_{14}$, $-\text{C}(=\text{O})\text{alkyl}$, $-\text{OC}(=\text{O})\text{alkyl}$,

- 25 $-\text{NR}_{13}\text{R}_{16}$, $-\text{SR}_{15}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})\text{alkyl}$, $-\text{S}(=\text{O})\text{aryl}$, $-\text{NHSO}_2\text{-aryl-R}_{17}$, $-\text{NHSO}_2\text{-alkyl}$, $-\text{SO}_2\text{NHR}_{17}$, $-\text{CONHR}_{17}$, and $-\text{NHC}(=\text{O})\text{NHR}_{17}$;

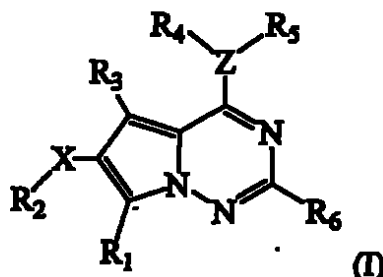
R_{14} is hydrogen, alkyl, or aryl;

R_{15} is hydrogen or alkyl;

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

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

3. A method of treating one or more conditions associated with p38 kinase activity comprising administering to a patient in need thereof at least one compound having the formula (I):

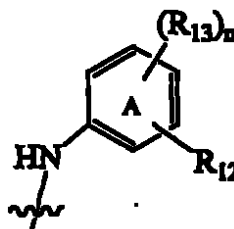


- 5 or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:
 R_3 is hydrogen, methyl, perfluoromethyl, methoxy, halogen, cyano or NH_2 ;
 X is selected from $-\text{O}-$, $-\text{OC}(=\text{O})-$, $-\text{S}-$, $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{C}(=\text{O})-$, $-\text{CO}_2-$,
 $-\text{NR}_{10}-$, $-\text{NR}_{10}\text{C}(=\text{O})-$, $-\text{NR}_{10}\text{C}(=\text{O})\text{NR}_{11}-$, $-\text{NR}_{10}\text{CO}_2-$, $-\text{NR}_{10}\text{SO}_2-$,
 $-\text{NR}_{10}\text{SO}_2\text{NR}_{11}-$, $-\text{SO}_2\text{NR}_{10}-$, $-\text{C}(=\text{O})\text{NR}_{10}-$, halogen, nitro, and cyano, or X
10 is absent;
 Z is O, S, N, or CR_{20} ;
 R_1 is hydrogen, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OC}(=\text{O})\text{R}_{21}$, $-\text{S}(=\text{O})\text{R}_{22}$,
 $-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{NH}_2$, $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{25}$,
 $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{25}$, $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, halogen,
15 nitro, or cyano;
 R_2 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo,
aralkyl, substituted aralkyl, or heterocycloalkyl, or substituted
heterocycloalkyl, or when X is halo, nitro or cyano, R_2 is absent, provided that
20 R_2 is not hydrogen when X is $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{NR}_{10}\text{CO}_2-$, or $-\text{NR}_{10}\text{SO}_2-$;
 R_4 is substituted aryl, aryl substituted with NHSO_2 alkyl, substituted heteroaryl, or an
optionally-substituted bicyclic 7-11 membered saturated or unsaturated
carbocyclic or heterocyclic ring system;
 R_5 is hydrogen, alkyl, or substituted alkyl, except that when Z is O or S, R_5 is absent;
25 R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted
heterocyclo, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, or halogen;
 R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen, alkyl,
substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted
heterocyclo;
30 R_{20} is hydrogen, lower alkyl, or substituted alkyl; and

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R_{22} is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo.

- 5 4. The method of claim 3 comprising administering to the patient at least one compound of formula (I), in which R_4 and R_5 taken together with Z form:

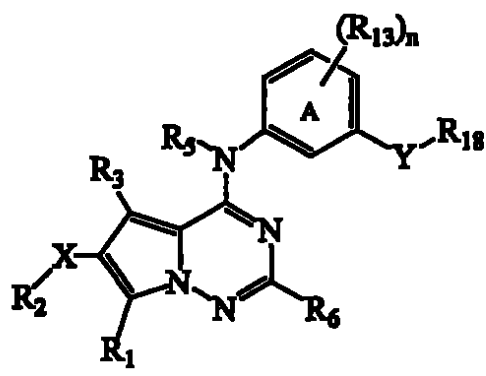


or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

- 10 R_{12} is attached to any available carbon atom of phenyl ring A and is selected from carbamyl, sulfonamido, arylsulfonylamine, and ureido, each of which is optionally substituted with up to one of hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, and aralkyl, or C_{1-4} alkylsulfonylamine;
- 15 R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, $-OR_{14}$, $-C(=O)alkyl$, $-OC(=O)alkyl$, $-NR_{15}R_{16}$, $-SR_{13}$, $-NO_2$, $-CN$, $-CO_2R_{13}$, $-CONH_2$, $-SO_3H$, $-S(=O)alkyl$, $-S(=O)aryl$, $-NHSO_2-aryl$, R_{17} , $-NHSO_2C_{1-4}alkyl$, $-SO_2NHR_{17}$, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;
- R_{14} is hydrogen, alkyl, or aryl;
- 20 R_{15} is hydrogen or alkyl;
- R_{16} is hydrogen, alkyl, aralkyl, or alkanoyl; and
- R_{17} is hydrogen, hydroxy, alkyl, substituted alkyl, alkoxy, aryl, substituted aryl, or aralkyl; and
- n is 0, 1, 2 or 3.

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5. The method of claim 3 comprising administering to the patient at least one compound having the formula (II):



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

R_3 is methyl or CF_3 ;

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

5 R_1 is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, halogen, nitro, or cyano;

Y is $-C(=O)NH-$, $-NHC(=O)NH-$, $-NHSO_2-$, or $-SO_2NH-$;

R_{10} is hydrogen or lower alkyl;

R_{18} is selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to

three R_{19} , except that when Y is $-NHSO_2-$, R_{18} is C_{1-4} alkyl, aryl or aryl

10 substituted with R_{19} ;

R_{13} is attached to any available carbon atom of phenyl ring A and at each occurrence is

independently selected from alkyl, substituted alkyl, halo, trifluoromethoxy,

trifluoromethyl, $-OR_{14}$, $-C(=O)alkyl$, $-OC(=O)alkyl$, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$,

$-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)alkyl$, $-S(=O)aryl$, $-NHSO_2-aryl-$

15 R_{17} , $-NHSO_2C_{1-4}alkyl$, $-SO_2NHR_{17}$, $-CONHR_{17}$, and $-NHC(=O)NHR_{17}$;

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

R_{19} at each occurrence is selected from alkyl, halo, trifluoromethoxy, trifluoromethyl,

hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano,

carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono,

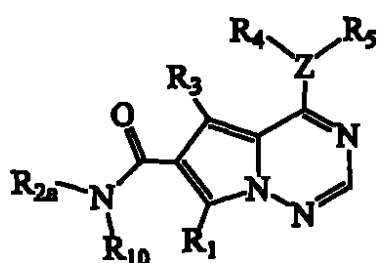
20 arylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy,

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

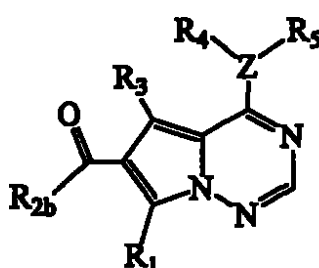
n is 0, 1 or 2.

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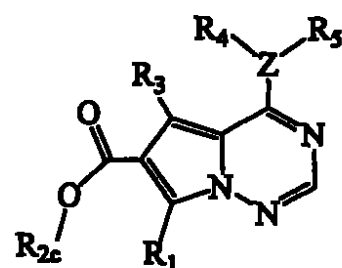
6. The method of claim 3, comprising administering to the patient at least one compound having the formula (Ia), (Ib), or (Ic):

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(Ia)



(Ib)



(Ic)

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

5 R_3 is methyl or CF_3 ;

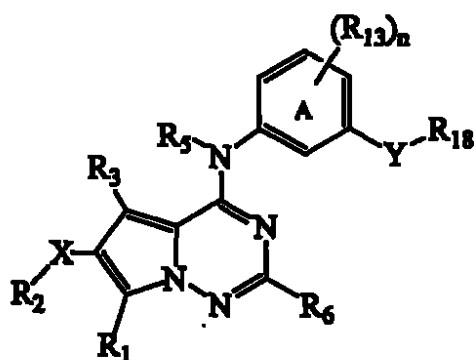
R_{2a} and R_{2c} are independently selected from hydrogen, C_{1-6} alkyl, substituted C_{1-4} alkyl, aryl, substituted aryl, benzyl, and substituted benzyl;

R_{2b} is heterocyclo or substituted heterocycle; and

R_{10} is hydrogen or lower alkyl.

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7. A compound having the formula (II):



(II),

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

R_3 is methyl, CF_3 , or CH_3 ; R_5 is hydrogen or alkyl;

Y is $-C(=O)NR_{21}$, $-NR_{21}C(=O)NR_{21}$, $-SO_2NR_{21}$, or $-NR_{21}SO_2$;

20 R_{18} and R_{21} are selected from hydrogen, alkyl, alkoxy, aryl, and aryl substituted with one to three R_{19} , except when Y is $-NR_{21}SO_2$, R_{18} is C_{1-4} alkyl or aryl optionally substituted with one to three R_{19} ;

X is selected from $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$,
 $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$,
 $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, and $-C(=O)NR_{10}-$, or X is absent;

R₁ is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$,
 5 $-SO_2R_{23}$, $-SO_2NR_{24}R_{25}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{25}$, $-NH_2$, $-NR_{24}R_{25}$,
 $-NR_{21}SO_2NR_{24}R_{25}$, $-NR_{21}SO_2R_{23}$, $-NR_{24}C(=O)R_{25}$, $-NR_{24}CO_2R_{25}$,
 $-NR_{21}C(=O)NR_{24}R_{25}$, halogen, nitro, or cyano;

R₂ is selected from

- a) hydrogen, provided that R₂ is not hydrogen when X is $-S(=O)-$, $-SO_2-$,
 10 $-NR_{10}CO_2-$, or $-NR_{10}SO_2-$;
 b) alkyl, alkenyl, and alkynyl optionally substituted with up to four R₂₆, or
 pentafluoroalkyl;
 c) aryl and heteroaryl optionally substituted with up to three R₂₇; and
 d) heterocyclo and cycloalkyl optionally substituted with keto ($=O$), up to
 15 three R₂₇, and/or having a carbon-carbon bridge of 3 to 4 carbon atoms;

R₄ is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted
 heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

R₁₀ is hydrogen or alkyl;

R₁₃ and R₁₉ at each occurrence are independently selected from alkyl, halo,
 20 trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy,
 thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl,
 alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, C₁,
 alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy,
 wherein each R₁₃ and/or R₁₉ group may be further substituted by hydroxy,
 25 alkyl, substituted alkyl, alkoxy, aryl, or aralkyl;

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

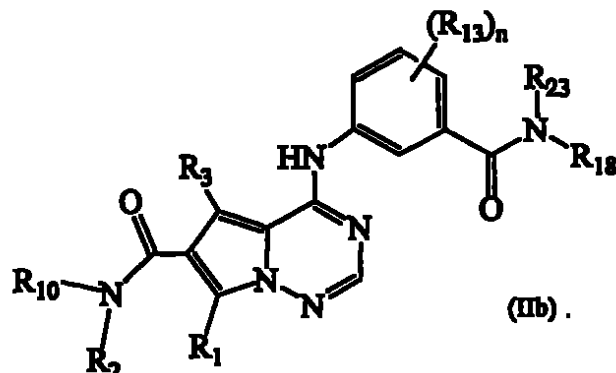
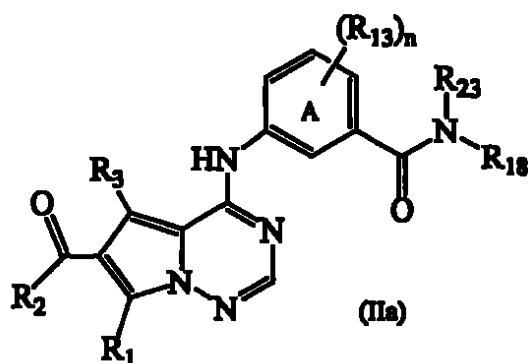
R₂₂ is alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted
 heterocyclo;

30 R₂₆ is selected from halogen, trifluoromethyl, haloalkoxy, keto ($=O$), nitro, cyano,
 $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$,
 $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$,
 $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alkyl; aryl optionally

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- substituted with one to three R_{27} ; cycloalkyl optionally substituted with keto(=O), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; and heterocycle optionally substituted with keto(=O), one to three R_{27} , or having a carbon-carbon bridge of 3 to 4 carbon atoms; wherein R_{28} and R_{29} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and C_{3-7} heterocycle, or may be taken together to form a C_{3-7} heterocycle; and wherein each R_{28} and R_{29} in turn is optionally substituted with up to two of alkyl, alkenyl, halogen, haloalkyl, haloalkoxy, cyano, nitro, amino, hydroxy, alkoxy, alkylthio, phenyl, benzyl, phenyloxy, and benzyloxy;
- 10 R_{27} is selected from alkyl, R_{32} , and C_{1-4} alkyl substituted with one to three R_{32} , wherein each R_{32} group is independently selected from halogen, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, and a 3 to 7 membered carbocyclic or heterocyclic ring optionally substituted with alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, amino, or cyano, wherein R_{30} and R_{31} are each independently selected from hydrogen, alkyl, alkenyl, aryl, aralkyl, C_{3-7} cycloalkyl, and heterocycle, or may be taken together to form a C_{3-7} heterocycle; and
- 15 n is 0, 1 or 2.

8. A compound according to claim 7, having the formula (IIa) or (IIb),



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

R_1 and R_{10} are hydrogen or $-CH_3$;

R_{13} is lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, or cyano;

R_{18} is hydroxy, C_{1-4} alkoxy, phenyl, or phenyl substituted with one or two R_{19} ;
 R_{23} is hydrogen or lower alkyl; and
 n is 0, 1 or 2.

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9. A compound according to claim 7, or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

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

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

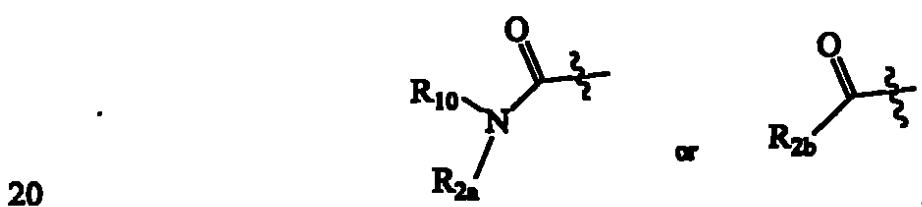
10 R_5 and R_{10} are hydrogen or $-CH_3$;

R_{13} and R_{19} at each occurrence are independently selected from lower alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, and cyano;

R_7 , R_8 , R_{21} , R_{24} , and R_{25} are independently selected from hydrogen and lower alkyl; R_{22} is lower alkyl; and

15 n is 0 or 1.

10. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which $X-R_2$ are:



R_{2a} is selected from:

- a) hydrogen;
 - b) straight or branched C_{2-6} alkyl;
 - 25 c) cycloalkyl optionally substituted with keto and/or up to two R_{27} ;
 - d) phenyl optionally substituted with up to two R_{27} ; and
 - e) heterocycle optionally substituted with keto and/or up to two R_{27} ;
 - f) pentafluoroalkyl or C_{1-4} alkyl substituted with up to three of halogen, trifluoromethyl, cyano, OR_{28} , $NR_{28}R_{29}$, CO_2R_{28} , aryl, heterocycle, and/or
 - 30 cycloalkyl, wherein the aryl, heterocycle, and/or cycloalkyl in turn are optionally optionally substituted with up to two of halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, nitro, cyano and alkyl; and
- R_{2b} is a monocyclic or bicyclic heterocycle optionally substituted with up to two R_{27} ;

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R_{27} at each occurrence is independently selected from hydrogen, alkyl, trifluoromethyl, trifluoromethoxy, halogen, cyano, nitro, amino, hydroxy, alkoxy, phenyl, benzyl, phenyloxy, and benzyloxy; and

5 R_{28} and R_{29} at each occurrence are independently selected from hydrogen, alkyl, alkenyl, phenyl, and benzyl.

11. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which:

10 R_{2a} is selected from:

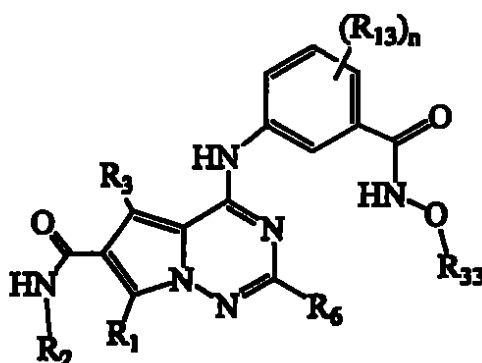
- a) straight or branched C_{2-6} alkyl;
- b) phenyl optionally substituted with up to two of halogen, C_{1-4} alkoxy, and trifluoromethyl;
- c) C_{3-6} cycloalkyl optionally substituted with up to two C_{1-4} alkyl and/or hydroxy;
- 15 d) straight or branched C_{1-4} alkyl substituted with up to three of
 - i) halogen,
 - ii) trifluoromethyl,
 - iii) cyano,
 - 20 iv) C_{1-4} alkoxy,
 - v) phenyloxy,
 - vi) benzyloxy,
 - vii) NH_2 , $NH(C_{1-4}alkyl)$, and/or $N(C_{1-4}alkyl)_2$,
 - viii) phenyl in turn optionally substituted with up to two of halogen and/or methoxy,
 - 25 ix) heterocycle selected from pyridinyl, indolyl, thiophenyl, furanyl, thiazolyl, thienyl, morpholinyl, tetrahydrofuranyl, triazinyl, piperazinyl, indenyl, and piperidinyl; said heterocycle optionally substituted with one to two C_{1-4} alkyl,
 - 30 x) C_{3-6} cycloalkyl; and

R_{2b} is a five to seven membered monocyclic heterocycle selected from diazepinyl, morpholinyl, piperidinyl, and pyrrolidinyl, said heterocycle optionally substituted with C_{1-4} alkyl, phenyl, and/or benzyl.

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12. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which R_1 and R_{10} are independently hydrogen or CH_3 .

13. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which R_4 is hydrogen.
- 5 14. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which Y is $-NHC(=O)NH-$ or $-NHSO_2-$; R_{18} is aryl or aryl substituted with alkyl, OCH_3 , CF_3 , cyano, or halogen.
15. A compound according to claim 7 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which Y is $-C(=O)NR_{23}$, R_{23} is hydrogen or lower alkyl, and R_{18} is C_{1-4} alkoxy or aryl optionally substituted with alkyl, OCH_3 , CF_3 , cyano or halogen.
- 10 16. A compound according to claim 7, having the formula:
- 15



in which R_{33} is lower alkyl.

17. A compound according to claim 16 or a pharmaceutically acceptable salt, prodrug or solvate thereof, in which R_3 and R_{33} are methyl, R_1 and R_6 are hydrogen, and R_2 is a straight or branched C_{2-6} alkyl or optionally-substituted benzyl.
- 20
18. A compound according to claim 7, which is selected from (i) N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 25 3-[[6-[(Hexahydro-4-methyl-1H-1,4-diazepin-1-yl)carbonyl]-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]-N-methoxy-4-methylbenzamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;

- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylpropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-(2,2-Dimethylpropyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 5 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-(1,1-Dimethylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 10 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyethyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-Methoxy-4-methyl-3-[[5-methyl-6-(4-morpholinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide;
N-Cyclohexyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 15 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-[(4-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-
- 20 methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(2-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 25 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-pyridinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(1-piperidinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[2-(4-
- 30 morpholinyl)ethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-[(1R,2S)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
N-[(1S,2R)-2,3-Dihydro-1H-inden-1-yl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 35 N-Methoxy-4-methyl-3-[[5-methyl-6-[[4-(phenylmethyl)-1-piperidinyl]carbonyl]pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide;

- N-Cyclopropyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-Cyclopentyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 5 N-[2-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-(Cyclohexylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(tetrahydro-2-furanyl)methyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 10 N-(2-1H-Indol-3-ylethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-Butyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 15 N-(Cyclopropylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylbutyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-(2-Furanylmethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 20 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-thienylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenoxyethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 25 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-methylcyclohexyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-N,5-dimethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,2-trifluoroethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 30 N-(2-Fluoroethyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-(2,3-Dihydro-1H-inden-2-yl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 35 N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;

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- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2,2,3,3,3-pentafluoropropyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5,7-dimethyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 5 N-(4-Fluorophenyl)-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-(2-methoxyphenyl)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-N-[(3-methoxyphenyl)methyl]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 10 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[3-(trifluoromethyl)phenyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-[(2,6-Dichlorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 15 N-[(1S)-1-Cyano-2-phenylethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-phenylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-Methoxy-4-methyl-3-[[5-methyl-6-(1-pyrrolidinylcarbonyl)pyrrolo[2,1-f][1,2,4]triazin-4-yl]amino]benzamide;
- 20 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(2-pyridinylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(phenylmethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 25 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(4-methyl-2-thiazolyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1R)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 30 N-[(3-Fluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- N-[1-(4-Fluorophenyl)ethyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide;
- 35 N-[(2,4-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; and

N-[(2,6-Difluorophenyl)methyl]-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[[4-Cyanophenyl]amino]carbonyl]-2-methylphenyl]amino]-N-ethyl-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[[4-Cyanophenyl]amino]carbonyl]-2-methylphenyl]amino]-5-methyl-N-[(1S)-1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[[4-Cyanophenyl]amino]carbonyl]amino]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; or is (ii) a pharmaceutically-acceptable salt, hydrate, or prodrug thereof.

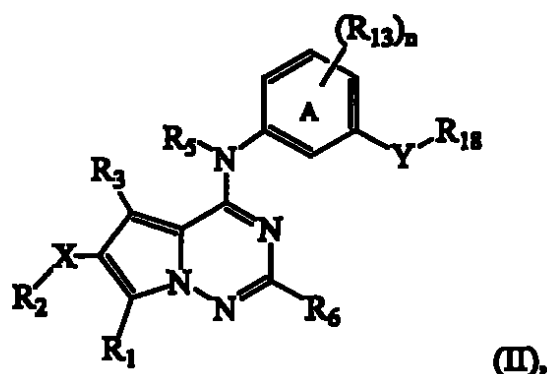
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19. A compound according to claim 7 which is selected from N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(1-methylethyl)pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; and 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; and a pharmaceutically-acceptable salt thereof.

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20. A compound having the formula (II):

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

30 R_3 is methyl or CF_3 ;

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R_3 is hydrogen or lower alkyl;

Y is $-C(=O)NR_{23}-$, $-NR_{23}C(=O)NR_{23}-$, $-NR_{23}SO_2-$, or $-SO_2NH_2-$;

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

X is selected from $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, and $-C(=O)NR_{10}-$, or X is absent;

R_1 is hydrogen, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$, $-SO_2R_{22}$, $-SO_2NR_{24}R_{23}$, $-CO_2R_{21}$, $-C(=O)NR_{24}R_{23}$, $-NH_2$, $-NR_{21}SO_2NR_{24}R_{23}$, $-NR_{21}SO_2R_{22}$, $-NR_{24}C(=O)R_{23}$, $-NR_{24}CO_2R_{23}$, $-NR_{21}C(=O)NR_{24}R_{23}$, halogen, nitro, or cyano;

R_2 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, heterocycloalkyl, or substituted heterocycloalkyl;

R_6 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, $-NR_7R_8$, $-OR_7$, or halogen;

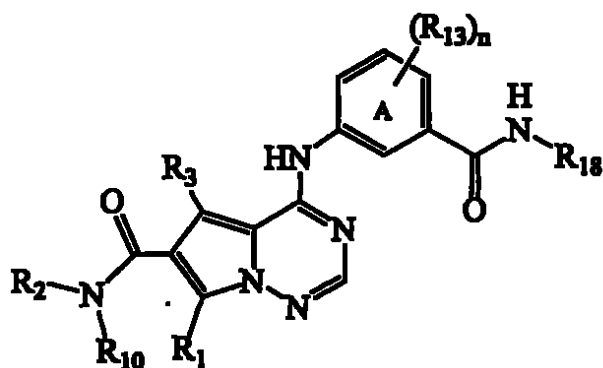
R_{13} and R_{19} at each occurrence are independently selected from alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, C_1 -alkylsulfonylamine, sulfonic acid, alkylsulfonyl, sulfonamido, and aryloxy, wherein each group R_{13} and R_{19} may be further substituted by hydroxy, alkyl, alkoxy, aryl, or aralkyl;

R_7 , R_8 , R_{21} , R_{24} , and R_{23} are independently selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

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

n is 0, 1 or 2.

21. A compound according to claim 20, having the formula:



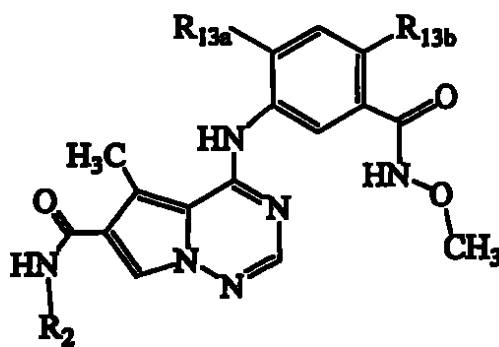
or a pharmaceutically acceptable salt, prodrug or solvate thereof; wherein.

R_{18} is alkoxy, aryl, or aryl substituted with R_{19} ;

R_1 and R_{10} are hydrogen or $-\text{CH}_3$; and

- 5 R_{13} is lower alkyl, halogen, trifluoromethoxy, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, or cyano.

22. A compound according to claim 20 having the formula:



or a pharmaceutically-acceptable salt, hydrate or prodrug thereof, in which R_2 is a straight or branched C_{2-6} alkyl or optionally-substituted benzyl, and R_{13a} and R_{13b} are selected from hydrogen, C_{1-4} alkyl, hydroxy, halogen, cyano, and trifluoromethyl.

23. A compound according to claim 20 which is N-Ethyl-4-[[5-[(methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; or a pharmaceutically acceptable salt comprising a methanesulfonic salt thereof.

24. A compound according to claim 20 which is 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-(1-methylethyl)pyrrolo [2,1-f][1,2,4]triazine-6-carboxamide; or a pharmaceutically acceptable salt thereof.

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25. A compound according to claim 20 which is 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; or a pharmaceutically acceptable salt thereof.
- 5 26. A compound according to claim 20 which is 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[1-phenylethyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; or a pharmaceutically acceptable salt thereof.
- 10 27. A compound according to claim 20 which is 4-[[5-[(Methoxyamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-[1-methylpropyl]pyrrolo[2,1-f][1,2,4]triazine-6-carboxamide; or a pharmaceutically acceptable salt thereof.
- 15 28. A pharmaceutical composition comprising at least one compound according to claim 7 and a pharmaceutically-acceptable carrier or diluent.
29. A pharmaceutical composition comprising at least one compound according to claim 20 and a pharmaceutically-acceptable carrier or diluent.
- 20 30. A method of treating an inflammatory disorder comprising administering to a patient in need of such treatment a pharmaceutical composition according to claim 28.
- 25 31. The method of claim 30 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 rheumatoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, gouty arthritis and osteoarthritis.

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60**CERTIFICATE OF MAILING**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Kenneth W. Peist
Type or print name

Kenneth W. Peist
Signature

February 28, 2001
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**IN RE APPLICATION OF****LEFOTHERIS ET AL.****APPLICATION NO: 60/249,877****FILED: NOVEMBER 17, 2000****FOR: USE OF PYRROLOTRIAZENE COMPOUNDS AS
ANTIINFLAMMATORY AGENT**

Assistant Commissioner for Patents
Washington, D.C. 20231

LETTER CORRECTING OFFICIAL FILING RECEIPT**Sir:**

The official filing receipt received in the above-identified application erroneously lists Joel Barrish's address. Please issue a corrected filing receipt listing the address as follows:

—38 Dorchester Lane, Richboro, PA 18954—

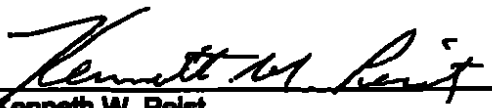
A copy of the filing receipt with the correction noted is enclosed.

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Applicants believe this error is ascribable to applicants. Accordingly, the Commissioner is hereby authorized to charge the \$25 fee under 37 CFR §1.19(h) and any additional fees that may be required to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company. An additional copy of this paper is here enclosed.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-3183
Date: February 28, 2001


Kenneth W. Peist
Attorney for Applicants
Reg. No. 45,008

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE RECD	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/249,877	11/17/2000		150	QA0237			

23814
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

FILING RECEIPT



0000000005771880

Date Mailed: 02/16/2001

Receipt is acknowledged of this provisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. 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 Customer Service Center. 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 PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Katerina Leftheris, Skillman, NJ ;
Joel Barrish, Holland, PA ;
John Hynes, Washington Crossing, PA ;

Continuing Data as Claimed by Applicant

Foreign Applications

If Required, Foreign Filing License Granted 02/15/2001

Title

Pyrrolotriazene compounds as antiinflammatory agent

Preliminary Class

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U.S. Patent Law

FEB 22 2001

Docketed Item _____
Due Date _____
Attorney Ken

Data entry by : YON, LOWUAN

Team : OIPE

Date: 02/16/2001



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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE RECD	ATTY DOCKET NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/310,581 ✓	08/07/2001 ✓		150 ✓	QA0237 PSP1 ✓			

CONFIRMATION NO. 2530

FILING RECEIPT



OC000000008951384

23914
MARLA J MATHIAS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P BOX 4000
PRINCETON, NJ 08543-4000

Date Mailed: 10/22/2001

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 Customer Service Center. 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)

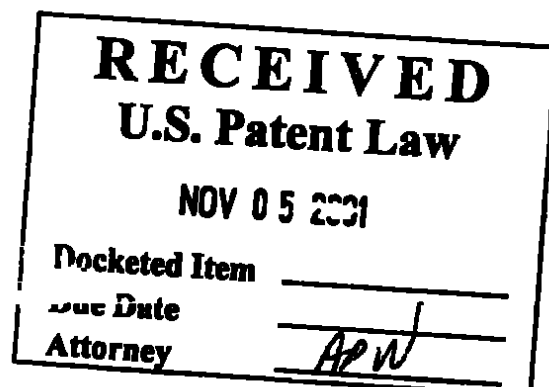
Katerina Leftheris, Skillman, NJ; ✓
John Hynes, Washington Crossing, PA; ✓
Stephen T. Wroblewski, Whitehouse Station, NJ; ✓

If Required, Foreign Filing License Granted 10/22/2001

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No



Title

Pyrrolotriazine carboxamide and benzamide compounds as kinase inhibitors ✓

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

66

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).

PCT

For receiving Office use only

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No. 67

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) QA237

Box No. I TITLE OF INVENTION

METHODS OF TREATING p38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS

Box No. II APPLICANT

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA

☐ This person is also inventor.Telephone No.
(800) 252-3342Facsimile No.
(800) 252-4626

Teleprinter No.

State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LEFTHERIS, Katerina
82 Richmond Drive
Skillman, NJ 08568
UNITED STATES OF AMERICA

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)State (that is, country) of nationality:
USState (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV 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



common representative

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
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000
UNITED STATES OF AMERICA
SEE SUPPLEMENTAL SHEET NO. 5

Telephone No.
(800) 252-3342Facsimile No.
(800) 252-4626

Teleprinter No.

☐ 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.

67
68

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet is not to be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BARRISH, Joel
38 Dorchester Lane
Richboro, PA 18954
UNITED STATES OF AMERICA

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HYNES, John
85 Dispatch Drive
Washington Crossing, PA 18977
UNITED STATES OF AMERICA

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WROBLESKI, Stephen T.
1507 South Branch Drive
Whitehouse Station, NJ 08889
UNITED STATES OF AMERICA

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (If other kind of protection or treatment desired, specify on dotted line)

National Patent (If other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☒ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☒ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☒ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☒ PT Portugal |
| ☒ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LU Luxembourg | |
| ☒ DE Germany | ☒ LV Latvia | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MA Morocco | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MD Republic of Moldova | ☒ UG Uganda |
| ☒ DZ Algeria | | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MG Madagascar | |
| ☒ EE Estonia | ☒ MK The former Yugoslav Republic of Macedonia | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MN Mongolia | ☒ VN Viet Nam |
| ☒ FI Finland | ☒ MW Malawi | ☒ YU Yugoslavia |
| ☒ GB United Kingdom | | ☒ ZA South Africa |
| ☒ GD Grenada | | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ Philippines
- ☐

Provisionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that these 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. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		☐ Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
Item (1) 17 NOVEMBER 2000 (17.11.00)	60/249,877	US		
Item (2) 07 AUGUST 2001 (07.08.01)	60/310,561	US		
Item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1) and (2)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(a)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY	
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA/EP	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)

Box No. VIII CHECK LIST: LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 5 description (excluding sequence listing part) : 88 claims : 19 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 123	This international application is accompanied by the item(s) marked below: 1. ☒ fee calculation sheet 2. ☒ separate signed power of attorney 3. ☐ copy of general power of attorney; reference number, if any: 4. ☐ statement explaining lack of signature 5. ☐ priority document(s) identified in Box No. VI as item(s): 6. ☐ translation of international application into (language): 7. ☐ separate indications concerning deposited microorganism or other biological material 8. ☐ nucleotide and/or amino acid sequence listing in computer readable form 9. ☒ other (specify): TRANSMITTAL LETTER, GENERAL POWER OF Attorney
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
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 request). ANASTASIA WINSLOW	

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA/	2. Drawings: ☐ received: ☐ not received: 6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

Supplemental Box *If the Supplemental Box is not used, this sheet need not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) If, in addition to the agent(s) indicated in Box IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continued from Page 1 - Box IV

ALGERI, Aldo; BABAJKO, Suzanne; BABCOCK, Timothy; DAVIS, Stephen; DUBOFF, Samuel; HERMENA, Ronald S.; KILCOYNE, John M.; KLEIN, Christopher; LOPEZ, Gabriel; MAKUJINA, Shah; MATHIAS, Marla; MORSE, David; O'BRIEN, Maureen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; BUCHHOLZ, Briana; DAMICO, Stephen; LANGE, Keith; PATEL, Rena; PEIST, Kenneth; MCNEIL, Scott; PROVOOST, Jonathan; FURMAN, Theodore; KRIEGER, Stuart; GIBBONS, Maureen S.

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 QA237	
International application No. PCT/US01/49982	International filing date (day/month/year) 07/November/2001	(Earliest) Priority date (day/month/year) 17/November/2000	
Title of invention METHODS OF TREATING p38 KINASE-ASSOCIATED CONDITIONS AND PYRROLOTRIAZINE COMPOUNDS USEFUL AS KINASE INHIBITORS			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America		Telephone No. 609-252-4000	
		Facsimile No. 609-252-4526	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: United States of America		State (that is, country) of residence: United States of America	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LEFThERIS, Katerina 92 Richmond Drive Skillman, New Jersey 08558 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.) BARRISH, Joel 38 Dorchester Lane Richboro, Pennsylvania 18954 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HYNES, John
95 Dispatch Drive
Washington Crossing, Pennsylvania 18977
United States of America

State *(that is, country)* of nationality:
USState *(that is, country)* of residence:
USName 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
1507 South Branch Drive
Whitehouse Station, New Jersey 08889
United States of America

State *(that is, country)* of nationality:
USState *(that is, country)* of residence:
USName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*State *(that is, country)* of nationality:State *(that is, country)* of residence:Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*State *(that is, country)* of nationality:State *(that is, country)* of residence:☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ 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.

609-252-3342

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 filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

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

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

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|----------|
| 1. translation of international application | : | 0 sheets |
| 2. amendments under Article 34 | : | 0 sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | 0 sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | 0 sheets |
| 5. letter | : | 0 sheets |
| 6. other (specify) | : | 0 sheets |

For International Preliminary
Examining Authority use only

received	not received
----------	--------------

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (Certification for POA): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



_____, Agent
Anastasia P. Winslow

Date: 13. June. 2002

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:

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WINSLOW, Anastasia
Bristol-Myers Squibb Company
P.O. Box 4000
Lawrenceville-Princeton Road
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 18 March 2002 (18.03.02)	
Applicant's or agent's file reference QA237	IMPORTANT NOTIFICATION
International application No. PCT/US01/49982	International filing date (day/month/year) 07 November 2001 (07.11.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 17 November 2000 (17.11.00)
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
17 Nove 2000 (17.11.00)	60/249,877	US	07 Marc 2002 (07.03.02)
07 Augu 2001 (07.08.01)	60/310,561	US	05 Marc 2002 (05.03.02)

BRIEF PENDING LAW

APR 01 2002

Docketed Item

Due Date

Attorney

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference QA237	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/US 01/49982	International filing date (day/month/year) 07/11/2001	(Earliest) Priority Date (day/month/year) 17/11/2000
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 4 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 36.2(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/US 01/49982

78 77

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 C07D519/00 A61K31/53 A61P29/00
//(C07D487/04,253:00,209:00),(C07D519/00,487:00,487:00),
(C07D519/00,487:00,471:00)

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)

IPC 7 C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 713 876 A (WAKAMOTO PHARMA CO LTD) 29 May 1996 (1996-05-29) claims 1,10	7,28,31
A	WO 99 24033 A (SHIONOGI & CO) 20 May 1999 (1999-05-20) page 3, paragraph 1 - paragraph 4; claim 1	7,28,31
P,X	WO 00 71129 A (SQUIBB BRISTOL MYERS CO) 30 November 2000 (2000-11-30) claims 1,3; examples 33,36,37,53,54,63,93	7,28

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

12 November 2002

Date of mailing of the international search report

21/11/2002

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/49982

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

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

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6, 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

PCT/US 01/49982

80 29

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0713876	A	29-05-1996	CA	2163399 A1		25-05-1996
			EP	0713876 A1		29-05-1996
			JP	8208654 A		13-08-1996
WO 9924033	A	20-05-1999	WO	9924033 A1		20-05-1999
			AU	9763098 A		31-05-1999
			CA	2308269 A1		20-05-1999
			EP	1037630 A2		27-09-2000
			WO	9924026 A2		20-05-1999
WO 0071129	A	30-11-2000	AU	4852400 A		12-12-2000
			BR	0010482 A		23-04-2002
			CN	1351498 T		29-05-2002
			EP	1183033 A1		06-03-2002
			NO	20015650 A		20-11-2001
			WO	0071129 A1		30-11-2000

MÉTODOS DE TRATAR CONDICIONES ASOCIADAS CON QUINASA p38 Y COMPUESTOS DE PIRROLOTRIAZINA ÚTILES COMO INHIBIDORES DE QUINASA

Inventiones Relacionadas

Esta solicitud reivindica el beneficio de la Solicitud Provisional de los Estados Unidos No. 60/249,877, presentada el 17 de noviembre de 2000, y la Solicitud Provisional de los Estados Unidos No. 60/310,561, presentada el 7 de agosto de 2001, las cuales se incorporan ambas aquí por referencia.

Campo de la Invención

Esta invención se relaciona con métodos de tratar condiciones asociadas con quinasas p38 α y β y con compuestos de pirrolotriazina, más particularmente, con compuestos de carboxamida y benzamida pirrolotriazina útiles para tratar condiciones asociadas con quinasa p38.

Antecedentes de la Invención

Un gran número de citocinas participan en la respuesta inflamatoria, incluyendo IL-1, IL-6, IL-8 y TNF- α . La sobreproducción de citocinas tal como IL-1 y TNF- α están implicadas en una amplia variedad de enfermedades, incluyendo la enfermedad inflamatoria intestinal, artritis reumatoide, psoriasis, esclerosis múltiple, shock endotóxico, osteoporosis, enfermedad de Alzheimer e insuficiencia cardíaca congestiva, entre otras [Henry y colaboradores, Drugs Fut., 24:1345-1354 (1999); Salituro y colaboradores, Curr. Med. Chem., 6:807-823 (1999)]. La evidencia en pacientes humanos indica que antagonistas de proteína de citocinas son efectivas en tratar enfermedades inflamatorias crónicas, tales como, por ejemplo, anticuerpo monoclonal a TNF- α (Enbrel) [Rankin y

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colaboradores, Br. J. Rheumatol., 34:334-342 (1995)], y receptor TNF- α soluble-proteína de fusión Fc (Etanercept) [Moreland y *colaboradores*, Ann. Intern. Med., 130:478-486 (1999)].

La biosíntesis de TNF- α ocurre en muchos tipos de células en respuesta a un estímulo externo, tal como, por ejemplo, un mitógeno, un organismo infeccioso, o trauma. Mediadores importantes de producción de TNF- α son las proteínas quinasas activadas por mitógeno (MAP), y en particular, quinasa p38. Estas quinasas se activan en respuesta a diferentes estímulos de estrés, incluyendo pero no limitadas a, citocinas proinflamatorias, endotoxina, luz ultravioleta y shock osmótico. La activación de p38 requiere fosforilación dual mediante quinasas quinasa MAP previas (MKK3 y MKK6) en treonina y tirosina en un motivo Thr-Gly-Tyr característico de isozimas p38.

Existen cuatro isoformas conocidas de p38, *i.e.*, p38- α , p38 β , p38 γ y p38 δ . Las isoformas α y β se expresan en células inflamatorias y son mediadores claves de producción de TNF- α . La inhibición de enzimas p38 α y β en células tiene como resultado niveles reducidos de expresión TNF- α . Igualmente, administrar inhibidores p38 α y β en modelos animales de enfermedad inflamatoria ha probado que dichos inhibidores son efectivos en tratar aquellas enfermedades. Por consiguiente, las enzimas p38 cumplen un papel importante en procesos inflamatorios mediados por IL-1 y TNF- α . Compuestos que, como se dice, inhiben la quinasa p38 y citocinas tales como IL-1 y TNF- α para uso en tratar enfermedades inflamatorias se divulgan en las Patentes de los Estados Unidos Nos. 6,277,989 y 6,130,235 a Scios, Inc; Patentes de los Estados Unidos Nos. 6,147,080 y 5,945,418 a Vertex Pharmaceuticals Inc; Patentes de los Estados Unidos Nos. 6,251,914, 5,977,103 y 5,658,903 a Smith-Kline Beecham Corp.; Patentes de los Estados Unidos Nos. 5,932,576 y 6,087,496 a G.D. Searle & Co.; WO 00/56738 y WO 01/27089 a Astra Zeneca; WO 01/34605 a Johnson & Johnson; WO 00/12497 (derivados de quinazolina como inhibidores de quinasa p38); WO 00/56738 (derivados de piridina y

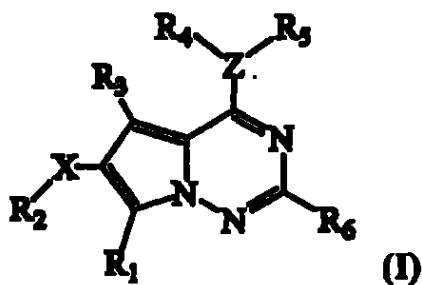
pirimidina para el mismo propósito); WO 00/12497 (discute la relación entre inhibidores de quinasa p38); y WO 00/12074 (compuestos de piperazina y piperidina útiles como inhibidores de p38).

La presente invención provee métodos de tratar condiciones asociadas con actividad de quinasa p38 que comprenden administrar a un paciente necesitado de ello ciertos compuestos de pirrolotriazina. La invención provee además compuestos seleccionados de pirrolotriazina, incluyendo compuestos de 5-metil y 5-trifluorometil pirrolotriazina-6-carboxamida útiles como inhibidores de quinasa, particularmente quinasas p38 α y β .

Compuestos de pirrolotriazina útiles como inhibidores de tirosina quinasa se divulgan en la solicitud de Patente de los Estados Unidos No. de Serial 09/573,829 presentada el 18 de mayo de 2000, asignada al presente beneficiario. Compuestos de pirrolotriazina sustituidos con un grupo ácido que, según se dice, poseen actividad inhibidora de sPLA₂ se divulgan en WO 01/14378 A1 a Shionogi & Co., Ltd, publicada el 1 de marzo de 2001 en japonés. Cada una de las solicitudes de patente, patentes y publicaciones mencionadas aquí se incorporan en este punto por referencia.

Sumario de la Invención

La presente invención se dirige a métodos de tratar una o más condiciones asociadas con actividad de quinasa p38 que comprenden administrar a un paciente necesitado de ello uno o más compuestos de acción farmacéutica que tienen la Fórmula (I):



o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R₃ es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano, o NH₂;

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X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -CO₂-,
-NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-,
-NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, -C(=O)NR₁₀-, halógeno, nitro y ciano, o
X está ausente;

Z se selecciona de O, S, N, y CR₂₀, en donde cuando Z es CR₂₀, dicho
átomo de carbono puede formar un arilo bicíclico o heteroarilo
opcionalmente sustituido con R₄ y R₅;

R₁ es hidrógeno, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂,
-SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₄R₂₅, -
NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -
NR₂₁C(=O)NR₂₄R₂₅, halógeno, nitro o ciano;

R₂ se selecciona de:

- a) hidrógeno, con la condición que R₂ no es hidrógeno si X es -
S(=O)-, -SO₂-, -NR₁₀CO₂-, o -NR₁₀SO₂-;
 - b) alquilo, alqueno y alquino opcionalmente sustituido con hasta
cuatro R₂₆;
 - c) arilo y heteroarilo opcionalmente sustituido con hasta tres R₂₇; y
 - d) heterociclo y cicloalquilo opcionalmente sustituido con ceto (=O),
hasta tres R₂₇, y/o que tiene un puente carbono-carbono de 3 a 4
átomos de carbono; o
 - e) R₂ está ausente si X es halógeno, nitro, o ciano;
- (i) R₄ es arilo sustituido, arilo sustituido con NHSO₂alquilo, heteroarilo
sustituido, o un anillo heterocíclico o carbocíclico saturado o
insaturado de 7-11 miembros opcionalmente sustituido, y
R₅ es hidrógeno, alquilo, o alquilo sustituido, salvo que cuando Z es
O ó S, R₅ está ausente, o alternativamente,
- (ii) R₄ y R₅ tomados junto con Z forman un arilo o heteroarilo bicíclico de
7-11 miembros opcionalmente sustituido;
- R₆ es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido,
heterociclo, heterociclo sustituido, -NR₇R₈, -OR₇, o halógeno;
- R₁₀ y R₁₁ se seleccionan independientemente de hidrógeno, alquilo, alquilo
sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido,

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heterociclo, y heterociclo sustituido;

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

R_{20} es hidrógeno, alquilo inferior, o alquilo sustituido, o R_{20} puede estar ausente si el átomo de carbono al cual se une junto con R_4 y R_5 es parte de un arilo o heteroarilo bicíclico insaturado;

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

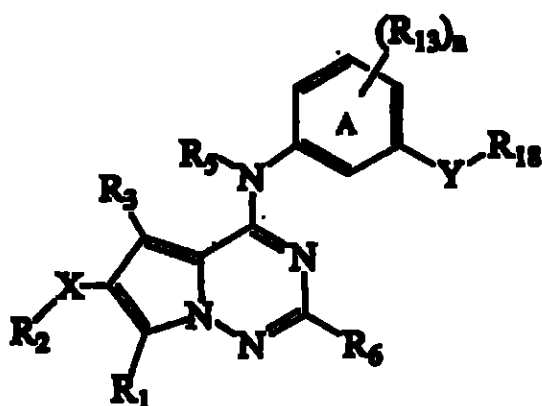
R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$,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

R_{27} se selecciona de alquilo, R_{32} , y C_{1-4} -alquilo sustituido con uno a tres R_{32} en donde cada grupo R_{32} se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, $-SR_{30}$, $-OR_{30}$, $-NR_{30}R_{31}$, $-NR_{30}SO_2$, $-NR_{30}SO_2R_{31}$, $-SO_2R_{30}$, $-SO_2NR_{30}R_{31}$, $-CO_2R_{30}$, $-C(=O)R_{30}$, $-C(=O)NR_{30}R_{31}$, $-OC(=O)R_{30}$, $-OC(=O)NR_{30}R_{31}$, $-NR_{30}C(=O)R_{31}$, $-NR_{30}CO_2R_{31}$, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros opcionalmente sustituido con alquilo, halógeno,

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hidroxi, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R_{30} y R_{31} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C_{3-7} cicloalquilo, y heterociclo, o pueden tomarse juntos para formar un C_{3-7} heterociclo.

La invención se dirige además a compuestos que, sorprendentemente, poseen una actividad ventajosa como inhibidores de quinasas p38 α y β y TNF- α que comprenden compuestos de Fórmula (II):



(II),

y sus sales, profármacos o solvatos de aceptación farmacéutica, en donde:

R_3 es metilo o CF_3 ;

R_4 es hidrógeno o alquilo;

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

R_{18} y R_{23} se seleccionan de hidrógeno, alquilo, alcoxi, arilo, y arilo sustituido con uno a tres R_{19} , salvo cuando Y es $-NR_{23}SO_2-$, R_{18} es C_{1-4} alquilo o arilo opcionalmente sustituido con uno a tres R_{19} ;

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

X, R_1 , R_2 , y R_6 son como se definieron más arriba en el texto para

compuestos de Fórmula (I).

Descripción de la Invención

Enumeradas a continuación se encuentran las definiciones de varios términos usados para describir esta invención. Estas definiciones se aplican a los términos tal como se emplean a lo largo de esta especificación, a menos que se limite en caso contrario en instancias específicas, individualmente o como parte de un grupo más amplio.

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

El término "alquilo sustituido" se refiere a un grupo alquilo sustituido por uno a cuatro sustituyentes seleccionados de halo, hidroxilo, alcoxi, oxo (=O), alcanilo, arilo, alcanoilo, amino, alquilamino, arilamino, aralquilamino, aminas disustituidas en las cuales los 2 sustituyentes amino se seleccionan de alquilo, arilo o aralquilo; alcanilamino, aroilamino, aralcanilamino, alcanilamino sustituido, arilamino sustituido, aralcanilamino sustituido, tiol, alquiltio, ariltio, aralquiltio, alquiltiono, ariltiono, aralquiltiono, alquilsulfonilo, arilsulfonilo, aralquilsulfonilo, sulfonamido, e.g. SO₂NH₂, sulfonamido sustituido, nitro, ciano, carboxi, carbamilo, e.g. CONH₂, carbamilo sustituido e.g. CONH-alquilo, CONH-arilo, CONH-aralquilo o casos en donde hay dos sustituyentes en el nitrógeno seleccionados de alquilo, arilo o aralquilo; alcóxicarbonilo, arilo, arilo sustituido, guanidino y heterociclos sustituidos o no sustituidos, tales como indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares. Cuando el sustituyente en el alquilo se sustituye adicionalmente, lo será con alquilo, alcoxi, arilo, o aralquilo.

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

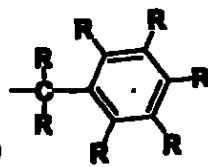
El término "halógeno" o "halo" se refiere flúor, cloro, bromo y yodo.

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

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

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

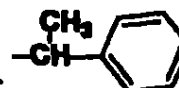
opcionalmente sustituido" se refiere al grupo



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grupo R puede ser hidrógeno o puede también seleccionarse de alquilo, halógeno, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi y benciloxi, y otros grupos enumerados más arriba en el texto. Por lo menos dos de estos grupos "R" deben ser hidrógeno y, preferiblemente, por lo menos cinco de los grupos "R" es hidrógeno. Un grupo bencilo

preferido incluye la porción alquilo que es ramificada para definir



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

Un "heteroarilo sustituido" tiene uno a cuatro sustituyentes en uno cualquiera o más de los anillos que comprenden el grupo heteroarilo. Los sustituyentes pueden seleccionarse de los enumerados a continuación para grupos heterociclo.

Grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo,

pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo (i.e.,



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

Grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxaxolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiraniilo, indoliziniilo, benzofuranilo, cromonilo, cumarinilo, benzopiraniilo, cinnolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

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

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

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

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

El término "alquinilo sustituido" se refiere a un grupo alquinilo sustituido por un sustituyente seleccionado de halo, hidroxilo, alcoxi, alcanilo, alcanoilo, alcanoilo, amino, alquilamino, dialquilamino, alcanilo, alcanoilamino, tiol, alquiltio, alquiltion, alquilsulfonilo, sulfonamido, nitro, ciano, carboxi, carbamilo, carbamilo sustituido, guanidino y heterociclo sustituido

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o no sustituido, e.g. imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares.

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

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

Grupos heterocíclicos monocíclicos ejemplares incluyen pirrolidinilo, pirrolilo, indolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahydrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxazepinilo, azepinilo, 4-piperidonilo, piridilo, N-oxo-piridilo, pirazinilo, pirimidinilo,

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piridazinilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, sulfota de tiamorfolinilo, 1,3-dioxolano y tetrahydro-1,1-dioxotienilo, dioxanilo, isotiazolidinilo, tietanilo, tiiranilo, triazinilo y triazolilo, y similares.

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

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

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

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

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

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

El término "perfluorometilo" significa un grupo metilo sustituido por uno, dos, o tres átomos de flúor, *i.e.*, CH_2F , CHF_2 y CF_3 . El término "perfluoroalquilo" significa un grupo alquilo que tiene de uno a 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 $-\text{OCF}_3$.

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

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

Definiciones de los demás diferentes grupos que se enumeran más arriba en el texto en conexión con alquilo sustituido, alqueno sustituido, alquino sustituido, arilo sustituido, heterociclo sustituido, cicloalquilo sustituido, etcétera, son las siguientes: alcoxi es $-\text{OR}^a$, alcanilo es $-\text{C}(=\text{O})\text{R}^a$, arilo es $-\text{OAr}$, alcanilo es $-\text{OC}(=\text{O})\text{R}^a$, amino es $-\text{NH}_2$, alquilamino es $-\text{NHR}^a$, arilamino es $-\text{NHAr}$, aralquilamino es $-\text{NH-R}^b\text{-Ar}$, amina disustituida o dialquilamino es $-\text{NR}^c\text{R}^d$, alcanilamino es $-\text{NH-C}(=\text{O})\text{R}^a$, aroilamino es $-\text{NH-C}(=\text{O})\text{Ar}$, aralcanilamino es $-\text{NH-C}(=\text{O})\text{R}^b\text{-Ar}$, tiol es $-\text{SH}$, alquiltio es $-\text{SR}^a$, ariltio es $-\text{SAr}$, aralquiltio es $-\text{S-R}^b\text{-Ar}$, alquiltiono es $-\text{S}(=\text{O})\text{R}^a$, ariltiono es $-\text{S}(=\text{O})\text{Ar}$, aralquiltiono es $-\text{S}(=\text{O})\text{R}^b\text{-Ar}$, alquilsulfonilo es $-\text{SO}_{(q)}\text{R}^a$, arilsulfonilo es $-\text{SO}_{(q)}\text{Ar}$, arilsulfonilamina es $-\text{NHSO}_{(q)}\text{Ar}$, alquilsulfonilamina es $-\text{NHSO}_2\text{R}^a$, aralquilsulfonilo es $-\text{SO}_{(q)}\text{R}^b\text{Ar}$, sulfonamido es $-\text{SO}_2\text{NH}_2$, nitro es $-\text{NO}_2$, carboxi es $-\text{CO}_2\text{H}$, carbamilo es $-\text{CONH}_2$, carbamilo sustituido es $-\text{C}(=\text{O})\text{NHR}^c$ o $-$

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$C(=O)NR^cR^d$, alcóxicarbonilo es $-C(=O)OR^a$, carboxialquilo es $-R^bCO_2H$, ácido sulfónico es $-SO_3H$, arilsulfonilamina es $-NHSO_{(q)}Ar$, guanidino es

$\begin{array}{c} \text{NH} \\ \parallel \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, y ureido es $\begin{array}{c} \text{O} \\ \parallel \\ \text{---N---C---NH}_2 \\ | \\ \text{H} \end{array}$, en donde R^a es alquilo como se define más arriba en el texto, R^b es alquilenos como se define más arriba en el texto, R^c y R^d se seleccionan de alquilo, arilo, y aralquilo, Ar es un arilo como se define más arriba en el texto, y q es 2 ó 3.

A todo lo largo de la especificación, grupos y sus sustituyentes pueden escogerse por un experto en el campo para proporcionar fracciones y compuestos estables.

Los compuestos de Fórmula (I) pueden formar sales las cuales se encuentran también en el ámbito de esta invención. Se prefieren sales de aceptación farmacéutica (*i.e.* no tóxicas, de aceptación fisiológica), aunque también son útiles otras sales, *e.g.*, en aislar o purificar los compuestos de esta invención. Todas las referencias a compuestos de Fórmula (I) contenidas aquí pretenden incluir sin limitación compuestos de Fórmulas (Ia) a (Ii) así como compuestos de Fórmula (II) y (IIa)-(IIh). Todas las referencias a compuestos de Fórmula (II) pretenden incluir compuestos de Fórmulas (IIa) a (IIh).

Los compuestos de Fórmula (I) pueden formar sales con metales alcalinos tales como sodio, potasio y litio, con metales alcalinotérreos tales como calcio y magnesio, con bases orgánicas tales como diciclohexilamina, tributilamina, piridina y aminoácidos tales como arginina, lisina y similares. Dichas sales pueden formarse tal como se conoce por expertos en el arte.

Los compuestos para Fórmula (I) pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. Dichas sales incluyen aquellas formadas con hidrógeno cloro, bromuro de hidrógeno, ácido metanosulfónico, ácido sulfúrico, ácido acético, ácido trifluoroacético, ácido oxálico, ácido maleico, ácido bencenosulfónico, ácido toluenosulfónico y varios otros (*e.g.*, nitratos, fosfatos, boratos, tartratos, citratos, succinatos, benzoatos, ascorbates, salicilatos y similares). Dichas sales pueden formarse como se conoce por aquellos que son expertos en el

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arte.

Formas de sales de los compuestos pueden ser útiles para mejorar la velocidad de disolución del compuesto y la biodisponibilidad oral. Para compuestos seleccionados de Fórmula (I), se obtuvieron exitosamente sales de mesilato y/o bisulfato (véase, e.g., Ejemplo 125 contenido aquí). Se descubrió que las dos sales de mesilato y bisulfato son no higroscópicas, son altamente solubles en agua, y estables en estado sólido.

Además, pueden formarse dobles iones dipolo ("sales internas").

Todos los estereoisómeros de los compuestos de la presente invención están contemplados, en mezcla o en forma pura o sustancialmente pura. La definición de compuestos de acuerdo con la invención abarca todos los estereoisómeros posibles y sus mezclas. Comprende las formas racémicas y los isómeros ópticos aislados que tienen la actividad especificada. Las formas racémicas pueden resolverse por métodos físicos, tales como, por ejemplo, cristalización fraccionaria, separación o cristalización de derivados diastereoméricos o separación mediante cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos a partir de los métodos convencionales, tales como, por ejemplo, formación de sales con un ácido ópticamente activo seguida por cristalización.

Compuestos de la Fórmula (I) pueden tener además formas de profármaco. Cualquier compuesto que se convertirá in vivo para proporcionar el agente bioactivo (i.e., el compuesto para fórmula I) es un profármaco en el ámbito y espíritu de la invención.

Varias formas de profármacos son bien conocidas en el arte. Para ejemplos de dichos derivados de profármacos, véase:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology, Vol. 42, página 309-396, editado por K. Widder, y colaboradores (Acamedic Press, 1985);

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

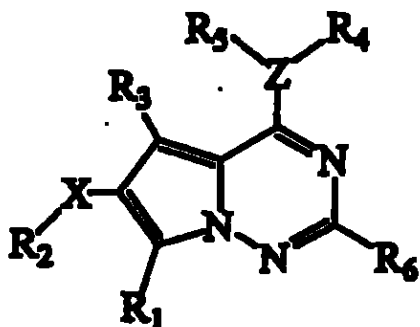
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c) H. Bundgaard, Advanced Drug Delivery Reviews, **8**, 1-38 (1992), cada uno de los cuales se incorpora aquí por referencia.

Debe entenderse además que solvatos (*e.g.*, hidratos) de los compuestos de Fórmula (I) se encuentran también en el ámbito de la presente invención. Métodos de solvatación son generalmente conocidos en el arte.

Compuestos Preferidos

Incorporaciones preferidas de la invención comprenden compuestos preferidos de Fórmulas (I) y (II), y métodos de tratar condiciones asociadas con actividad de quinasa p38 que comprenden administrar compuestos preferidos de Fórmulas (I) y (II). Compuestos preferidos son aquellos que tienen la Fórmula (I),



(I)

y sus sales, profármacos o solvatos de aceptación farmacéutica, en donde:

R₃ es metilo, -CF₃, ó -OCF₃,

X se selecciona de -C(=O)-, -CO₂-, -NR₁₀C(=O)-, y -C(=O)NR₁₀-, ó X está ausente;

Z es N;

R₁ es hidrógeno, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halógeno, nitro, o ciano;

R₂ es hidrógeno, C₂₋₆alquilo, C₁₋₄alquilo sustituido, arilo, aralquilo, arilo sustituido, aralquilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, o heterociclo sustituido, o cicloalquilalquilo o

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heterocicloalquilo opcionalmente sustituido;

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

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

R_6 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, o halógeno;

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

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

R_{14} es hidrógeno, alquilo, o arilo;

R_{15} es hidrógeno o alquilo;

R_{16} es hidrógeno, alquilo, aralquilo, o alcanilo;

R_{17} es hidrógeno, hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, o aralquilo;

R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno y alquilo; y R_{22} es alquilo o alquilo sustituido.

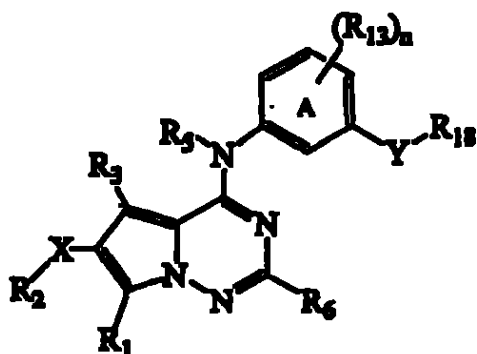
En compuestos de Fórmula (I), preferiblemente el grupo R_3 es metilo, trifluorometilo, o metoxi, muy preferiblemente metilo; X es preferiblemente $-CO_2-$, $-NR_{10}C(=O)-$, o $-C(=O)NR_{10}-$, más preferiblemente $-C(=O)NH-$; Z es preferiblemente N; R_4 es preferiblemente arilo sustituido o heteroarilo sustituido, más preferiblemente fenilo sustituido con por lo menos uno de carbamilo, carbamilo sustituido, arilsulfonilamido, arilsulfonilamido sustituido, ureido, o ureido sustituido, y sustituido opcionalmente con uno o dos $C_{1-4}alquilo$ o halógeno. Muy preferiblemente R_4 es fenilo sustituido con por lo menos uno de $-C(=O)NHO(C_{1-4}alquilo)$ o $-C(=O)NH(fenilo$ opcionalmente sustituido), y además se sustituye opcionalmente con $C_{1-4}alquilo$. R_5 es preferiblemente hidrógeno o alquilo inferior o, más

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preferiblemente, hidrógeno.

En compuestos preferidos, R_1 y R_6 pueden seleccionarse de grupos de sustituyentes como se definen aquí; no obstante, ventajosamente se seleccionan de hidrógeno, CH_3 , $-OH$, $-OCH_3$, halógeno, nitro, y ciano, y muy preferiblemente R_1 y R_6 son hidrógeno. R_2 es preferiblemente alquilo, arilo, arilo sustituido, aralquilo, aralquilo sustituido, heteroarilo, o heteroarilo sustituido, más preferiblemente C_{2-6} alquilo recto o ramificado o bencilo opcionalmente sustituido. La sal de mesilato es la forma preferida de sal.

En consecuencia, compuestos preferidos comprenden asimismo aquellos que poseen la Fórmula (II),



(II),

y sus sales, profármacos o solvatos de aceptación farmacéutica, en donde:

R_3 es metilo, $-CF_3$, ó $-OCH_3$;

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

Y es $-C(=O)NH$ -, $-NHC(=O)NH$ -, o $-NH SO_2$ -;

R_{10} es hidrógeno o alquilo inferior;

R_{18} se selecciona de hidrógeno, alquilo, alcoxi, arilo, y arilo sustituido con uno a tres R_{19} , salvo que cuando Y es $-NH SO_2$ -, R_{18} es $-C_{1-4}$ alquilo, arilo o arilo sustituido con R_{19} ;

R_{13} se une a cualquier átomo de carbono disponible del anillo fenilo A y en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, $-C(=O)$ alquilo, $-OC(=O)$ alquilo, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, -

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CO_2R_{15} , $-\text{CONH}_2$, $-\text{SO}_3\text{H}$, $-\text{S}(=\text{O})\text{alquilo}$, $-\text{S}(=\text{O})\text{aril}$, $-\text{NHSO}_2\text{-aril-}$
 R_{17} , $-\text{SO}_2\text{NHR}_{17}$, $-\text{CONHR}_{17}$, y $-\text{NHC}(=\text{O})\text{NHR}_{17}$;

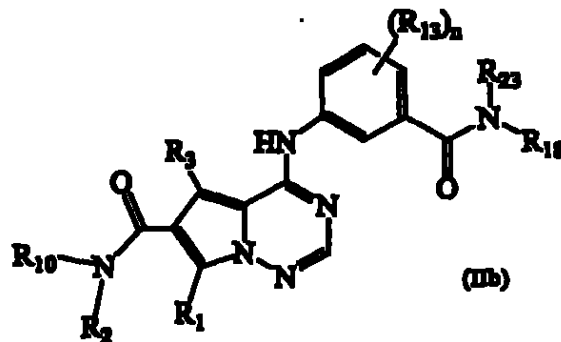
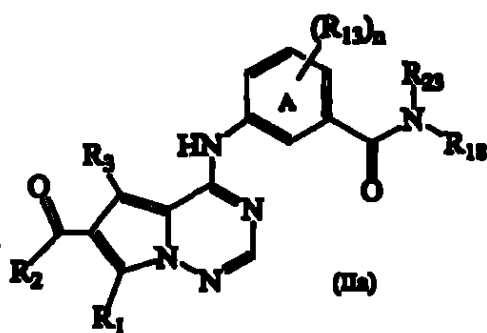
R_{14} , R_{15} , R_{16} y R_{17} son hidrógeno o alquilo;

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

n es 0, 1 ó 2, y

R_1 , R_2 y R_6 son como se define más arriba en el texto para compuestos de Fórmula (I).

Más preferidos son compuestos que tienen la Fórmula (IIa) o (IIb):



y sus sales, profármacos o solvatos de aceptación farmacéutica, en donde:

R_3 es metilo;

R_1 y R_{10} son hidrógeno o $-\text{CH}_3$;

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

haloalquilo, haloalcoxi, nitro, ciano y alquilo;

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

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

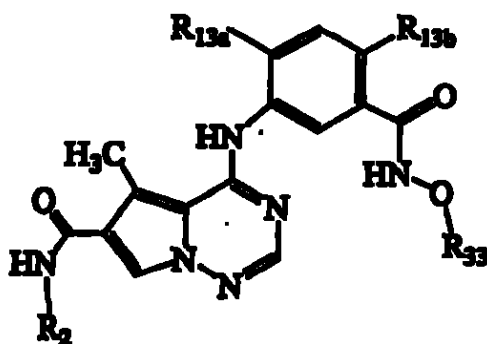
R_{27} en cada ocurrencia se selecciona independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, hidroxilo, alcoxi, fenilo, bencilo, feniloxi, y benciloxi;

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

n es 0, 1 ó 2.

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

Muy preferidos son compuestos que poseen la fórmula,



en la cual R_{13a} y R_{13b} son hidrógeno, CH_3 , OH , OCH_3 , CF_3 , ciano, o halógeno, R_2 es C_{2-6} alquilo o bencilo opcionalmente sustituido, R_{33} es alquilo inferior, y n es 0 ó 1.

Utilidad

Los compuestos de la invención son inhibidores selectivos de actividad de quinasa p38, y en particular, isoformas p38 α y p38 β . Por lo tanto, compuestos de fórmula (I) poseen utilidad en tratar condiciones asociadas con actividad de quinasa p38. Dichas condiciones incluyen

enfermedades en las cuales los niveles de citocina se modulan como una consecuencia de señalización intracelular mediante p38 y, en particular, enfermedades que están asociadas con una sobreproducción de citocinas IL-1, IL-4, IL-8 y TNF- α . Tal como se usa aquí, los términos "tratar" o "tratamiento" abarcan cualquiera de las dos, o ambas, medidas de reacción favorable y profilaxis, e.g., diseñadas para inhibir o retrasar la iniciación de la enfermedad o desorden, lograr una reducción completa o parcial de los síntomas o estado patológico, y/o aliviar, mejorar, atenuar, o curar la enfermedad o desorden y/o sus síntomas. Cuando se hace referencia aquí a inhibición de "quinasa p-38 α/β ", esto significa que quinasa p38 α y/o quinasa p38 β se inhiben. Por consiguiente, la referencia a un valor IC₅₀ para inhibir quinasa p-38 α/β significa que el compuesto posee tal efectividad para inhibir por lo menos una, o ambas, de las quinasas p38 α y p38 β .

En vista de su actividad como inhibidores de quinasas p-38 α/β , los compuestos de fórmula (I) son útiles en tratar condiciones asociadas con p-38 incluyendo, pero no limitadas a, enfermedades inflamatorias, enfermedades autoinmunes, desórdenes destructivos de los huesos, desórdenes proliferativos, desórdenes angiogénicos, enfermedades infecciosas, enfermedades neurodegenerativas y enfermedades virales.

Más particularmente, las condiciones o enfermedades específicas que pueden tratarse con los compuestos inventivos incluyen, sin limitación, pancreatitis (aguda o crónica), asma, alergias, enfermedad de la membrana hialina en adultos, enfermedad pulmonar obstructiva crónica, glomerulonefritis, artritis reumatoide, lupus eritematoso sistémico, escleroderma, tiroiditis crónica, enfermedad de Graves, gastritis autoinmune, diabetes, anemia hemolítica autoinmune, neutropenia autoinmune, trombocitopenia, dermatitis atópica, hepatitis activa crónica, miastenia grave, esclerosis múltiple, enfermedad inflamatoria intestinal, colitis ulcerativa, enfermedad de Crohn, psoriasis, enfermedad injerto vs.

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anfitrión, reacción inflamatoria inducida por endotoxina, tuberculosis, aterosclerosis, degeneración muscular, caquexia, artritis psoriática, síndrome de Reiter, gota, artritis traumática, artritis rubéola, sinovitis aguda, enfermedad de las células β pancreáticas; enfermedades caracterizadas por infiltración masiva de neutrófilos; espondilitis reumatoide, artritis gotosa y otras condiciones artríticas, malaria cerebral, enfermedad inflamatoria pulmonar crónica, silicosis, sarcoidosis pulmonar, enfermedad de reabsorción ósea, rechazos de aloinjertos, fiebre y dolores musculares debidos a infección, caquexia secundaria a una infección, formación mieloide, formación de tejido cicatrizante, colitis ulcerativa, piresis, influenza, osteoporosis, osteoartritis y desorden óseo relacionado con mieloma múltiple, leucemia mielógena aguda, leucemia mielógena crónica, melanoma metastásico, sarcoma de Kaposi, mieloma múltiple, sepsis, shock séptico, y shigellosis; enfermedad de Alzheimer, mal de Parkinson, isquemias cerebrales o enfermedad neurodegenerativa causada por lesión traumática; desórdenes angiogénicos incluyendo tumores sólidos, neovascularización ocular, y hemangiomas infantiles; enfermedades virales incluyendo infección por hepatitis aguda (inclusive hepatitis A, hepatitis B y hepatitis C), infección por VIH y retinitis CMV, SIDA < ARC o malignidad, y herpes; infarto, isquemia del miocardio, isquemia en ataques cardíacos de infarto, hipoxia de los órganos, hiperplasia vascular, lesión de repercusión cardíaca y renal, trombosis, hipertrofia cardíaca, agregación plaquetaria inducida por trombina, endotoxemia y/o síndrome de shock tóxico, y condiciones asociadas con prostaglandina-endoperoxidasa-sintasa-2.

Adicionalmente, los inhibidores de p38 de esta invención inhiben la expresión de proteínas pro-inflamatorias inducibles tales como prostaglandina endoperoxido sintasa-2 (PGHS-2), también designada como ciclooxigenasa-2 (COX-2). En consecuencia, condiciones adicionales asociadas con p38 incluyen edema, analgesia, fiebre y dolor, tales como dolor neuromuscular, dolor de cabeza, dolor causado por el cáncer, dolor dental y dolor artrítico. Los compuestos inventivos pueden usarse

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igualmente para tratar infecciones virales veterinarias, tales como infecciones por lentivirus, incluyendo, pero no limitadas a virus de anemia infecciosa equina; o infecciones por retrovirus, incluyendo virus de inmunodeficiencia felina, virus de inmunodeficiencia bovina, y virus de inmunodeficiencia canina.

Cuando los términos "condición asociada con p38" o "enfermedad o desorden asociado con p38" se usan aquí, cada uno pretende abarcar todas las condiciones identificadas más arriba en el texto, repetidas en su extensión, así como cualquier otra condición que sea afectada por la actividad de la quinasa p38.

Por lo tanto, la presente invención provee métodos para tratar dichas condiciones, que comprenden administrar a un sujeto necesitado de una cantidad efectiva de por lo menos un compuesto de fórmula (I) o su sal. Los métodos de tratar condiciones asociadas con quinasa p38 pueden incluir administrar compuestos de fórmula (I) solos o en combinación uno con otro y/o otros agentes terapéuticos adecuados útiles en tratar dichas condiciones. Ejemplares de dichos otros agentes terapéuticos incluyen corticosteroides, rolipram, calfofina, CSAIDs, 4-sustituidas imidazo [1,2-A]quinoxalinas como se divulgan en la Patente de los Estados Unidos No. 4,200,750 y en S. Ceccarelli y colaboradores, "Imidazo[1,2-a]quinoxalin-4-amine: A Novel Class of Nonxanthine A₁-Adenosine Receptor Antagonists," European Journal of Medicinal Chemistry Vol. 33, (1998), en páginas 943-955; Interleukin-10, glucocorticoides, salicilatos, óxido nítrico, y otros inmunosupresores; inhibidores de translocación nuclear, tales como deoxispergualina (DSG); fármacos antiinflamatorios no esteroideos (NSAIDs) tales como ibuprofeno, celecoxib y rofecoxib; esteroides tales como prednisona o dexametasona; agentes antivirales tales como abacavir; agentes antiproliferativos tales como metotrexato, leflunomida, FK506 (tacrolimus, Prograf); fármacos citotóxicos tales como azatioprina y ciclofosfamida; inhibidores de TNF- α tales como tenidap, anticuerpos anti-TNF o receptor de TNF soluble, y rapamicina (sirolimus o Rapamune) o sus

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derivados.

Los otros agentes terapéuticos ya mencionados, cuando se emplean en combinación con los compuestos de la presente invención, pueden usarse, por ejemplo, en aquellas cantidades indicadas en la Physicians' Desk Reference (PDR) o como se determine en otra forma por alguien de habilidades ordinarias en el arte. En los métodos de la presente invención, dicho(s) otro(s) agente(s) terapéutico(s) puede(n) administrarse antes de, simultáneamente con, o a continuación de la administración de los compuestos inventivos.

La presente invención provee también composiciones farmacéuticas capaces de tratar condiciones asociadas con la quinasa p38, incluyendo condiciones mediadas por TNF- α , IL-1, y/o IL-8, como se describe anteriormente. Las composiciones inventivas pueden contener otros agentes terapéuticos como se describe más arriba en el texto y pueden formularse, por ejemplo, empleando vehículos convencionales sólidos o líquidos o diluyentes, así como aditivos farmacéuticos de un tipo apropiado al modo de administración deseada (e.g., excipientes, aglutinantes, preservativos, estabilizantes, sabores, etc.) de acuerdo con técnicas tales como aquellas bien conocidas en el arte de la formulación farmacéutica.

Los compuestos de fórmula (I) pueden administrarse por medios cualesquiera apropiados para la condición a tratarse, los cuales pueden depender de la necesidad de tratamiento específico del sitio o cantidad de fármaco a administrarse. Generalmente se prefiere la administración tópica para enfermedades relacionadas con la piel, y se prefiere el tratamiento sistemático para condiciones cancerosas o pre-cancerosas, si bien se contemplan otros modos de administración. Por ejemplo, los compuestos pueden administrarse oralmente, tal como en forma de tabletas, cápsulas, gránulos, polvos, o formulaciones líquidas incluyendo jarabes; tópicamente, tal como en la forma de soluciones, suspensiones, geles o ungüentos;

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sublingualmente; bucalmente; parenteralmente, tal como mediante inyección subcutánea, intravenosa, intramuscular o intrasternal o técnicas de infusión (e.g., como soluciones o suspensiones estériles inyectables acuosas o no acuosas); nasalmente tal como mediante nebulizador de inhalación; tópicamente, tal como en la forma de crema o ungüento; rectalmente tal como en la forma de supositorios; o liposomalmente. Pueden administrarse formulaciones de dosis unitaria que contienen vehículos o diluyentes no tóxicos, de aceptación farmacéutica. Los compuestos pueden administrarse en una forma apropiada para liberación inmediata o liberación extendida. La liberación inmediata o la liberación extendida puede lograrse con composiciones farmacéuticas apropiadas o, particularmente el caso de liberación extendida, con dispositivos tales como implantes subcutáneos o bombas osmóticas.

Composiciones ejemplares para administración tópica incluyen un transportador tópico tal como PLASTIBASE® (aceite mineral gelatinizado con polietileno).

Composiciones ejemplares para administración oral incluyen suspensiones que pueden contener, por ejemplo, celulosa microcristalina para imprimir volumen, ácido algínico o alginato de sodio como agente de suspensión, metilcelulosa como un promotor de viscosidad, y edulcorantes o agentes saborizantes tales como aquellos conocidos en el arte; y tabletas de liberación inmediata que pueden contener, por ejemplo, celulosa microcristalina, fosfato dicálcico, almidón, magnesio estearato y/o lactosa y/o otros excipientes, aglutinantes, extensores, desintegrantes, diluyentes y lubricantes tales como aquellos conocidos en el arte. Los compuestos inventivos pueden administrarse también oralmente mediante administración sublingual y/o bucal, e.g., con tabletas moldeadas, comprimidas, o secadas por congelamiento. Composiciones ejemplares pueden incluir diluyentes de rápida disolución tales como manitol, lactosa, sucrosa, y/o ciclodextrinas. Igualmente en dichas formulaciones puede

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haber excipientes de alto peso molecular tales como celulosas (AVICEL®) o polietilen glicoles (PEG); un excipiente para fomentar la adhesión mucosal tal como celulosa hidroxipropílica (HPC), hidroxipropil metil celulosa (HPMC), carboximetil celulosa de sodio (SCMC), y/o copolímero de anhídrido maleico (*e.g.*, GANTREZ®); y agentes para controlar la liberación tal como copolímero poliacrílico (*e.g.*, CARBOPOL 934®). Lubricantes, deslizantes, sabores, agentes colorantes y estabilizantes pueden agregarse igualmente para facilidad de fabricación y uso.

Composiciones ejemplares para administración nasal en aerosol o inhalación incluyen soluciones que pueden contener, por ejemplo, alcohol bencílico u otros preservativos apropiados, promotores para mejorar la absorción y/o biodisponibilidad, y/o otros agentes solubilizantes o dispersantes tales como aquellos conocidos en el arte.

Composiciones ejemplares para administración parenteral incluyen soluciones inyectables o suspensiones que pueden contener, por ejemplo, diluyentes o solventes no tóxicos, de aceptación parenteral, tal como manitol, 1,3-butanodiol, agua, solución de Ringer, una solución de cloruro de sodio isotónico, u otros agentes dispersantes o humectantes apropiados y agentes de suspensión, incluyendo mono o diglicéridos sintéticos, y ácidos grasos, incluyendo ácido oleico.

Composiciones ejemplares para administración rectal incluyen supositorios que pueden contener, por ejemplo, excipientes apropiados no irritantes, tales como manteca de cacao, ésteres glicéricos sintéticos o polietilen glicoles, que son sólidos a temperaturas ordinarias pero se licúan y/o disuelven en la cavidad rectal para liberar el fármaco.

La cantidad efectiva de un compuesto de la presente invención pueden determinarse por alguien de habilidades ordinarias en el arte, e incluye cantidades de dosificación ejemplares para un mamífero de desde

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alrededor de 0.05 a 100 mg/kg de peso corporal de compuesto activo por día, que pueden administrarse en una dosis única o en la forma de dosis individuales divididas, tales como desde 1 a 4 veces por día. Se entenderá que el nivel de dosis específica y la frecuencia de dosificación para cualquier sujeto particular pueden variarse y dependerán de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y hora de administración, velocidad de excreción, combinación de fármacos, y gravedad de la condición particular. Sujetos preferidos para tratamiento incluyen animales, muy preferiblemente especies mamíferas tales como humanos, y animales domésticos tales como perros, gatos, caballos, y similares. Por lo tanto, cuando aquí se usa el término "paciente", este término pretende incluir todos los sujetos, muy preferiblemente especies mamíferas, que están afectados por la mediación de niveles de enzima p38.

Compuestos de fórmula (I), incluyendo los compuestos descritos en sus ejemplos, se han probado en uno o más de los ensayos descritos más adelante y han mostrado actividad como inhibidores de enzimas p38 α / β y TNF- α .

Ensayos Biológicos

Generación de Quinasas p38

cDNAs de p38 α humana, isozimas β y γ se clonaron mediante PCR. Estas cDNAs se subclonaron en el vector de expresión pGEX (Pharmacia). La proteína de fusión GST-p38 se expresó en *E. Coli* y se purificó de comprimidos bacterianos mediante cromatografía de afinidad usando glutatión agarosa. La proteína de fusión p38 se activó incubando con MKK6 constitutivamente activa. La p38 activa se separó de MKK6 mediante cromatografía de afinidad. La MKK6 constitutivamente activa se generó de acuerdo con Raingeaud y colaboradores [*Mol. Cell. Biol.*, 1247-

1255 (1996)].

Producción de TNF- α mediante PBMCs estimuladas por LPS

Sangre entera humana heparinizada se obtuvo de voluntarios sanos. Células mononucleares de sangre periférica (PBMCs) se purificaron de sangre entera humana mediante centrifugación de gradiente de densidad Ficoll-Hypaque y se resuspendieron a una concentración de $5 \times 10^6/\text{ml}$ en medio de ensayo (medio RPMI que contenía 10% de suero bovino fetal). 50 μl de suspensión de células se incubaron con 50 μl de compuesto de prueba (concentración 4X en medio de ensayo que contenía 0.2% DMSO) en placas con tejido de cultivo de 96-pozos durante 5 minutos a RT. A continuación se agregaron 100 μl LPS (200 ng/ml solución madre) a la suspensión de células y luego la placa se incubó durante 6 horas a 37°C. Luego de la incubación, el medio de cultivo se recogió y almacenó a -20°C. La concentración de TNF- α en el medio se cuantificó usando un estuche ELISA estándar (Pharmingen-San Diego, CA). Concentraciones de TNF- α y valores IC₅₀ para compuestos de prueba (concentración del compuesto que inhibía la producción de TNF- α estimulada por LPS en un 50%) se calcularon mediante análisis de regresión lineal.

Ensayo p38

Los ensayos se llevaron a cabo en placas de 96 pozos con fondo en V. El volumen de ensayo final era 60 μl preparado de tres adiciones de 20 μl de enzima, sustratos (MBP y ATP) y compuestos de prueba en tampón de ensayo (50 mM Tris pH 7.5, 10 mM MgCl₂, 50 mM NaCl y 1 mM DTT). Bacterianamente expresado, p38 activada se pre-incubó con compuestos de prueba durante 10 minutos antes de la iniciación de la reacción con sustratos. La reacción se incubó a 25°C durante 45 minutos y se terminó agregando 5 μl de 0.5 MEDTA a cada muestra. La mezcla de reacción se aspiró en un filtermat pre-humedecido usando un Skatron Micro96 Cell Harvester (Skatron, Inc.), luego se lavó con PBS. Seguidamente el filtermat se secó en un horno microondas durante 1 minuto, se trató con cera de

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escintilación MeltiLex A (Wallac), y se contó en contador de escintilación Microbeta Model 1450 (Wallac). Los datos de la inhibición se analizaron mediante regresión no lineal de mínimos cuadrados usando Prism (GraphPadSoftware). La concentración final de reactivos en los ensayos son ATP, 1 μ M; [γ - ^{33} P]ATP, 3 nM; MBP (Sigma, #M1891), 2 μ g/pozo; p38, 10 nM; y DMSO, 0.3%.

Producción de TNF- α mediante Ratones estimulados con LPS

Ratones (femeninos Balb/c, de 6-8 semanas de edad, Harlan Labs; n=8/grupo de tratamiento) se inyectaron intraperitonealmente con 50 μ g/kg lipopolisacárido (LPS; cepa de *E coli* 0111:B4, Sigma) suspendido en solución salina estéril. Noventa minutos más tarde, los ratones se sedaron mediante inhalación CO₂:O₂ y se obtuvo una muestra de sangre. Se separó suero y se analizó para detectar concentraciones de TNF-alfa por medio de un ensayo ELISA comercial de acuerdo con las instrucciones del fabricante (R&D Systems, Minneapolis, MN).

Se administraron los compuestos de prueba oralmente en varios momentos antes de la inyección de LPS. Los compuestos se dosificaron como suspensiones o como soluciones en diferentes vehículos o agentes solubilizantes.

Abreviaturas

Para facilidad de referencia, se emplean aquí 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

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Iso-P = isopropilo

MeOH = metanol

EtOH = etanol

EtOAc = acetato de etilo

Boc = tert-butiloxicarbonilo

CBZ = carbobenciloxi o carbobenzoxi o benciloxicarbonilo

DCM = diclorometano

DCE = 1,2-dicloroetano

DMF = dimetil formamida

DMSO = sulfóxido de dimetilo

TFA = ácido trifluoroacético

THF = tetrahidrofurano

HATU = O-(7-Azabenzotriazol-1-il-*N,N,N',N'*-tetrametiluronio

hexafluorofosfato

KOH = hidróxido de potasio

K₂CO₃ = carbonato de potasio

POCl₃ = oxiclورو de fósforo

KOtBu = t-butóxido de potasio

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

DIPEA = diisopropiletilamina

HOBt = 1-hidroxibenzotriazol hidrato

m-CPBA = ácido m-cloroperbenzoico

NaH = hidruro de sodio

NaOH = hidróxido de sodio

Na₂S₂O₃ = tiosulfato de sodio

Pd = paladio

Pd/C = paladio en carbono

min == minuto(s)

L = litro

mL = milímetro

μL = microlitro

g = gramo(s)

mg = miligramo(s)

mol = moles

mmol = milimole(s)

meq = miliequivalente

RT o rt = temperatura ambiente

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

sat or sat'd = saturado

aq. = acuoso

TLC = cromatografía de capa delgada

HPLC = cromatografía líquida de alto rendimiento

RP HPLC = HPLC de fase reversa

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

MS = espectrometría de masa

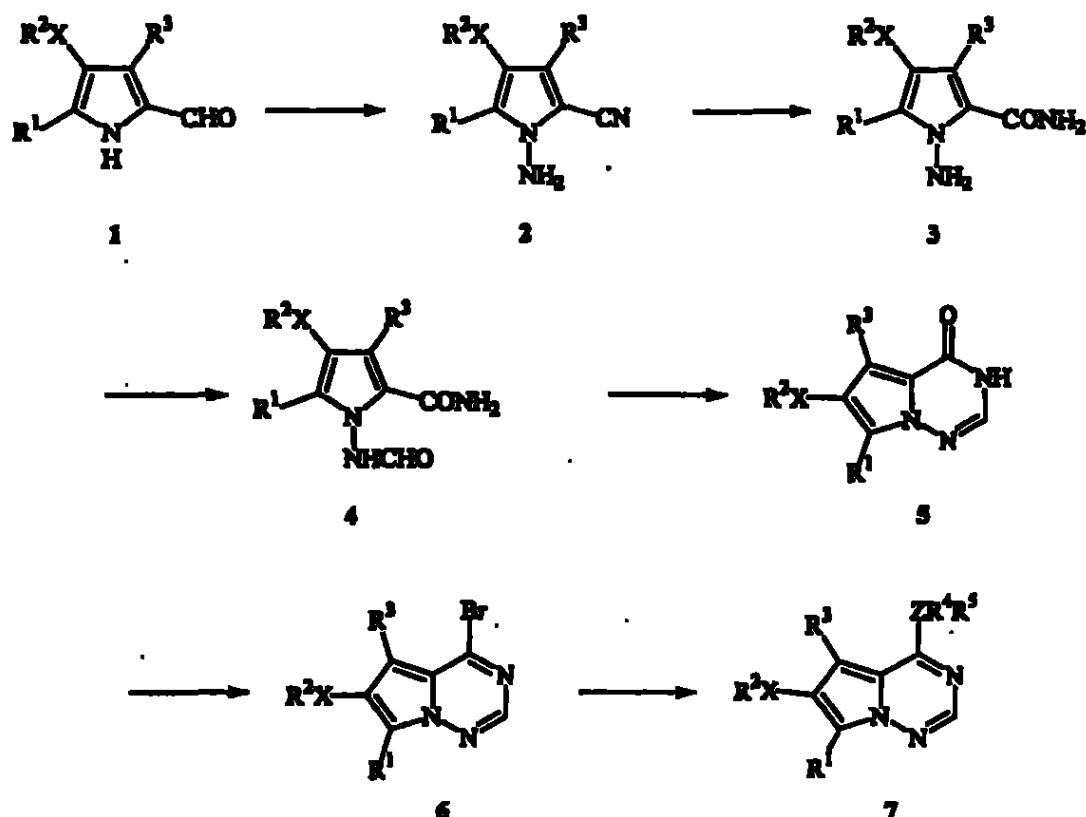
NMR = resonancia magnética nuclear

mp = punto de fusión

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

Métodos de Preparación

Generalmente los compuestos de fórmula I pueden prepararse de acuerdo con los siguientes esquemas y el conocimiento de un experto en el arte. En los esquemas, los grupos R₁-R₆, R₁₀, R₁₃, R₁₈, R₂₃, X y Z son como se describen aquí para compuestos de fórmula (I).

Esquema 1

Un 2-formilpirrol opcionalmente sustituido (1) se hace reaccionar con un reactivo aminante, tal como ácido hidroxilamina-O-sulfónico, en un solvente acuoso a temperatura ambiente, seguido por tratamiento bajo enfriamiento con una base tal como KOH, para formar compuesto (2).

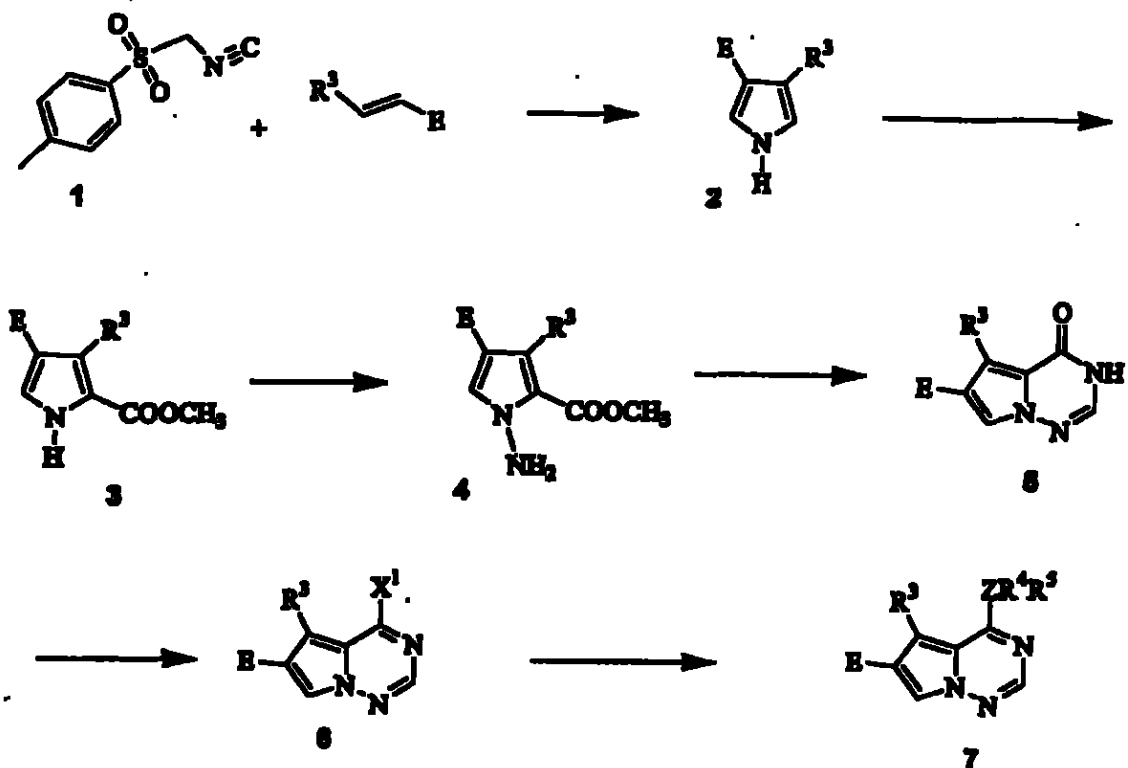
Compuesto (2) se hizo reaccionar con una base acuosa tal como KOH a temperatura ambiente para formar compuesto (3). Compuesto (3) se hizo reaccionar con un agente acilante, tal como ácido fórmico, en un solvente acuoso, para formar compuesto (4). Compuesto (4) se cicliza con una base tal como metóxido de sodio en MeOH con calentamiento para formar compuesto (5). Compuesto (5) se halogena, *e.g.*, con oxibromuro de fósforo a temperatura elevada, para formar compuesto (6). Compuesto (6) se hizo reaccionar con una amina tal como una anilina en un solvente orgánico, tal como acetonitrilo, para formar producto (7) de Esquema 1.

Compuesto (7) de Esquema 1 donde R_1 = halógeno puede prepararse de compuesto (7) de Esquema 1 donde R_1 = hidrógeno mediante reacción con un agente halogenante tal como bromo en un solvente apropiado tal

como ácido acético.

Compuestos (1) pueden obtenerse de pirroles sustituidos mediante formulación, *e.g.*, mediante reacción con oxiclورو de fósforo y DMF. Un metilpirrol puede obtenerse mediante reducción de un formilpirrol, *e.g.*, mediante reacción con hidruro de aluminio de litio.

Esquema 2



E = grupo extractor de electrones tal como éster, nitro o cetona

X¹ = halógeno

Hacer reaccionar un anión de isocianuro de tosilmétilo (TosMIC) (1) con un aceptor de Michael tal como crotonato de etilo provee pirrol (2) disustituido. El tratamiento de pirrol (2) con un agente acilante tal como cloruro de tricloroacetilo en presencia de un ácido de Lewis tal como cloruro de aluminio a desde temperatura ambiente hasta 50 °C, seguido por tratamiento con metóxido de sodio, proporciona pirrol (3) trisustituido. Compuesto (3) puede obtenerse calentando un aldehído, tal como acetaldehído, con 2 equivalentes de isocianoacetato de etilo en presencia de una base, tal como DBU, en un solvente orgánico, tal como THF.

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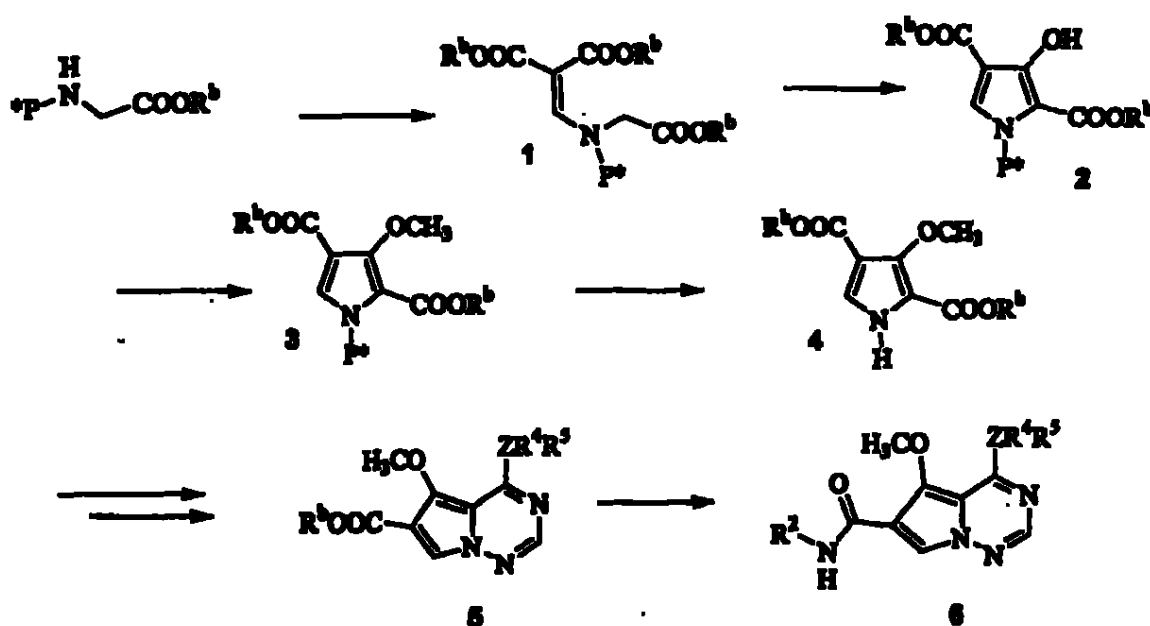
Alternativamente, compuesto (3) puede obtenerse siguiendo el procedimiento de M. Suzuki, M. Miyoshi, y K. Matsumoto J. Org. Chem. 1974,39 (1980).

Pirrol (3) puede aminarse mediante un reactivo aminante, tal como difenil fosforil hidroxilamina, en presencia de una base, tal como NaH, a temperatura ambiente en solventes orgánicos, tal como DMF, para formar pirrol (4) N-aminado. Compuesto (4) se ciclizó calentando a desde 120 a 195 °C con formamida para proporcionar 1,2,4-triazina (5). El tratamiento de compuesto (5) con un agente halogenante, tal como oxibromuro de fósforo, a desde 60 a 115°C, en presencia o ausencia de un co-solvente tal como DCE, proporciona compuesto (6).

Compuesto (6) se hizo reaccionar con una amina, tal como una anilina en un solvente orgánico, tal como DMF, para obtener compuesto (7). Alternativamente, compuesto (7) puede obtenerse tratando (6) con un anion de un compuesto heterocíclico, tal como oxindol, en un solvente orgánico tal como THF.

Un anión de TosMIC (1) puede elaborarse tratando una solución de él en DMSO con una base tal como NaH a temperatura ambiente o una solución de él en THF con hexametildisilazana a -78 °C.

Esquema 3



en donde P^+ = grupo protector, $\text{R}^b = \text{R}^c$ descrito más arriba en el texto

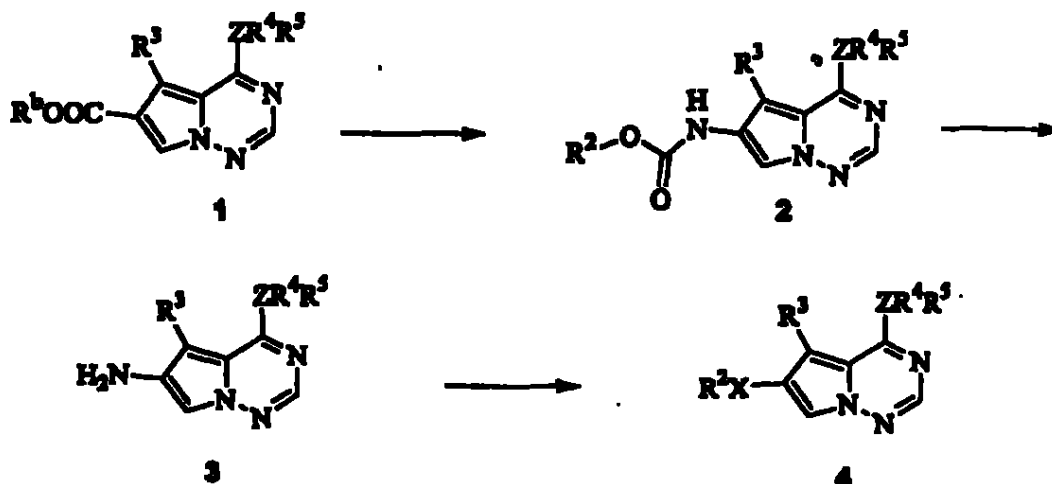
HA
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Un éster apropiado N-prottegido de glicina, tal como con un grupo bencilo, puede agregarse a malonato de dialquil metileno a desde temperatura ambiente hasta 80°C para obtener compuesto (1). Compuesto (1) se ciclizó para formar pirrol (2) bajo tratamiento con una base fuerte, tal como hexametildisilazana de litio, a desde -78°C hasta temperatura ambiente en un solvente orgánico tal como THF. Pirrol (2) se alquiló mediante tratamiento con un agente alquilante, tal como yodometano o sulfato de dimetilo, en presencia de una base, tal como K₂CO₃, en un solvente orgánico, tal como acetona o DMF para producir compuesto (3).

Desprotección de compuesto (3) puede lograrse, cuando protegido opcionalmente por grupos tales como bencilo, mediante hidrogenación sobre un catalizador, tal como Pd, en presencia de formato de amonio. Compuesto (4) se convirtió en compuesto (5) mediante ciclización como se describe para compuesto (5) de Esquema 2.

Hidrólisis del grupo ester en compuesto (5) puede lograrse mediante tratamiento con una base tal como KOH acuoso. El ácido resultante puede acoplarse con una amina en presencia de un agente acoplante, tal como DCC o PyBrop.

Esquema 4



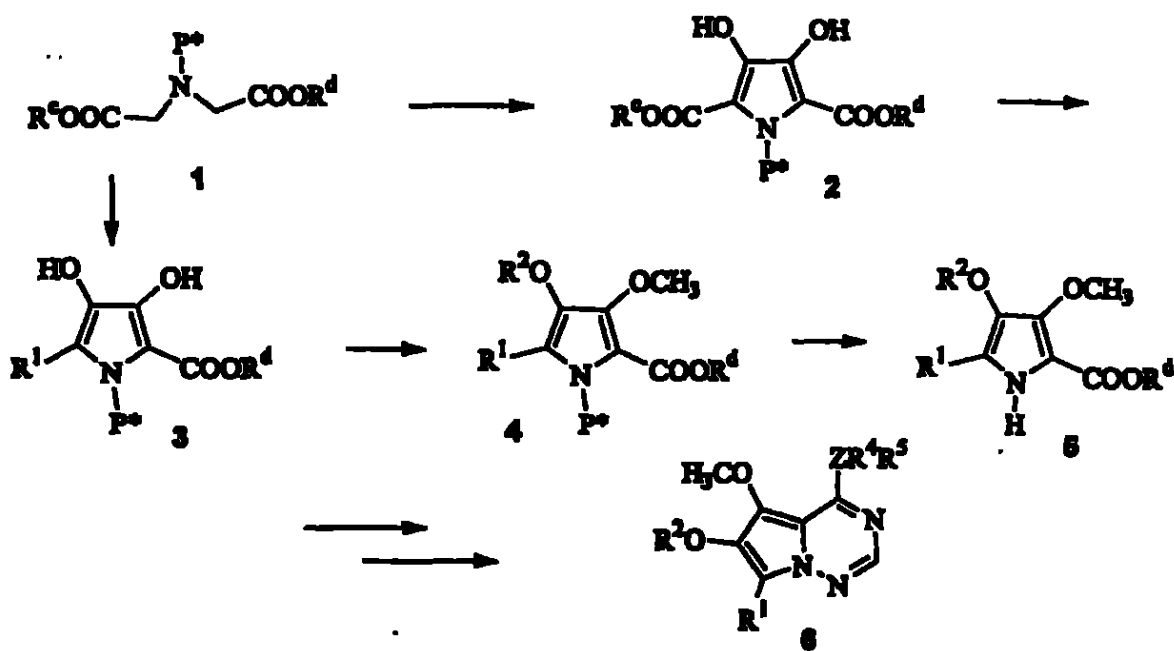
en donde X = NR¹⁰, NR¹⁰CO, NR¹⁰CONR¹¹, NR¹⁰COO,
NR¹⁰SO₂, NR¹⁰SO₂NR¹¹, como se describe más arriba en el texto.

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Compuesto (5) de Esquema 3 puede convertirse en ácido carboxílico (1) (en donde R_3 es metoxi o como se define aquí en otra forma) mediante tratamiento con una base tal como KOH acuoso. Este ácido experimenta reordenación de Curtis mediante tratamiento con difenil fosforil azida en presencia de un alcohol, tal como alcohol bencílico, en un solvente orgánico, tal como 1,4-dioxano, para proporcionar compuesto (2).

El grupo carbamato de compuesto (2) puede desprotegerse, cuando protegido opcionalmente por grupos tales como CBZ, mediante hidrogenación sobre un catalizador, tal como Pd, para obtener compuesto (3). El grupo amino de compuesto (3) puede acilarse para formar compuesto (4), *e.g.*, mediante tratamiento con un ácido carboxílico en presencia de un agente acoplante tal como DCC, o sulfonarse, *e.g.*, mediante tratamiento con un cloruro de sulfonilo. Alternativamente, el grupo amino de compuesto (3) puede alquilarse con halogenuros alquílicos o puede experimentar aminación reductora con aldehídos en presencia de un agente reductor, tal como cianoborohidruro de sodio.

Esquema 5



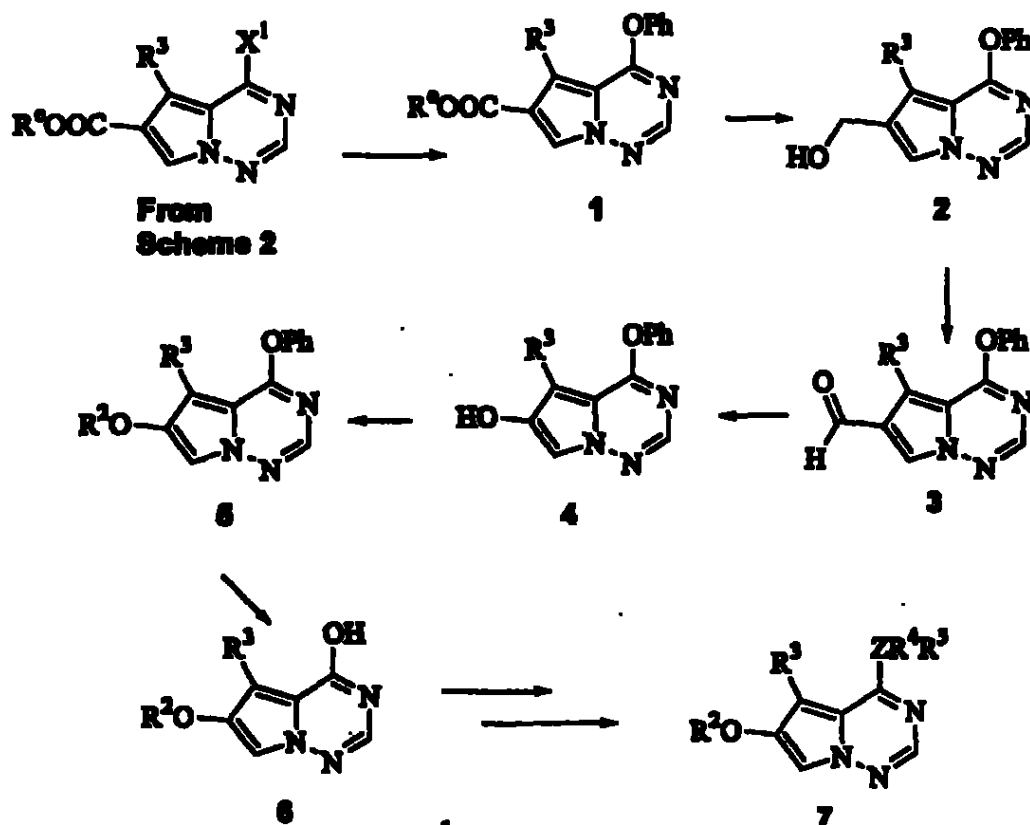
en donde P^* = grupo protector; R^e , $R^d = R^6$; y $R^1 = H$ o $COOR^{21}$ como se describe más arriba en el texto

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Compuesto (1) (imino dicarboxilato) apropiadamente protegido puede ciclizarse mediante tratamiento con oxalato de alquilo en presencia de una base, tal como metóxido de sodio, en un solvente orgánico, tal como MeOH. Compuesto (2) bajo desprotección selectiva, tal como con TFA cuando protegido opcionalmente mediante éster tert-butilico, experimenta descarboxilación para proporcionar compuesto (3) donde $R^1 = H$. Este paso se omitió para formar compuesto (3) donde $R^1 = COOR^{21}$.

El grupo hidroxilo de compuesto (3) puede eterificarse mediante reacción con un agente alquilante, tal como sulfato de dimetilo. Compuesto (4) puede desprotegerse mediante hidrogenación, cuando protegido opcionalmente tal como con un grupo bencilo, para obtener compuesto (5). Compuesto (5) se convirtió entonces en compuesto (6) en una manera análoga a la descrita para compuesto (4) de Esquema 3 y compuestos (4) a (7) de Esquema 2.

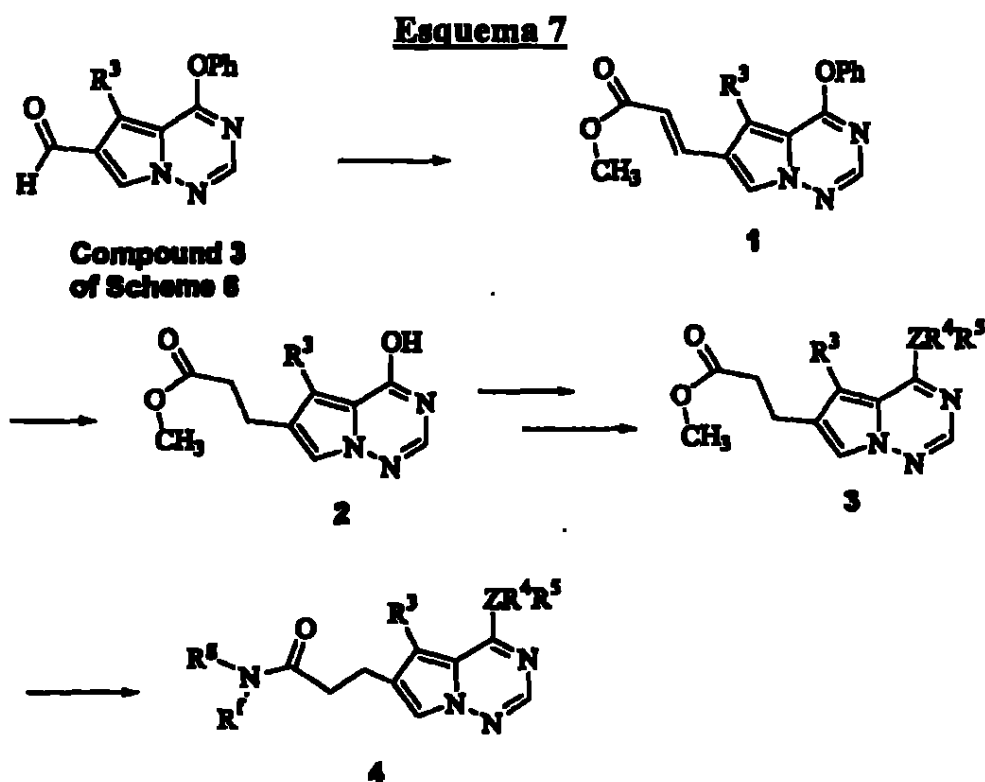
Esquema 6



$X^1 = \text{halógeno}$

Compuesto (6) de Esquema 2 puede eterificarse en la posición 4, *e.g.*, mediante tratamiento con anión fenóxido para formar compuesto (1). Reducción de compuesto (1) con un agente reductor, tal como DIBAL, en un solvente orgánico, tal como tolueno, proporciona alcohol (2). Oxidación del alcohol (2) puede lograrse mediante tratamiento con MnO_2 a una temperatura elevada en un solvente orgánico, tal como tolueno, para formar (3). Tratamiento de compuesto (3) con un oxidante, tal como *m*-CPBA en un solvente orgánico, tal como DCM, seguido por hidrólisis acuosa con una base, tal como bicarbonato de potasio, proporciona el compuesto hidroxilado (4).

Alquilación del grupo fenólico de compuesto (4) con un agente, tal como yodometano, en presencia de una base, tal como NaH, a desde temperatura ambiente hasta 100°C , proporciona compuesto (5). Hidrólisis de compuesto (5) puede lograrse mediante tratamiento con un ácido, tal como HCl acuoso, a una temperatura elevada para proporcionar (6). Compuesto (6) puede convertirse en compuesto (7) con procedimiento análogos a aquellos descritos en Esquema 2.

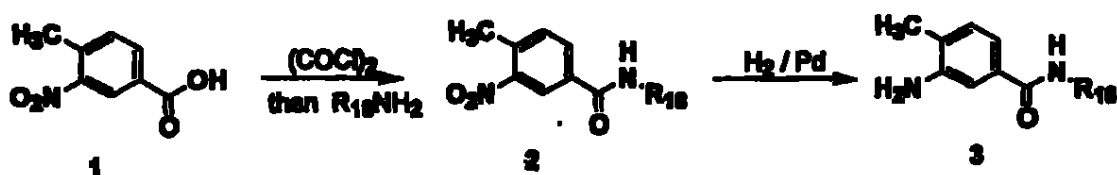


en donde $\text{R}^1, \text{R}^5 = \text{R}^2$ como se describe más arriba en el texto

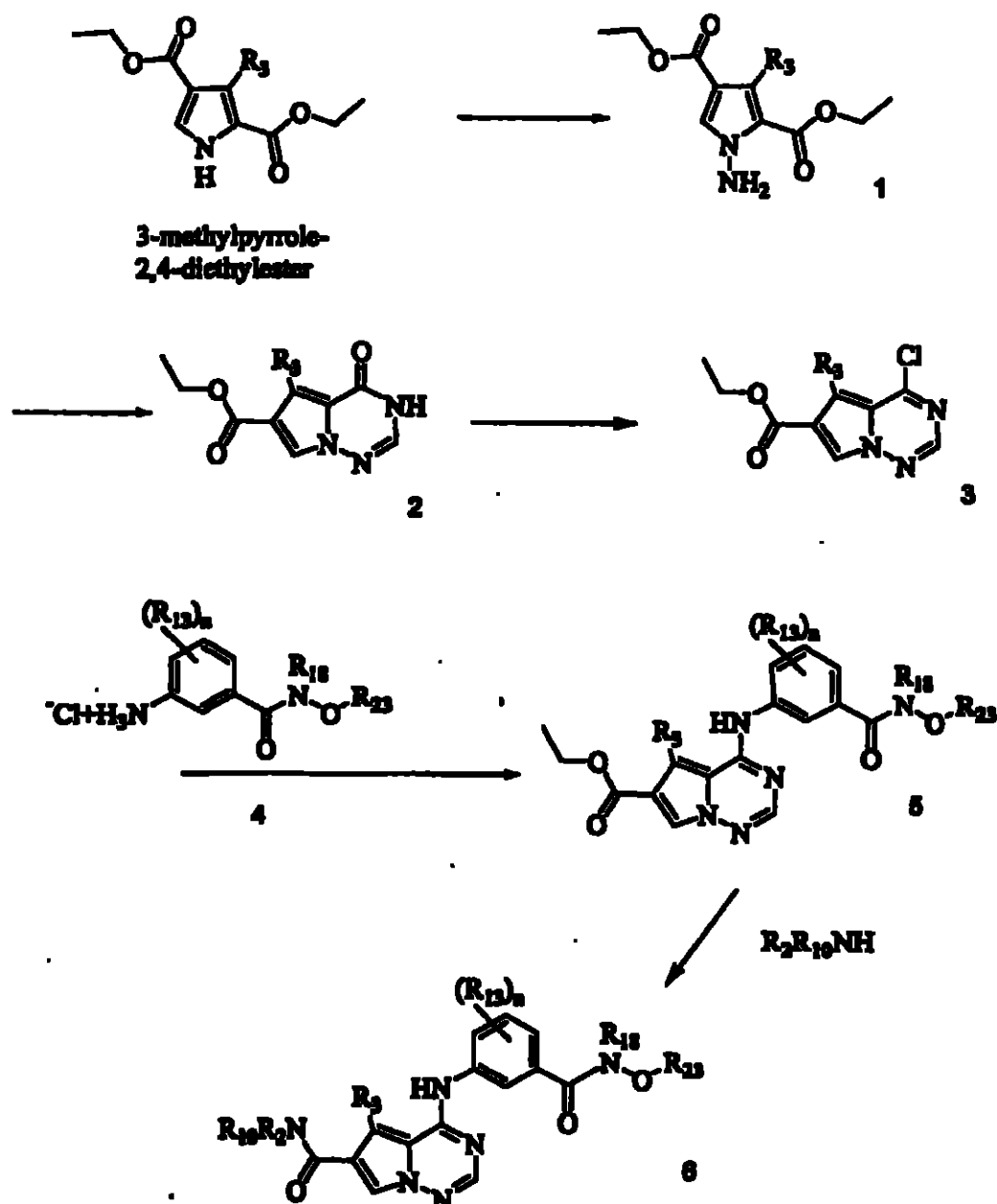
Compuesto (3) de Esquema 6 puede experimentar un reacción de Wittig, e.g., con fosfonatos tal como dietilfosfonoacetato de metilo, en un solvente orgánico, tal como DCE, en presencia de una base, tal como NaH, para proporcionar compuesto (1). El doble enlace de compuesto (1) puede hidrogenarse mediante tratamiento con hidrógeno en presencia de un catalizador, tal como Pd. Compuesto (2) puede convertirse en (3) mediante procedimientos descritos en Esquema 2.

Hidrólisis del éster, como se describe más arriba en el texto, seguido por acoplamiento del ácido resultante con una amina en presencia de un agente acoplante, tal como DCC, proporciona el compuesto (4).

Esquema 8



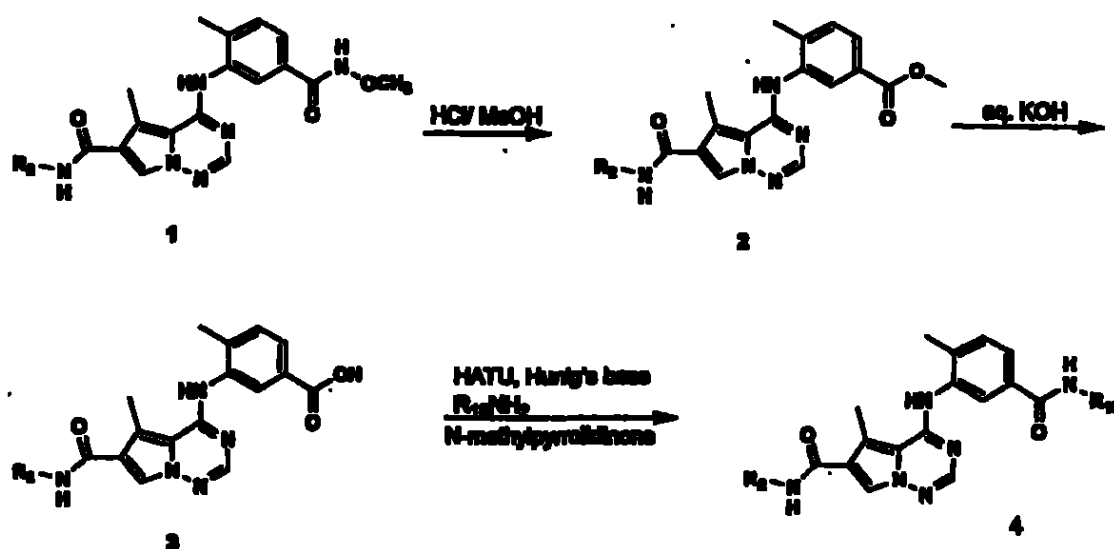
Compuesto (1) disponible en el comercio puede hacerse reaccionar con cloruro de oxalilo con calentamiento y luego concentrarse *in vacuo* y hacerse reaccionar con una amina R_{18}NH_2 en presencia de una base, tal como diisopropilamina, en un solvente orgánico, tal como DCM para proporcionar compuesto (2). 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 compuesto (3). Compuesto (3) puede entonces usarse como en Esquema 9 para producir compuestos (6) de Esquema 9.

Esquema 9

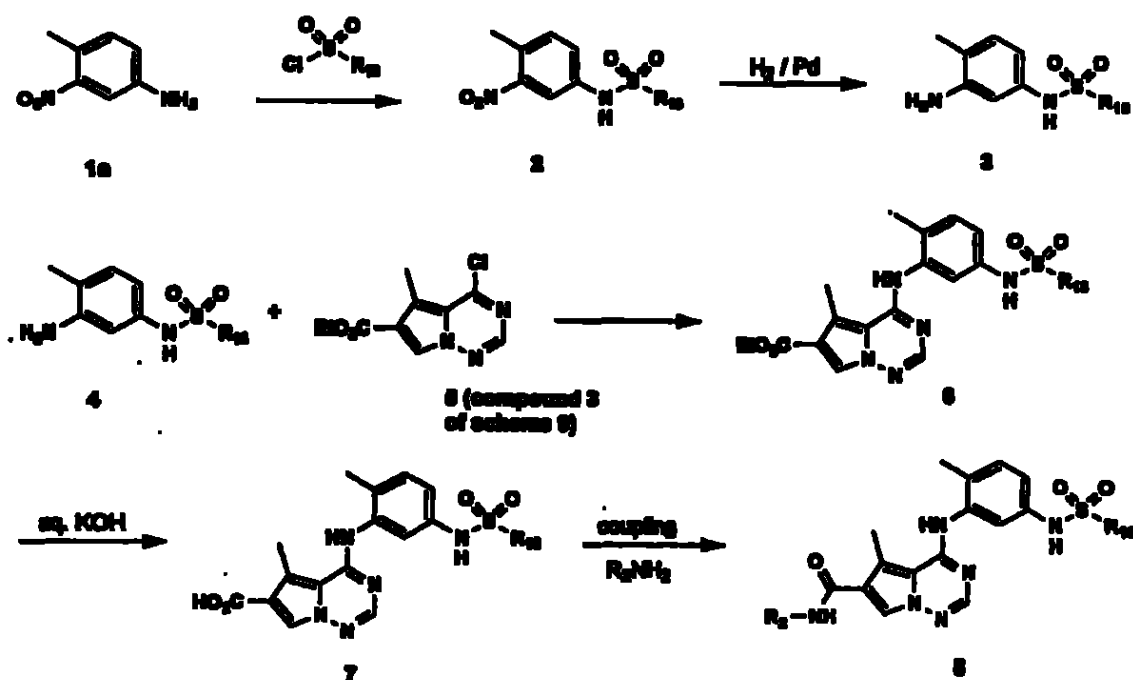
Éster 3-metil-1-pirrol-2,4-diétilico puede hacerse reaccionar con cloramina en éter para producir compuesto (1). Hacer reaccionar compuesto (1) en formamida con ácido acético produce compuesto (2). Compuesto (2) puede hacerse reaccionar con DIPEA y POCl₃ en tolueno para producir compuesto (3). Compuesto (3) puede hacerse reaccionar con DIPEA y compuesto (4) en DMF para producir compuesto (5). Compuesto (5) puede hacerse reaccionar en THF con NaOH para producir un ácido intermedio el cual, bajo tratamiento con HOBt, EDCI y la amina apropiada (NR₂R₁₀) en DMF produce compuestos (6).

Compuesto (4) puede prepararse 1) haciendo reaccionando ácido 4-amino-3-metilbenzoico disponible en el comercio y N-(*tert*-butoxicarbonil)anhídrido en THF para producir una anilina intermedia BOC-protegida; 2) haciendo reaccionar la anilina intermedio con clorhidrato de -(3-dimetilaminopropil)-3-etilcarbodiimida, HOBt, y DMF, seguido por adición de clorhidrato de metoxiamina y DIPEA para producir una N-metoxiamida intermedio BOC-protegida; y 3) haciendo reaccionar esa metoxiamida intermedio en una solución de HCl en dioxano para producir compuesto (4) como un sal clorhidrato. Alternativamente, compuesto (4) puede prepararse como se indica en Esquema 8.

Esquema 10

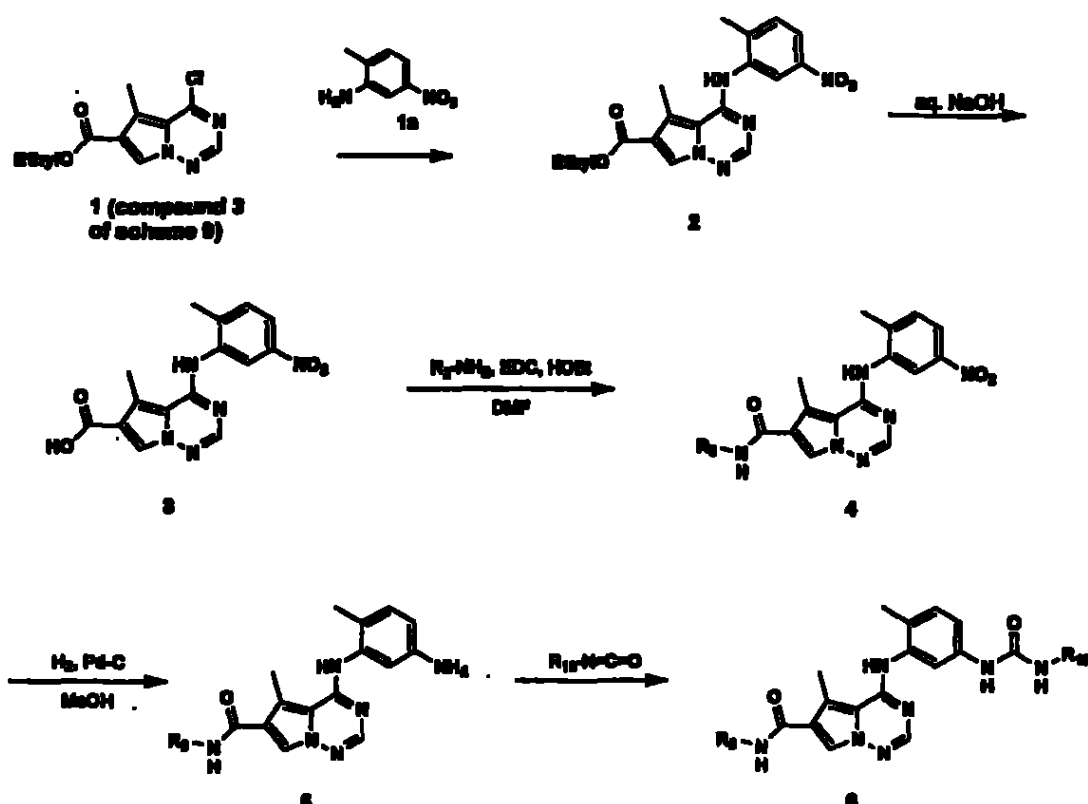


Un hidroxamato (1) sustituido puede hacerse reaccionar con ácido, tal como HCl, en MeOH anhidro, para proporcionar compuesto (2). Compuesto (2) puede hacerse reaccionar con una base acuosa tal como KOH con calentamiento para formar compuesto (3). Compuesto (3) se hizo reaccionar con una amina $R_{18}NH_2$ en presencia de un reactivo acoplante, tal como HATU, y una base tal como diisopropilamina, en un solvente orgánico, tal como N-metilpirrolidinona para proporcionar compuestos (4). Alternativamente, compuestos (4) pueden prepararse generalmente como se describe en Esquemas 8 y 9.

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122**Esquema 11**

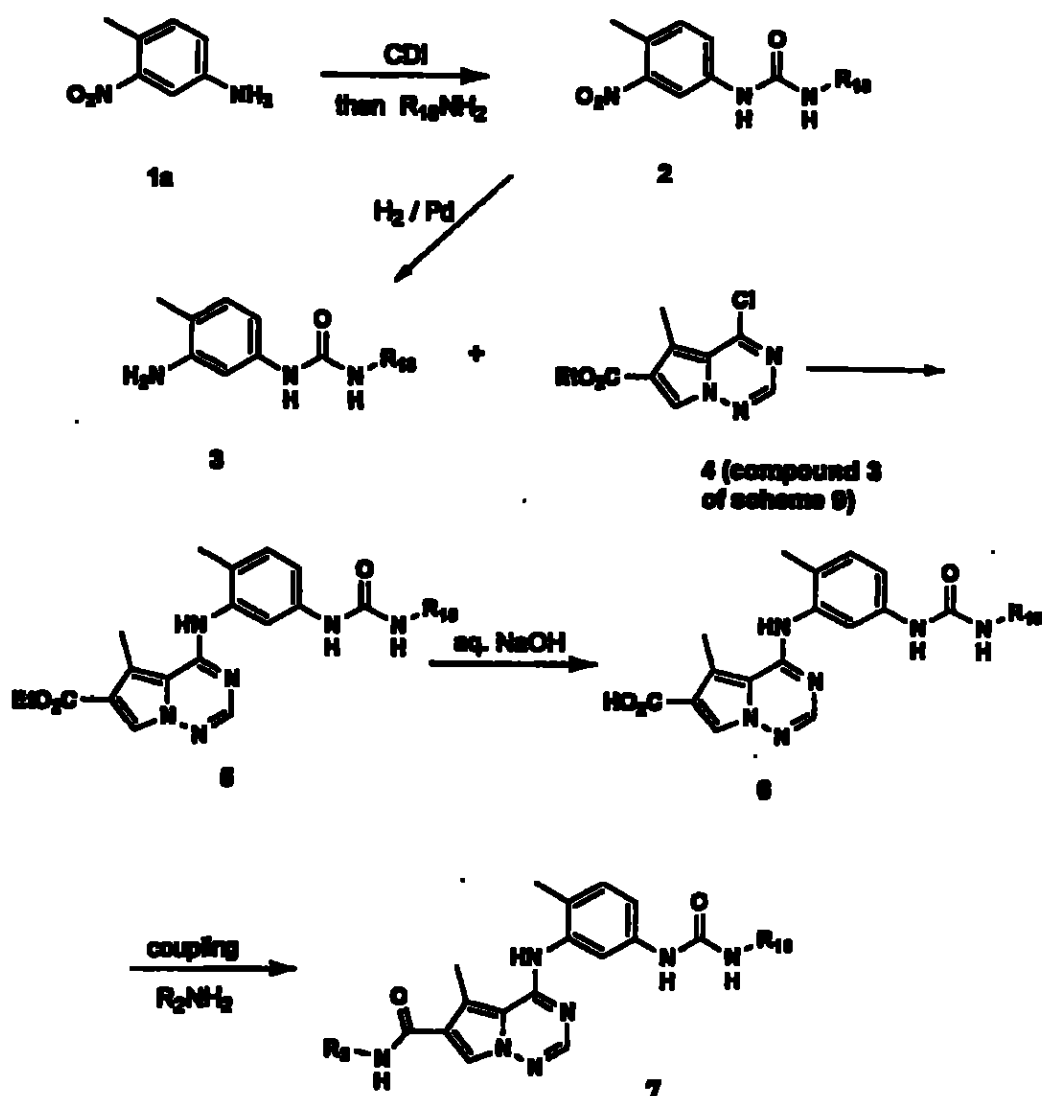
Compuesto (1a) disponible en el comercio puede hacerse reaccionar con un cloruro de sulfonilo en presencia de una base, tal como TEA, en un solvente orgánico, tal como DCM para proporcionar compuesto (2). Reacción de compuesto (2) con hidrógeno en presencia de un catalizador, tal como Pd en un solvente, tal como MeOH, produce compuesto (3). Reacción de compuesto (3) con cloruro (5) (compuesto 3 de esquema 9) en un solvente orgánico, tal como DMF, a temperatura ambiente proporciona compuesto (6).

Reacción de compuesto (6) con KOH acuoso con calentamiento proporciona compuesto (7). Compuesto (7) puede hacerse reaccionar con una amina R_2NH_2 en presencia de un reactivo acoplante, tal como EDCI, y una base tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar compuesto (8).

Esquema 12

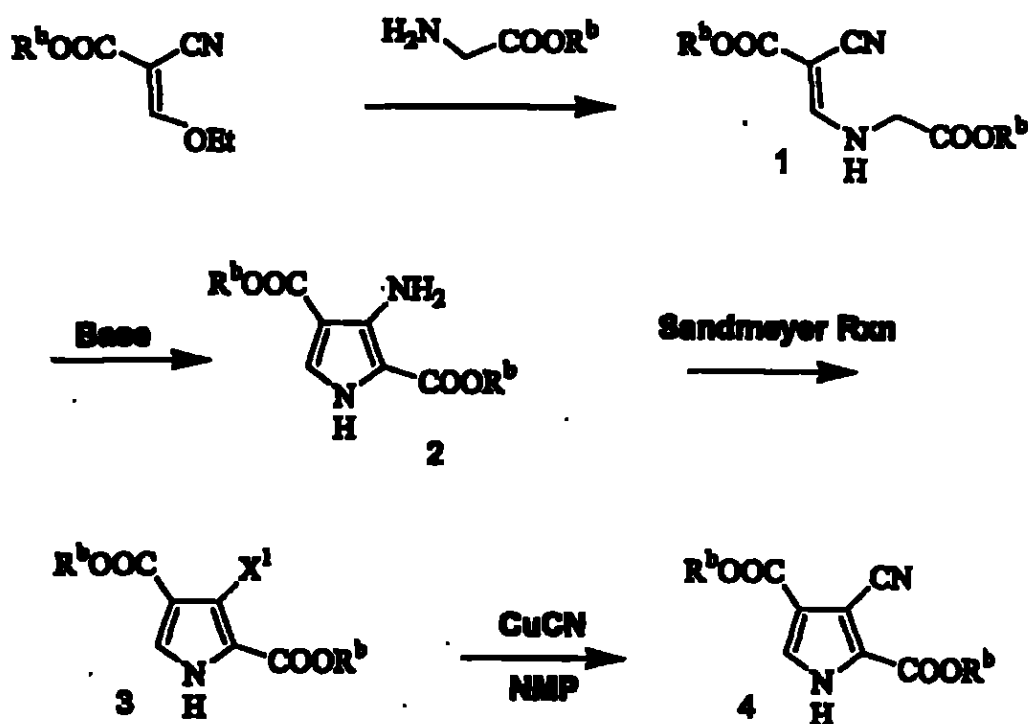
Cloropirrolotriazina (1) (compuesto 3 de Esquema 9) puede hacerse reaccionar con una anilina (1a) (e.g., compuesto 1 de Esquema 11) en DMF anhidro a temperatura ambiente para proporcionar compuesto (2). Reacción de compuesto (2) con una base acuosa tal como NaOH con calentamiento produce compuesto (3). Compuesto (3) puede hacerse reaccionar con una amina R_2NH_2 en presencia de un reactivo acoplante, tal como HOBt, con o sin una base tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar compuesto (4). Compuesto (4) puede hacerse reaccionar con hidrógeno en presencia de un catalizador, tal como Pd/C, en un solvente orgánico, tal como MeOH para producir compuesto (5). Reacción de compuesto (5) con un isocianato en un solvente orgánico, tal como DCE produce compuesto (6).

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Esquema 13

Compuesto (1a) disponible en el comercio (compuesto 1a de Esquemas 11 y 12), puede hacerse reaccionar con carbonil diimidazol y con una amina $R_{18}NH_2$ en un solvente orgánico, tal como DCE, para producir compuesto (8). Reacción de compuesto (8) con hidrógeno en presencia de un catalizador, tal como Pd, en un solvente alcohólico tal como EtOH proporciona compuesto (9). Reacción de (9) con cloruro (1) en un solvente orgánico, tal como DMF, produce compuesto (10). Reacción de (10) con NaOH acuoso con calentamiento proporciona producto (11). Producto (11) puede hacerse reaccionar con una amina R_2NH_2 en presencia de un reactivo acoplante, tal como EDCI, y una base tal como diisopropilamina, en un solvente orgánico, tal como DMF para proporcionar compuesto (7).

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Esquema 14

X^1 es halógeno

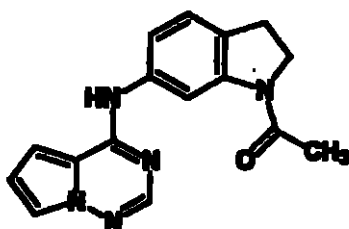
Éster etílico de glicina puede agregarse a cianoacetato de alquil alcoxi metileno a desde temperatura ambiente hasta $80^\circ C$ para obtener compuesto (1). Compuesto (1) se ciclizó para formar pirrol (2) bajo tratamiento con una base fuerte, tal como hexametildisilazana de litio, a desde $-78^\circ C$ hasta temperatura ambiente en un solvente orgánico tal como THF. Pirrol (2) se convirtió en haluro usando nitrito de sodio en un solvente orgánico, tal como DMF, y una fuente haluro, tal como CuBr para producir compuesto (3). Compuesto (3) puede convertirse en compuesto (4) usando CuCN en un solvente orgánico tal como NMP a temperaturas elevadas. Alternativamente, compuesto (2) puede convertirse directamente en compuesto (4) usando nitrito de sodio en un solvente orgánico, tal como DMF, y una fuente cianuro tal como CuCN. Compuestos (3) y (4) pueden usarse luego como se describe en esquemas previos (e.g., como compuesto 3 de Esquema 2), para formar compuestos de fórmula (I) en donde R_3 es halógeno o ciano.

Además, otros compuestos de fórmula I pueden prepararse empleando procedimientos generalmente conocidos por aquellos expertos en el arte. En particular, los siguientes ejemplos proveen métodos adicionales para la preparación de los compuestos de esta invención.

La invención se describirá ahora con más detalles mediante los siguientes ejemplos de trabajo, los cuales son incorporaciones preferidas de la invención. Se realizaron purificaciones HPLC en columnas de fase reversa (RP) C18 usando mezclas agua MeOH y TFA como solución tampón. Estos ejemplos son ilustrativos más que limitantes. Puede haber otras incorporaciones que caen dentro del espíritu y ámbito de la invención como se define por las reivindicaciones adjuntas.

Ejemplo 1

1-[2,3-Dihidro-6-(pirrolo[2,1-f][1,2,4]triazina-4-ilamino)-1H-indol-1-il]etanona



A. 4-Bromo-pirrolo[2,1-f][1,2,4]triazina

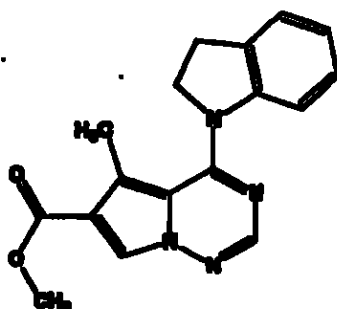
Una mezcla de 50 mg (0.37 mmol) de pirrolo[2,1-f][1,2,4]triazina-4(3H)-ona [preparada como se describe en S.A. Patil, B.A. Otter y R.S. Klein, *J. Het. Chem.*, 31, 781-786 (1994)] y 0.5 g de oxibromuro de fósforo se calentó y mantuvo a 60°C durante 20 minutos bajo argón. Inicialmente se obtuvo una fusión de color anaranjado claro que se solidificó a un sólido amarillo con calentamiento continuado. Se agregó hielo agitando vigorosamente. La mezcla se extrajo dos veces con EtOAc. Los extractos combinados se lavaron con NaHCO₃ saturado y salmuera, se secaron (MgSO₄), y el solvente se retiró para proporcionar 63 mg de Compuesto A crudo como un aceite anaranjado que se cristalizó al reposar. (M+H)⁺ = 198⁺, 200⁺.

B. Ejemplo 1

Una solución de 60 mg (0.3 mmol) de Compuesto A y 1-acetil-6-aminoindolina en 1.5 ml de acetonitrilo se agitó durante la noche a temperatura ambiente bajo argón. Se obtuvo un precipitado blanco el cual se retiró por filtración. La torta de filtrado se suspendió en 10% de cloruro de isopropanol/metileno para extracción. Se agregó NaHCO_3 saturado y la mezcla se agitó hasta que se obtuvo una solución. La capa orgánica se separó y se lavó con salmuera, se secó (MgSO_4), y se retiró el solvente. Purificación mediante cromatografía en gel de sílice con EtOAc produjo 4% de Ejemplo 1 como un sólido blanco. $(\text{M}+\text{H})^+ = 294$.

Ejemplo 2

Éster metílico de ácido 4-(2,3-dihidro-1H-indol-1-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico

**A. Éster metílico de ácido metilpirrol-3-carboxílico**

A una solución 1.0 M de hexametildisilazida de litio en THF (41 mL, 41 mmol) a -78°C se agregó gota a gota durante 45 minutos una solución de tosilmetil isocianuro (8.1 g, 41 mmol) en THF. Luego de agitar la reacción durante 45 minutos más, se agregó una solución de crotonato de metilo en THF durante 40 minutos. La reacción se calentó a 25°C y se agitó durante 5 horas. La reacción se diluyó con EtOAc y se lavó con NaHCO_3 acuoso saturado. La capa acuosa se extrajo tres veces con EtOAc, se secó (Na_2SO_4), se concentró, y purificó mediante cromatografía en gel de sílice fluyendo con una gradiente de 20-30% EtOAc en hexanos para proporcionar Compuesto A.

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128**B. Éster dimetílico de ácido 3-metilpirrol-2,4-dicarboxílico**

A una suspensión de cloruro de aluminio (106.4 g, 798 mmol) en DCE (700 mL) a -40°C bajo nitrógeno se agregó gota a gota cloruro de tricloroacetilo (89 mL, 798 mmol). Se agregó una solución de Compuesto A (37 g, 266 mmol) en DCE (200 mL). La mezcla de reacción se calentó gradualmente a temperatura ambiente y se agitó durante el fin de semana (65 horas). Una mezcla fría y pre-preparada de cloruro de aluminio (53.2 g) y cloruro de tricloroacetilo (44.6 g) en DCE (450 mL) se agregó a la mezcla de reacción. Luego de 24 horas más, la mezcla se vertió cuidadosamente en un baño agua-hielo (2 L) y el pH la solución se ajustó a 2.0. La capa orgánica se separó y la capa acuosa se extrajeron con DCM. Los extractos orgánicos combinados se lavaron con 3 N HCl, salmuera, se secaron (Na_2SO_4), y concentraron *in vacuo* para producir un aceite oscuro. Este aceite se disolvió en MeOH (400 mL), y la solución resultante se enfrió a 0°C bajo nitrógeno. A esta solución se agregó metóxido de sodio (25 % en MeOH) hasta que el pH de la solución fue 10. Trascorrida 1 hora, la mezcla se concentró y luego se diluyó con agua helada (1 L) y el pH de la mezcla se ajustó a 6. La mezcla se extrajo con DCM (3 x 1 L). Los extractos combinados se lavaron con NaHCO_3 , salmuera, se secaron (Na_2SO_4), y se concentraron *in vacuo*. El sólido café obtenido se purificó mediante cromatografía en gel de sílice fluyendo con EtOAc en hexanos para proporcionar 44.3 g (84%) de Compuesto B. MS: $[\text{M}+\text{H}]^+ = 196$.

C. Éster dimetílico de ácido 1-amino-3-metilpirrol-2,4-dicarboxílico

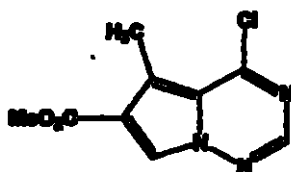
A una suspensión de NaH (60% en aceite, 33 mg, 0.83 mmol) en DMF (5 mL) a 0°C se agregó Compuesto B (46 g, 213 mmol) en DMF (3 mL). Después de 10 minutos a 0°C, se agregó difenil fosforil hidroxilamina (0.19 g, 0.83 mmol) pura seguida por DMF (3 mL). La mezcla de reacción se agitó durante 2 horas a 25°C y luego se extinguió con tampón de fosfato de pH 7 (15 mL). La mezcla se extrajo con EtOAc (4 x 20 mL). Los extractos combinados se secaron (Na_2SO_4) y luego de purificación mediante

cromatografía en gel de sílice fluyendo con 25-30% EtOAc en hexanos, se obtuvieron 38 g (84%) de Compuesto C como un sólido blanco. ESI $[M+H]^+ = 213.1$.

D. Éster metílico de ácido 5-metilpirrolo[2,1-f][1,2,4]triazina-4(3H)-ona-6-carboxílico

Compuesto C (38 g, 179 mmol) se combinó con formamida (400 mL) y se calentó a 165°C durante 6 horas. La reacción se diluyó con agua (5 mL), se extrajo con EtOAc (3 x 10 mL), se secó (Na_2SO_4), y se concentró. El material crudo se purificó lavando con éter/hexanos (7/3) para proporcionar 33.4 g (90%) de Compuesto D como un sólido blanco. ESI MS: $[M-H]^- = 206.0$

E. 4-Cloro-5-metil-6-carbometoxipirrolo[2,1-f][1,2,4] triazina



Oxicloruro de fósforo (2.5 mL) se combinó con Compuesto D (100 mg, 0.483 mmol) y se calentó a 100°C durante la noche. La fusión se dejó enfriar a temperatura ambiente en EtOAc. La mezcla se neutralizó con $NaHCO_3$ acuoso y se extrajo dos veces con EtOAc. Los lavados orgánicos combinados se secaron (Na_2SO_4), y se concentraron para proporcionar 101 mg (93%) de Compuesto E. MS: $(M+H)^+ = 226.6$.

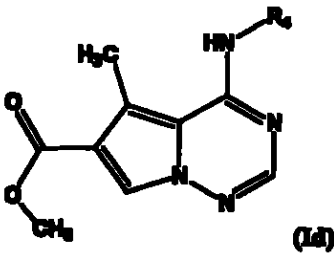
F. Ejemplo 2

Una mezcla de Compuesto E (20 mg, 0.09 mmol) e indolina (21 mg, 0.177 mmol) en CH_3CN (1 mL) se agitó durante 4 horas. Seguidamente se agregó DMF (0.2 mL), y la mezcla cruda se purificó mediante HPLC preparativa para proporcionar 12.2 mg (45 %) de Ejemplo 2 como un sólido blanco. $[M+H]^+ = 309.2$; ^1H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.91 (s, 1H), 7.20 (m, 1H), 7.01 (m, 1H), 6.93-6.91 (m, 2H), 4.15 (t, $J=7.8$ Hz, 2H), 3.81

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(s, 3H), 3.09 (t, J=7.8 Hz, 2H), 2.35 (s, 3H).

Ejemplo 3-6

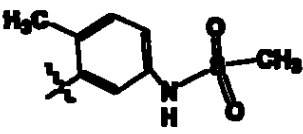


Compuestos que tienen la fórmula (Id), en donde el grupo R₄ tiene los valores relacionados en Tabla 1, se prepararon siguiendo los métodos de Ejemplo 2, usando un compuesto de amina apropiadamente seleccionada en lugar de indolita en paso F.

TABLA 1

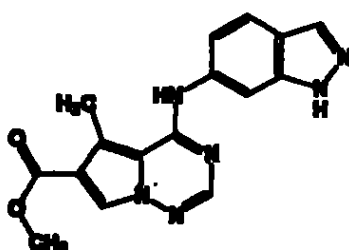
Ej.	R ₄	Nombre del Compuesto	Datos
3		Éster metílico de ácido 4-[[3-(hidrazinocarbonil)fenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS:[M+H] ⁺ =341.2; ¹ HNMR(d-DMSO):δ 7.79 (s, 1H), 7.58 (s, 1H), 7.11-7.05 (m, 3H), 6.72 (d, J= 8.1Hz, 1H), 5.23 (brs,2H), 3.76(s, 3H), 2.67 (s, 3H)
4		Éster metílico de ácido 4-[3-(acetilamino)fenil]amino]- 5-metilpirrolo[2,1-f][1,2,4] triazina-6-carboxílico	MS: [M+H] ⁺ = 340.2; ¹ HNMR(CDCl ₃):δ 7.81 (s, 1H), 7.75 (s,1H), 7.51 (s, 1H), 7.20-7.07 (m, 3H), 3.80 (s, 3H), 2.84 (s, 3H), 1.90 (s, 3H)
5		Éster metílico de ácido 4-[(1 -acetil-2,3 -dihidro-1H-indol-6-il)amino]-5-metilpirrolo [2,1-f][1,2,4] triazina-6-carboxílico	MS: [M+H] ⁺ = 366.2; ¹ HNMR(CDCl ₃):δ 8.14 (d, J= 8.6Hz, 1H), 7.95 (s, 1H), 7.82 (s, 1H), 7.51 (s, 1H), 7.12 (d, J= 8.6 Hz, 1H), 4.03 (t, J= 7.8Hz, 2H), 3.81 (s, 3H), 3.18 (t, J= 7.8 Hz, 2H), 2.67 (s, 3H), 2.19 (s, 3H)

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6		Éster metílico de ácido 5-metil-4-[[2-metil-5-[(metilsulfonyl)amino]fenil]amino]pirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: $[M+H]^+ = 390.2$; $^1\text{H NMR}(\text{CDCl}_3)$: δ 8.04 (br s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.09-6.99 (m, 2H), 3.82 (s, 3H), 3.00 (s, 3H), 2.89 (s, 3H), 2.28 (s, 3H)
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Ejemplo 7

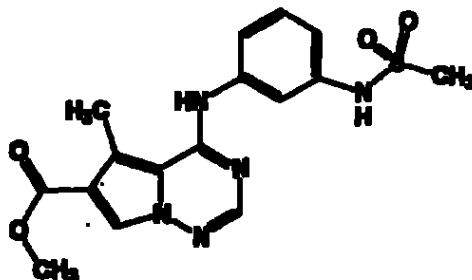
Éster metílico de ácido 4-(1H-Indazol-6-ilamino)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico



Una mezcla de Compuesto E de Ejemplo 2 (20 mg, 0.09 mmol) y 6-aminoindazol (18 mg, 0.13 mmol) en CH_3CN (1 mL) y DMSO (0.5 mL) se agitó durante 4 horas. La mezcla se filtró, se lavó con CH_3CN , y el material crudo se purificó mediante HPLC preparativa para proporcionar Ejemplo 7 como un sólido blanco (13 mg, 45 %). $[M+H]^+ = 323.1$; $^1\text{H NMR}(\text{CDCl}_3)$: δ 8.37 (s, 1H), 7.99 (s, 1H), 7.94 (d, $J=7.4$ Hz, 1H), 7.68 (d, $J=4.2$ Hz, 1H), 7.00 (dd, $J=7.4, 4.2$ Hz, 1H), 3.83 (s, 3H), 2.91 (s, 3H).

Ejemplo 8

Éster metílico de ácido 5-Metil-4-[[3-[(metilsulfonyl)amino]fenil]amino]pirrolo[2,1-f][1,2,4]triazina-6-carboxílico

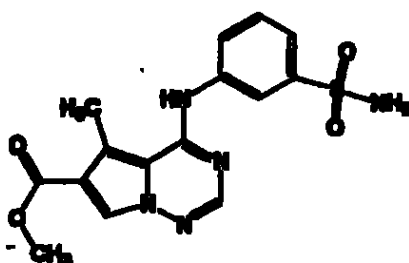


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Compuesto E de Ejemplo 2 se disolvió en DMF (2 mL), y seguidamente se agregó 3-(metilsulfonilamino)anilina (54 mg, 0.3 mmol). La mezcla de reacción se agitó durante 4 horas bajo argón a 25 °C. La mezcla de reacción cruda se purificó mediante HPLC preparativa. El material obtenido resultó ser una sal del compuesto deseado. El material se disolvió en EtOAc y se lavó con NaHCO₃ saturado. Evaporar el solvente produjo 24 mg (40 %) de Ejemplo 8. MS: [M+H]⁺ 376.2; ¹H NMR (*d*-DMSO): δ 8.89 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.55 (s, 1H), 7.38 (s, 1H), 7.34-7.32 (m, 2H), 7.01 (d, *J*=8.0 Hz, 1H), 3.81 (s, 3H), 3.02 (s, 3H), 2.82 (s, 3H).

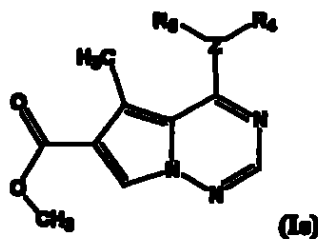
Ejemplo 9

Éster metílico de ácido 4-[[3-(Aminosulfonil)fenil]amino]-5-metilpirrolo[2,1-*f*] [1,2,4]triazina-6-carboxílico



Compuesto E de Ejemplo 2 (20 mg, 0.09 mmol) se mezcló con 3-aminobencenosulfonamida (23 mg, 0.13 mmol) en DMF (1 mL) y se agitó durante 4 horas. La evaporación del solvente extractor y purificación mediante HPLC preparativa produjeron 8.6 mg (58 %) de Ejemplo 9 como un sólido. MS: [M+H]⁺ = 362; ¹H NMR (*d*-DMSO): δ 9.08 (s, 1H), 8.18 (s, 2H), 7.98 (s, 1H), 7.91-7.89 (m, 1H), 7.62-7.58 (m, 2H), 7.42 (s, 2H), 3.81 (s, 3H), 2.84 (s, 3H)

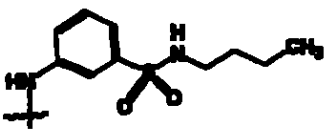
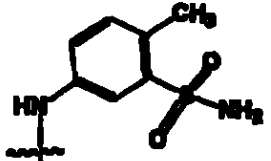
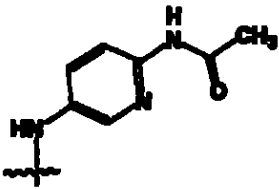
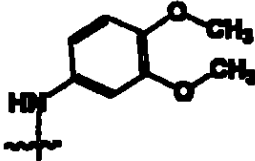
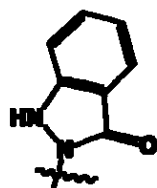
Ejemplos 10-14



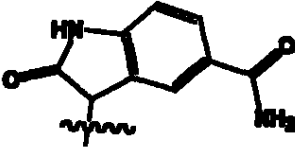
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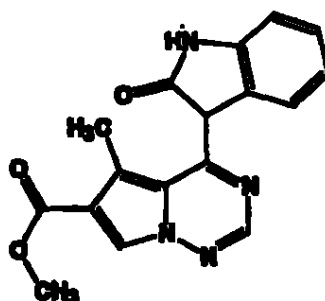
Compuestos que tienen la fórmula (Ie), en donde los grupos Z, R₄, y R₅ juntos tienen los valores enumerados en Tabla 2, se prepararon siguiendo el método de Ejemplo 9, salvo que en vez de 3-aminobencenosulfonamida, se empleó un compuesto amino apropiadamente seleccionado.

TABLA 2

Ej.	-ZR ₄ R ₅	Nombre del Compuesto	Datos
10		Éster metílico de ácido 4-[[3-[(Butilamino)sulfonyl]fenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 418.2; ¹ H NMR (CDCl ₃): δ 8.07 (s, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 7.84-7.82 (m, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.49-7.45 (m, 2H), 3.82 (s, 3H), 2.93-2.89 (m, 2H), 2.81 (s, 3H), 1.44-1.18 (m, 4H), 0.84 (t, J=7.4 Hz, 3H)
11		Éster metílico de ácido 4-[[3-(Aminosulfonyl)-4-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 376.2; ¹ H NMR (CDCl ₃): δ 8.05 (s, 1H), 7.91 (s, 1H), 6.97 (d, J=7.8 Hz, 1H), 6.31 (s, 1H), 6.23 (d, J=7.8 Hz, 1H), 4.22 (t, J=7.7 Hz, 2H), 3.84 (s, 3H), 2.84 (t, J=7.7 Hz, 2H), 2.55 (s, 3H).
12		Éster metílico de ácido 4-[[6-(Acetilamino)-3-piridinil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 341.2; ¹ H NMR (d-DMSO): δ 10.51 (s, 1H), 8.87 (s, 1H), 8.53 (s, 1H), 8.14-8.01 (m, 3H), 7.93 (s, 1H), 3.80 (s, 3H), 2.83 (s, 3H), 2.32 (s, 3H).
13		Éster metílico de ácido 4-[(3,4-Dimetoxi-fenil)amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 343.2; ¹ H NMR (CDCl ₃): δ 7.91 (s, 1H), 7.85 (s, 1H), 7.21 (s, 1H), 7.00 (dd, J=8.6, 2.8 Hz, 1H), 6.82 (d, J=8.6 Hz, 1H), 3.84-3.82 (3s, 9H), 2.88 (s, 3H)
14		Éster metílico de ácido 4-(2,3 -Dihidro-3 -oxo-1H-indazol-2-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 324.2; ¹ H NMR (CDCl ₃): δ 9.65 (s, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 7.42-7.37 (m, 2H), 7.14-7.12 (m, 1H), 3.86 (s, 3H), 2.84 (s, 3H)

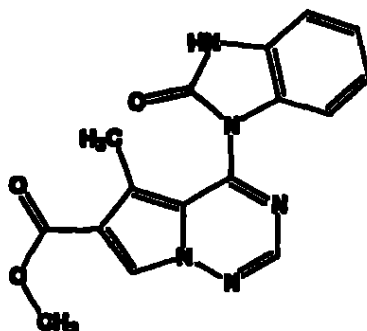
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15		Éster metílico de ácido 4-[5-(Aminocarbonil)-2,3-dihidro-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: $[M+H]^+ = 366.2$; ^1H NMR ($CDCl_3/CD_3OH$): δ 7.92 (s, 1H), 7.76 (s, 1H), 7.48 (d, $J=8.0$ Hz, 1H), 7.25 (s, 1H), 7.05 (d, $J=8.0$ Hz, 1H), 3.82 (s, 3H), 2.25 (s, 3H)
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Ejemplo 16**Éster metílico de ácido 4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico**

Una solución de oxindol (5.32 g, 40 mmol) en THF (150 ml) y DMF (35 ml) se desoxigenó purgándola con argón. Esta mezcla se puso en un baño de hielo, y se agregó NaH (60% en aceite, 1.7 g, 42 mmol). Después de 30 minutos se agregó 4-cloro-5-metil-6-carbometoxipirrolo[2,1-f][1,2,4]triazina (Compuesto E de Ejemplo 2) (3.38 g, 15 mmol). Trascorrida 1 hora a temperatura ambiente, la mezcla resultante se neutralizó con ácido acético. El solvente se retiró *in vacuo*. El residuo se disolvió en DCM, se lavó con salmuera, y se secó ($MgSO_4$). La solución se concentró a un residuo sólido que se trituró con DCM y éter dietílico para proporcionar el compuesto del título como un sólido anaranjado (3.5 g, 72%). MS: $[M+H]^+ = 323.1$; ^1H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.74 (s, 1H), 7.37 (s, 1H), 7.19 (d, $J=7.6$ Hz, 1H), 7.11 (t, $J=7.6$ Hz, 1H), 7.10 (t, $J=7.6$ Hz, 1H), 7.06 (d, $J=7.6$ Hz, 1H), 3.84 (s, 3H), 2.34 (s, 3H).

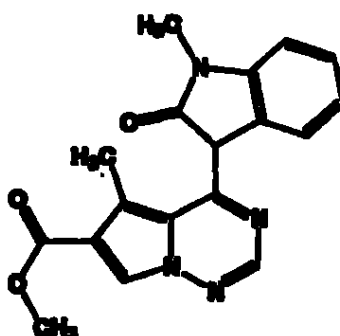
Ejemplo 17**Éster metílico de ácido 4-(2,3-Dihidro-3-oxo-1H-indazol-1-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico**



El anterior Ejemplo 17 se preparó siguiendo el método de Ejemplo 16, excepto que se empleó 3-indazolinona en lugar de oxindol. $[M+H]^+ = 324$; $^1\text{H NMR}$ (CDCl_3): δ 8.16 (s, 1H), 8.02-7.99 (m, 2H), 7.83-7.81 (m, 1H), 7.58-7.54 (m, 1H), 7.46 (s, 1H), 3.87 (s, 3H), 2.66 (s, 3H).

Ejemplo 18

Éster metílico de 4-(2,3-Dihidro-1-metil-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico

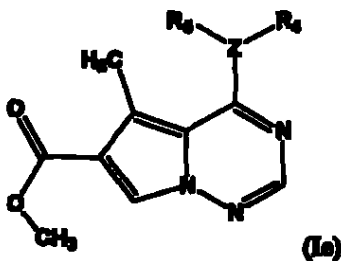


A una mezcla a 0°C de NaH (60%, 5 mg, 0.106 mmol) en DMF (0.5 mL) se agregó N-metiloxindol (22 mg, 0.15 mmol). La mezcla de reacción se agitó durante 10 minutos a 0°C . Se agregó Compuesto E de Ejemplo 2 (22 mg, 0.10 mmol) en DMF (1 mL). La mezcla de reacción se agitó durante 45 minutos a 25°C y a continuación se extinguió con tampón de fosfato a pH 7. La mezcla se extrajo con EtOAc. Los extractos combinados se secaron (Na_2SO_4) y purificaron por HPLC preparativa para proporcionar Ejemplo 18 como un sólido amarillo. MS: $[M+H]^+ 337.2$; $^1\text{H NMR}$ (CDCl_3): δ 7.90 (s, 1H), 7.40 (s, 1H), 7.16 (m, 2H), 7.02 (t, $J=7.6$ Hz, 1H), 6.90 (d, $J=7.6$ Hz, 1H), 5.28 (s, 1H), 3.86 (s, 3H), 3.36 (s, 3H), 2.37 (s,

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3H).

Ejemplos 19-24



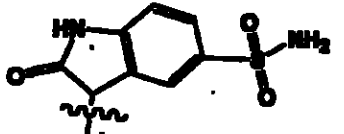
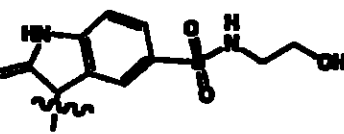
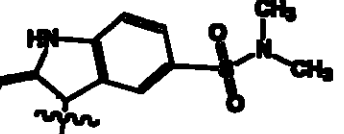
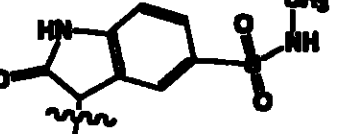
Compuestos que tienen la fórmula (Ie), en donde los grupos Z, R₄, y R₅ juntos tienen los valores relacionados en Tabla 3, se prepararon siguiendo el método de Ejemplo 18, excepto que en lugar de oxindol, se empleó un oxindol apropiadamente sustituido, y para los Ejemplos 19 y 20, se utilizaron 2,3-dihidro-2-oxo-1H-benzimidazol (40.2 mg, 0.3 mmol) y (metilsulfonil)amino]-2-oxo-1H-indol (90 mg, 0.4 mmol), respectivamente, en lugar de oxindol. Luego de purificación mediante HPLC preparativa, el material deseado puede recogerse, concentrarse, y neutralizarse con NaHCO₃ acuoso o desililarse con fluoruro de tetrabutilamonio.

TABLA 3

Ej.	-ZR ₄ R ₅	Nombre del Compuesto	Datos
19		Éster metílico de ácido 4-(2,3-Dihidro-2-oxo-1H-benzimidazol-1-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	¹ H NMR(CDCl ₃): δ 8.37 (s, 1H), 8.32 (s, 1H), 7.95 (br, s, 1H), 7.21-7.10 (m, 4H), 3.88 (s, 3H), 2.51 (s, 3H).
20		Éster metílico de ácido 4-[2,3-Dihidro-5-[(metilsulfonil)amino]-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	¹ HNMR (CD ₃ OD): δ 7.99 (s, 1H), 7.69 (s, 1H), 7.04-7.02 (m, 2H), 6.92 (d, J= 8.8 Hz, 1H), 3.86 (s, 3H), 2.87 (s, 3H), 2.39 (s, 3H).

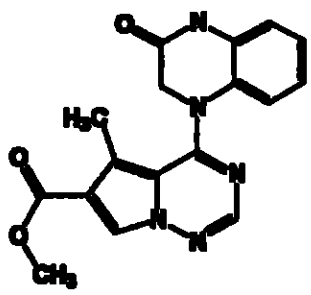
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21		Éster metílico de ácido 4-[5-(Aminosulfonyl)-2,3-dihidro-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M-H] ⁻ = 400.1; ¹ H NMR (CD ₃ OD): δ 8.05 (s, 1H), 7.83 (s, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.07 (d, J=8.3 Hz, 2H), 3.84 (s, 3H), 2.28 (s, 3H).
22		Éster metílico de ácido 4-[2,3-Dihidro-5-[(2-hidroxietyl)amino]sulfonyl]-2-oxo-1H-indol-3-il]-5-metilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 446.2; ¹ H NMR (CDCl ₃ /CD ₃ OH): δ 7.84 (s, 1H), 7.55 (s, 1H), 7.28 (d, J=8.6 Hz, 1H), 7.20 (s, 1H), 6.78 (d, J=8.6 Hz, 1H), 3.78 (s, 3H), 3.60 (t, J=7.4Hz, 2H), 2.77 (t, J=7.4 Hz, 2H), 2.20 (s, 3H).
23		Éster metílico de ácido 4-[5-[(Dimetilamino)sulfonil]-2,3 -dihidro-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M+H] ⁺ = 430. ¹ H NMR (CDCl ₃): δ 9.56 (s, 1H), 8.05 (s, 1H), 7.65-7.54 (m, 3H), 7.15 (d, J=8.2 Hz, 1H), 3.87 (s, 3H), 2.73 (s, 6H), 2.43 (3H, s)
24		Éster metílico de ácido 4-[2,3-Dihidro-5-[(metilamino)sulfonyl]-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	MS: [M-H] ⁻ = 414. ¹ H NMR (CDCl ₃ /CD ₃ OH): δ 7.98 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.31 (d, J=7.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 3.82 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H).

Ejemplo 25

Éster metílico de ácido 5-Metil-4-(1,2,3,4-tetrahidro-3-oxo-1-quinoxalini)lpirrolo[2,1-f] [1,2,4]triazina-6-carboxílico

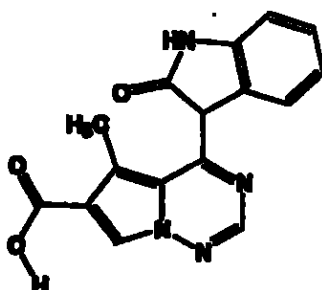


Ejemplo 2, Compuesto E (23 mg, 0.1 mmol) se agitó con 1,2,3,4-tetrahidroquinoxalin-2-ona (44.4 mg, 0.3 mmol) en DMF (0.5 mL) durante

1 hora a 50°C. Se agregó agua, y el material sólido resultante se recogió, se lavó con agua, y se secó. El material se trituró con MeOH, se filtró, y se secó nuevamente para proporcionar 20 mg (59%) de Ejemplo 25 como un sólido blanco. ^1H NMR (*d*-DMSO): δ 8.30-8.25 (m, 2H), 7.12-7.03 (m, 2H), 6.83 (br s, 2H). 4.38 (s, 2H), 3.73 (s, 3H), 2.49 (s, 3H), 1.72 (s, 3H).

Ejemplo 26

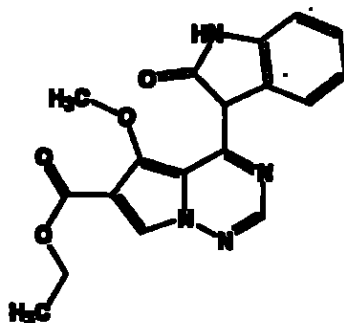
Ácido 4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico



A una solución de Ejemplo 16 (3.3 g, 10.2 mmol) en MeOH (600 mL) se agregó KOH (1N solución acuosa, 200 mL), y la mezcla se desoxigenó purgándola con argón. La mezcla de reacción se calentó a 60°C durante 20 horas, luego se enfrió y concentró a alrededor de 50 mL. El residuo se acidificó con HCl concentrado a pH 4. El sólido Amarillo se recogió, se lavó con agua, y se secó *in vacuo* para producir el Compuesto del título (2.9 g, 92%). MS: $[\text{M}+\text{H}]^+ = 307.1$; ^1H NMR (CD_3OD): δ 7.94 (s, 1H), 7.71 (s, 1H), 7.18-7.10 (m, 2H), 6.94-6.86 (m, 2H), 2.45 (s, 3H).

Ejemplo 27

Éster etílico de ácido 4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metoxipirrolo[2,1-f][1,2,4] triazina-6-carboxílico



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A. Éster dietílico de ácido [(2-Etoxi-2-oxoetil)(fenilmetil)amino]metileno]propanodióico

Éster etílico de N-bencilglicina (5.79 g, 30 mmol) se combinó con malonato de etoximetileno dietílico (6.48 g, 30 mmol) y se agitó a 120°C durante 1 hora. El material crudo se empleó directamente para la siguiente reacción.

B. Éster dietílico de ácido 1-fenilmetil-3-hidroxipirrol-2,4-dicarboxílico

A una suspensión de NaH (60% en aceite, lavada con hexanos, 500 mg, 12.5 mmol) en tolueno (10 mL) se agregó Compuesto A (3.63 g, 10 mmol) en tolueno (30 mL) gota a gota a 50°C. Después de 2 horas, la mezcla se vertió en agua helada y se acidificó con 1 N HCl acuoso. La mezcla se extrajo tres veces con EtOAc. Los extractos orgánicos combinados se secaron (MgSO₄) y concentraron *in vacuo*. El material crudo se purificó mediante cromatografía en gel de sílice eluyendo con 50% EtOAc en hexanos para proporcionar 2.70 g (85%) de Compuesto B como un aceite rosado.

C. Éster dietílico de ácido 1-fenilmetil-3-metoxipirrol-2,4-dicarboxílico

Compuesto B (634 mg, 2 mmol) se agitó en acetona durante 10 horas a temperatura ambiente con yoduro de metilo (300 mg, 2.1 mmol) y K₂CO₃ (500 mg). La mezcla se filtró, concentró, y purificó mediante cromatografía en gel de sílice eluyendo con 33% EtOAc en hexanos para proporcionar 470 mg (71%) de Compuesto C como un gel.

D. Éster dietílico de ácido 3-metoxipirrol-2,4-dicarboxílico

Compuesto C (27 g, 81.5 mmol) en EtOH (1 L) se mezcló con Pd/C (10%, 4g) y formato de amonio (28 g) y se hidrogenó a 40 psi a 90°C durante 18 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y concentró. El material crudo (aceite café) se purificó mediante

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cromatografía en gel de sílice eluyendo con 25% EtOAc en hexanos para proporcionar 13 g (66%) de un sólido marrón.

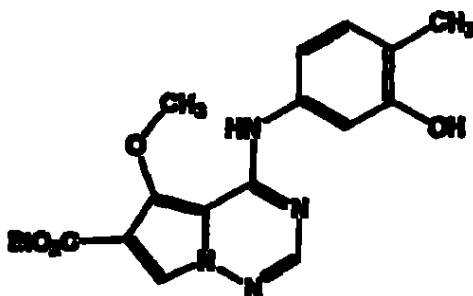
E. Éster dietílico de ácido 1-amino-3-metoxipirrol-2,4-dicarboxílico

A una suspensión agitada de NaH (60% en aceite, 1.76 g, 70 mmol) en DMF (350 mL) bajo nitrógeno a 0° C se agregó gota a gota una solución de Compuesto D (13 g, 54 mmol) en DMF (200 mL). Trascurridos 30 minutos, la mezcla se diluyó con DMF (750 mL), y luego se agregó difenil fosforil hidroxilamina (15.7 g, 67.4 mmol) y la mezcla de reacción se dejó calentar a temperatura ambiente. Después de 6 horas, la mezcla se concentró y el residuo se diluyó con agua (1 L) y se extrajo con EtOAc (3x1 L). Los extractos orgánicos combinados se secaron (MgSO₄), se concentraron, y purificaron mediante cromatografía en gel de sílice eluyendo con 20% EtOAc en hexanos para proporcionar 13 g (93%) de sólido.

F. Éster etílico de ácido 4-hidroxi-5-metoxipirrolo[2,1-f][1,2,4]triazina-6-carboxílico

Compuesto E (100 mg, 0.39 mmol) se combinó con formamida (1 mL) y se calentó a 180°C durante 6 horas. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua (5 mL). El sólido que se formó se recogió, se lavó con agua, y se secó para proporcionar 70 mg (76%) de Compuesto F.

G. Éster etílico de ácido 4-cloro-5-metoxipirrolo[2,1-f][1,2,4]triazina-6-carboxílico



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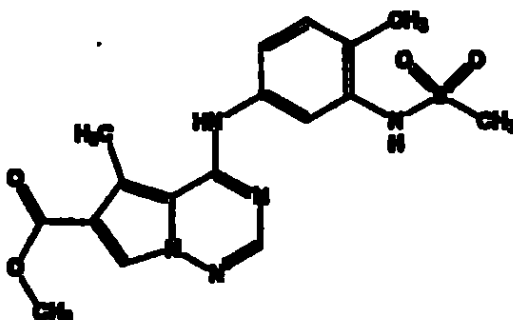
Oxícloruro de fósforo (1 mL) se combinó con Compuesto F (23.7 mg, 0.1 mmol) y se calentó a reflujo durante 2 horas. La fusión se dejó enfriar a temperatura ambiente y el oxícloruro de fósforo se retiró en un evaporador rotatorio.

H. Ejemplo 27

A una suspensión de NaH (60%, 44 mg, 1.1 mmol) en THF (1 mL) se agregó oxindol (133 mg, 1 mmol). La mezcla de reacción se agitó durante 20 minutos a temperatura ambiente y se agregó Compuesto G (0.1 mmol). La reacción se agitó durante 2 horas a 25 °C. El material crudo se purificó mediante HPLC preparativa seguida por cromatografía en gel de sílice eluyendo con EtOAc para proporcionar 5.5 mg (16%) de Ejemplo 27 como un sólido amarillo. MS: $[M+H]^+ = 353$; $^1\text{H NMR}$ (CDCl_3): δ 8.42 (s, 0.4H), 8.10 (s, 0.6H), 7.79 (s, 1H), 7.75-6.88 (m, 4H), 4.33 (m, 2H), 3.57 (s, 3H), 1.37 (m, 3H).

Ejemplo 28

Éster metílico de ácido 5-metil-4-[[4-metil-3-[(metilsulfonil)amino]fenil]amino]pirrolo[2,1-f][1,2,4]triazina-6-carboxílico

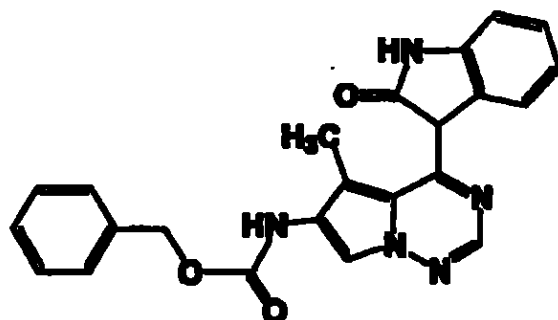


A una solución de Ejemplo 6 (16 mg, 51 μmol) en piridina (1 mL) a 0°C se agregó 4-metil-3-[(metilsulfonil)anilina (4.4 μL , 87 μmol). La mezcla de reacción se agitó durante 1 hora a 0°C y luego se calentó a 25°C y se agitó durante 4 horas. Se agregó agua y la mezcla se extrajo con EtOAc (3 x 5 mL). Los extractos orgánicos combinados se lavaron con agua (10 mL) y salmuera (10 mL) y se secaron (Na_2SO_4). El material crudo se purificó mediante cromatografía en gel de sílice eluyendo con 2% MeOH

en cloroformo para proporcionar 6.9 mg (30%) de sólido. MS: $[M+H]^+$ 390.2; ^1H NMR ($CDCl_3$): δ 7.93 (s, 1H), 7.86 (s, 1H), 7.77 (s, 1H), 7.35 (d, $J=8.2$ Hz, 1H), 7.27 (s, 1H), 7.18 (d, $J=8.2$ Hz, 1H), 6.25 (s, 1H), 3.82 (s, 3H), 3.03 (s, 3H), 2.86 (s, 3H), 2.24 (s, 3H)

Ejemplo 29

Éster fenilmetílico de ácido [4-(2,3-dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4] triazina-6-il]carbámico



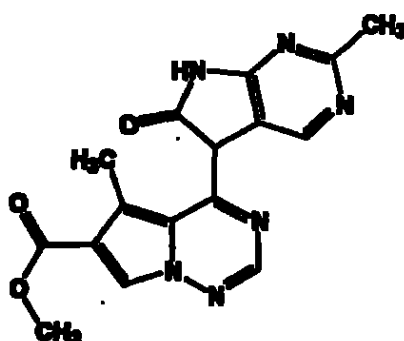
A una solución de Ejemplo 26 (29 mg, 0.09 mmol) en 1,4-dioxano (0.6 mL) bajo Ar con mallas moleculares de 4 Å recubiertas de polvo se agregó TEA (10 μ L, 71 μ mol), difenilfosforil azida (15 μ L, 71 μ mol) y alcohol bencílico (12 μ L, 0.12 mmol). La reacción se calentó a 50°C durante 15 horas. La mezcla se concentró *in vacuo* y se cromatografió directamente en gel de sílice eluyendo con una gradiente de 2-5% MeOH en cloroformo para proporcionar 8 mg (50%) de un producto intermedio como un sólido blanco. Oxibromuro de fósforo (5 eq.) se combinó con este intermedio (16 mg, 0.054 mmol) y se calentó a 60°C durante 20 minutos. La fusión se vertió en agua helada y se extrajo con EtOAc (4 x 5 mL). Los extractos se lavaron con $NaHCO_3$ acuoso, se secaron (Na_2SO_4), y se concentraron *in vacuo*. El residuo se disolvió en una mezcla de CH_3CN (0.5 mL) y DMF (0.1 mL), y a continuación se agregó 5-amino-o-cresol (10 mg, 0.081 mmol). La mezcla de reacción se agitó durante la noche bajo argón a 25°C. El solvente se retiró *in vacuo*, y el material crudo se purificó mediante cromatografía rotatoria en una placa de gel de sílice de 1 mm eluyendo con 2% MeOH en cloroformo para proporcionar el Compuesto del título como un aceite amarillo (5 mg, 13%). MS: $[M+H]^+ = 414$; ^1H NMR

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(CDCl₃): δ 7.94 (s, 1H), 7.82 (s, 1H), 7.41-7.34 (m, 5H), 7.17-7.14 (m, 1H), 7.04-7.02 (m, 1H), 6.93-6.90 (m, 2H), 6.44 (s, 1H), 5.23 (s, 2H), 2.12 (s, 3H).

Ejemplo 30

Éster metílico de ácido 4-(2,3-dihidro-6-metil-2-oxo-1H-pirazolo[2,3-d]pirimidin-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico



A. 6-Metil-5,7-diazaoxindol

A una solución de (4-amino-2-metilpirimidin-5-il)acetato de etilo (WO 99/10349, 0.975 g, 5 mmol) en THF (30 ml), se agregó lentamente t-butoxido de potasio (1 M en THF, 5 mL). Luego de una hora, la mezcla se neutralizó con ácido acético a pH 5. Los volátiles se retiraron *in vacuo* y el residuo se purificó mediante cromatografía de columna de destello (gel de sílice, 5-8 % MeOH en DCM) para producir un sólido amarillo (680 mg, 91%).

B. Éster metílico de ácido metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico

A una solución de 6-metil-5,7-diazaoxindol (67 mg, 0.45 mmol) en DMF (2 ml) y THF (1 ml) se agregó NaH (60% en aceite, 20 mg, 0.5 mmol). Luego de agitar durante 20 minutos se agregó Compuesto E de Ejemplo 2 (34 mg, 0.15 mmol). La mezcla se agitó a temperatura ambiente durante la noche y seguidamente se neutralizó con ácido acético. Se agregó DCM (10 ml) y el precipitado resultante se recogió y lavó con pequeñas cantidades de DCM y agua y entonces se secó *in vacuo* para producir el Compuesto del título como un sólido anaranjado (32 mg, 63%). MS:

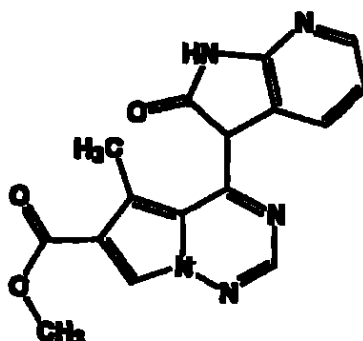
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(M+H)=359

Ejemplo 31

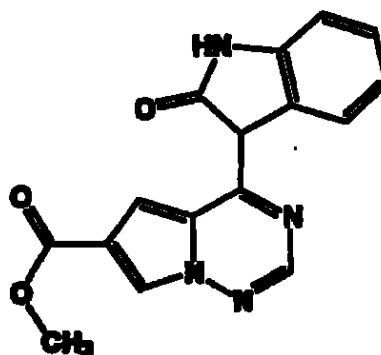
Éster metílico de ácido 4-(2,3-dihidro-2-oxo-1H-pirazolo[2,3-b]piridin-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico



A una solución de 7-azaioxindol (véase Tetrahedron-Lett., Vol. 28 (1987), en página 4027) (60 mg, 0.45 mmol) en DMF (2 mL) y THF (1 mL) se agregó NaH (60% en aceite, 20 mg, 0.5 mmol). Luego de agitar durante 20 minutos se agregó Compuesto E de Ejemplo 2 (34 mg, 0.15 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. La solución se neutralizó con ácido acético, y seguidamente se agregó DCM (10 ml) a la mezcla. El sólido resultante se recogió, se lavó con pequeñas cantidades de DCM y agua y se secó *in vacuo* para producir un sólido amarillo (35 mg, 72%). LC-MS: (M+H)⁺ = 324.

Ejemplo 32

Éster metílico de ácido 4-(2,3-dihidro-2-oxo-1H-indol-3-il)pirrolo[2,1-f][1,2,4]triazina-6-carboxílico

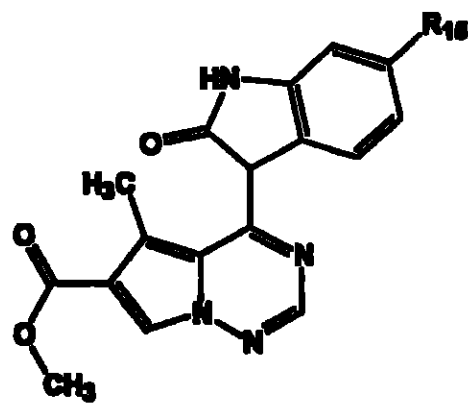


Se siguió Ejemplo 2 usando 2-metoxycarbonil pirrol como el pirrol inicial para proporcionar 4-cloro-6-carbometoxipirrolo[2,1-f]

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[1,2,4]triazina, la cual se convirtió luego en Ejemplo 32 utilizando el mismo o un procedimiento similar de Ejemplo 31.

Ejemplos 33-36



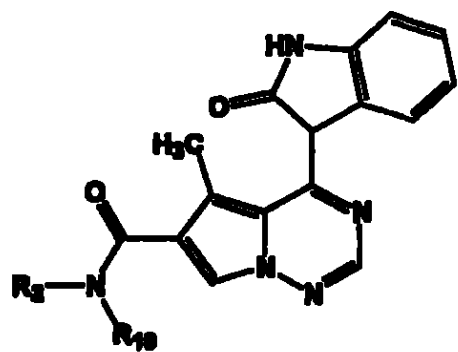
Compuestos que tienen la fórmula (If), en donde R₁₅ tiene los valores enumerados en Tabla 4, se prepararon mediante el siguiente procedimiento de Ejemplo 32 empleando reactivos apropiados conocidos en la literatura (véase, WO 97/42187).

TABLA 4

Ej.	R ₁₅	Nombre del Compuesto
33	F	Éster metílico de ácido 4-[6-fluoro-2-hidroxi-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico
34	Br	Éster metílico de ácido 4-[6-bromo-2-hidroxi-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico
35	CF ₃	Éster metílico de ácido 4-[2,3-dihidro-2-oxo-6-(trifluorometil)-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico
36	SO ₂ Me	Éster metílico de ácido 4-[2,3-dihidro-6-(metilsulfonil)-2-oxo-1H-indol-3-il]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico

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Ejemplos 37-49



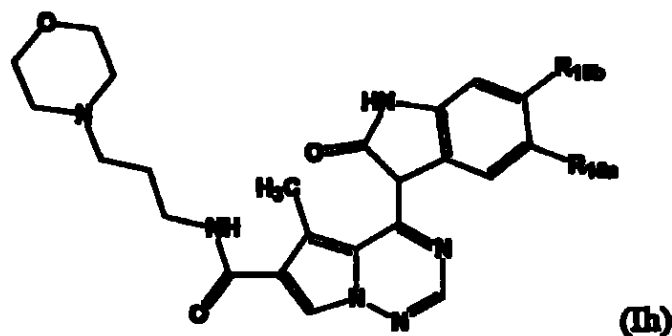
A Ejemplo 26 (50 mg, 0.16 mmol) en DMF (1 mL) y DCM (0.5 mL) se agregaron PyBrop (113 mg, 0.24 mmol) y DIPEA (0.08 mL, 0.5 mL). Después de 10 minutos se agregó una amina apropiada. Luego de 15 horas, la mezcla de reacción se purificó mediante RP HPLC preparativa para proporcionar los compuestos de fórmula (Ig), arriba en el texto, en donde R₂ y R₁₀ tienen los valores relacionados en Tabla 5.

TABLA 5

EJ.	R ₂	R ₁₀	Nombre del Compuesto
37		CH ₃	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-N,5-dimetil-N-[2-(1-pirrolidinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
38		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[2-(1-pirrolidinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
39		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(4-morfolinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
40		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida

41		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(4-metil-1-piperazinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
42		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(1H-1,2,3-triazol-1-il)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
43		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(2H-1,2,3-triazol-2-il)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
44		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(1H-1,2,4-triazol-1-il)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
45		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(2-metil-1H-imidazol-1-il)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
46		H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[4-(4-morfolinil)butil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
47		CH ₃	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-N,5-dimetil-N-[3-(4-morfolinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida
48	H	H	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida
49	H	CH ₃	4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-N,5-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida

Ejemplos 50-52



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Compuestos que tienen la fórmula (Ih), en donde R_{15a} y R_{15b} tienen los valores enumerados en la siguiente Tabla 6, se prepararon mediante el siguiente proceso, empleando el oxoindol apropiadamente sustituido en paso C.

A. Ácido 5-metilpirrolo [2,1-f] [1,2,4]triazina-4(3H)-ona-6-carboxílico

A una solución de éster metílico de ácido 5-metilpirrolo[2,1-f][1,2,4]triazina-4(3H)-ona-6-carboxílico (Compuesto D de Ejemplo 2, 1.035 g, 5.00 mmol) en una mezcla de THF/MeOH/agua (50 mL, 3:1:1) se agregó hidróxido de litio (2.062 g, 49.1 mmol). La mezcla de reacción se agitó a 55°C durante 12 horas, seguidamente se enfrió a 0°C y se neutralizó mediante 3N HCl. Los solventes orgánicos se retiraron y la solución acuosa se llevó a pH 4 con 1 N HCl. El precipitado resultante se filtró, se enjuagó con agua fría, y se secó con aire para producir Compuesto A como un sólido blancuzco (0.965 g, 100%).

B. 4-Cloro-5-metil-N-[3-(4-morfolinil)propil]pirrolo [2,1-f] [1,2,4]triazina-6-carboxamida

Una suspensión de Compuesto A (2.00 g, 10.4 mmol) en oxiclورو de fósforo (8 mL) se agitó a 100°C durante 4 horas. El solvente se retiró *in vacuo* usando tolueno para ayudar en el retiro. El sólido verde resultante se suspendió en acetonitrilo (20 mL) a 0°C y se trató con suficiente TEA (5 mL) para llevar la solución a pH 10. Se agregó 4-(3-aminopropil)morfolina (1.5 mL, 10.3 mmol), y la solución se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de reacción se vertió en solución de bicarbonato de sodio saturado y se extrajo con EtOAc. La capa orgánica se secó (MgSO₄) y los volátiles se retiraron *in vacuo* para producir Compuesto B como un sólido amarillo (1.75 g, 50%).

C. Ejemplos 50-52

A una solución de un oxoindol apropiadamente sustituido, *i.e.*, 5-

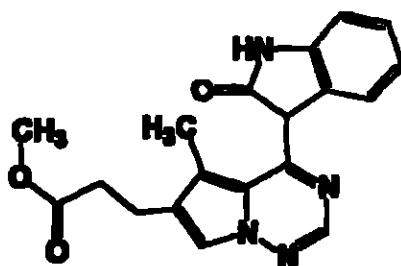
fluoro oxindol para el Ejemplo 50 (36 mg, 0.24 mmol) en DMF (1 mL) se agregó NaH (5.9 mg, 0.23 mmol). Después de 30 minutos a temperatura ambiente, se agregó una solución de Compuesto B (24 mg, 0.072 mmol) en DMF (1 mL) y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. El solvente se retiró *in vacuo* y la mezcla se purificó mediante RP HPLC. Se retiró *in vacuo* MeOH en las fracciones HPLC deseadas y la solución acuosa resultante se neutralizó utilizando solución de bicarbonato de sodio saturado, luego se extrajo EtOAc. La capa orgánica se secó (MgSO₄) y los volátiles se retiraron *in vacuo*. El sólido obtenido se disolvió en acetonitrilo/MeOH y se trató con 1 N HCl en éter dietílico. La mezcla se agitó a temperatura ambiente durante 1 hora y los solventes se retiraron *in vacuo*. La sal de HCl del Compuesto del título se obtuvo como un sólido anaranjado (18 mg, 51%).

TABLA 6

Ej.	R _{15a}	R _{15b}	Nombre del Compuesto	Datos
50	F	H	4-(5-Fluoro-2,3-dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(4-morfolinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	MS: (M+H) ⁺ = 453.
51	H	F	4-(6-Fluoro-2,3-dihidro-2-oxo-1H-indol-3-il)-5-metil-N-[3-(4-morfolinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;	—
52	-SO ₂ NH ₂	H	4-[5-(Aminosulfonil)-2,3-dihidro-2-oxo-1H-indol-3-il]-5-metil-N-[3-(4-morfolinil)propil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	—

Ejemplo 53

Éster metílico de ácido 4-(2,3-dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4] triazina-6-propanoico



A. 4-Fenoxi-5-metil-6-carbometoxipirrolo[2,1-f][1,2,4]triazina

A una solución de fenol (705 mg, 7.5 mmol) en una mezcla de THF (10 mL) y DMF (10 mL) se agregó NaH (60% en aceite, 300 mg, 7.5 mmol). Después de 30 minutos, se agregó 4-cloro-5-metil-6-carbometoxipirrolo[2,1-f][1,2,4]triazina (675 mg, 3.0 mmol - Compuesto E de Ejemplo 2). Luego de 1 hora, el solvente se retiró y el residuo se vertió en 5% solución de K_2CO_3 acuoso. Se recogió el precipitado, se lavó con agua, y se secó *in vacuo* para proporcionar Compuesto A como un sólido blanco (800 mg, 94%). MS: $(M+H)^+ = 284$.

B. 4-Fenoxi-5-metil-6-hidroximetilpirrolo[2,1-f][1,2,4]triazina

A una solución de Compuesto A (700 mg, 2.47 mmol) en tolueno (20 mL) a $-60^\circ C$, se agregó DIBAL (1.5 M en tolueno, 6 mmol). Luego de agitar a $0^\circ C$ durante 1 hora, se agregó 1N HCl (30 mL) acuoso y la mezcla se agitó durante 30 minutos. Seguidamente la mezcla se diluyó con DCM. La capa orgánica se separó, se secó ($MgSO_2$), y se concentró. El residuo se purificó mediante cromatografía de columna de destello (gel de sílice, 2 % MeOH en DCM) para producir Compuesto B como un sólido (610 mg, 96%). MS: $(M+H)^+ = 256$.

C. 4-Fenoxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxaldehído

Una mezcla de Compuesto B (500 mg, 1.96 mmol) y MnO_2 (3.0 g) en tolueno (30 mL) se calentó a $60^\circ C$ durante 1 hora. Luego de enfriar a temperatura ambiente, la mezcla se filtró a través de una almohadilla de gel

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de sílice y se lavó con EtOAc. Luego de la concentración *in vacuo*, se obtuvo Compuesto C como un sólido blanco (420 mg, 85%). MS: $(M+H)^+ = 254$

D. Éster metílico de ácido 4-fenoxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-propenoico.

DBU (1.42 mL, 9.49 mmol) se agregó a una solución de Compuesto C (600 mg, 2.37 mmol) y metil dietilfosfonoacetato (1.74 mL, 9.49 mmol) en DCE (20 mL). Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se diluyó con DCM y se lavó con 2% ácido cítrico acuoso, salmuera, se secó ($MgSO_4$), y se concentró. El extracto orgánico se concentró y el residuo se purificó mediante cromatografía en gel de sílice y elución con 20% EtOAc/DCM para producir un sólido blanco (710 mg, 97%). MS: $(M+H)^+ = 310$.

E. Éster metílico de ácido 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazina-6-propanoico.

Pd/C (10%, 70 mg) se agregó a una solución de Compuesto D (710 mg, 2.30 mmol) en una mezcla de solvente EtOAc/MeOH/THF/AcOH (100 mL/100 mL/20 mL/2 mL). La suspensión se agitó bajo hidrógeno durante 2 horas. La mezcla de reacción se pasó a través de Celita, la Celita se lavó con MeOH, y el filtrado se concentró *in vacuo* para proporcionar el producto crudo. La trituración con hexanos produjo Compuesto E como un sólido blanco (430 mg, 88%). MS: $(M+H)^+ = 236$.

F. Éster metílico de ácido 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazina-6-propanoico.

Una mezcla de DIPEA (0.24 mL, 1.4 mmol), Compuesto E (220 mg, 0.94 mmol) y $POCl_3$ (3 mL) se calentó en un frasco sellado a 80°C. Después de 2 horas, la mezcla se enfrió a temperatura ambiente y se concentró *in vacuo* para producir un residuo. El residuo se dividió en porciones entre DCM y solución de $NaHCO_3$ acuoso. La capa DCM se

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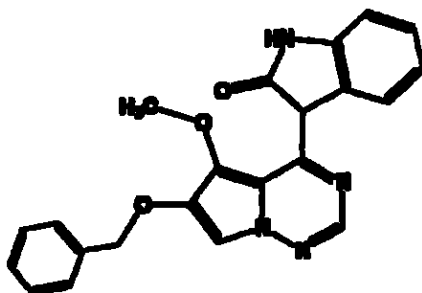
separó, se secó (MgSO_4), y se concentró *in vacuo* para producir un sólido verde oscuro. Purificación mediante cromatografía en gel de sílice y elución con 20% EtOAc/DCM proporcionó Compuesto F como un sólido amarillo (220 mg, 92%). MS: $(\text{M}+\text{H})^+ = 254$.

G. Éster metílico de ácido 4-(2,3-dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-propanoico.

NaH (60% en aceite, 28 mg, 0.71 mmol) se agregó a una solución de oxindol (94 mg, 0.71 mmol) en DMF (2 mL) bajo argón. La mezcla se agitó durante 10 minutos y se agregó Compuesto F (60 mg, 0.24 mmol). Luego de 1 hora a temperatura ambiente, la reacción se extinguió mediante la adición de ácido acético y se diluyó con DCM. La solución orgánica se lavó con agua, se secó (MgSO_4), y se concentró *in vacuo* para proporcionar el producto crudo. Purificación mediante cromatografía en gel de sílice y elución con 20% EtOAc/DCM produjo el Compuesto del título como un sólido amarillo puro (78 mg, 94%). MS: $(\text{M}+\text{H})^+ = 351$.

Ejemplo 54

1,3-Dihidro-3-[5-metoxi-6-(fenilmetoxi)pirrolo[2,1-f][1,2,4] triazina-4-il]-2H-indol-2-ona



A. 4-Hidroxi-5-metoxipirrolo[2,1-f][1,2,4]triazina-6-metanol

Éster etílico de ácido 4-hidroxi-5-metoxipirrolo[2,1-f][1,2,4]triazina-6-carboxílico (Compuesto F de Ejemplo 27 - 3.56 g, 15 mmol) se combinó con tri-*tert*-butoxialuminohidruro de litio (solución 1 M en THF, 60 mL, 60 mmol) y se calentó a reflujo durante la noche. La mezcla de reacción se dejó enfriar a temperatura ambiente y se extinguió con 1 N HCl acuoso. La mezcla se concentró para retirar los volátiles y el material restante se

combinó con 100 g de gel de sílice y se aplicó a una columna de gel de sílice de destello la cual se eluyó con EtOAc para proporcionar 2.65 g (90%) de Compuesto A. MS: $[M+H]^+ = 196$.

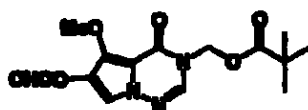
B. Éster [6-(hidroximetil)-5-metoxi-4-oxopirrólo[2,1-f][1,2,4]triazina-3(4H)-il]metílico de ácido 2,2-dimetilpropanoico

Compuesto A (195 mg, 1 mmol) se disolvió en 1.5 mL de DMF. Se agregó NaH (60% en aceite, 48 mg, 1.2 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 0.5 horas. Se agregó pivalato de clorometilo (181 mg, 1.2 mmol) y la mezcla se agitó durante 1 hora. Se agregó agua y la mezcla se extrajo con EtOAc (3 x 10 mL). Los extractos combinados se secaron (Na_2SO_4), se concentraron *in vacuo* y se purificaron cromatografía de columna de destello en gel de sílice eluyendo con 33% EtOAc en hexanos para proporcionar 260 mg (84%) de Compuesto B como un sólido. MS: $[M+H]^+ = 310$.

C. Éster [6-formil-5-metoxi-4-oxopirrólo[2,1-f][1,2,4]triazina-3(4H)-il]metílico de ácido 2,2-dimetilpropanoico

Compuesto B (740 mg, 2.39 mmol) se suspendió en tolueno (10 mL) con dióxido de manganeso (835 mg, 9.6 mmol) y se calentó a 100°C durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente se filtró, y el precipitado se lavó con EtOAc. El filtrado se concentró *in vacuo* para proporcionar 660 mg (90%) de Compuesto C como un sólido. MS: $[M+H]^+ = 308$.

D. Éster [6-formiloxi-5-metoxi-4-oxopirrólo[2,1-f][1,2,4]triazina-3(4H)-il]metílico de ácido 2,2-dimetilpropanoico



Compuesto C (660 mg, 2.15 mmol) se disolvió en CH_2Cl_2 (10 mL). Se agregó ácido M-cloroperoxibenzoico (57%, 745 mg, 2.46 mmol) con

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MgSO₄ (2.0 g), y la mezcla de reacción se agitó a temperatura ambiente durante 5 horas. La mezcla se filtró y el filtrado se lavó con solución de NaHCO₃ acuoso dos veces, se secó (MgSO₄), y se concentró para proporcionar 680 mg (98%) de Compuesto D como un sólido. MS: [M+H]⁺ 324.

E. Éster [5-metoxi-4-oxo-6-(fenilmetoxi)pirrolo[2,1-f][1,2,4]triazina-3(4H)-il]metílico de ácido 2,2-dimetilpropanoico

Compuesto D (680 mg, 2.10 mmol, 1 eq) se disolvió en acetona (10 mL) seguido por la adición de bromuro de bencilo (430 mg, 2.5 mmol) y K₂CO₃ (1.0 g, 7.25 mmol). La mezcla de reacción se agitó a 60°C durante 10 horas, se enfrió a temperatura ambiente, y se filtró. El filtrado se concentró y se purificó mediante cromatografía de destello en gel de sílice eluyendo con 25% EtOAc en hexanos para proporcionar 485 mg (60%) de Compuesto E como un gel. MS: [M+H]⁺=386;

F. 5-Metoxi-6-(fenilmetoxy)pirrolo[2,1-f][1,2,4]triazina-4(3H)-ona

Compuesto E (65 mg, 0.17 mmol) se agitó a temperatura ambiente en una mezcla de MeOH (1 mL) e hidróxido de amonio (0.2 mL) durante 6 horas. La mezcla se concentró *in vacuo*, se disolvió en CH₂Cl₂, y se purificó mediante cromatografía de destello en gel de sílice eluyendo con 33% EtOAc en hexanos para proporcionar 45 mg (97%) de Compuesto F como un sólido. MS: [M+H]⁺=272.

G. 4-Cloro-5-metoxi-6-(fenilmetoxi)pirrolo[2,1-f][1,2,4]triazina

Compuesto F (44 mg, 0.16 mmol) se agitó con POCl₃, (0.5 mL) a 60°C durante 3 horas. La mezcla se concentró *in vacuo*, se disolvió en CH₂Cl₂ (2 mL), y se agitó con NaHCO₃ sólido durante 10 minutos. La mezcla se filtró y concentró para proporcionar 46 mg (99%) de Compuesto G como un sólido. MS: [M+H]⁺=286. (el sustituyente Cl puede

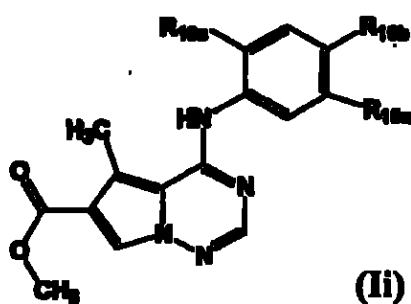
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reemplazarse con OCH₃ luego de estar en MeOH); R.T.=3.265 min (YMC S5 ODS columna 4.6 x 50 mm, 10-90% MeOH acuoso durante 4 minutos que contenía 0.2% ácido fosfórico, 4 mL/min, monitoreando a 220 nm); ¹H NMR (CDCl₃): δ 8.01 (s, 1H), 7.45-7.30 (m, 6H), 5.15 (s, 2H), 4.03 (s, 3H).

H. 1,3-Dihidro-3-[5-metoxi-6-(fenilmetoxi)pirrolo[2,1-f][1,2,4] triazina-4-il]-2H-indol-2-ona

A una suspensión de NaH (60% en aceite, 19.2 mg, 0.48 mmol) en DMF (0.5 mL) se agregó oxindol (63.4 mg, 0.48 mmol). La mezcla de reacción se agitó durante 1 hora a RT. Se agregó Compuesto G (38 mg, 0.16 mmol, 1 eq), y la mezcla se agitó durante 1 hora. La mezcla se diluyó con agua y se filtró. El sólido resultante se trituró con MeOH y se secó para proporcionar 38 mg (62%) del Compuesto del título. MS: [M+H]⁺= 387; ¹H NMR (d-DMSO): δ 12.83 (br s, 1H), 10.64 (br s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.50-7.31 (m, 6H), 7.02-6.94 (m, 1H), 6.89-6.82 (m, 2H), 5.10 (s, 2H), 3.55 (s, 3H).

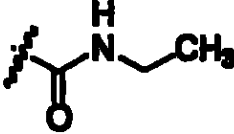
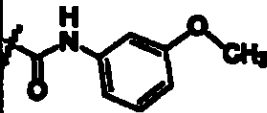
Ejemplos 55-60



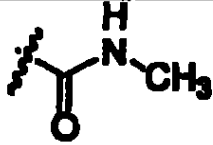
Compuestos que tienen la fórmula (II), en donde R_{16a}, R_{16b} y R_{16c} tienen los valores indicados en Tabla 7, a continuación, se prepararon siguiendo el procedimiento descrito para Ejemplo 54, excepto que utilizando una fenilamina diferente.

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TABLA 7

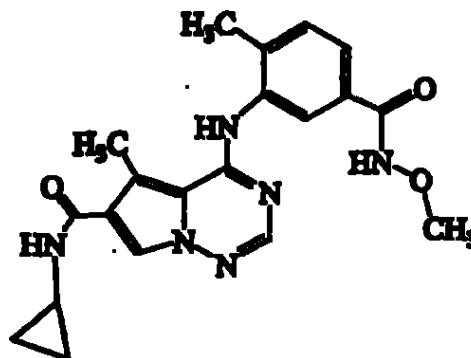
Ej.	R _{16a}	R _{16b}	R _{16c}	Nombre del Compuesto	Datos
55	F	H	CH ₃	Éster metílico de ácido 4-[(5-fluoro-2-metilfenil)amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	[M+H] ⁺ =315.2; ¹ H NMR(CDCl ₃) δ 7.97 (br s, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.13 (t, J=8.2 Hz, 1H), 6.77 (dt, J=2.7, 8.3 Hz, 1H), 3.87 (s, 3H), 2.82 (s, 3H), 2.27 (s, 3H)
56		H	CH ₃	Éster metílico de ácido 4-[[5-[(etilamino) carbonil]-2-metilfenil]amino]-5-metilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	[M+H] ⁺ =368.23; ¹ H NMR(CDCl ₃) δ 8.17 (brs, 1H), 7.92 (s, 1H), 7.83 (s, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.23 (d, J=7.7 Hz, 1H), 3.82 (s, 3H), 3.40 (m, 2H), 2.88 (s, 3H), 2.30 (s, 3H), 1.85 (m, 3H).
57	H	F	CH ₃	Éster metílico de ácido 4-[(4-fluoro-2-metilfenil)amino]-5-metilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	[M+H] ⁺ = 315.1; ¹ H NMR (CDCl ₃) δ 7.99 (s, 1H), 7.87 (s, 1H), 7.68 (br s, 1H), 6.99 (m, 2H), 3.88 (s, 3H), 2.85 (s, 3H), 2.31 (s, 3H).
58	H	F	H	Éster metílico de ácido 4-[(4-fluorofenil) amino]-5-metilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	[M+H] ⁺ =301.1; ¹ H NMR (CDCl ₃) δ 7.94 (s, 1H), 7.85 (s, 1H), 7.54 (m, 2H), 7.05 (t, J=8.8 Hz, 2H), 3.82 (s, 3H), 2.82 (s, 3H).
59		H	CH ₃	Éster metílico de ácido 4-[[5-[[3-metoxifenil] amino]carbonil]-2-metil fenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxílico	[M+H] ⁺ =446.2.

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60		H	CH ₃	Éster metílico de ácido 5-metil-4-[2-metil-5-[(metilamino) carbonil]Fenoxi] pirrolo[2,1-f][1,2,4] triazina-6-carboxílico	[M+H] ⁺ =355.1.
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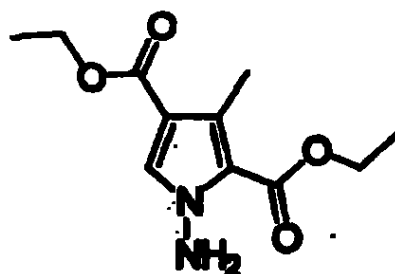
Ejemplo 61

N-Ciclobutil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil] amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida



El Compuesto de Ejemplo 61 se preparó como se indica a continuación, usando el Esquema 9 descrito más arriba en el texto, en donde Compuestos (A)-(E) poseen las estructuras señaladas a renglón seguido.

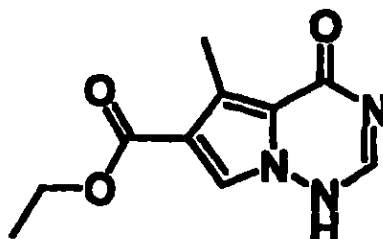
A.



A una solución de éster 3-metil-1-pirrol-2,4-diético (100 mg) (J. Heterocyclic Chem. Vol. 34 (1997), en páginas 177-193; Heterocycles, Vol. 50 (1999), en páginas 853-866; Synthesis (1999), en páginas 479-482) en DMF (0.44M) se agregó NaH o KOtBu (1.2 equiv) a temperatura ambiente. Esta solución se agitó durante 30-45 minutos. Se agregó cloramina en éter (ca. 0.15M, 1 eq.) por medio de una jeringa. La solución se agitó durante 1.5 hora o hasta que el material inicial se convirtió en el producto como se juzgó mediante análisis HPLC. La reacción se extinguió seguidamente con Na₂S₂O₃ acuoso y se extrajo con EtOAc o Et₂O. Los extractos orgánicos se

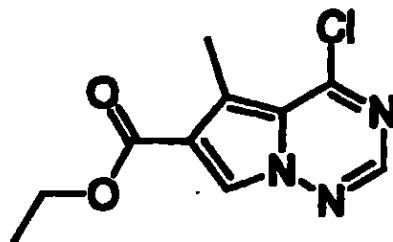
lavaron con agua y salmuera y después se secaron sobre sulfato de sodio. Compuesto A se obtuvo en un rendimiento >90%. NH_2Cl en éter se preparó de acuerdo con el procedimiento de Nunn, J. Chem. Soc. (C), (1971) en página 823.

B.



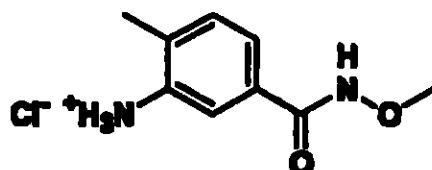
A una solución de Compuesto A (2 g) en formamida (8 mL) se agregó ácido acético (20% en peso), y la mezcla se calentó a 120°C durante 24 horas. La mezcla de reacción se enfrió y se agregó agua (32 mL) para precipitar el producto. Se recogieron los sólidos mediante filtración y se lavaron con EtOAc para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

C.



A una solución de Compuesto B (10 g, 45.2 mmol) en tolueno (150 mL) se agregó DIPEA (6.31 mL, 36.2 mmol, 0.8 equiv) y POCl_3 (5.05 mL, 54.2 mmol, 1.2 equiv) y la mezcla de reacción se calentó a 120-125 °C (temperatura de baño de aceite) durante 20 horas. La mezcla de reacción se enfrió y se vertió en NaHCO_3 -agua-tolueno helado saturado (450 mL-450 mL-150 mL) y se agitó rápidamente para asegurar la extinción del exceso de POCl_3 . Se separaron las capas (se filtran a través de celita si se forma una suspensión) y la capa orgánica se lavó nuevamente con NaHCO_3 saturado. La capa orgánica se secó sobre Na_2SO_4 , se filtró y concentró *in vacuo* para producir Compuesto C como un sólido amarillo marrón (9.9g, 95%).

D.



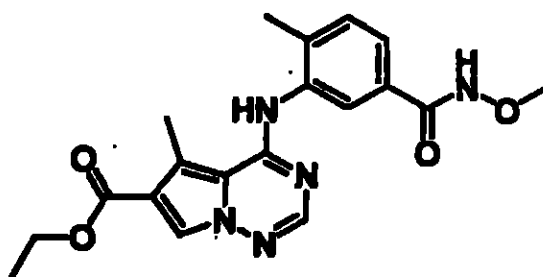
Una mezcla de ácido 4-amino-3-metilbenzoico disponible en el comercio (100 g, 0.66 mol) y N-(*tert*-butoxicarbonil)anhídrido (150 g, 0.68 mol) en THF (1000 mL) se calentó lentamente a 50°C durante la noche. La mezcla resultante se enfrió a temperatura ambiente y el solvente se retiró en un evaporador rotatorio. Los sólidos resultantes se trituraron con hexanos y se secaron *in vacuo* para producir 151 g (91%) de la anilina intermedio cruda protegida BOC como un sólido rosado claro.

Al sólido rosado pálido anterior se agregó EDCI (127 g, 0.66 mol), HOBt (90 g, 0.66 mol), y DMF (1000 ml), y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos seguida por la adición de clorhidrato de metoxiamina (55 g, 0.66 mol) en una porción. Luego de agitar durante 10 minutos, la mezcla se enfrió usando un baño helado. Se agregó DIPEA (250 ml, 1.4 mol) a una velocidad tal que se mantuviera la temperatura de reacción interna por debajo de 25 °C. Una vez concluida la adición, se retiró el baño helado y la reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se dividió en partes entre 0.5 L de agua y 1.5 L de EtOAc y se separaron las capas resultantes. La porción acuosa se extrajo con EtOAc adicional (400 mL x 3), y los extractos orgánicos combinados se lavaron con agua (300 mL x 3), 0.5 N HCl acuoso frío (400 mL x 2), y agua (500 mL). Seguidamente el producto se extrajo con 0.5 N NaOH acuoso frío (300 mL x 3) y los extractos acuosos básicos combinados se neutralizaron a pH = 8 mediante una lenta adición de 0.5 N HCl acuoso frío. El sólido resultante que se precipitó se recogió mediante filtración y se lavó con agua fría. El sólido húmedo se decoloró en EtOH caliente con carbón vegetal activo para producir 106 g de sólido blanco como la N-metoxiamida intermedio protegida BOC.

A una lechada del sólido anterior (91 g, 0.32 mol) en 1,4-dioxano (400 mL) a temperatura ambiente se agregó una solución 4M de HCl en

dioxano (400 mL), y la mezcla resultante se agitó a temperatura ambiente durante la noche. Se agregó éter dietílico (1000 mL) y el sólido precipitado se recogió mediante filtración y se trituro con una mezcla caliente de EtOH/H₂O (4:1 v/v). Secar el sólido resultante *in vacuo* produjo 53 g de la sal hidrociorato puro (Compuesto D) como un sólido blanco. ¹H NMR (d₆-DMSO): δ 9.5-9.9 (br. s, 1H), 7.75 (s, 1H), 7.55 (d, 1H), 7.36 (d, 1H), 3.70 (s, 3H), 2.38 (s, 3H).

E.



A una solución del Compuesto D (41.2 g, 190 mmol) en DMF (230 mL) se agregó DIPEA (33.1 mL, 180.7 mmol, 0.95 equiv), y el recipiente de reacción se calentó a 55 °C (temperatura de baño de aceite). Se agregó Compuesto C (45.6 g, 190 mmol) sólido en varias porciones durante 10 minutos y el frasco se enjuagó con DMF (150 mL) y se agregó a la reacción. La reacción se calentó durante 10 horas a 55 °C y se enfrió a temperatura ambiente. A continuación la mezcla se vertió en 1.5 L agua diluida a 2.2 L con hielo lentamente durante 10 minutos. Se ajustó el pH a 6 y los sólidos se agitaron durante 1 hora. Se filtraron los sólidos, se lavaron con agua (2x200 mL) y se secaron sobre el filtro para producir 71.9 g de éster crudo. Seguidamente el sólido se suspendió en acetonitrilo (450 mL) y se calentó agitando simultáneamente a 50 °C durante 1 hora. La mezcla se enfrió y se filtró para producir 64.2 g de producto (pureza >99%). Estos sólidos se disolvieron luego en EtOH caliente (2.8 L) y se agregó carbón decolorante (6.4 g) seguido por calentamiento a reflujo durante 15 minutos. La mezcla se filtró entonces a través de una almohadilla de celita y el frasco de reacción se enjuagó con EtOH caliente (1 L). Después se concentró el filtrado caliente a ~1 L de EtOH mediante destilación tras lo cual el producto comenzó a cristalizar de una solución a un volumen de 2.5

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L. La solución se enfrió y puso en un lugar fresco agitando simultáneamente durante 40 horas. Se filtraron los sólidos y se enjuagaron con 1/1 EtOH/Et₂O (500 mL) para producir 58.5 g de Compuesto E como un sólido blanco (80%).

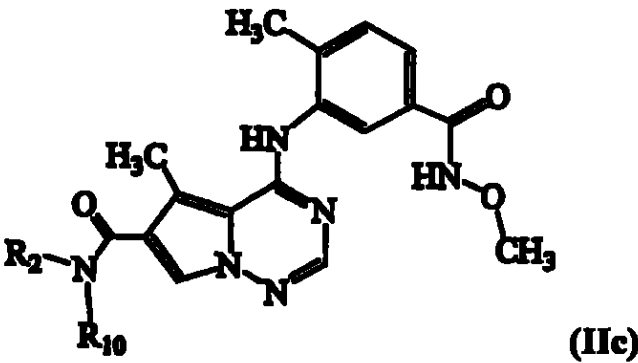
F. Ejemplo 61

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

A una solución de del ácido húmedo en 300 mL de DMF se agregó HOBt (11.9 g, 88.0 mmol), EDCI (16.9 g, 88.0 mmol) y 1.3 equivalentes (117 mmol) de ciclopropil-amina como la base libre o como la sal clorhidrato. La mezcla se agitó durante 30 minutos para solubilizar los sólidos, se puso en un baño de agua fría, y se agregó DIPEA (20.4 mL, 117 mmol) se agregó lentamente a través de una jeringa. La mezcla de reacción se dejó agitar a temperatura ambiente durante 1 hora, luego se vertió en agua helada agitada rápidamente (1.2 L) para precipitar el producto. Después de agitar durante 3 horas, se recogieron los sólidos mediante filtración de succión, se lavaron con agua (150 mL) y éter (2x100mL), y se pusieron a secar con aire mediante filtración de succión para producir Ejemplo 61 (92-98%) como un sólido blanco.

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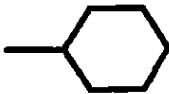
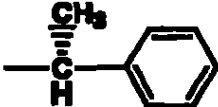
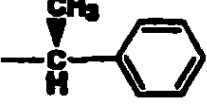
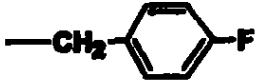
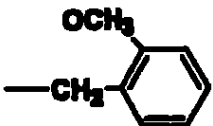
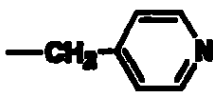
Ejemplos 62-115



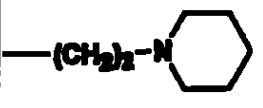
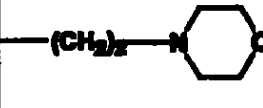
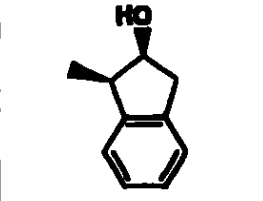
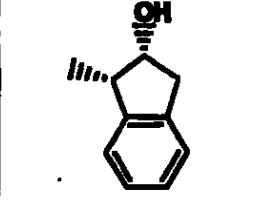
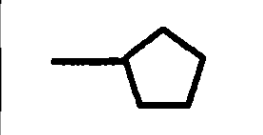
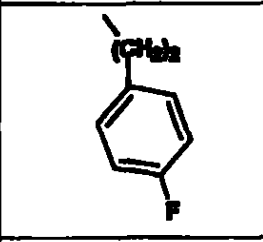
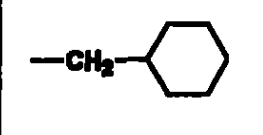
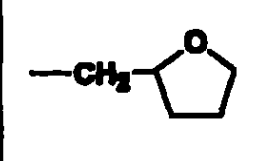
Compuestos que tienen la fórmula (IIc), en donde R₂ y R₁₀ poseen los valores indicados en Tabla 8 se prepararon siguiendo los mismos métodos expuestos más arriba en el texto en Esquema 9 y Ejemplo 61, utilizando diferentes aminas (NR₂R₁₀) en el último paso. Adicionalmente, cada Compuesto puede recristalizarse usando una mezcla 7 a 1 EtOH/agua para producir producto analíticamente puro como un sólido cristalino blanco.

TABLA 8

Ej.	R ₂	R ₁₀	Nombre del Compuesto	Datos MS/HPLC
62	$\text{---CH}_2\text{---C(CH}_3)_3$	CH ₃	N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo [2,1-f][1,2,4]triazina -6-carboxamida	439.3 3.43 min
63	$\text{---CH---(CH}_3)_2$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(1-metiletil)pirrolo[2,1-f][1,2,4] triazina-6-carboxamida	397.3 2.79 min
64	$\text{---CH}_2\text{---CH(CH}_3)_2$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilpropil)pirrolo [2,1-f] [1,2,4] triazina-6-carboxamida	411.4 3.14 min
65	$\text{---CH}_2\text{---C(CH}_3)_3$	H	N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino) Carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	425.3 3.35 min

66	$-(CH_2)_2CH_3$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	397.2 2.88 min
67	$-C(CH_3)_3$	H	N-(1,1-Dimetiletil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	411.2 3.11 min
68	$-(CH_2)_2-OCH_3$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-(2-metoxietil)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	413.2 1.99 min
69		H	N-Ciclohexil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	437.4 2.88 min
70		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-fenilettil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	459.3 2.85 min
71		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-fenilettil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	459.3 2.85 min
72		H	N-[(4-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	463.4 2.83 min
73		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-[(2-metoxifenil)metil]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	475.4 2.83 min
74		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(4-piridinilmetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	446.2 1.45 min
75		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(4-piridinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	460.3 1.81 min

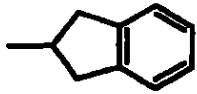
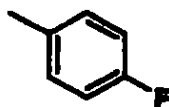
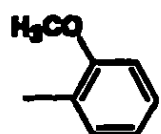
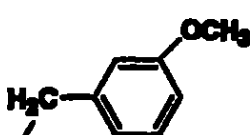
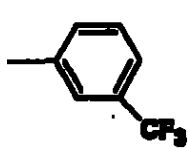
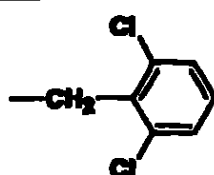
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76		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(1-piperidil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	466.4 1.56min
77		H	4-H5-l(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	468.3 1.38 min
78		H	N-[(1R, 2S)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	487.4 2.74 min
79		H	N-[(1S, 2R)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	487.2 2.74 min
80		H	N-Ciclopropil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	395.3 2.64 min
81		H	N-Ciclopentil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	423.0 3.15 min
82		H	N-[2-(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	477.3 3.53 min
83		H	N-(Ciclohexilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	451.3 3.70 min
84		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(tetrahidro-2-furanil)metil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	439.3 2.76 min

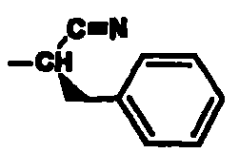
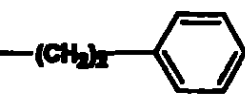
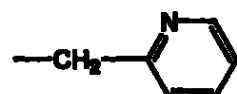
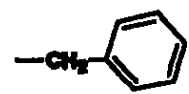
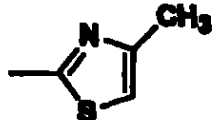
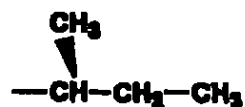
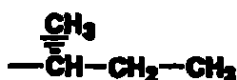
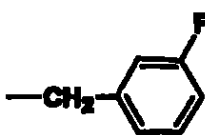
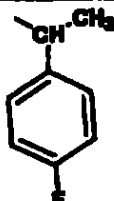
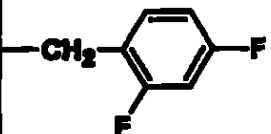
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85		H	N-(2-1H-indol-3-iletìl)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	498.3 3.39 min
86	$-(CH_2)_3-CH_3$	H	N-Butil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	411.2 3.16 min
87		H	N-(Ciclopropilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	409.1 2.90 min
88		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilbutil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	425.3 3.43 min
89		H	N-(2-Furanilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	435.1 2.95 min
90		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-tienilmetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	451.2 3.16 min
91		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-fenoxietil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	475.3 3.43 min
92		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilciclohexil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	451.2 3.56 min
93	$-CH_2-CH_3$	CH3	N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	397.2 2.59 min
94	$-CH_2-CF_3$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	437.1 3.01 min

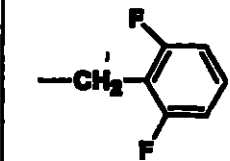
T65
166

95	$\text{—CH}_2\text{—CH}_2\text{—F}$	H	N-(2-Fluoroetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	401.2 2.44 min
96		H	N-(2,3-Dihidro-1H-inden-2-il)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	471.2 3.56 min
97	$\text{—CH}_2\text{—CH}_3$	H	N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	383.3 2.58 min
98		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2,2,3,3,3-pentafluoropropil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	487.2 3.40 min
99	$\text{—(CH}_2\text{)}_2\text{—N(CH}_3\text{)}_2$	H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	426.5 1.38 min
100		H	N-(4-Fluorofenil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	449.2 2.92 min
101		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-(2-metoxifenil)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	461.2 2.97 min
102		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-[(3-metoxifenil)metil]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	475.4 2.75 min
103		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[3-(trifluorometil)fenil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	499.1 3.39 min
104		H	N-[(2,6-Diclorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	513.1 3.10 min

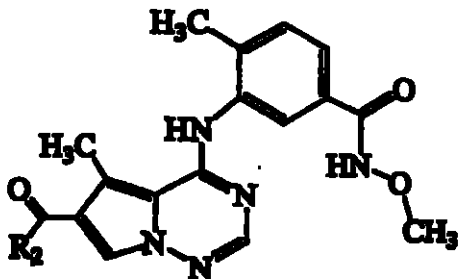
167

105		H	N-[(1S)-1-Ciano-2-feniletìl]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	484.3 2.88 min
106		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-feniletìl)pirrolo[2,1-f][1,2,4] triazina-6-carboxamida	459.3 2.91 min
107		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-piridinilmetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	446.2 1.51 min
108		H	4-[[5-l(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(fenilmetil)pirrolo[2,1-f][1,2,4] triazina-6-carboxamida	445.2 2.69 min
109		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(4-metil-2-tiazolil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	452.3 3.50 min
110		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	411.2 3.20 min
111		H	4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	411.2 3.20 min
112		H	N-[(3-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	463.2 2.84 min
113		H	N-[1 -(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	477.3 2.93 min
114		H	N-[(2,4-Difluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	481.2 2.92 min

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115		H	N-[(2,6-Difluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	481.1 2.70 min
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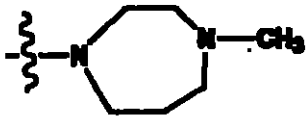
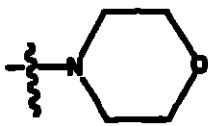
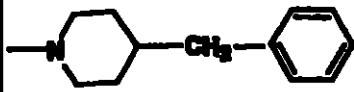
Ejemplos 116-119



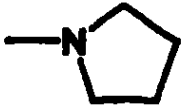
(IIId)

Compuestos que tienen la fórmula (IIId), en donde los grupos R₂ poseen los valores indicados en Tabla 9, se prepararon siguiendo los mismos métodos expuestos más arriba en el texto en Esquema 9 y Ejemplos 62-115.

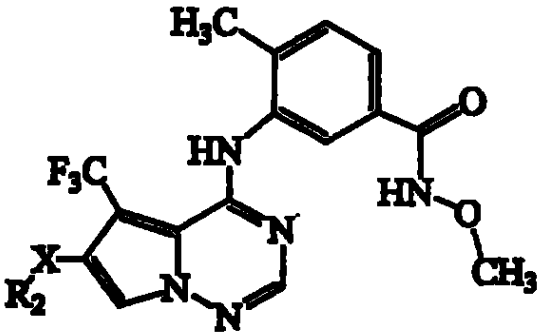
TABLA 9

Ej.	R ₂	Nombre del Compuesto	Datos
116		3-[[6-[(Hexahidro-4-metil-1H-1,4-diazepin-1-il) carbonil]-5-metil pirrolo[2,1-f][1,2,4]triazina-4-il]amino]-N-metoxi-4-metilbenzamida	452.1 1.63 min
117		N-Metoxi-4-metil-3-[[5-metil-6-(4-morfolinilcarbonil) pirrolo[2,1-f][1,2,4]triazina-4-il]amino]benzamida	425.2 1.82 min
118		N-Metoxi-4-metil-3-[[5-metil-6-[[4-(fenilmetil)-1-piperidinil]carbonil] pirrolo[2,1-f][1,2,4]triazina-4-il]amino]benzamida	513.4 3.45 min

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119		N-Metoxi-4-metil-3-[[5-metil-6-(1-pirrolidinilcarbonyl)pirrolo[2,1-f][1,2,4]triazina-4-il]amino]benzamida	409.2 2.16 min
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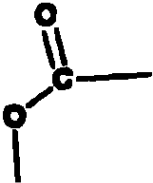
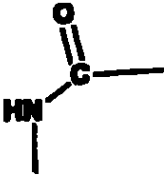
Ejemplos 120-124



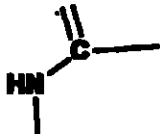
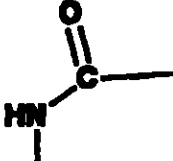
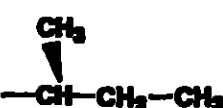
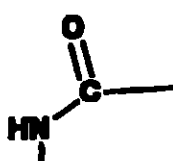
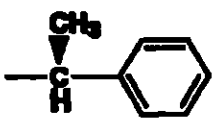
(IIe)

Compuestos que tienen la fórmula (IIe), en donde X y R₂ poseen los valores indicados en Tabla 10, se prepararon siguiendo el mismo o similar procedimiento como en Esquema 9 y Ejemplo 61, salvo que en el primer paso se utilizó éster 3-trifluorometil-1-pirrol-2,4-dietílico disponible en el comercio en lugar de éster 3-metil-1-pirrol-2,4-dietílico.

TABLA 10

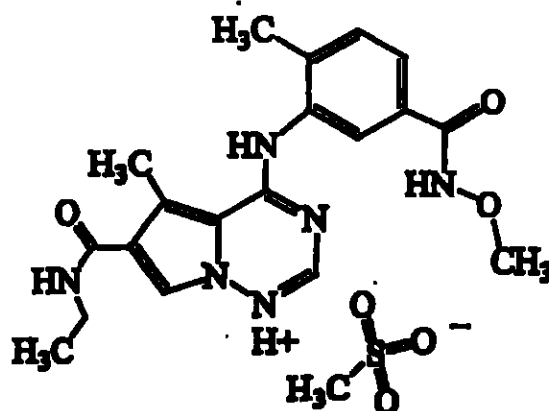
Ej. No.	X	R ₂	Nombre del Compuesto	Datos MS/HPLC
120		-CH ₂ -CH ₃	Éster etílico de ácido 4-[[5-[(Metoxiamino)carbonyl]-2-metilfenil] amino]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazina-6-carboxílico	438.2 3.76 min
121		-CH ₂ -CH ₃	N-Etil-4-[[5-[(metoxiamino)carbonyl]-2-metilfenil] amino]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	437.2 2.99 min

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122		$-\text{CH}_2-\text{CH}_2-\text{CH}_3$	4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-propil-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	451.3 3.21 min
123			4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-[(1S)-1-metilpropil]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	465.3 3.36 min
124			4-[[5-[(Metoxiamino) carbonil]-2-metilfenil] amino]-N-[(1S)-1-feniletil]-5-(trifluorometil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	513.2 1.72 min

Ejemplo 125

Ácido metanosulfónico de N-etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida



Ejemplo 97 como una base libre se cargó con acetona (10 ml/g Ej. 106), y la funda se calentó a 50-60°C. Se inició el reflujo a 55-57°C, y la mezcla se agitó durante 30 minutos a 50-60°C. Se agregó ácido metanosulfónico (1.2 eq.), y se observó una leve exoterma. La lechada se agitó a 50-60°C hasta que DSC mostró en dos muestras consecutivas la conversión completa de la base libre (mp 220-222°C) en la sal de mesilato (mp 259-261 °C). La lechada se enfrió a 20-25°C durante aproximadamente 30 minutos y, a continuación, se agitó durante por lo menos 30 minutos con la temperatura mantenida a 20-25 °C. Entonces se

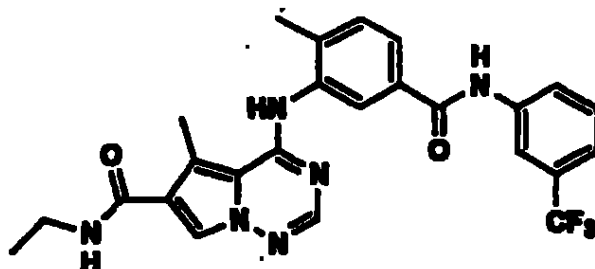
171

filtró la lechada, se lavó con acetona, y se secó *in vacuo* a 40-50°C a un LOD (límite de detección) <0.5% para proporcionar Ejemplo 125 como un sólido blanco cristalino (rendimiento 90-95%).

$[M+H]^+ = 478.4$. El procedimiento anterior puede emplearse para preparar sales de mesilato de otros compuestos de Fórmulas (I) y (II) contenidas aquí.

Ejemplo 126

N-Etil-5-metil-4-[[[2-metil-5-[[[3-(trifluorometil)fenil]amino]carbonil]fenil]amino]pirrolo[2,1-*f*][1,2,4]triazina-6-carboxamida

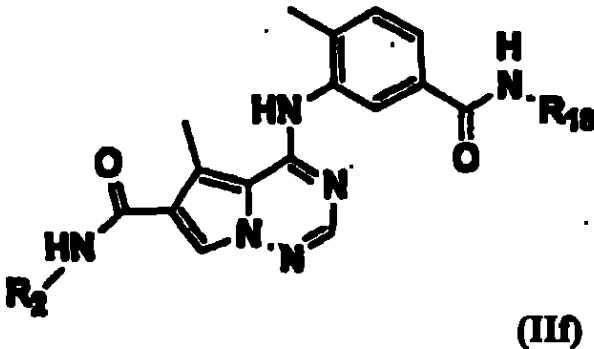


A. A una lechada de 2.0 g (4.2 mmol) de Compuesto (1) de Esquema 10, en donde R_2 es etilo, en 12 mL de MeOH anhidro se agregaron 18 mL de una solución 4N solución de HCl anhidro en dioxano a temperatura ambiente. La solución transparente resultante se agitó a temperatura ambiente durante 16 horas y la mezcla de reacción se concentró *in vacuo*. El aceite resultante se disolvió en 16 mL de solución 1.5 N de KOH acuoso y se calentó a 50°C durante 3 horas. Luego de enfriar a temperatura ambiente, la mezcla se diluyó con 50 mL de agua y se agregó 10% HCl acuoso hasta que el pH era apropiadamente 3 ó 4. El producto precipitado resultante se recogió mediante filtración de vacío y se lavó con 50 mL de agua y se secó *in vacuo* para producir 1.47 g (99%) de Compuesto (3) de Esquema 10. Una muestra analítica de este producto se preparó mediante recristalización de 10% acetonitrilo acuoso. ^1H 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 (Condición A): 2.24 minutos.

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B. Una mezcla de Compuesto A (40 mg, 0.11 mmol), HATU (65 mg, 0.17 mmol), diisopropilamina (20 μ L, 0.11 mmol), y 3-trifluorometilanilina (36 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 mediante RP HPLC preparativa para producir 41 mg (74%) de Ejemplo 126 como un sólido marrón claro. ¹H NMR (CD₃OD w/ TFA): δ 8.28 (s, 1H), 8.19 (s, 1H), 8.16 (d, 1H), 8.11 (d, 1H), 7.84 (s, 1H), 7.71 (d, 1H), 7.58 (t, 2H), 7.47 (d, 1H), 3.44 (q, 2H), 2.94 (s, 3H), 2.47 (s, 3H), 1.26 (t, 3H). LCMS (M+H⁺) = 497.47. HPLC (Condición A) : 3.30 minutos.

Ejemplos 127-129

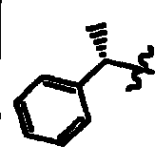
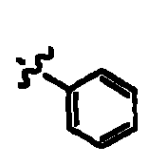
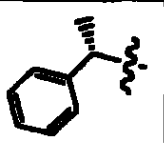
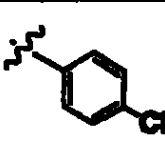


Compuestos de Fórmula (IIf) se prepararon como se describe para Ejemplo 126, salvo que se seleccionaron sustratos y aminas apropiados para producir compuestos donde R₂ y R₁₈ tienen los valores indicados en Tabla 11.

TABLA 11

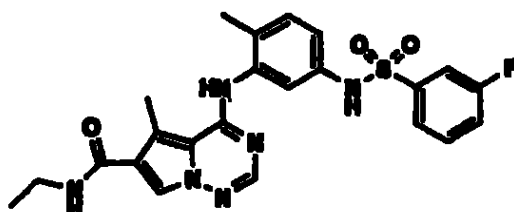
Ej.	R ₂	R ₁₈	Nombre del Compuesto	Datos
127	Et		4-[[5-[[[4-Cianofenil]amino]carbonil]-2-metilfenil]amino]-N-etil-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	¹ H NMR (CD ₃ OD): δ 7.93 (brs, 1H), 7.84-7.86 (d, 3H), 7.74 (d, 1H), 7.62 (d, 2H), 7.58 (s, 1H), 7.40 (d, 1H), 3.30 (q, 2H), 3.21 (s, 3H), 2.76 (s, 3H), 1.14 (t, 3H). LCMS (M+H ⁺)=454.18. HPLC (Condición A) : 2.86 min.

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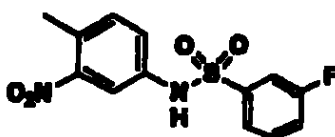
128			5-Metil-4-[[2-metil-5-[(fenilamino)carbonil]fenil]amino]-N-[(1S)-1-feniletíl]pirrólo[2,1-f][1,2,4]triazina-6-carboxamida	LCMS (M+H ⁺) = 505.27. HPLC (Condición A): 3.34 min.
129			4-[[5-[[[(4-Ciano-fenil)amino]carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletíl]pirrólo[2,1-f][1,2,4]triazina-6-carboxamida	LCMS (M+H ⁺) = 530.23. HPLC (Condición A): 3.35 min.

Ejemplo 130

N-Etil-4-[[5-[[[(3-fluorofenil)sulfonil]amino]-2-metilfenil] amino]-5-metilpirrólo[2,1-f][1,2,4]triazina-6-carboxamida



A.

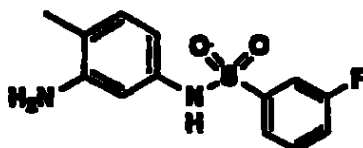


A una solución de 4-metil-3-nitroanilina [Compuesto (11) de Esquema 11)(3.72 g, 24.5 mmol)] en 150 ml de DCM a temperatura ambiente se agregó cloruro de 3-fluorobencenosulfonilo (5.00 g, 25.7 mmol), seguido por TEA (7.0 ml, 50.2 mmol) *vía* una jeringa. La mezcla resultante se agitó durante 20 horas y el solvente se retiró *in vacuo*. El residuo se disolvió en DCM (600 ml), se lavó con NaHCO₃ acuoso saturado, se secó sobre sulfato de sodio, se filtró, y se concentró *in vacuo* para producir 8.00 g de un sólido oscuro el cual se trituró con DCM para producir 5.46 g de sólido amarillo. Una porción de este sólido (1.63g) se

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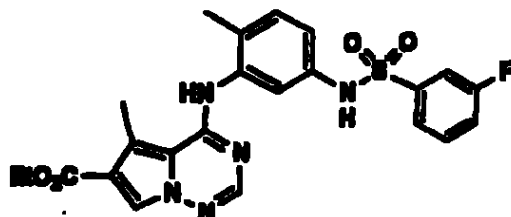
disolvió en 10 ml 1N NaOH acuoso y 20 ml THF, y la solución se agitó a temperatura ambiente durante 20 horas. El solvente se retiró *in vacuo* y el residuo se acidificó con 3N HCl a un pH de 2. El sólido precipitado resultante se recogió mediante filtración para producir 1.02 g (94%) de un sólido amarillo claro como el Compuesto A deseado. HPLC (Condición A) = 2.99 min. $^1\text{H NMR}(\text{DCl}_3)$ δ 7.67 (d, 1H), 7.59 (dd, 1H), 7.49 (m, 2H), 7.32 (m, 1H), 7.28 (m, 2H), 2.54 (s, 3H).

B.



A 0.20 g (0.64 mmol) de Compuesto A en MeOH (10 ml) se agregó 10% Pd/C (20 mg) y la mezcla se agitó bajo un balón de hidrógeno durante 6 horas a temperatura ambiente. La solución se filtró a través de una almohadilla de celita y el solvente se retiró *in vacuo* para producir 0.18 g (100%) de Compuesto B como un sólido vidrioso, incoloro. HPLC (Condición A): 1.77 minutos. LCMS $\text{M}+\text{H}^+$ (m/z) 281.

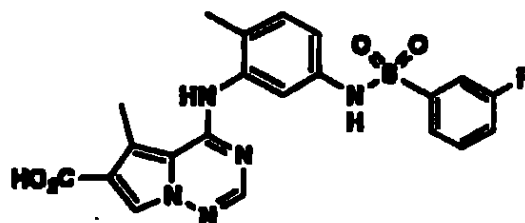
C.



Compuesto B (0.18 g, 0.64 mmol) y 0.15 g (0.64 mmol) de 4-cloro-5-metilpirrolotriazina-6-etilcarboxilato (Compuesto 8 de Esquema 11) en DMFanhidro se agitó a temperatura ambiente durante 20 horas. La reacción se extinguió con la adición de agua fría y NaHCO_3 acuoso saturado. El sólido se recogió, se lavó con agua, y se secó *in vacuo* para producir 0.27 g (91%) de Compuesto C como un sólido amarillo claro. HPLC (Condición A: 3.49 minutos. LCMS $\text{M}+\text{H}^+$ (m/z) 484.

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175

D.



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

E. Ejemplo 130

Una mezcla de 30 mg (66 µmol) de Compuesto D, EDCI (19 mg, 98 µmol), HOBt (13 mg, 98 µmol) y base de Hunig (43 µL, 0.25 mmol) se agitó a temperatura ambiente durante 0.5 hora. Se agregó clorhidrato de etilamina (10 mg, 0.13 mmol) y la mezcla se agitó durante 16 horas. La mezcla cruda se purificó mediante cromatografía RP HPLC preparativa para producir Ejemplo 130. HPLC (Condición A): 2.83 minutos. LCMS M+H⁺ (m/z) 483.

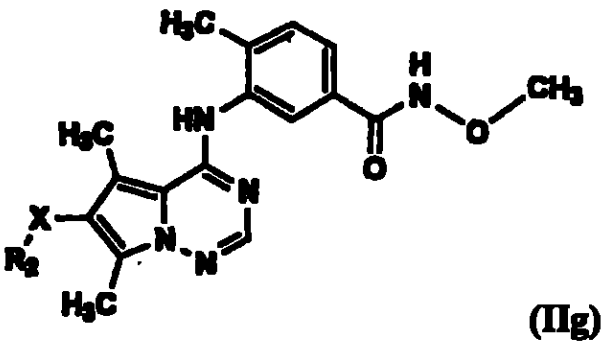
Ejemplos 131-132

Ejemplos 131 y 132 como se muestra en la Tabla 12 se prepararon de Compuesto D de Ejemplo 130 y una amina apropiada como se describe en Ejemplo 130, paso E.

TABLA 12

Ej.	Compuesto	Nombre del Compuesto	Datos
131		4-[[5-[[[(3-Fluorofenil)sulfonyl]amino]-2-metilfenil]amino]-N-[(1S)-2-metoxi-1-metiletil]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	HPLC (Condición A): 2.89 min. MH ⁺ (m/z) 527.
132		4-[[5-[[[(3-Fluorofenil)sulfonyl]amino]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	HPLC (Condición A): 3.23 min. MH ⁺ (m/z) 559.

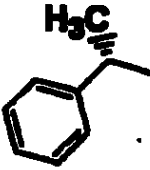
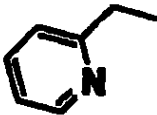
Ejemplos 133-141

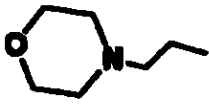
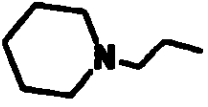
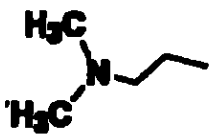


Compuestos que tienen la fórmula (IIg), en donde X y R₂ poseen los valores indicados en Tabla 13 se prepararon de dietil-2,4-dimetilpirrol-3,5-dicarboxilato disponible en el comercio siguiendo el mismo procedimiento o uno similar descrito más arriba en el texto para la preparación de 5-desmetil pirrolotriazina.

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177

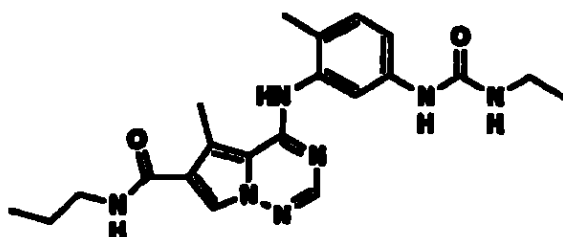
TABLA 13

Ej.	X	R ₂	Nombre del Compuesto	Datos
133	-CO ₂ -	Et	Éster etílico de ácido 4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	398.2, M+H 3.13 min, A
134	-C(=O)NH-	Et	N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	397.2, M+H 1.70 min, A
135	-C(=O)NH-		4-[[5-L(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[(1S)-1-feniletil]pirrolo [2,1-f][1,2,4]triazina-6-carboxamida	473.3, M+H 2.51 min, A
136	-C(=O)NH-	-CH(CH ₃) ₂	4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(1-metiletil)pirrolo [2,1-f][1,2,4]triazina-6-carboxamida	411.2, M+H 1.81 min, A
137	-C(=O)NH-		4-[[5-[(Metoxi-amino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(2-piridinilmetil)pirrolo [2,1-f][1,2,4]triazina-6-carboxamida	460.2, M+H 1.30 min, A
138	-CO ₂ -	H	Ácido 4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo [2,1-f][1,2,4]triazina-6-carboxílico	370.2, M+H 2.21 min, A

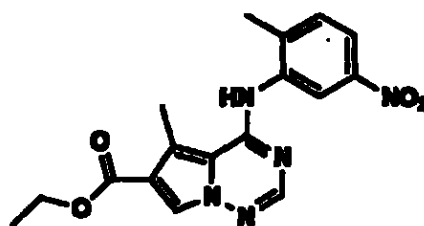
139	-C(=O)NH-		4-[[5-[(Metoxi-amino) carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	482.1, M+H 1.21 min, A
140	-C(=O)NH-		4-[[5-[(Metoxi-amino) carbonil]-2-metilfenil]amino]-5,7-dimetil-N-[2-(1-piperidinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida	480.2, M+H 1.39 min, A
141	-C(=O)NH-		N-[2-(Dimetilamino)etil]-4-[[5-[(metoxiamino) carbonil]-2-metilfenil]amino]-5,7-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	440.2, M+H 1.09min, A

Ejemplo 142

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



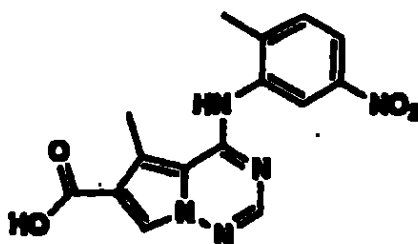
A. Éster etílico de ácido 5-metil-4-[(2-metil-5-nitrofenil)amino]pirrolo[2,1-f][1,2,4]triazina-6-carboxílico



Una suspensión de cloropirrolotriazina (Compuesto 1 de Esquema 12)

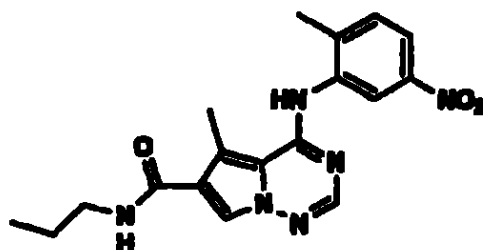
(2.03 g, 8.47 mmol) y 3-nitro-5-metil anilina (1.41 g, 9.3 mmol) en DMF (25 mL) se agitó a temperatura ambiente durante 24 horas. Se agregó agua (125 mL) durante 30 minutos y la solución se agitó durante 1 hora tras la cual el pH se ajustó a neutro con NaHCO_3 acuoso saturado. Los sólidos se filtraron,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

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



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

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

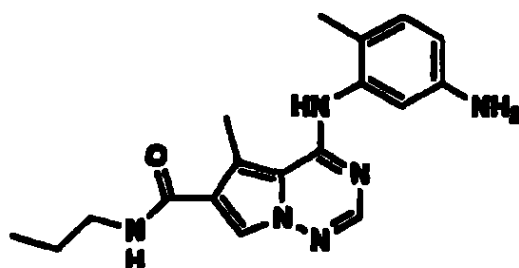


Una solución de Compuesto B (2.32 mmol), EDCI (489 mg, 2.55 mmol), y HOBt (345 mg, 2.55 mmol) en DMF (6 mL) se agitó a temperatura ambiente durante 1 hora, y luego se agregó n-propil amina

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(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 purificaron mediante cromatografía de columna en sílice (33% acetato de etilo/hexanos) para producir Compuesto C (0.79 g, rendimiento 93%) como un sólido blanco. ^1H 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 ($\text{M}+\text{H}^+$) = 369.3. HPLC (Condición A): 3.42 minutos.

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



Una solución de Compuesto C (794 mg, 2.16 mmol) y 10% Pd/C (250 mg, húmedo) en MeOH (20 mL) se desgasificó y se volvió a llenar con hidrógeno tres veces y se agitó durante 2 horas. La solución se filtró y concentró para producir Compuesto D (691 mg, rendimiento 95%). ^1H 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 ($\text{M}+\text{H}^+$) = 339.2. HPLC (Condición A): 2.39 minutos.

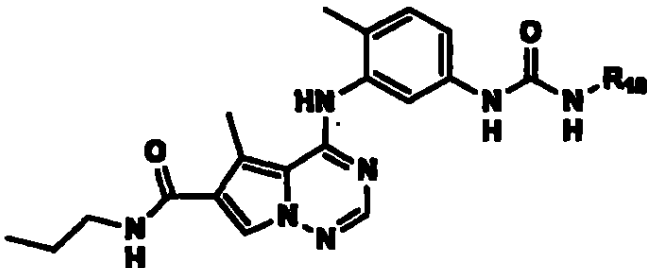
E. Ejemplo 142

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

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isopropanol y se secó *in vacuo* para producir 19.6 mg (63%) del Compuesto del título como un producto puro. ¹H NMR (CD₃OD): δ 7.94 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.23 (br s, 2H), 7.44 (d, 1H), 3.23 (q, 2H), 2.84 (s, 3H), 2.24 (s, 3H), 1.66 (m, 2H), 1.16 (t, 3H), 1.02 (t, 3H). LCMS (M+H⁺) = 410.2. HPLC (Condición A): 2.82 minutos.

Ejemplos 143-148



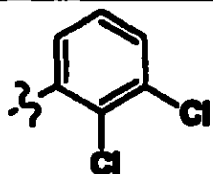
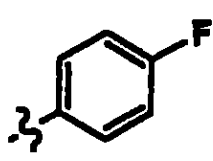
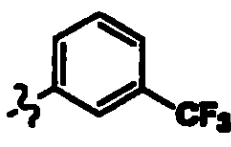
(IIh)

Compuestos que tienen la fórmula (IIh), en donde R₁₈ posee los valores relacionados en la Tabla 14 se prepararon siguiendo el procedimiento indicado para Ejemplo 142, usando diferentes isocianatos en el último paso.

TABLA 14

Ej.	R ₁₈	Nombre del Compuesto	Datos MS/HPLC
143		5-Metil-4-[[2-metil-5-[[[(fenilamino)carbonil]amino]fenil]amino]-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	458.2 3.40 min
144		5-Metil-4-[[2-metil-5-[[[(3-metilfenil)amino]carbonil]amino]fenil]amino]-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	472.5 3.60
145		4-[[5-[[[(4-Cianofenil)amino]carbonil]amino]-2-metilfenil]amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	483.3 3.48

7A
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146		4-[[5-[[[(2,3-Diclorofenil)amino] carbonil]amino]-2-metilfenil] amino]-5-metil-N-propilpirrolo [2,1-f][1,2,4]triazina-6-carboxamida	526.2 3.98
147		4-[[5-[[[(4-Fluorofenil)amino] carbonil]amino]-2-metilfenil] amino]-5-metil-N-propilpirrolo [2,1-f][1,2,4]triazina-6-carboxamida	476.2 3.48
148		5-Metil-4-[[2-metil-5-[[[(3-(trifluorometil)fenil]amino] carbonil]amino]fenil]amino]-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida	526.1 3.87min

Ejemplos 149-152

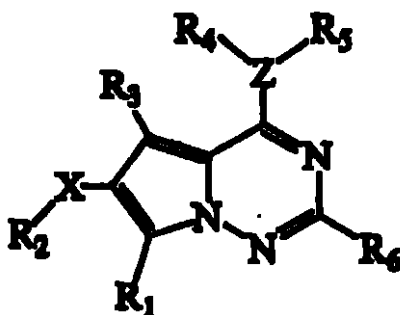
Los compuestos nombrados a continuación se prepararon usando métodos análogos a los procedimientos descritos más arriba en el texto:

- 149) 1,3-Dihidro-3-[5-metoxi-6-[[4-(4-metil-1-piperazinil) butil]amino]pirrolo[2,1-f][1,2,4]triazina-4-il]-2H-indol-2-ona;
- 150) 1,3 -Dihidro-3-[5-metoxi-6-[[4-(4-morfolinil)butil]amino] pirrolo [2,1-f][1,2,4]triazina-4-il]-2H-indol-2-ona;
- 151) 1-[3-[4-(2,3-Dihidro-2-oxo-1H-indol-3-il)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-il]-1-oxopropil]-4-metilpiperazina; y
- 152) 2-Metil-5-[[5-metil-6-[3-(2H-1,2,3-triazol-2-il)propoxi] pirrolo [2,1-f][1,2,4]triazina-4-il]amino]fenol.

REIVINDICACIONES

Reivindicamos:

1. Un método de tratar una o más condiciones asociadas con actividad de quinasa p38 que comprende administrar a un paciente necesitado de ello por lo menos un Compuesto que tiene la fórmula (I):



(I)

o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R₃ es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano o NH₂;

X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -CO₂-,

-NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-,

-NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, -C(=O)NR₁₀-, halógeno, nitro, y ciano, o

X está ausente;

Z se selecciona de O, S, N, y CR₂₀, en donde cuando Z es CR₂₀, dicho átomo de carbono puede formar un arilo o heteroarilo bicíclico opcionalmente sustituido con R₄ y R₅;

R₁ es hidrógeno, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂,

-SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)-NR₂₄R₂₅, -NH₂-, -NR₂₄R₂₅,

-NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅,

-NR₂₁C(=O)NR₂₄R₂₅, halógeno, nitro, o ciano;

R₂ se selecciona de:

a) hidrógeno, con la condición que R₂ no es hidrógeno cuando X es -S(=O)-, -SO₂-, -NR₁₀CO₂-, o -NR₁₀SO₂-;

b) alquilo, alquenilo, cuatro R₂₆ o pentafluoroalquilo;

c) arilo y heteroarilo opcionalmente sustituido con hasta tres R₂₇; y

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- d) heterociclo y cicloalquilo opcionalmente sustituido con ceto ($=O$), hasta tres R_{27} , y/o que tienen un puente carbono-carbono de 3 a 4 átomos de carbono; o
- e) R_2 está ausente si X es halógeno, nitro o ciano;
- (i) R_4 es arilo sustituido, arilo sustituido con $NHSO_2$ alquilo, heteroarilo sustituido, o un anillo carboxílico o heterocíclico bicíclico saturado o insaturado de 7-11 miembros opcionalmente sustituido, y
- R_5 es hidrógeno, alquilo, o alquilo sustituido, excepto cuando Z es O ó S, R_5 está ausente, o alternatively,
- (ii) R_4 y R_5 tomados juntos con Z forman un arilo o heteroarilo bicíclico de 7-11 miembros opcionalmente sustituido;
- R_6 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, o halógeno;
- R_{10} y R_{11} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclo, y heterociclo sustituido;
- R_7 , R_8 , R_{21} , R_{24} , y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;
- R_{20} es hidrógeno, alquilo inferior, o alquilo sustituido, o R_{20} puede estar ausente si al átomo de carbono al cual se une, junto con R_4 y R_5 es parte de un arilo o heteroarilo bicíclico insaturado;
- R_{22} es alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido;
- R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alquilo; arilo opcionalmente sustituido con uno a tres R_{27} ; cicloalquilo opcionalmente sustituido con ceto ($=O$), uno a tres R_{27} , o que tiene un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo opcionalmente sustituido con ceto ($=O$), uno a tres R_{27} , o

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que tiene un puente carbono-carbono de 3 a 4 átomos de carbonono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C_{3-7} cicloalquilo, y C_{3-7} heterociclo, o pueden tomarse juntos para formar un C_{3-7} heterociclo; y en donde cada R_{28} y R_{29} a su vez se sustituyen opcionalmente con hasta dos de alquilo, alquenilo, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y benciloxi; y

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

2. El método de la reivindicación 1 que comprende administrar a un paciente por lo menos un Compuesto que tiene la fórmula (I), o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R_3 es metilo, $-CF_3$, ó $-OCH_3$;

X se selecciona de $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-SO_2NR_{10}-$, y $-C(=O)NR_{10}-$, o X está ausente;

Z es N;

R_2 es hidrógeno, C_{2-6} alquilo, C_{1-4} alquilo sustituido con hasta cuatro R_{26} pentafluoroalquilo, o arilo o heteroarilo opcionalmente sustituido con hasta dos R_{27} ;

R_4 es fenilo sustituido con un R_{12} y cero a tres R_{13} ;

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

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

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

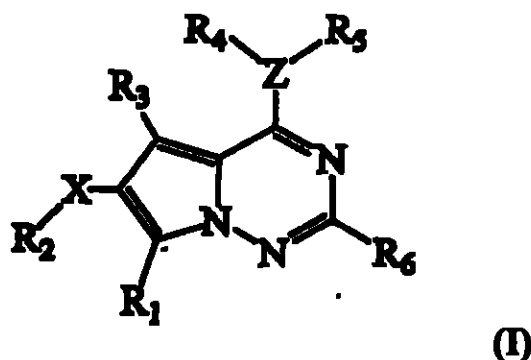
R_{14} es hidrógeno, alquilo, o arilo;

R_{15} es hidrógeno o alquilo;

R_{16} es hidrógeno, alquilo, aralquilo, o alcenoilo; y

R_{17} es hidrógeno, hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, o aralquilo.

3. Un método de tratar una o más condiciones asociadas con la actividad de quinasa p38 que comprende administrar a un paciente necesitado de ello por lo menos un compuesto que tiene la fórmula (I):



o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R_3 es hidrógeno, metilo, perfluorometilo, metoxi, halógeno, ciano o NH_2 ;

X se selecciona de $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$,

$-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$,

$-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, $-C(=O)NR_{10}-$, halógeno, nitro, y ciano, o

X está ausente;

Z es O, S, N, o CR_{20} ;

R_1 es hidrógeno, $-CH_3$, $-OH$, $-OCH_3$, $-SH$, $-SCH_3$, $-OC(=O)R_{21}$, $-S(=O)R_{22}$,

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$-\text{SO}_2\text{R}_{22}$, $-\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{CO}_2\text{R}_{21}$, $-\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, $-\text{NH}_2$, $-\text{NR}_{21}\text{SO}_2\text{NR}_{24}\text{R}_{25}$, $-\text{NR}_{21}\text{SO}_2\text{R}_{22}$, $-\text{NR}_{24}\text{C}(=\text{O})\text{R}_{25}$, $-\text{NR}_{24}\text{CO}_2\text{R}_{25}$, $-\text{NR}_{21}\text{C}(=\text{O})\text{NR}_{24}\text{R}_{25}$, halógeno, nitro, o ciano;

R_2 es hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, aralquilo, aralquilo sustituido, o heterocicloalquilo, o heterocicloaralquilo sustituido,, o cuando X es halo, nitro o ciano, R_2 está ausente, a condición que R_2 no es hidrógeno cuando X es $-\text{S}(=\text{O})-$, $-\text{SO}_2-$, $-\text{NR}_{10}\text{CO}_2-$, ó $-\text{NR}_{10}\text{SO}_2-$;

R_4 es arilo sustituido, arilo sustituido con NHSO_2 alquilo, heteroarilo sustituido, o un sistema de anillo carbocíclico o heterocíclico bicíclico saturado o insaturado de 7-11 miembros opcionalmente sustituido;

R_5 es hidrógeno, alquilo, o alquilo sustituido, excepto que cuando Z es O o S, R_5 está ausente;

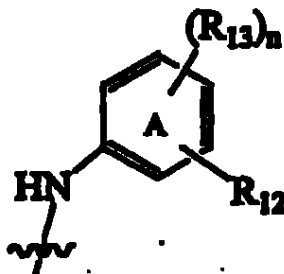
R_6 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-\text{NR}_7\text{R}_8$, $-\text{OR}_7$, o halógeno;

R_7 , R_8 , R_{10} , R_{11} , R_{21} , R_{24} y R_{25} se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;

R_{20} es hidrógeno, alquilo inferior, o alquilo sustituido; y

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

4. El método de la reivindicación 3 que comprende administrar al paciente por lo menos un compuesto de fórmula (I), en la cual R_4 y R_5 tomados juntos con Z forman:



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o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R_{12} se une a cualquier átomo de carbono disponible del anillo fenilo A y se selecciona de carbamilo, sulfonamido, arilsulfonilamina, y ureido, cada uno de los cuales se sustituye opcionalmente con hasta uno de hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, y aralquilo, o C_{1-4} alquilsulfonilamina;

R_{13} se une a cualquier átomo de carbono disponible del anillo fenilo A y en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, $-C(=O)alquilo$, $-OC(=O)alquilo$, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)alquilo$, $-S(=O)arilo$, $-NHSO_2-aril-R_{17}$, $-NHSO_2C_{1-4}alquilo$, $-SO_2NHR_{17}$, $-CONHR_{17}$, y $-NHC(=O)NHR_{17}$;

R_{14} es hidrógeno, alquilo, o arilo;

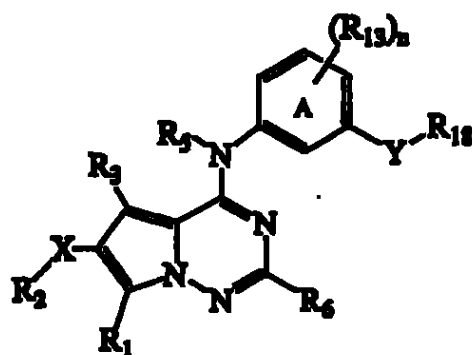
R_{15} es hidrógeno o alquilo;

R_{16} es hidrógeno, alquilo, aralquilo, o alcanoilo; y

R_{17} es hidrógeno, hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, arilo sustituido, o aralquilo; y

n es 0, 1, 2 ó 3.

5. El método de la reivindicación 3 que comprende administrar al paciente por lo menos un compuesto que tiene la fórmula (II):



(II),

o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R_3 es metilo o CF_3 ;

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

R_1 es hidrógeno, $-CH_3$, $-OH$, $-OCH_3$, halógeno, nitro, o ciano;

Y es $-C(=O)NH-$, $-NHC(=O)NH-$, $-NHSO_2-$, o $-SO_2NH-$;

R_{10} es hidrógeno o alquilo inferior;

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

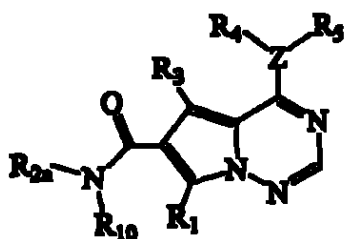
R_{13} se une a cualquier átomo de carbono disponible del anillo fenilo A y en cada ocurrencia se selecciona independientemente de alquilo, alquilo sustituido, halo, trifluorometoxi, trifluorometilo, $-OR_{14}$, $-C(=O)$ alquilo, $-OC(=O)$ alquilo, $-NR_{15}R_{16}$, $-SR_{15}$, $-NO_2$, $-CN$, $-CO_2R_{15}$, $-CONH_2$, $-SO_3H$, $-S(=O)$ alquilo, $-S(=O)$ arilo, $-NHSO_2$ -aril- R_{17} , $-NHSO_2C_{1-4}$ alquilo, $-SO_2NHR_{17}$, $-CONHR_{17}$, y $-NHC(=O)NHR_{17}$;

R_{14} , R_{15} , R_{16} y R_{17} son hidrógeno o alquilo;

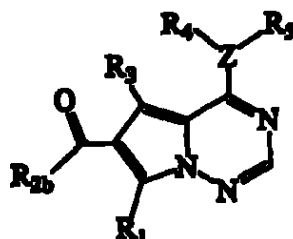
R_{19} en cada ocurrencia se selecciona de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanoilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, ácido sulfónico, alquilsulfonilo,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

n es 0, 1 ó 2.

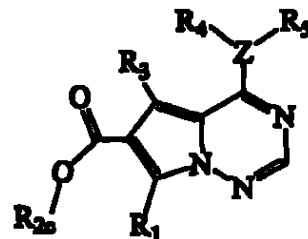
6. El método de la reivindicación 3, que comprende administrar al paciente por lo menos un compuesto que tiene la fórmula (Ia), (Ib), o (Ic):



(Ia)



(Ib)



(Ic)

o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

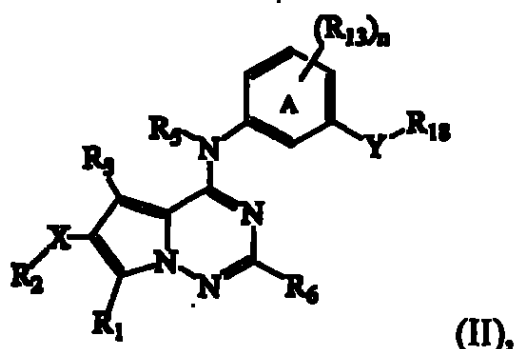
R_3 es metilo o CF_3 ;

R_{2a} y R_{2c} se seleccionan independientemente de hidrógeno, C_{2-4} alquilo, C_{1-4} alquilo sustituido, arilo, arilo sustituido, bencilo, y bencilo sustituido;

R_{2b} es heterociclo o heterociclo sustituido; y

R_{10} es hidrógeno o alquilo inferior.

7. Un compuesto que tiene la fórmula (II):



o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R_3 es metilo, CF_3 , o CH_3 ; R_5 es hidrógeno o alquilo;

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

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

X se selecciona de $-O-$, $-OC(=O)-$, $-S-$, $-S(=O)-$, $-SO_2-$, $-C(=O)-$, $-CO_2-$, $-NR_{10}-$, $-NR_{10}C(=O)-$, $-NR_{10}C(=O)NR_{11}-$, $-NR_{10}CO_2-$, $-NR_{10}SO_2-$, $-NR_{10}SO_2NR_{11}-$, $-SO_2NR_{10}-$, y $-C(=O)NR_{10}-$, o X está ausente;

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

R_2 se selecciona de

a) hidrógeno, a condición que R_2 no es hidrógeno cuando X es $-S(=O)-$, $-SO_2-$, $-NR_{10}CO_2-$, o $-NR_{10}SO_2-$;

b) alquilo, alqueno, y alquino opcionalmente sustituido con hasta

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cuatro R_{26} , o pentafluoroalquilo;

c) arilo y heteroarilo opcionalmente sustituido con hasta tres R_{27} ; y

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

R_6 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, $-NR_7R_8$, $-OR_7$, o halógeno;

R_{10} es hidrógeno o alquilo;

R_{13} y R_{19} en cada ocurrencia se seleccionan independientemente de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, alcanoiloxi, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcóxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, C_{1-4} alquilsulfonilamina, ácido sulfónico, alquilsulfonilo, sulfonamido, y ariloxi, en donde cada grupo R_{13} y/o R_{19} puede sustituirse adicionalmente por hidroxilo, alquilo, alquilo sustituido, alcoxi, arilo, o aralquilo;

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

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

R_{26} se selecciona de halógeno, trifluorometilo, haloalcoxi, ceto ($=O$), nitro, ciano, $-SR_{28}$, $-OR_{28}$, $-NR_{28}R_{29}$, $-NR_{28}SO_2$, $-NR_{28}SO_2R_{29}$, $-SO_2R_{28}$, $-SO_2NR_{28}R_{29}$, $-CO_2R_{28}$, $-C(=O)R_{28}$, $-C(=O)NR_{28}R_{29}$, $-OC(=O)R_{28}$, $-OC(=O)NR_{28}R_{29}$, $-NR_{28}C(=O)R_{29}$, $-NR_{28}CO_2R_{29}$, $=N-OH$, $=N-O$ -alquilo; arilo opcionalmente sustituido con uno a tres R_{27} ; cicloalquilo opcionalmente sustituido con ceto ($=O$), uno a tres R_{27} , o que tiene un puente carbono-carbono de 3 a 4 átomos de carbono; y heterociclo opcionalmente sustituido con ceto ($=O$), uno a tres R_{27} , o que tiene un puente carbono-carbono de 3 a 4 átomos de carbono; en donde R_{28} y R_{29} se seleccionan cada uno independientemente de hidrógeno, alquilo, alqueno, arilo, aralquilo, C_{3-7} cicloalquilo, y C_3 -

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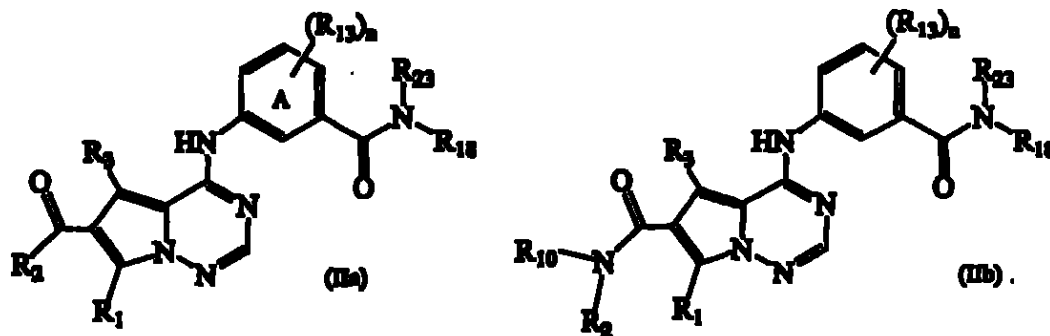
heterociclo, o pueden tomarse juntos para formar un C₃₋₇heterociclo; y en donde cada R₂₈ y R₂₉ a su vez se sustituyen opcionalmente con hasta dos de alquilo, alquenilo, halógeno, haloalquilo, haloalcoxi, ciano, nitro, amino, hidroxilo, alcoxi, alquiltio, fenilo, bencilo, feniloxi, y benciloxi;

R₂₇ se selecciona de alquilo, R₃₂, y C₁₋₄alquilo sustituido con uno a tres R₃₂, en donde cada grupo R₃₂ se selecciona independientemente de halógeno, haloalquilo, haloalcoxi, nitro, ciano, -SR₃₀, -OR₃₀, -NR₃₀R₃₁, -NR₃₀SO₂-NR₃₀SO₂R₃₁, -SO₂R₃₀, -SO₂NR₃₀R₃₁, -CO₂R₃₀, -C(=O)R₃₀, -C(=O)NR₃₀R₃₁, -OC(=O)R₃₀, -OC(=O)NR₃₀R₃₁, -NR₃₀C(=O)R₃₁, -NR₃₀CO₂R₃₁, y un anillo carbocíclico o heterocíclico de 3 a 7 miembros opcionalmente sustituido con alquilo, halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, amino, o ciano, en donde R₃₀ y R₃₁ se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, arilo, aralquilo, C₃₋₇cicloalquilo, y heterociclo, o pueden tomarse juntos para formar un C₃₋₇heterociclo;

y

n es 0, 1 ó 2.

8. Un compuesto de acuerdo con la reivindicación 7, que tiene la fórmula (IIa) o (IIb),



o su sal, profármaco o solvato de aceptación farmacéutica, en donde:

R₁ y R₁₀ son hidrógeno ó -CH₃;

R₁₃ es alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxilo, C₁₋₄alcoxi, nitro, o ciano;

R₁₈ es hidroxilo, C₁₋₄alcoxi, fenilo, o fenilo sustituido con uno o dos R₁₉;

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R_{23} es hidrógeno o alquilo inferior; y
 n es 0, 1 ó 2.

9. Un compuesto de acuerdo con la reivindicación 7, o su sal, profármaco o solvato de aceptación farmacéutica, en donde

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

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

R_3 y R_{10} son hidrógeno o $-CH_3$;

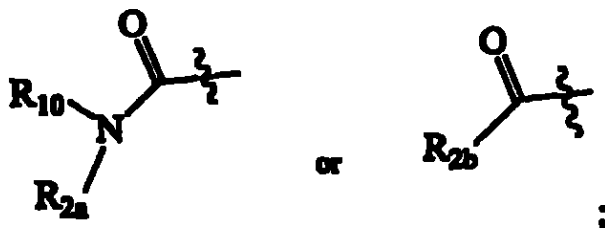
R_{13} y R_{19} en cada ocurrencia se seleccionan independientemente de alquilo inferior, halo, trifluorometoxi, trifluorometilo, hidroxilo, C_{1-4} alcoxi, nitro, y ciano;

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

R_{22} es alquilo inferior; y

n es 0 ó 1.

10. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual $X-R_2$ son:



R_{2a} se selecciona de:

- hidrógeno;
- C_{2-6} alquilo recto o ramificado;
- cicloalquilo opcionalmente sustituido con ceto y/o hasta dos R_{27} ;
- fenilo opcionalmente sustituido con hasta dos R_{27} ; y
- heterociclo opcionalmente sustituido con y/o hasta dos R_{27} ;
- pentafluoroalquilo o C_{1-4} alquilo sustituido con hasta tres de halógeno, trifluorometilo, ciano, OR_{28} , $NR_{28}R_{29}$, CO_2R_{28} arilo, heterociclo, y/o cicloalquilo, en donde el arilo, heterociclo, y/o

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cicloalquilo a su vez se sustituyen opcionalmente con hasta dos de halógeno, hidroxilo, alcoxi, haloalquilo, haloalcoxi, nitro, ciano y alquilo; y

R_{2b} es un heterociclo monocíclico o bicíclico opcionalmente sustituido con hasta dos R₂₇;

R₂₇ en cada ocurrencia se selecciona independientemente de hidrógeno, alquilo, trifluorometilo, trifluorometoxi, halógeno, ciano, nitro, amino, hidroxilo, alcoxi, fenilo, bencilo, feniloxi, y benciloxi; y

R₂₈ y R₂₉ en cada ocurrencia se seleccionan independientemente de hidrógeno, alquilo, alquenilo, fenilo, y bencilo.

11. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual:

R_{2a} se selecciona de:

- a) C₂₋₆alquilo recto o ramificado;
- b) fenilo opcionalmente sustituido con hasta dos de halógeno, C₁₋₄alcoxi, y trifluorometilo;
- c) C₃₋₆cicloalquilo opcionalmente sustituido con hasta dos C₁₋₄alquilo y/o hidroxilo;
- d) C₁₋₄alquilo recto o ramificado sustituido con hasta tres de
 - i) halógeno,
 - ii) trifluorometilo,
 - iii) ciano,
 - iv) C₁₋₄alcoxi,
 - v) feniloxi,
 - vi) benciloxi,
 - vii) NH₂, NH(C₁₋₄alquilo), y/o N(C₁₋₄alquilo)₂,
 - viii) fenilo sustituido opcionalmente a su vez con hasta dos de halógeno y/o metoxi,
 - ix) heterociclo seleccionado de piridinilo, indolilo, tiofenilo, furanilo, tiazolilo, tienilo, morfolinilo, tetrahidroruranilo, triazinilo, piperazinilo, indenilo, y piperadinilo; dicho

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heterociclo opcionalmente sustituido con uno a d s C₁₋₄alquilo,

x) C₃₋₆cicloalquilo; y

R_{2b} es un heterociclo monocíclico de cinco a siete miembros seleccionado de diazepinilo, morfolinilo, piperidinilo, y pirrolidinilo, dicho heterociclo opcionalmente sustituido con C₁₋₄alquilo, fenilo, y/o bencilo.

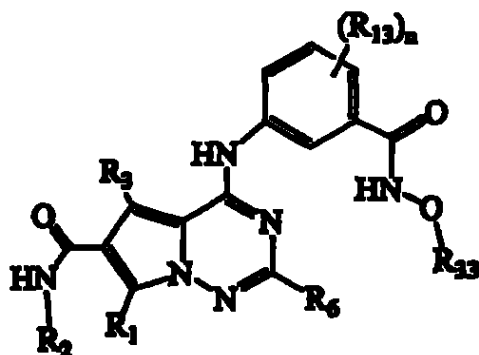
12. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual R₁ y R₁₀ son independientemente hidrógeno o CH₃.

13. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual R₆ es hidrógeno.

14. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual Y es -NHC(=O)NH- o -NHSO₂-; R₁₈ es arilo o arilo sustituido con alquilo, OCH₃, CF₃, ciano, o halógeno.

15. Un compuesto de acuerdo con la reivindicación 7 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual Y es -C(=O)NR₂₃-, R₂₃ es hidrógeno o alquilo inferior, y R₁₈ es C₁₋₄alcoxi o arilo opcionalmente sustituido con alquilo, OCH₃, CF₃, ciano o halógeno.

16. Un compuesto de acuerdo con la reivindicación 7, que tiene la fórmula:



en la cual R_{33} es alquilo inferior.

17. Un compuesto de acuerdo con la reivindicación 16 o su sal, profármaco o solvato de aceptación farmacéutica, en el cual R_3 y R_{33} son metilo, R_1 y R_6 son hidrógeno, y R_2 C_{2-6} alquilo recto o ramificado o bencilo opcionalmente sustituido.

18. Un compuesto de acuerdo con la reivindicación 7, que se selecciona de (i) N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
3-[[6-[(Hexahidro-4-metil-1H-1,4-diazepin-1-il)carbonil]-5-metilpirrolo[2,1-f][1,2,4]triazina-4-il]amino]-N-metoxi-4-metilbenzamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilpropil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-(2,2-Dimetilpropil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-(1,1-Dimetiletil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-(2-metoxietil)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-Metoxi-4-metil-3-[[5-metil-6-(4-morfolinilcarbonil)pirrolo[2,1-f][1,2,4]triazina-4-il]amino]benzamida;
N-Ciclohexil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

N-[(4-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amin]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-[(2-metoxifenil)metil]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(4-piridinilmetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(4-piridinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(1-piperidinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[2-(4-morfolinil)etil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[(1R,2S)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[(1S,2R)-2,3-Dihidro-1H-inden-1-il]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-Metoxi-4-metil-3-[[5-metil-6-[[4-(fenilmetil)-1-piperidinil]carbonil]pirrolo [2,1-f][1,2,4]triazina-4-il]amino]benzamida;
N-Ciclopropil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-Ciclopentil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[2-(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-(Ciclohexilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(tetrahidro-2-furanil)metil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-(2-1H-Indol-3-iletil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-Butil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

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N-(Ciclopropilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilbutil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

N-(2-Furanilmetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-tienilmetil)pirrolo [2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-fenoxietil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-metilciclohexil)pirrolo [2,1-f][1,2,4]triazina-6-carboxamida;

N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-N,5-dimetilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2,2,2-trifluoroetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

N-(2-Fluoroetil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

N-(2,3-Dihidro-1H-inden-2-il)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

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

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2,2,3,3,3-pentafluoropropil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5,7-dimetil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

N-(4-Fluorofenil)-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-(2-metoxifenil)-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-N-[(3-metoxifenil)metil]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

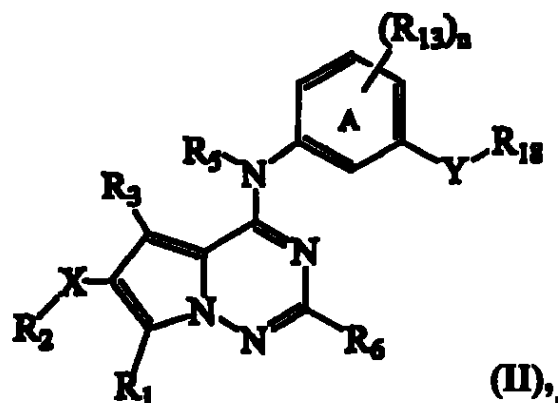
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[3-(trifluorometil)fenil]pirrolo [2,1-f][1,2,4]triazina-6-carboxamida;
N-[(2,6-Diclorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[(1S)-1-Ciano-2-feniletil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-feniletil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-Metoxi-4-metil-3-[[5-metil-6-(1-pirrolidinilcarbonil)pirrolo[2,1-f][1,2,4]triazina-4-il]amino]benzamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(2-piridinilmetil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(fenilmetil)pirrolo [2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(4-metil-2-tiazolil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1R)-1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[(3-Fluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[1-(4-Fluorofenil)etil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
N-[(2,4-Difluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida; y
N-[(2,6-Difluorofenil)metil]-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[[4-Cianofenil]amino]carbonil]-2-metilfenil]amino]-N-etil-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[[4-Cianofenil]amino]carbonil]-2-metilfenil]amino]-5-metil-N-[(1S)-1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;

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4-[[5-[[[(4-Cianofenil)amino]carbonil]amino]-2-metilfenil]amino]-5-metil-N-propilpirrolo [2,1-f][1,2,4]triazina-6-carboxamida;
o es (ii) su sal, hidrato o profármaco de aceptación farmacéutica.

19. Un compuesto de acuerdo con la reivindicación 7 que se selecciona de
N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(1-metiletil)pirrolo[2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-propilpirrolo [2,1-f][1,2,4]triazina-6-carboxamida;
4-[[5-(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida; y
4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida; y su sal de aceptación farmacéutica.

20. Un compuesto que tiene la fórmula (II):



o su sal, profármaco o solvato de aceptación farmacéutica, en donde R_3 es metilo o CF_3 ;

R_5 es hidrógeno o alquilo inferior;

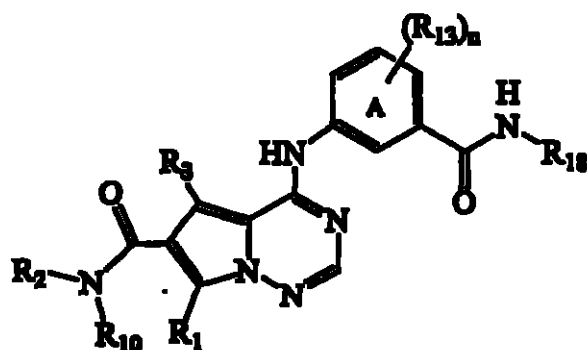
Y es $-C(=O)NR_{23}$ -, $-NR_{23}C(=O)NR_{23}$ -, $-NR_{23}SO_2$ -, o $-SO_2NH_2$ -;

R_{18} y R_{23} se seleccionan de hidrógeno, alquilo, alcoxi, arilo, y arilo sustituido con uno a tres R_{19} , excepto cuando Y es $-NR_{23}SO_2$ -, R_{18} es

- C_{1-4} alquilo o arilo opcionalmente sustituido con uno a tres R_{19} ;
- X se selecciona de -O-, -OC(=O)-, -S-, -S(=O)-, -SO₂-, -C(=O)-, -CO₂-, -NR₁₀-, -NR₁₀C(=O)-, -NR₁₀C(=O)NR₁₁-, -NR₁₀CO₂-, -NR₁₀SO₂-, -NR₁₀SO₂NR₁₁-, -SO₂NR₁₀-, y -C(=O)NR₁₀-, o X está ausente;
- R_1 es hidrógeno, -CH₃, -OH, -OCH₃, -SH, -SCH₃, -OC(=O)R₂₁, -S(=O)R₂₂, -SO₂R₂₂, -SO₂NR₂₄R₂₅, -CO₂R₂₁, -C(=O)NR₂₄R₂₅, -NH₂, -NR₂₁SO₂NR₂₄R₂₅, -NR₂₁SO₂R₂₂, -NR₂₄C(=O)R₂₅, -NR₂₄CO₂R₂₅, -NR₂₁C(=O)NR₂₄R₂₅, halógeno, nitro, o ciano;
- R_2 es alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, aralquilo, aralquilo sustituido, heterocicloalquilo, o heterocicloalquilo sustituido;
- R_6 es hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, -NR₇R₈, -OR₇ o halógeno;
- R_{13} y R_{19} en cada ocurrencia se seleccionan independientemente de alquilo, halo, trifluorometoxi, trifluorometilo, hidroxilo, alcoxi, alcanilo, alcanilo, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;
- R_7 , R_8 , R_{21} , R_{24} , y R_{25} , se seleccionan independientemente de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido;
- R_{22} es alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido; y
- n es 0, 1 ó 2.

21. Un compuesto de acuerdo con la reivindicación 20, que tiene la fórmula:

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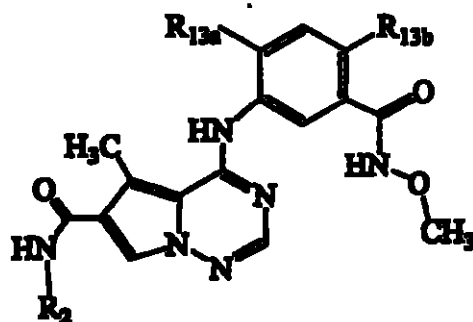


o su sal, profármaco o solvato de aceptación farmacéutica; en donde R_{18} es alcoxi, arilo, o arilo sustituido con R_{19} ;

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

R_{13} es alquilo inferior, halógeno, trifluorometoxi, trifluorometilo, hidroxilo, C_{1-4} alcoxi, nitro, o ciano.

22. Un compuesto de acuerdo con la reivindicación 20 que tiene la fórmula:



o su sal, hidrato o profármaco de aceptación farmacéutica, en el cual R_2 es un C_{2-6} alquilo recto o ramificado o bencilo opcionalmente sustituido, y R_{13a} y R_{13b} se seleccionan de hidrógeno, C_{1-4} alquilo, hidroxilo, halógeno, ciano, y trifluorometilo.

23. Un compuesto de acuerdo con la reivindicación 20 que es N-Etil-4-[[5-[(metoxiamino)carbonil]-2-metilfenil]amino]-5-metilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida; o su sal de aceptación farmacéutica que comprende una sal metanosulfónica.

24. Un compuesto de acuerdo con la reivindicación 20 que es 4-[[5-

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[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-(1-metiletil) pirrolo[2,1-f][1,2,4]triazina-6-carboxamida; o su sal de aceptación farmacéutica.

25. Un compuesto de acuerdo con la reivindicación 20 que es 4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-propilpirrolo[2,1-f][1,2,4]triazina-6-carboxamida; o su sal de aceptación farmacéutica.

26. Un compuesto de acuerdo con la reivindicación 20 que es 4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[1-feniletil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida; o su sal de aceptación farmacéutica.

27. Un compuesto de acuerdo con la reivindicación 20 que es 4-[[5-[(Metoxiamino)carbonil]-2-metilfenil]amino]-5-metil-N-[1-metilpropil]pirrolo[2,1-f][1,2,4]triazina-6-carboxamida; o su sal de aceptación farmacéutica.

28. Una composición farmacéutica que comprende por lo menos un compuesto de acuerdo con la reivindicación 7 y un transportador o diluyente de aceptación farmacéutica.

29. Una composición farmacéutica que comprende por lo menos un compuesto de acuerdo con la reivindicación 20 y un transportador o diluyente de aceptación farmacéutica.

30. Un método de tratar un desorden inflamatorio que comprende administrar a un paciente necesitado de dicho tratamiento una composición farmacéutica de acuerdo con la reivindicación 28.

31. El método de la reivindicación 30 en el cual el desorden inflamatorio se selecciona de asma, enfermedad de la membrana hialina en adultos, enfermedad pulmonar obstructiva crónica, diabetes, enfermedad

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inflamatoria intestinal, osteoporosis, psoriasis, rechazo injerto vs. anfitrión, aterosclerosis, y artritis incluyendo artritis rematoide, artritis psoriática, artritis traumática, artritis rubéola, artritis gotosa y osteoartritis.