

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

Division de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 EXPEDIENTE No

05-1141

54 TITULO

PROCESO PARA LA REPARACION DE CIERTOS COMPUESTOS DE PIRROLOTRIAZINA

51

CLASIFICACION INTERNACIONAL

A61K31/53 A61P13/08,
A61P29/00, A61P27/00

71

SOLICITANTE

BRISTOL MYERS SQUIBB COMPANY

DOMICILIO

PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74

APODERADO

HECTOR GOMEZ MEJIA

22

SANTAFE DE BOGOTA, D C

07/01/2005

SS

PETITORIO

AS: 96.054



SUPERINTENDENCIA Y COMERCIO
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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, Route 206 and Princeline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: HECTOR GOMEZ MEJÍA Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>22720</u> TP <u>19436</u>
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Título (54): <u>PROCESO PARA LA PREPARACION DE CIERTOS COMPUESTOS DE PIRROLOTRIAZINA</u>			
7 Clasificación Internacional (51) <u>A61K31/53; A61P13/08; A61P29/00</u> <u>A61P33/00</u>			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	US	19-07-2002	60/397,256
	US	13-02-2003	60/447,213
	US	18-07-2003	10/622,280
9 Comparación de Prioridad No. <u>04-90191 y 05-511</u> Fecha <u>07-01-2005</u>			

10

ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$443.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que 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 Tarjeta de Propietarios

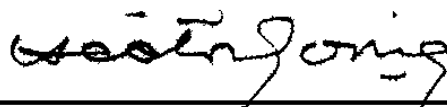
11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: HECTOR GOMEZ MEJÍA

FIRMA:



C.C. 22720 de Bogotá T.P. 19436 del C.S.J.

3
SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

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FECHA : NOVIEMBRE 19 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21591365	19/11/2004	8,480,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CERTIFICACION DE EXCEDENTE : 05 - 611
FECHA : ENERO 4 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028773	04/01/2005	1,747,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	21,000.00
		TOTAL :	21,000.00

SOM: VEINTIUNO MIL PESOS

RESPONSABLE : 

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ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

Folios 1000
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A61K 31/53, A61P 13/08, 29/00, 37/00

Hills Dr., Belle Mead, NJ 08502 (US). GIBSON, Francis,
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(21) International Application Number:
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(74) Agents: KORSEN, Elliott et al.; Bristol-Myers Squibb
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(22) International Filing Date: 21 July 2003 (21.07.2003)

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(71) Applicant (*for all designated States except US*): BRIS-
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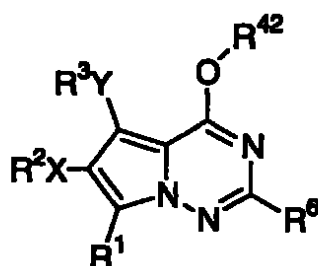
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(75) Inventors/Applicants (*for US only*): BHIDE, Rajeev
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BOSA, Stephanie [US/US]; 2 Big Top Dr., Lambertville,
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(88) Date of publication of the International search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE COMPOUNDS



(I)

(57) Abstract: The present invention relates to a process for preparing certain pyrrolotriazine compounds of the formula (I) and pharmaceutically acceptable salts thereof. The formula (I) compounds inhibit the tyrosine kinase activity of growth factor receptors such as VEGFR-2 and FGFR-1, thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

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

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

(72) Inventors; and

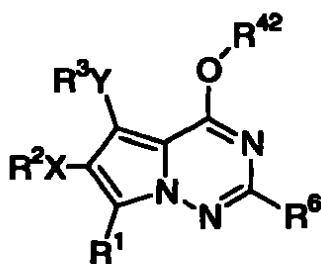
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— without international search report and to be republished upon receipt of that report

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**PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE
COMPOUNDS**

Field of the Invention

5 This invention relates to novel, improved processes for the preparation of certain pyrrolotriazine compounds that inhibit the tyrosine kinase activity of growth factor receptors such as VEGFR-2, and FGFR-1, thereby making them useful as anti-cancer agents. The compounds prepared by the processes of the invention are also useful in the treatment of diseases, other than cancer, which are associated with signal
10 transduction pathways operating through growth factors and anti-angiogenesis receptors such as VEGFR-2.

Background of the Invention

 Normal angiogenesis plays an important role in a variety of processes
15 including embryonic development, wound healing, obesity and several components of female reproductive function. Undesirable or pathological angiogenesis had been associated with disease states including diabetic retinopathy, psoriasis, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma, asthma, cancer and metastatic disease (Fan et al, 1995, Trend Pharmacol. Sci. 16: 57-66; Folkman, 1995,
20 Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathophysiological processes (Cullinan-Bove et al, 1993,, Endocrinology 133: 829-837; Senger et al, 1993 Cancer and Metastasis Reviews, 12: 303-324).

 Receptor tyrosine kinases (RTKs) are important in the transmission of
25 biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity that leads to phosphorylation of tyrosine
30 residues on both the receptor and other intracellular proteins, leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is

presently comprised of the fms-like tyrosine kinase receptor, Flt or Flt1 (VEGFR-1), the kinase insert domain-containing receptor, KDR (also referred to as Flk-1 or VEGFR-2), and another fms-like tyrosine kinase receptor, Flt4 (VEGFR-3). Two of these related RTKs, Flt and KDR, have been shown to bind vascular endothelial growth factor (VEGF) with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells had been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes. VEGF, along with acidic and basic fibroblast growth factor (aFGF & bFGF) have been identified as having in vitro endothelial cell growth promoting activity. It is noted that aFGF and bFGF bind to and activate the receptor tyrosine kinase termed FGFR-1. By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36: 139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024).

In adults, endothelial cells have a low proliferation index except in cases of tissue remodeling, such as wound healing and the female reproductive cycle, and adipogenesis. However in pathological states such as cancer, inherited vascular diseases, endometriosis, psoriasis, arthritis, retinopathies and atherosclerosis, endothelial cells are actively proliferating and organizing into vessels. Upon exposure to angiogenic stimuli with growth factors such as VEGF and bFGF, endothelial cells re-enter the cell cycle, proliferate, migrate and organize into a three-dimensional network. It is now widely accepted that the ability of tumors to expand and metastasize is dependent upon the formation of this vascular network.

Binding of VEGF or bFGF to their corresponding receptor results in dimerization, autophosphorylation on tyrosine residues and enzymatic activation. These phosphotyrosine residues serve as "docking" sites for specific downstream signaling molecules and enzymatic activation results in EC activation. Disruption of these pathways should inhibit endothelial cell activation. Disruption of the FGFR-1 pathway should also affect tumor cell proliferation since this kinase is activated in

many tumor types in addition to proliferating endothelial cells. Finally, recent evidence also suggests that disruption of VEGF signaling inhibits endothelial cell migration, a critical process in vascular network formation.

The over-expression and activation of VEGFR-2 and FGFR-1 in tumor-associated vasculature has suggested a role for these molecules in tumor angiogenesis. Angiogenesis and subsequent tumor growth is inhibited by antibodies directed against VEGF ligand and VEGF receptors, and by truncated (lacking a transmembrane sequence and cytoplasmic kinase domain) soluble VEGFR-2 receptors. Dominant mutations introduced into either VEGFR-2 or FGFR-1 which result in a loss of enzymatic activity inhibits tumor growth *in vivo*. Antisense targeting of these receptors or their cognate ligands also inhibits angiogenesis and tumor growth. Recent evidence has elucidated, in part, the temporal requirements of these receptors in tumor growth. It appears that VEGF signaling is critical in early tumor growth and bFGF is more important at a later time associated with tumor expansion.

Compounds that can benefit from the processes of the invention include those in the priority applications as well as compounds disclosed in WO 00/71129, which are hereby incorporated by reference in their entirety.

Summary of the Invention

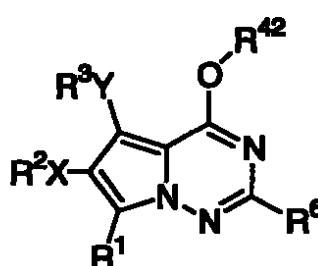
The present invention provides a process for the preparation of certain pyrrolotriazine compounds. The process of the invention provides a useful, convenient and improved preparation of pyrrolotriazine derivatives containing a hydroxyl group attached directly to the pyrrolotriazine ring.

The process of the invention comprises, in one embodiment, the steps of reacting a chloro-substituted pyrrolotriazine with an oxide anion to form an ether; converting the ester to a benzylic alcohol, oxidatively rearranging the alcohol to form a phenol. The hydroxyl compound is subsequently alkylated with an electrophilic agent to afford a phenoxy substituted compound which is hydrolyzed to afford an amide. This is converted to the final compound by first forming a chloroimide and reacting this with an alkylating agent such as hydroxy fluoroindole in the presence of a base in a polar solvent to afford the final compound.

In a second embodiment, the invention provides a process for preparing the fluoroindole portion of the compounds using a novel and improved process that is amenable to large scale preparations and provides fluoroindole derivatives of high quality. In addition, fluoroindole derivatives prepared using the process described herein are stable solids that are easy to isolate and have long term stability, giving products of higher quality than fluoroindole derivatives prepared using alternative methods.

Detailed Description of the Invention

The present invention provides a process for the preparation of certain pyrrolotriazine compounds of the formula



(I)

their enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof which inhibit the tyrosine kinase activity of growth factor receptors such as VEGFR-2. In formula I and throughout the specification, the above symbols are defined as follows:

X and Y are independently selected from O, OCO, S, SO, SO₂, CO, CO₂, NR¹⁰, NR¹¹CO, NR¹²CONR¹³, NR¹⁴CO₂, NR¹⁵SO₂, NR¹⁶SO₂NR¹⁷, SO₂NR¹⁸, CONR¹⁹, halogen, nitro, cyano, or X or Y are absent;

R¹ is hydrogen;

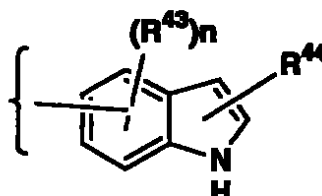
R² and R³ are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl or substituted heterocycloalkyl; with the proviso that when X is halo,

nitro or cyano, R^2 is absent, and, when Y is halo, nitro or cyano, R^3 is absent;

R^6 is H;

$R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}$ and R^{19} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, or substituted heterocyclo;

R^{42} is



$(R^{43})_n$ wherein n equals 0, 1 or 2 and each R^{43} is independently selected from the group consisting of hydrogen, fluorine, chlorine and methyl; and

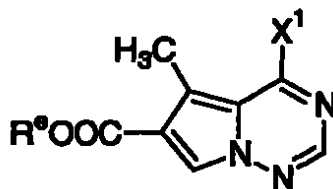
R^{44} is methyl, or hydrogen,

with the further provisos that:

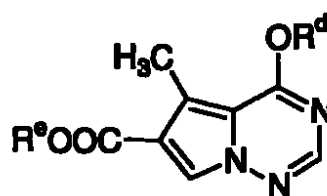
- a. R^2 may not be hydrogen if X is SO, SO₂, NR¹³CO₂, or NR¹⁴SO₂; and
- b. R^3 may not be hydrogen if Y is SO, SO₂, NR¹³CO₂, or NR¹⁴SO₂.

The process of the invention comprises, in one embodiment, the steps of

- a) converting a compound of the formula



where R^e is lower alkyl or aryl and X^1 is halogen, to a compound 1 of the formula

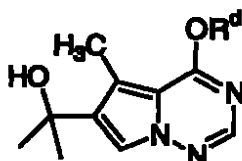


1

where R^d is lower alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl by treatment with a phenoxide or alkoxide,

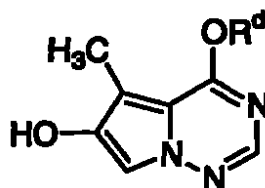
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b) alkylating Compound 1 to afford Compound 2 of the formula



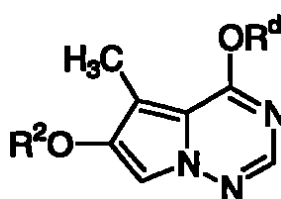
2

10 c) treating compound 2 with a peroxide in the presence of a Lewis acid to afford compound 3 of the formula



3

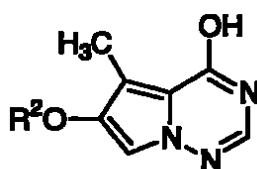
15 d) alkylating the phenol group in compound 3 to afford Compound 4 of the formula



4

where R² is benzyl or substituted benzyl,

- 5 e) hydrolyzing Compound 4 to afford Compound 5 of the formula

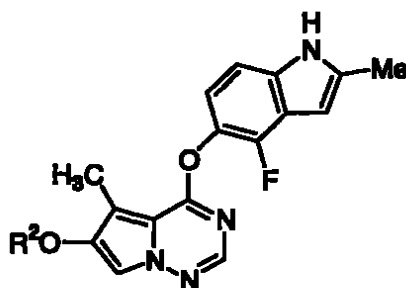


5

where R² is benzyl or substituted benzyl, and

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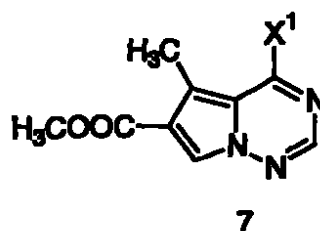
- f) converting Compound 5 to Compound 6 of the formula



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- 15 by first converting compound 5 to a chloroimidate and subsequently alkylating the chloroimidate to afford Compound 6 wherein R² is benzyl. The deprotection of phenol is accomplished by treatment with hydrogen donor in presence of a catalyst to afford compound 6 where R² is hydrogen.

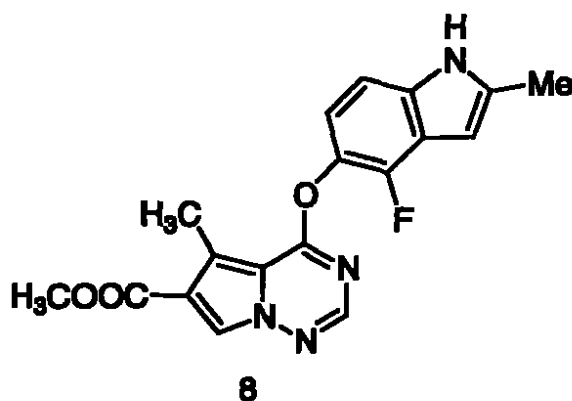
In a second embodiment of the invention, the starting compound of the formula



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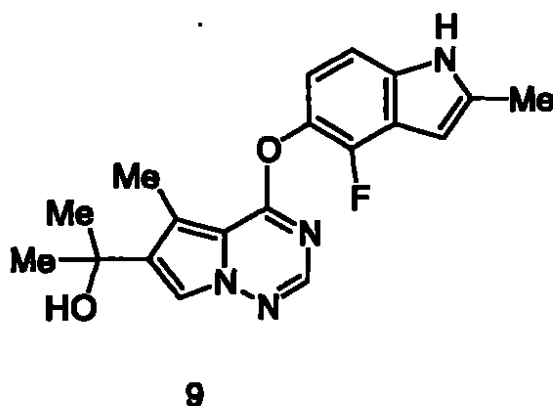
where X_1 is halogen;

is reacted with a nucleophile to afford Compound 8 of the formula



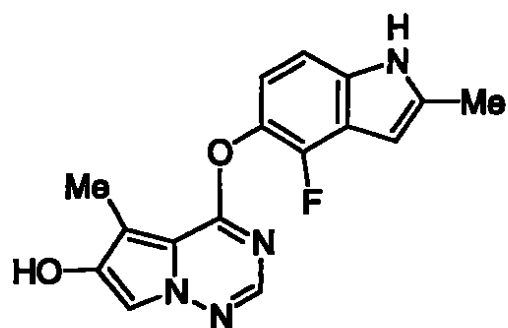
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which is treated with an alkylating agent at low temperature, to afford Compound 9 of the formula



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Compound 9 is then treated with a peroxide in the presence of a Lewis acid to afford Compound 10 of the formula



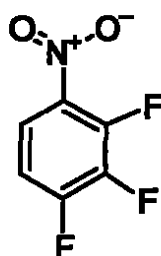
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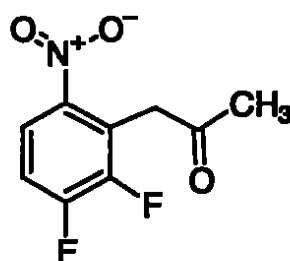
In a further embodiment of the invention, the fluoroindole piece can be prepared as follows:

a) reacting a fluorinated compound of the formula

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with a nucleophile to afford Compound 11 of the formula

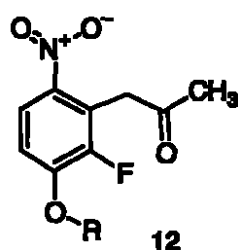


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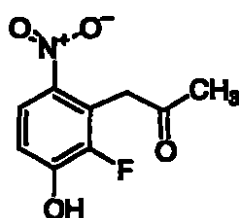
b) reacting Compound 11 with an alkoxy anion to afford Compound 12 of

the formula



5 wherein R is a protecting group,

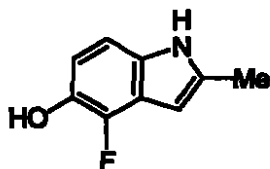
c) deprotecting the alkoxy group by treatments with deprotecting reagents to afford Compound 13 of the formula



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, and

d) cyclizing Compound 13 under reducing conditions to afford Compound 14 of the formula



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In a preferred embodiment, step 1 of scheme 1 involved the conversion of the compound to an ether by treatment with a nucleophile such as a phenoxide or alkoxide anion. Preferably, the alkoxide anion is a methoxide or ethoxide anion.

Preferred alkylating agents in step 2 of scheme 1 include an alkyl magnesium halide, i.e., methyl magnesium bromide or methyl magnesium chloride at low temperature from about -25°C to about 25°C.

Compound 2 in step 3 is preferably treated with an peroxide such as hydrogen peroxide or sodium perborate in the presence of a Lewis acid such as boron trifluoride in an organic solvent such as dichloromethane (DCM) to afford compound 3.

Compound 3 is alkylated with an electrophilic agent such as benzyl bromide or benzyl chloride in the presence of a base such as NaH at a temperature from about 0°C to about 100°C.

Compound 4 is hydrolyzed by treatment with an acid, preferably aqueous HCl at an elevated temperature to afford Compound 5. Compound 5 is finally converted to Compound 6 through the chloroimidate which is subsequently alkylated, preferably with hydroxy fluoroindole, in the presence of a base such as potassium carbonate or sodium hydride in a polar solvent such as dimethylformamide (DMF) or toluene, preferably DMF. The benzylic deprotection is achieved by treatment with a hydrogen source such as ammonium formate in the presence of a catalyst such as Palladium on carbon.

Preferred conditions for the second embodiment include in step 1, the use of a nucleophile such as fluoroindole in the presence of a base such as potassium carbonate or sodium hydride to treat Compound 7 to afford Compound 8. This reaction takes place, preferably, in a polar solvent such as DMF. Step 2 involves treating Compound 8 with an alkylating agent, such as an alkyl magnesium halide, i.e., methyl magnesium bromide or methyl magnesium chloride at low temperature from about -25°C to about 25°C. In a preferred embodiment, Step 3 involves treating Compound 9 with a peroxide such as hydrogen peroxide or sodium perborate in the presence of a Lewis acid such as boron trifluoride at a temperature from about -25°C to about 25°C to afford Compound 10.

In the preparation of the indole side chain, the starting fluorinated compound, in this case, trifluoronitrobenzene, can be reacted with a nucleophile such as ethyl acetoacetate or tet-butylacetoacetate, which is followed by decarboxylation of the ester group in the presence of an acid or base, preferably an aqueous acid. In step 2, Compound 11 is reacted with an alkoxy anion such as sodium methoxide or methanol

in the presence of a base such as potassium carbonate or the sodium salt of benzyl alcohol to afford Compound 12. The alkoxy or benzyloxy group is then deprotected by treatment with a deprotecting reagent such as pyridinium chloride or hydrogen bromide in acetic acid to afford Compound 13. In the final step, Compound 13 is
5 cyclized under reducing conditions preferably using reduction agents such as sodium dithionate or palladium on carbon in the presence of a hydrogen source to afford the desired indole compounds.

The invention also provides a pharmaceutical composition comprising a
10 compound of formula I or II and a pharmaceutically acceptable carrier.

The invention also provides a pharmaceutical composition comprising a compound of formula I or II in combination with pharmaceutically acceptable carrier and an anti-cancer or cytotoxic agent. In a preferred embodiment said anti-cancer or cytotoxic agent is selected from the group consisting of linomide; inhibitors of
15 integrin $\alpha v \beta 3$ function; angiostatin; razoxane; tamoxifen; toremifene; raloxifene; droloxifene; idoxifene; megestrol acetate; anastrozole; letrozole; borazole; exemestane; flutamide; nilutamide; bicalutamide; cyproterone acetate; gosereline acetate; leuprolide; finasteride; metalloproteinase inhibitors; inhibitors of urokinase plasminogen activator receptor function; growth factor antibodies; growth factor
20 receptor antibodies such as Avastin® (bevacizumab) and Erbitux® (cetuximab); tyrosine kinase inhibitors; serine/threonine kinase inhibitors; methotrexate; 5-fluorouracil; purine; adenosine analogues; cytosine arabinoside; doxorubicin; daunomycin; epirubicin; idarubicin; mitomycin-C; dactinomycin; mithramycin; cisplatin; carboplatin; nitrogen mustard; melphalan; chlorambucil; busulphan;
25 cyclophosphamide; ifosfamide nitrosoureas; thiotepa; vincristine; Taxol® (paclitaxel); Taxotere® (docetaxel); epothilone analogs; discodermolide analogs; eleutherobin analogs; etoposide; teniposide; amsacrine; topotecan; flavopyridols; biological response modifiers and proteasome inhibitors such as Velcade® (bortezomib).

30 The invention also provides a method of inhibiting protein kinase activity of growth factor receptors which comprises administering to a mammalian species in

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need thereof, a therapeutically effective protein kinase inhibiting amount of a compound of formula I.

Additionally, there is disclosed a method of inhibiting tyrosine kinase activity of at least one growth factor receptor such as which comprises administering to a mammalian species in need thereof, a therapeutically effective amount of a compound of formula I or II. In a preferred embodiment said growth factor receptor is selected from the group consisting of VEGFR-2 and PGFR-1.

Finally, there is disclosed a method for treating a proliferative disease, comprising administering to a mammalian species in need thereof, a therapeutically effective amount of a compound of formula I. In a preferred embodiment the proliferative disease is cancer.

The following are definitions of terms that may be used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

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.

The term "substituted alkyl" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, hydroxy, alkoxy, oxo, 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. SO_2NH_2 , substituted sulfonamido, nitro, cyano, carboxy, carbamyl, e.g. CONH_2 , 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 heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with alkyl, alkoxy, aryl or aralkyl.

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, each of which may be substituted.

5 The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

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

15 The term "heteroaryl" refers to an optionally substituted, 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, for example, pyridine, tetrazole, indazole, indole.

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

 The term "substituted alkenyl" refers to an alkenyl group substituted by, for example, one to two substituents, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio,
25 alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

 The term "alkynyl" refers to straight or branched chain hydrocarbon groups of
30 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.

 The term "substituted alkynyl" refers to an alkynyl group substituted by, for example, a substituent, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino,

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alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, substituted carbamyl, guanidino and heterocyclo, e.g. imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like.

5 The term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring systems, 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. Exemplary
10 substituents include one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

 The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered
15 bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen 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
20 quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

 Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl,
25 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,
30 isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

 Exemplary bicyclic heterocyclic groups include 2,3-dihydro-2-oxo-1H-indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl,

quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl
5 (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzimidazolyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothieryl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, indolyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl,
10 pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothieryl, and the like.

Exemplary substituents include one or more alkyl or aralkyl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclos, such as, epoxides and aziridines.

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

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.

20 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.

25 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,
30 salicylates and the like). Such salts can be formed as known to those skilled in the art.

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

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All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

Compounds of 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 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);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

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.

Thus according to a further aspect of the invention, there is provided the use of a compound of formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a mammalian animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a

mammalian animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined herein before.

The compounds described herein also inhibit other receptor tyrosine kinases including HER1 and HER2 and are therefore useful in the treatment of proliferative disorders such as psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including non-small cell lung, colorectal, and breast cancer. Similarly, the HER2 receptor kinase has been shown to be overexpressed in breast, ovarian, lung and gastric cancer. Monoclonal antibodies that downregulate the abundance of the HER2 receptor or inhibit signaling by the HER1 receptor have shown anti-tumor efficacy in preclinical and clinical studies. It is therefore expected that inhibitors of the HER1 and HER2 kinases will have efficacy in the treatment of tumors that depend on signaling from either of the two receptors. The ability of these compounds to inhibit HER1 further adds to their use as anti-angiogenic agents. See the following documents and references cited therein: Cobleigh, M. A., Vogel, C. L., Tripathy, D., Robert, N. J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D. J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", *J. of Clin. Oncol.* 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M. R., Cohen, R., Burtress, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", *J. Clin. Oncol.* 18(4), p. 904-914 (2000).

The antiproliferative, antiangiogenic and/or vascular permeability reducing treatment defined herein before may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. The compounds of this invention may also be useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a

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fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its approved dosage range. Compounds of formula I may be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate.

In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiproliferative, antiangiogenic and/or vascular permeability reducing treatment defined herein before may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

- (i) antiangiogenic agents that work by different mechanisms from those defined hereinbefore (for example, linomide, inhibitors of integrin $\alpha v \beta 3$ function, angiostatin, razoxane);
- (ii) cytostatic agents such as antiestrogens (for example, tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example, megestrol acetate), aromatase inhibitors (for example, anastrozole, letrozole, boraazole, exemestane), antihormones, antiprogestogens, antiandrogens (for example, flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example, gosereline acetate, leuprolide), inhibitors of testosterone 5 α -dihydroreductase (for example, finasteride), farnesyltransferase inhibitors, anti-invasion agents (for example, metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example, EGF, FGF, platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies such as Avastin® (bevacizumab) and Erbitux® (cetuximab); tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and
- (iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example, antifolates

like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); Intercalating antitumour antibiotics (for example, anthracyclines such as doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example, cisplatin, carboplatin); alkylating agents (for example, nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa; antimetabolic agents (for example, vinca alkaloids such as vincristine and taxoids such as Taxol® (paclitaxel), Taxotere® (docetaxel) and newer microtubule agents such as epothilone analogs, discodermolide analogs, and eleutherobin analogs); topoisomerase inhibitors (for example, epipodophyllotoxins such as etoposide and teniposide, amsacrine, topotecan); cell cycle inhibitors (for example, flavopyridols); biological response modifiers and proteasome inhibitors such as Velcade® (bortezomib).

As stated above, the formula I compounds of the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, obesity, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation and ocular diseases associated with retinal vessel proliferation such as diabetic retinopathy.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell

lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

-hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

-tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

-other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of kinases in the regulation of cellular proliferation in general, inhibitors can act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of formula I may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic

injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

The compounds of formula I are especially useful in treatment of tumors having a high incidence of tyrosine kinase activity, such as colon, lung, and pancreatic tumors. By the administration of a composition (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

Compounds of formula I may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through growth factor receptors such as VEGFR-2 and FGFR-1.

The compounds of this invention may be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds may also be administered as suspensions using carriers appropriate to this mode of administration. The compounds may be administered in a dosage range of about 0.05 to 300 mg/kg/day, preferably less than 200 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Methods of Preparation

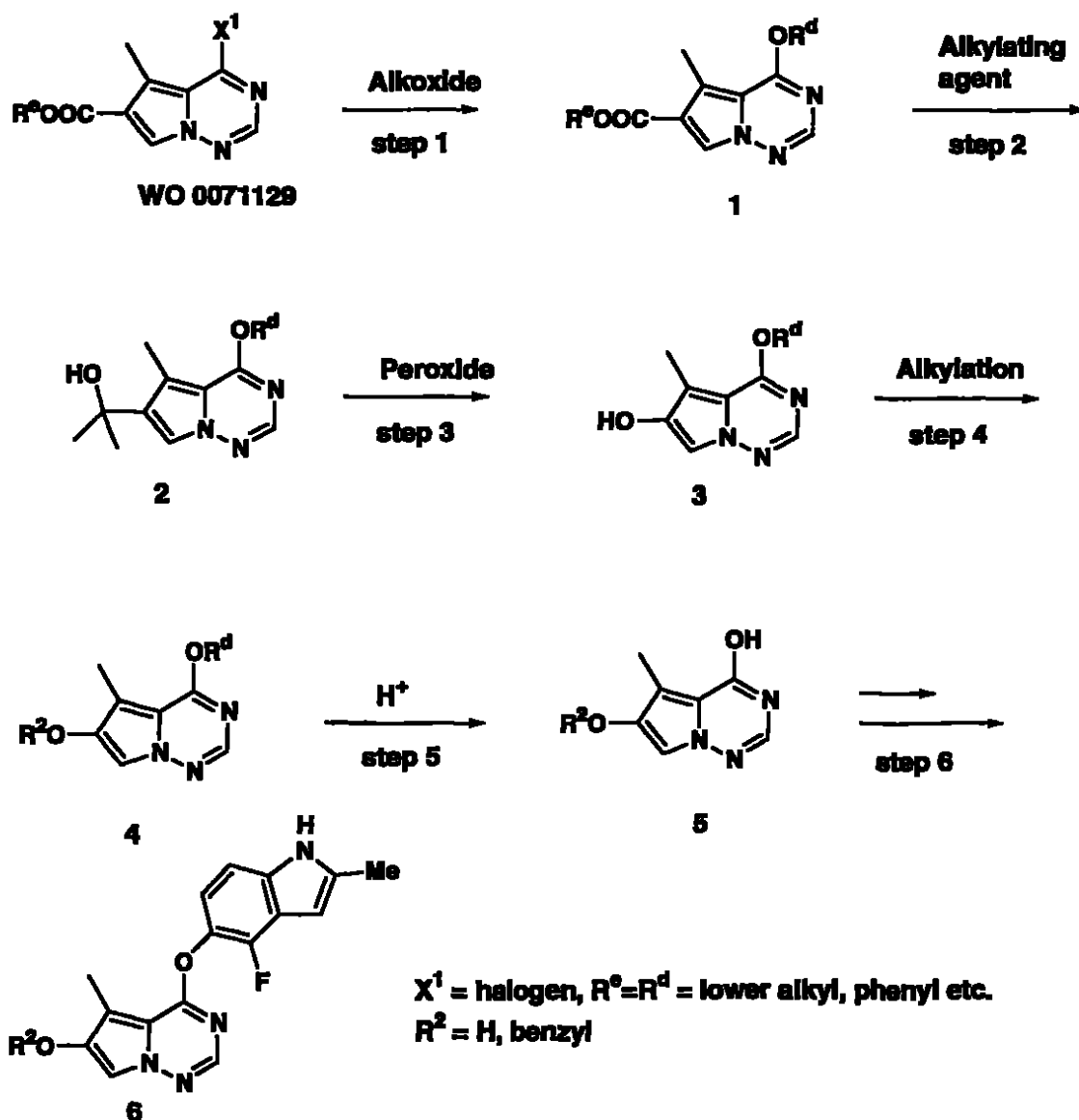
Certain compounds of formula I may be prepared according to the following schemes and the knowledge of one skilled in the art.

All temperatures are in degrees Celsius (°C) unless otherwise indicated. Preparative Reverse Phase (RP) HPLC purifications were done on C18 reverse phase (RP) columns YMC S5 ODS columns eluting with 90% aqueous methanol containing 0.1% TFA as buffer solution and monitoring at 220 nm. For analytical HPLC 0.2% phosphoric acid was used instead of TFA. All of the synthesized compounds were characterized by at least proton NMR and LC/MS. During work up of reactions, the

organic extract was dried over magnesium sulfate (MgSO_4), unless mentioned otherwise.

The following abbreviations are used for the commonly used reagents. Et_2O ; diethyl ether, Na_2SO_4 ; sodium sulfate; HCl ; hydrochloric acid, NaOH ; sodium hydroxide, NaCl ; sodium chloride, Pd/C ; palladium on carbon, K_2HPO_4 ; potassium monohydrogen phosphate, K_2CO_3 ; potassium carbonate, NaHCO_3 ; sodium bicarbonate, LiOH ; lithium hydroxide, RT ; room temperature, TFA ; trifluoroacetic acid, h ; hour.

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Scheme 1

Step 1

A compound from PCT Publication WO 0071129 is converted to an ether (etherified) at the 4-position, for example, by treatment with phenoxide or methoxide or ethoxide anion.

Step 2

Compound 1 can then be treated with an alkylating agent such as methyl magnesium bromide or methyl magnesium chloride, at low temperatures to afford compound 2.

Step 3

Compound 2 can then be treated with a peroxide such as hydrogen peroxide or sodium perborate in the presence of a Lewis acid, such as boron trifluoride, at low temperature to afford phenolic compound 3.

Step 4

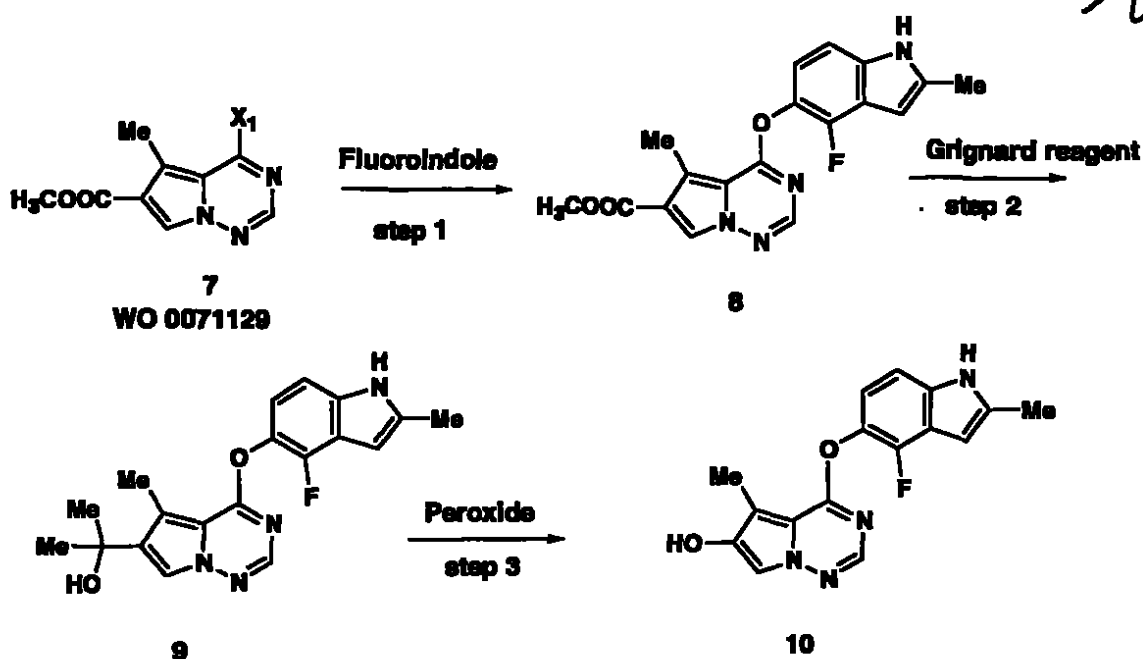
Alkylation of the phenol group in compound 3 with an electrophilic agent, such as benzyl bromide, in the presence of a base, such as NaH, at from 0 °C to 80 °C, affords compound 4.

Step 5

Hydrolysis of compound 4 of this scheme is achieved by treatment with an acid, such as aqueous HCl, at an elevated temperature, to afford compound 5.

Step 6

Compound 5 of this scheme is converted to compound 6 by first converting to chloroimidate as described above followed by alkylation of the resulting chloroimidate with a hydroxy fluoroindole in the presence of a base such as potassium carbonate in a polar solvent such as dimethyl formamide to afford protected compound 6.

Scheme 2

5 Step 1

A compound from PCT Publication WO 0071129, wherein X_1 is halogen, such as chlorine, can be treated with a nucleophile such as fluoroindole in the presence of a base such as potassium carbonate in a polar solvent such as dimethyl formamide to afford compound 8.

10

Step 2

Compound 8 can then be treated with an alkylating agent such as methyl magnesium bromide or methyl magnesium chloride, at low temperatures to afford compound 9.

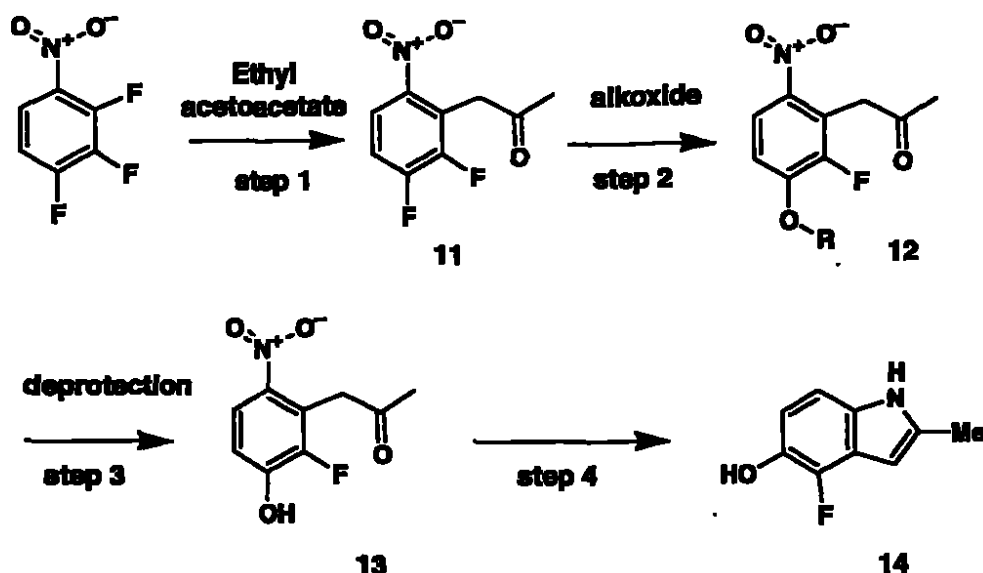
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Step 3

Compound 9 can then be treated with a peroxide such as hydrogen peroxide or sodium perborate in the presence of a Lewis acid, such as boron trifluoride, at low temperature to afford phenolic compound 10.

20

Scheme 3



Step 1

- 5 A fluorinated compound such as trifluoro nitrobenzene can be reacted with a nucleophile such as ethyl acetoacetate followed by decarboxylation of ester group in the presence of an acid or base to give compound 11.

Step 2

- 10 Compound 11 can then be reacted with an alkoxy anion such as sodium methoxide or sodium salt of benzyl alcohol to give compound 12.

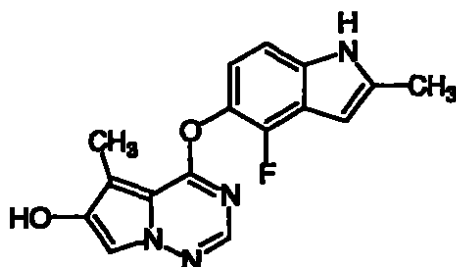
Step 3

- 15 Deprotection of the alkoxy group of Compound 12 of this scheme then can be accomplished by treatment with reagents like pyridinium chloride or hydrogen bromide in acetic acid to give compound 13.

Step 4

- 20 Compound 13 then could be cyclized under reducing conditions such as sodium dithionite or palladium on carbon in the presence of hydrogen to give the indole derivatives of the formula 14.

Compound 12 could directly be converted to compound 14 by treatment with palladium on carbon in the presence of hydrogen source such as ammonium formate.

Example 15 **4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-ol****A. 4-Chloro-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester**

A mixture of 4-hydroxy-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester (60.0g, 271.2 mmol, for preparation see WO 0071129), phosphorus oxychloride (30.3 mL, 325.4 mmol) and diisopropylethyl amine (37.7 mL, 217 mmol) in toluene (800 mL) was heated to reflux under argon for 18 h and then cooled to room temperature. The mixture was concentrated on rotovap and the residue was diluted with dichloromethane (1000 mL) and cold sodium bicarbonate solution (300 mL). The resulting mixture was stirred at room temperature for 10 min. The separated organic layer was washed with cold brine (300 mL), dried, and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel eluting with dichloromethane to provide the desired compound (64.8 g, 99%) as a yellow solid.

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B. 4-Ethoxy-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester

To a solution of compound A of this example (23 g, 96 mmol) in tetrahydrofuran (0.6 L) under argon at 0 °C was added sodium ethoxide in ethanol (21% w/w, 43 mL, 115.2 mmol) dropwise over 20 min. The reaction was stirred at 0 °C for 1 hr, diluted with ethyl acetate and washed with ammonium chloride solution and brine. The organic layer was dried, concentrated and the residue was purified by chromatography on silica gel eluting with dichloromethane followed by 50% ethyl

acetate in hexanes to provide the desired compound (23.5 g, 98%) as a white solid.

LC/MS; (M+H)⁺ = 250.17

C. 2-(4-Ethoxy-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yl)-propan-2-ol

5 To a solution of compound B of this example in THF (2.5 L) at 0 °C was slowly added methyl magnesium bromide (3M in Et₂O, 360 mL, 1.08 mol) with addition funnel. The mixture was allowed to warm to room temperature, whereupon stirring was continued for 4 h. The reaction was quenched by ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with sodium
10 chloride solution and dried, to afford the desired compound (78 g, 100%) as a yellow solid. LC/MS; (M+H)⁺ = 236.1

D. 4-Ethoxy-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-ol

A mixture of hydrogen peroxide (30%, 10.3 mL, 178.5 mmol) and boron
15 trifluoride diethyl etherate (271.4 mL, 2.14 mol) was stirred at 0 °C for 30 min. It was then cooled to -20 °C and a solution of Compound C of this example (30g, 129.5 mmol) in dichloromethane (1.45 L) at -15 °C was added. The reaction mixture reached -3 °C, and then cooled to -40°C. To this mixture was added a saturated solution of sodium sulfite with stirring. The resulting mixture was extracted with ethyl
20 acetate, dried, and concentrated *in vacuo* to provide Compound D (26g, 76%).
LC/MS; (M+H)⁺ = 194.2

E. 6-Benzyloxy-4-ethoxy-5-methylpyrrolo[2,1-f][1,2,4]triazine

A mixture of compound D of this example (1 g, 5.2 mmol), benzyl bromide
25 (0.62 mL, 5.2 mmol) and potassium carbonate (2.1 g, 15.5 mmol) in dimethyl formamide (10 mL) was stirred at room temperature for 12 h. The reaction was diluted with ethyl acetate and washed with water, 10% lithium chloride solution and brine. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give Compound E (1g) as yellow solid which was used without further purification for the
30 next step.

F. 6-Benzyloxy-5-methylpyrrolo[2,1-f][1,2,4]triazin-4-ol

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Compound E of this example (90 g, crude) in 1N HCl (600 mL) and ethanol (800 mL) was heated to reflux for 4 h. A solid precipitated which was collected by filtration, washed with a mixed solvent (water /ethanol/ methanol = 4/4/2) and dried to give a off-white solid, which was washed with dichloromethane to afford Compound F (65 g) as a white solid. LC/MS; (M+H)⁺ = 256.2

G. 6-Benzyloxy-4-chloro-5-methylpyrrolo[2,1-f][1,2,4]triazine

A mixture of compound F of this example (10 g, 39.2 mmol), phosphorus oxychloride (4.4 mL, 47.1 mmol) and diisopropylethyl amine (5.5 mL, 31.4 mmol) in toluene (150 mL) was stirred at 85 °C for 2 h and then more phosphorus oxychloride (1.1 mL, 11.8 mmol) was added. After 2 h, additional phosphorus oxychloride (1.1 mL, 11.8 mmol) was added. The reaction mixture was continuously stirred at 85 °C for 1h and then concentrated. The residue was dissolved in dichloromethane, washed with cold sodium bicarbonate solution, dried, and concentrated *in vacuo*. The crude material was purified by chromatography on silica gel eluting with dichloromethane to provide Compound G (9.9 g, 93%) as a yellow solid.

H. 6-Benzyloxy-4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazine

A solution of 4-fluoro-2-methyl-1H-indol-5-ol (6.47 g, 39.2 mmol, Example 2) in dimethyl formamide (100 mL) was degassed with argon and then cooled to -20 °C. Sodium hydride (60% in oil, 1.57 g, 39.2 mmol) was added in one portion. The reaction mixture was allowed to warm to 0 °C with stirring over 30 min, cooled back to -20°C and a solution of Compound G of this example in dimethyl formamide (100 mL) was added in one portion. The reaction was warmed to room temperature. After 30 min, the mixture was acidified with 1N HCl (200 mL), diluted with ethyl acetate (1.8 L), and washed with a 10% lithium chloride solution (0.4 L x 2), 1N NaOH solution (0.3 L x 2), buffer (pH = 2, 200 mL), and NaCl solution (0.4 L). The organic layer was dried, and concentrated *in vacuo* to provide Compound H (15 g, 95%) as a tan solid. LC/MS; (M+H)⁺ = 403.1

**I. 4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-
f][1,2,4]triazin-6-ol**

A mixture of Compound H of this example (15 g, 37.3 mmol), ammonium formate (12 g, 190 mmol) and Pd/C (10%, 1.5 g) in dimethyl formamide (100 mL) was stirred at room temperature for 2 h. The mixture was filtered through Celite® and the filtrate was diluted with ethyl acetate and washed successively with 10% lithium chloride solution (2X), 5% sodium bicarbonate solution (2X) and brine. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo* to gave a light-brown solid, which was washed with dichloromethane to afford the title compound (7.8 g, 64%) as an off-white solid. MS: [M+H]⁺ = 313.2. ¹HNMR (CDCl₃): δ 2.44 (s, 3H), 2.51 (s, 3H), 6.31 (s, 1H), 6.95 (dd, 1H), 7.07 (d, 1H, J = 8.8 Hz), 7.38 (s, 1H), 7.78 (s, 1H).

Example 1 can also be prepared by the alternate route described below.

15 A-1. 4-Chloro-5-methyl-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester

A 10 L reactor was charged with 4-hydroxy-5-methyl-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ethyl ester (155.1 g, 0.7 mol) and toluene (2.7 L). Phosphorous oxychloride (128.8 g, 78 mL, 0.84 mol) was then added followed by the addition of diisopropylethylamine (94.2 g, 127 mL, 0.7 mol). The reaction mixture was stirred for 5 min at room temperature and then heated at reflux for 20 h. HPLC analysis indicated complete disappearance of starting material. The reaction mixture was then cooled to 0 °C and cold K₂HPO₄ solution (527 g in 2.4 L of water) was added at a rate to maintain the internal temperature of the reaction mixture below 5 °C. The final pH of the mixture was 8. The mixture was then stirred at between 0°C to 5 °C for 20 min and then at room temperature for 1 h. The organic phase was separated and washed with K₂HPO₄ solution (85 g in 405 mL of water) and water (345 mL) and then filtered and concentrated *in vacuo* until yellow solids began to precipitate. Dimethyl formamide (1 L) was added and the remaining toluene was removed *in vacuo* (bath temperature = 38 °C, pressure = 9 Torr). After concentration, approximately 4% toluene was observable by HPLC.

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**J. 4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-
f][1,2,4]triazine-6-carboxylic acid ethyl ester**

The residue from previous step A-1 was transferred to a 10 L reactor and dimethyl formamide (1.1 L) was added followed by K₂CO₃ (276 g, 2.1 mol) and 4-fluoro-2-methyl-1*H*-indol-5-ol (109.5 g, 0.7 mol). The reaction mixture was stirred at ambient temperature for 16 h and then cooled to 0 °C. Water (2.0 L) and ethyl acetate (2 L) were added at a rate so as to maintain the internal temperature below 20 °C. The phases were then separated and the aqueous phase was extracted with ethyl acetate (2 L). The combined organic extracts were then washed with water (2 L), 10% aqueous LiCl (2 L) and water (2 L). Toluene (1 L) was then added and the organic extracts were concentrated *in vacuo*. Additional toluene (500 mL) was added and the mixture was reconcentrated *in vacuo*. LC/MS; (M+H)⁺ = 369.4. ¹HNMR (CDCl₃): δ 1.41 (t, 3H, J = 7.15 Hz), 2.45 (s, 3H), 2.87 (s, 3H), 4.39 (q, 2H, J = 7.15 Hz), 6.34 (s, 1H), 6.98 (dd, 1H), 7.08 (d, 1H, J = 8.25 Hz), 7.90 (s, 1H), 8.15 (s, 1H).

15

**K. 2-[4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methyl-pyrrolo[2,1-
f][1,2,4]triazin-6-yl]-propan-2-ol**

The residue from the previous step (step J) was transferred to a 10 L reactor and enough toluene was added to provide a total reaction volume of 1.1 L. THF (1.1 L) was then added followed by the addition of LiCl (140 g) and the reaction mixture was cooled to 0 °C. Methyl magnesium bromide [1.4 M in toluene, THF (75:25), 2.1 L, 2.8 mol] was then added at a rate so as to maintain an internal temperature below 5 °C. Total addition time was approximately 2 h. The reaction mixture was stirred at 0 °C for an additional 2 h and then warmed to 15 °C over 3 h, at which time 5% of the starting material was still observable by HPLC. The reaction mixture was then recooled to 5 °C and an additional 100 mL of methylmagnesium bromide was added and the mixture was stirred for an additional 1.5 h. Ethyl acetate (1.5 L and a solution of 15% NH₄Cl (3.2 L) and) were then added so as maintain an internal temperature below 5 °C. The layers were then separated and the aqueous phase was extracted with ethyl acetate (2 L). The combined organic layers were washed with 15% NH₄Cl (2 x 2 L) and water (2 x 2L) and then concentrated *in vacuo* to afford the desired product as an amorphous yellow solid. The crude product was dissolved in dichloromethane

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(5 L) using a water bath (T=37 °C) to aid dissolution. The solution was then passed through a short pad of silica gel (400 g) and the pad was washed with dichloromethane (7 L) and 5% ethyl acetate/dichloromethane (1.2 L). The filtrate was evaporated to yield an off-white solid to which ethyl acetate (1.2 L) was added. The resulting slurry was transferred to a 10 L reactor and a clear solution was obtained after stirring for 2 h at 50 °C. The solution was then cooled to ambient temperature and a white solid precipitated. Heptane (2.6 L) was then added and the mixture was stirred at room temperature for 20 h. The resulting solids were filtered, washed with heptane (1 L) and dried under reduced pressure at 50 °C for 24 h. 2-[4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-propan-2-ol was obtained as a white solid (186 g, 75% over 3 steps). LC/MS; (M+H)⁺ = 355.4

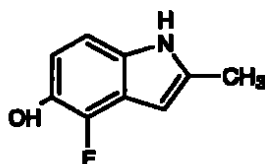
I-1. 4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol

To a solution of BF₃•OEt₂ (120 mL, 0.948 mol) in dichloromethane (200 mL) at 0 °C was added H₂O₂ (50% aqueous solution, 4.6 mL, 0.079 mol). The reaction mixture was stirred at 0 °C for 30 min and then cooled to -20 °C. In a separate flask, 2-[4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-propan-2-ol from previous step (20 g, 0.0564 mol) was dissolved in dichloromethane (400 mL) using indirect heat to achieve complete dissolution. This solution was then added rapidly via canula (addition time = 20 min) to the peroxide solution. The reaction temperature during the addition was between -15 °C and -25 °C. After the addition was complete, the reaction temperature was raised to -15 °C and maintained at that temperature for an additional 40 min. The reaction mixture was quenched by the addition of Na₂SO₃ (200 mL, 20% aqueous solution) and ethanolamine (33% aqueous solution, 300 mL). Both reagents were added at a rate so as to maintain the internal temperature below 0 °C. The cooling bath was removed and the reaction mixture was stirred for 2 h and then poured into a separatory funnel. The layers were separated and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic layers were washed with 5% aqueous citric acid (100 mL), 10% aqueous NaHCO₃ (100 mL), water (2 x 100 mL), and brine (100 mL) and then dried, filtered and concentrated *in vacuo* to afford an orange foam. The crude material was

loaded onto a Florisil[®] column using tetrahydrofuran as the loading solvent and the column was eluted with 30% ethyl acetate/heptane. The fractions containing the desired product were collected and concentrated *in vacuo* and then recrystallized from ethyl acetate/heptane. The solids were collected and washed with heptane to afford (9.1 g, 52%) of the desired product as an off-white solid. The filtrate was concentrated *in vacuo* and purified on silica gel using 40% ethyl acetate/heptane as the eluent to afford an additional 2.5 g (14%) of the desired product. Total yield of 4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ol was (11.6 g, 66%).

Reverse phase HPLC: 3.75 min (YMC SS ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). LC/MS; (M+H)⁺ = 313.2

Example 2



4-Fluoro-2-methyl-1*H*-indol-5-ol

A. 1-(2,3-Difluoro-6-nitrophenyl)-propan-2-one

A 10 liter reactor was charged with potassium *tert*-butoxide (570.6 g, 5.082 mol) and tetrahydrofuran (2 L). Overhead stirring was initiated and the resulting suspension was cooled to 11 °C before ethyl acetoacetate (668 mL, 5.082 mol) was added. The addition of the ethyl acetoacetate required 1 h and an exotherm was observed. The rate of addition was controlled so that the internal temperature of the reactor did not exceed 25 °C. The resulting mixture became homogeneous and was pale yellow in color. After addition was completed, the reaction mixture was cooled between 10°C and 15 °C and then 1,2,3-trifluoronitrobenzene (260 mL, 600 g, 2.259 mol) was added dropwise as a solution in tetrahydrofuran (1 L). The addition required 35 min and an exotherm was observed. The rate of addition was controlled so an internal temperature of 21 °C was not exceeded. After addition was complete, the

resulting brown reaction mixture was warmed to RT and stirred for 2.5 h, at which time, LC analysis indicated 100% conversion with no trace of 1,2,3-trifluoronitrobenzene remaining. The reaction mixture was recooled to 15 °C and 3 L of 1 N HCl were slowly added over 15 min and the brown solution eventually became a clear yellow solution. The pH of the aqueous phase was ~ pH 4. The mixture was extracted with ethyl acetate (2 x 1 L) and the combined organic extracts were washed with brine (1 L) and concentrated *in vacuo* to afford an orange oil.

The oil obtained was charged into a 10 L reactor and dissolved in glacial acetic acid (1 L). Sulfuric acid (conc., 1 L) was then added and a vigorous evolution of gas was observed in addition to a slight exotherm. Mechanical stirring was initiated and the reaction mixture was heated at 70 °C for 3 h, after which time LC analysis indicated 100% conversion. The reaction mixture was cooled to between 15°C to 20 °C and ethyl acetate (3 L) was added followed by the addition of water (6 L). No visible interface was observable. Seven liters of aqueous phase were separated and then extracted with ethyl acetate (2 x 2 L). At this time, a visible interface was observable. The combined organic extracts were washed with 1 N NaOH (6 x 1 L) (the pH of the aqueous phase was 6.6) and brine (3 x 1 L). The brown organic extracts were concentrated under reduced pressure (bath temperature 35 °C, 36 torr) for ~10 h to afford 569 g of the desired compound as a crude brown oil which was 82% AP by HPLC. Residual ethyl acetate was 3% by GC. KF: 0.25%. ¹H and ¹³C NMR matched reported data. Major impurity: para regioisomer.

B. A mixture of 1-(2,3-difluoro-6-nitrophenyl)-propan-2-one (183 g) and potassium carbonate (100 g) in methanol (1 L) was heated at reflux for 3 h. The reaction mixture was then cooled and concentrated *in vacuo* to remove most of the methanol. The residue was diluted with ethyl acetate (1 L), filtered and washed with water. The separated aqueous layer was neutralized with 2N HCl and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated *in vacuo* to give a brown solid. The solid was triturated with diethyl ether and filtered to provide 1-(2-fluoro-3-methoxy-6-nitrophenyl)-

propan-2-one (121 g, 71%) as a yellow solid. LC/MS; (M+H)⁺ = 228.2.

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C. A mixture of 1-(2-fluoro-3-methoxy-6-nitrophenyl)-propan-2-one from previous step (454 mg, 21 mmol) and pyridinium chloride (0.9 g, 7.8 mmol) was stirred at 180°C for 75 min. The reaction was cooled to room temperature, diluted with 1N HCl (3mL) and ethyl acetate (10 mL) and filtered. The filtrate was washed with brine (2x), dried and concentrated *in vacuo* to give 1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one (410 mg, 96 %) as a grey solid, which was used without further purification for the next step. LC/MS; (M+H)⁺ = 214. ¹H NMR (CDCl₃): δ 2.37 (s, 3H), 4.22 (s, 2H), 6.95 (dd, 1H), 7.95 (d, 1H, J= 9.35 Hz).

D. 1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one from previous step (50 g, 0.234 mol) was added to 2 liter round bottom flask. Water (1 L) was added, and the yellow suspension was stirred at RT. Sodium dithionite (225 g, 5.5 eq) was added in one portion and the reaction mixture was stirred and kept <30 °C until HPLC analysis indicated no starting material remained (typically less than 1 hour). Upon completion, the reaction mixture was cooled to 0 °C and the tan solid product was collected by vacuum filtration. The wet product was dried at <50 °C under house vacuum to afford 4-fluoro-2-methyl-1*H*-indol-5-ol (31.4 g, 81% yield) which was isolated as a tan crystalline powder. The material had an HPLC purity of >99.8. ¹H NMR (CDCl₃, 400 MHz) δ 7.8 (s, 1H), 6.9-6.7 (m, 2H), 6.2 (s, 1H), 4.7 (s, 1H), 2.4 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 145.7, 143.4, 137.5, 136.7, 134.4, 120.1, 112.7, 106.8, 95.4, 13.3.

25 Also, 1-(2,3-difluoro-6-nitrophenyl)-propan-2-one could be converted to the title compound by an alternate route as described below.

E. 1-(3-Benzyloxy-2-fluoro-6-nitro-phenyl)-propan-2-one
To a solution of 1-(2,3-difluoro-6-nitrophenyl)-propan-2-one (2.5 g, 82% purity by HPLC analysis, 9.54 mmol) were added benzyl alcohol (2.5 mL) and LiOH•H₂O (1.07 g, 25.58 mmol). The reaction mixture was then heated to 100-110 °C and stirred for 4 hours until HPLC analysis indicated complete reaction. After

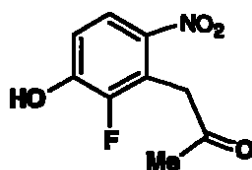
cooling to RT, the reaction mixture was diluted with dichloromethane (18 mL) and neutralized to pH 6-7 with 1 N HCl. The layers were separated and the organic phase was washed with brine and collected. With stirring, heptane (30-25 mL) was added to the organic solution whereupon crystallization was initiated. The resulting slurry was cooled to 0-5 °C and stirred for an additional 1 h. The slurry was then filtered and the filter cake was washed with heptane. The yellow-brown solids were then dried *in vacuo* at 50 °C for 12-15 h to afford of the desired compound (1.6 g) which was 95 % pure by HPLC analysis. HPLC method: Column: YMC Pack Cyano 3µm, 4.6x50 mm Solvent A: 0.05% TFA in MeOH:Water (20:80), Solvent B: 0.05% TFA in MeOH: water (20:80), Wavelength: 254 nm Flow Rate: 3 mL/min. Gradient Time: 3 min. Final %B: 100 Initial Hold: 0.5 min. Start %B: 0. Typical Retention Times: SM, 1.2 min; Product 2.2-2.3 min.

F. 4-Fluoro-2-methyl-1*H*-indol-5-ol

To a solution of compound E from previous step (20.00 g, 66.03.30 mmol) in methanol under a nitrogen atmosphere (300 mL) at room temperature in the absence of light were added 10% Pd/C (2.0 g) and ammonium formate (60.0 g, 0.95 mol). The reaction mixture was stirred for 3.5 h and then diluted with ethyl acetate (200 mL) and filtered through a Celite®/silica gel pad. The residue can then be purified by either of the following methods:

After concentration *in vacuo*, the resulting residue was purified by chromatography eluting with 30% ethyl acetate/hexanes to afford (7.32 g, 67%) of the desired compound as a white solid after trituration with dichloromethane/hexanes. After concentration *in vacuo*, the residue was dissolved in dichloromethane and passed through a silica gel pad washing with dichloromethane. The filtrate was concentrated *in vacuo* to afford (6.66 g, 61%) of the title compound as a white solid.

Compound E of this example can also be converted to 1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one by the following two alternate methods.



1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one

5 **Method G-1:** To a solution of 1-(3-benzyloxy-2-fluoro-6-nitrophenyl)-propan-2-one (3.03 g, 10 mmol) in acetic anhydride (5 mL) and acetic acid (5 mL) at room temperature was added hydrobromic acid (48% aqueous solution, 3 mL). After addition, the reaction was heated at 100 °C for 30 min and then cooled to room temperature. To this mixture was added 10 mL of hexanes with stirring. The solution
10 was decanted and concentrated. The residue was diluted with ethyl acetate (50 mL) and washed with brine (3 x 20 mL). The organic layer was dried and concentrated *in vacuo* to provide 1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one (1.7 g, 80%) as a brown solid, which was used in the next step without further purification. LC/MS; (M+H)⁺ = 213.2

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Method G-2: A mixture of 1-(3-benzyloxy-2-fluoro-6-nitrophenyl)-propan-2-one (65.0 g, 0.214 mol) and pyridinium chloride (60.74 g, 0.526 mol) was stirred at 180 °C for 1 hr. The reaction mixture was cooled to room temperature, diluted with 3N HCl (100 mL) and ethyl acetate (500 mL) and filtered. The aqueous layer was
20 extracted with ethyl acetate (2X) and the combined organic layers were washed with brine, dried (MgSO₄), filtered through a pad of silica gel and concentrated *in vacuo*. The residue was decolorized with charcoal in methanol, filtered and concentrated *in vacuo* to afford 1-(2-fluoro-3-hydroxy-6-nitrophenyl)-propan-2-one (37 g, 81%) as a brown solid. LC/MS; (M+H)⁺ = 213.2

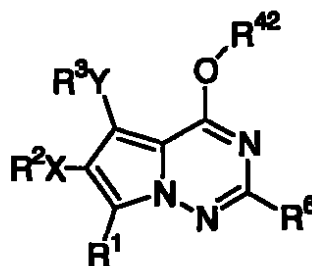
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Alternatively, 1-(3-benzyloxy-2-fluoro-6-nitrophenyl)-propan-2-one can be cyclized to 5-benzyloxy-4-fluoro-2-methyl-1*H*-indole as described below, which then can be debenzylated as described before.

H. A mixture of 1-(3-benzyloxy-2-fluoro-6-nitrophenyl)-propan-2-one (9.09 g, 30 mmol) and Raney nickel (~ 5 g) in methanol (100 mL) was heated to 40 °C and then a solution of hydrazine in methanol (15 mL) was added dropwise with vigorous stirring over a period of 30 min. After refluxing for 1 h, the reaction mixture was cooled to room temperature, filtered through Celite and concentrated. The crude material was passed through a pad of silica gel eluting with dichloromethane and concentrated *in vacuo* to provide 5-benzyloxy-4-fluoro-2-methyl-1*H*-indole (6.1 g, 80%) as a yellowish oil. LC/MS; (M+H)⁺ = 256.3⁺.

What is Claimed is:

1. A process for preparing a compound of formula (I)



(I)

wherein

X and Y are independently selected from O, OCO, S, SO, SO₂, CO, CO₂, NR¹⁰, NR¹¹CO, NR¹²CONR¹³, NR¹⁴CO₂, NR¹⁵SO₂, NR¹⁶SO₂NR¹⁷, SO₂NR¹⁸,

10 CONR¹⁹, halogen, nitro, cyano, or X or Y are absent;

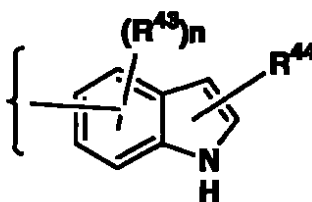
R¹ is hydrogen;

R² and R³ are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, aralkyl, substituted aralkyl, heteroaryl, substituted heteroaryl, 15 heterocycloalkyl or substituted heterocycloalkyl; with the proviso that when X is halo, nitro or cyano, R² is absent, and, when Y is halo, nitro or cyano, R³ is absent;

R⁶ is H;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, 20 substituted aryl, heteroaryl, substituted heteroaryl, heterocyclo, or substituted heterocyclo;

R⁴² is



$(R^{43})_n$ wherein n equals 0, 1 or 2 and each R^{43} is independently selected from the group consisting of hydrogen, fluorine, chlorine and methyl; and

R^{44} is methyl, or hydrogen,

5 with the further provisos that:

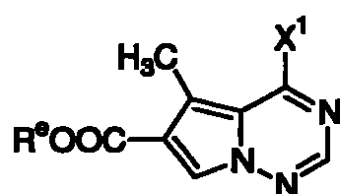
a. R^2 may not be hydrogen if X is SO, SO₂, NR¹³CO₂, or NR¹⁴SO₂; and

b. R^3 may not be hydrogen if Y is SO, SO₂, NR¹³CO₂, or NR¹⁴SO₂;

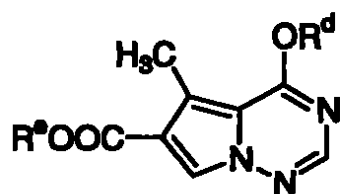
or an enantiomer, diastereomer, or pharmaceutically acceptable salt, prodrug, or solvate thereof,

10 which comprises the steps of

a) converting a compound of the formula



15 where R^e is lower alkyl or aryl and X^1 is a halogen to a compound 1 of the formula



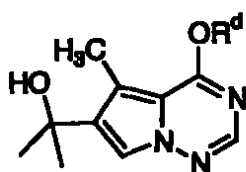
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where R^d is lower alkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, by

20 treatment with a phenoxide, or alkoxide,

b) alkylating Compound 1 to afford Compound 2 of the formula

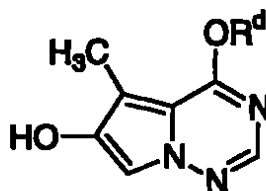
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2

c) treating compound 2 with a peroxide in the presence of a Lewis acid to afford compound 3 of the formula

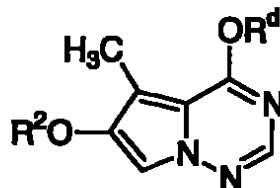
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d) alkylating the phenol group in compound 3 to afford Compound 4 of the formula

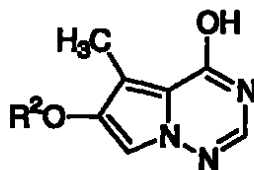
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4

where R² is benzyl or substituted benzyl,

15 e) hydrolyzing Compound 4 to afford Compound 5 of the formula

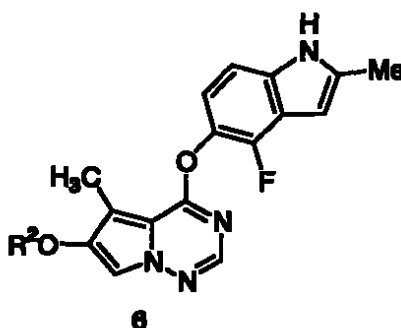


5

where R^2 is benzyl or substituted benzyl, and

f) converting Compound 5 to Compound 6 of the formula

5

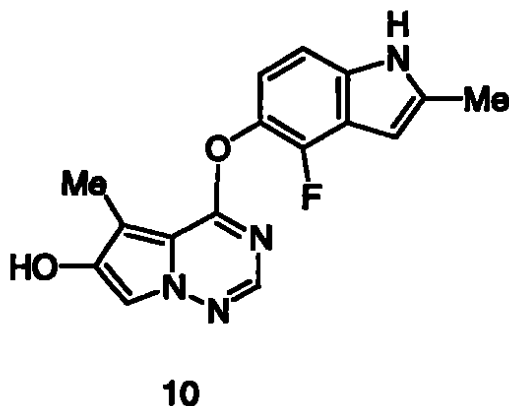


by first converting compound 5 to a chloroimidate, subsequently alkylating the chloroimidate to afford Compound 6 wherein R^2 is benzyl and deprotecting the phenol by treatment with a hydrogen donor in the presence of a catalyst to afford compound 6 where R^2 is hydrogen.

2. The process according to Claim 1 wherein in step c), hydrogen peroxide is used in the presence of a Lewis acid to convert the benzylic alcohol to the phenol.

3. A process for preparing a compound of the formula

15

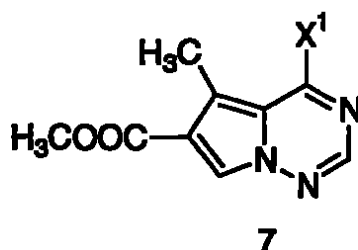


which comprises the steps of

a) reacting a compound of the formula

20

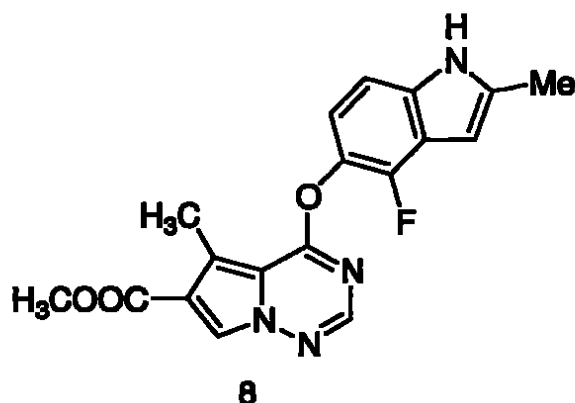
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where X₁ is halogen;

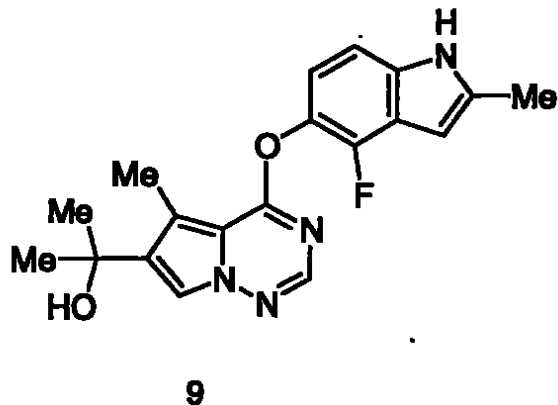
with a nucleophile to afford Compound 8 of the formula

5



b) treating Compound 8 with an alkylating agent at low temperature, to afford Compound 9 of the formula

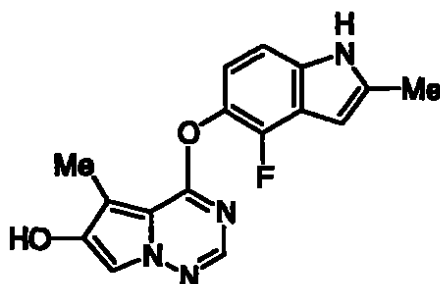
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, and

c) treating Compound 9 with a peroxide in the presence of a Lewis acid to afford Compound 10 of the formula

15



10

4. The process according to Claim 3 wherein the alkylating agent in step (b) is an alkyl magnesium halide.

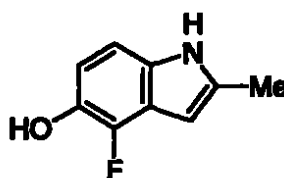
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5. The process according to Claim 4 wherein the alkyl magnesium halide is methyl magnesium bromide or methyl magnesium chloride.

6. The process according to Claim 4 wherein the peroxide used in step c) is hydrogen peroxide or sodium perborate.

7. The process according to Claim 4 wherein the Lewis acid used in step c) is boron trifluoride.

8. A process for preparing a compound of the formula



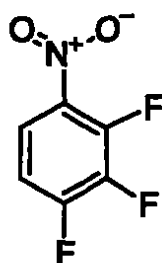
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which comprises the steps of

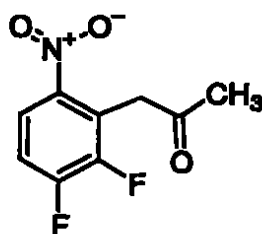
a) reacting a fluorinated compound of the formula

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30



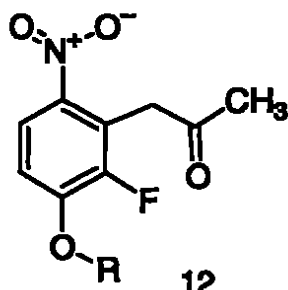
b) with a nucleophile to afford Compound 11 of the formula



11

5

c) reacting Compound 11 with an alkoxy anion to afford Compound 12 of the formula

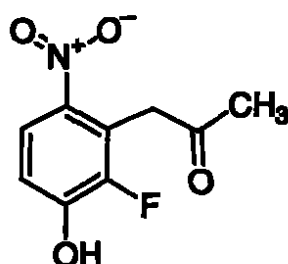


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10

wherein R is a protecting group,

d) deprotecting the alkoxy group by treatments with deprotecting reagents
15 to afford Compound 13 of the formula

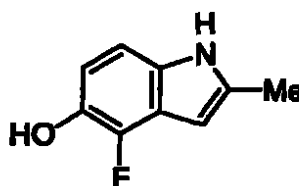


13 , and

e) cyclizing Compound 13 under reducing conditions to afford Compound

14 .

5



14

9. The process according to Claim 8 wherein the reduction in step (e) utilizes sodium dithionite in water or a mixture of water and an organic solvent such as THF.

10. The process according to Claim 8 wherein the reduction in step (d) utilizes pyridinium chloride or pyridinium iodide or hydrogen bromide.

11. A pharmaceutical composition comprising at least one or more compounds of Claim 1 in combination with a pharmaceutically acceptable carrier and at least one additional anti-cancer or cytotoxic agent.

12. A method for producing an antiangiogenic effect which comprises administering to a mammalian species in need thereof, an effective antiangiogenic producing amount of at least one compound made by the process of Claim 1.

13. A method for producing a vascular permeability reducing effect which comprises administering to a mammalian species in need thereof an effective vascular

permeability reducing amount of at least one compound made by the process of Claim 1.

14. A method of inhibiting protein kinase activity of growth factor receptors
5 which comprises administering to a mammalian species in need thereof, an effective protein kinase inhibiting amount of at least one compound made by the process of Claim 1.

15. A method of inhibiting tyrosine kinase activity of growth factor
10 receptors which comprises administering to a mammalian species in need thereof, an effective tyrosine kinase inhibiting amount of at least one compound made by the process of Claim 1.

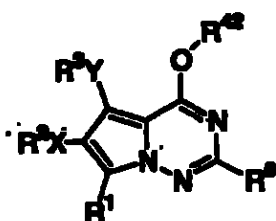
16. A method for treating diseases associated with signal transduction
15 pathways operating through growth factor receptors, which comprises administering to a mammalian species in need thereof a therapeutically effective amount of at least one compound made by the process of Claim 1.

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

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(71) Solicitante (para todos los estados designados excepto US): BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).		
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	Publicada: - Sin el reporte de búsqueda internacional y para publicarlo en el caso de recibir tal reporte.	
	Para los códigos de dos letras y abreviaciones, consultar las "Guías y Notas sobre los Códigos y Abreviaciones" que aparecen al comienzo de cada publicación regular de la Gaceta del PCT.	

(54) título: **PROCESO PARA LA PREPARACIÓN DE CIERTOS COMPUESTOS DE
PIRROLOTRIAZINA**



(I)

(57) Resumen: La presente invención se refiere a un proceso para preparar ciertos compuestos de pirrolo-triazina de la fórmula (I) y sales farmacéuticamente aceptables de los mismos. Los compuestos de la fórmula (I) inhiben la actividad de la tirosina cinasa de los receptores del factor de crecimiento, tales como VEGFR-2 y FGFR-1, por lo que los hacen útiles como agentes anti-cáncer. Los compuestos de la fórmula I también son útiles para el tratamiento de otras enfermedades asociadas con las trayectorias de transducción de señal que operan a través de los receptores del factor de crecimiento.

PROCESO PARA LA PREPARACION DE CIERTOS COMPUESTOS DE
PIRROLOTRIAZINA

CAMPO DE LA INVENCION

Esta invención se refiere a procesos nuevos, mejorados para la preparación de ciertos compuestos de pirrolootriazina que inhiben la actividad de la tirosina cinasa de los receptores del factor de crecimiento, tales como VEGFR-2 FGFR-1, por lo cual se hacen útiles como agentes anti-cáncer. Los compuestos preparados mediante los procesos de la invención son también útiles en el tratamiento de enfermedades, además de cáncer, que se asocian con las trayectorias de transducción de señal que operan a través de los factores de crecimiento y receptores anti-angiogénicos tales como VEGFR-2.

ANTECEDENTES DE LA INVENCION

La angiogénesis normal juega un papel importante en una variedad de procesos que incluyen el desarrollo embrionario, curación de heridas, obesidad y varios componentes de la función reproductora femenina. La angiogénesis indeseable o patológica se ha asociado con estados de enfermedad que incluyen retinopatía diabética, psoriasis, artritis reumatoide, ateroma, sarcoma de Kaposi y hemangioma, asma, cáncer y enfermedad metastática (Fan et al., 1995, Trend

Pharmacol. Sci. 16: 57-66, Folkman, 1995, Nature Medicine 1: 27-31). La alteración de la permeabilidad vascular se considera que juega un papel tanto en los procesos normal como en el fisiopatológico (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al., 1993 Cancer and Metastasis Reviews, 12: 303-324).

Los receptores de la tirosina cinasa (RTKs) son importantes en la transmisión de señales bioquímicas a través de la membrana de plasma de las células. Estas moléculas de transmembrana consisten característicamente de un dominio de ligando-enlace extracelular conectado a través de un segmento en la membrana de plasma a un dominio de tirosina cinasa intracelular. El enlace del ligando al receptor resulta en la estimulación de la actividad de la tirosina cinasa asociada con el receptor que lleva a la fosforilación de los residuos de tirosina tanto en el receptor como en otras proteínas intracelulares, lo que lleva a una variedad de respuestas celulares. A la fecha, se han identificado por lo menos diecinueve subfamilias de RTK distintas, definidas por la homología de secuencia de aminoácidos. Una de estas subfamilias comprende actualmente el receptor de tirosina cinasa tipo fms, Flt o Flt1 (VEGFR-1), el receptor que contiene el dominio insertado en la cinasa, KDR (también referido como Flk-1 o VEGFR-2), y otro receptor de tirosina cinasa tipo fms, Flt4 (VEGFR-3). Dos de estos RTKs

relacionados, Flt y KDR, han demostrado ligar el factor de crecimiento endotelial vascular (VEGF) con alta afinidad (De Vries et al., 1992, Science 255:989-991; Terman et al., 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). La unión de VEGF a estos receptores expresados en células heterólogas se ha asociado con cambios en el estado de fosforilación de la tirosina de proteínas celulares y flujos de calcio. El VEGF, junto con el factor de crecimiento de fibroblastos ácidos y básicos (aFGF y bFGF), se ha identificado como que tiene actividad para promover el crecimiento celular endotelial *in vitro*. Se ha notado que el aFGF y bFGF se ligan a y activan el receptor de tirosina cinasa llamado FGFR-1. En virtud de la expresión restringida de estos receptores, la actividad del factor de crecimiento de VEGF, en contraste con la de los FGFs, es relativamente específica hacia células endoteliales. La evidencia reciente indica que el VEGF es un estimulador importante de la angiogénesis tanto normal como patológica (Jakeman et al., 1993, Endocrinology, 133: 848-859; Kolch et al., 1995, Breast Cancer Research and Treatment, 36: 139-155) y permeabilidad vascular (Connolly et al., 1989, J. Biol. Chem. 264: 20017-20024).

En adultos, las células endoteliales tienen un índice de proliferación bajo, excepto en casos de remodelación de tejido, tales como curación de heridas y en el ciclo reproductor femenino, y adipogénesis. Sin embargo, en estados

patológicos tales como el cáncer, enfermedades vasculares hereditarias, endometriosis, psoriasis, artritis, retinopatías y aterosclerosis, las células endoteliales proliferan y se organizan activamente en los vasos. Durante la exposición a un estímulo angiogénico con factores de crecimiento tales como VEGF y bFGF, las células endoteliales vuelven a entrar al ciclo celular, proliferando, migrando y organizándose en un canal tridimensional. Ahora, es ampliamente aceptado que la capacidad de los tumores para expandirse y formar metástasis depende de la formación de este canal vascular.

El enlace de VEGF o bFGF a su receptor correspondiente resulta en la dimerización, autofosforilación en residuos de tirosina y activación enzimática. Estos residuos de fosfotirosina sirven como sitios de "acoplamiento" para moléculas de señalización 3' específicas y la activación enzimática que resulta en la activación EC. La interrupción de estas trayectorias debería inhibir la activación celular endotelial. La interrupción de la trayectoria FGFR-1 también debería afectar la proliferación celular del tumor, ya que esta cinasa se activa en muchos tipos de tumores además de proliferar en células endoteliales. Finalmente, la evidencia reciente también sugiere que la interrupción de la señalización VEGF inhibe la migración celular endotelial, un proceso crítico en la formación de canales vasculares.

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La sobreexpresión y activación de VEGFR-2 y FGFR-1 en la vascularidad asociada con el tumor, sugiere un papel para estas moléculas en la angiogénesis del tumor. La angiogénesis y el crecimiento posterior del tumor se inhibe por anticuerpos dirigidos contra el ligando VEGF y receptores VEGF, y por receptores VEGFR-2 solubles truncados (que carecen de la secuencia de transmembrana y dominio de cinasa citoplásmico). Las mutaciones dominantes introducidas ya sea por VEGFR-2 o FGFR-1 que resultan en una pérdida de actividad enzimática, inhiben el crecimiento del tumor *in vivo*. La dirección antisentido de estos receptores o sus ligandos similares también inhibe la angiogénesis y el crecimiento del tumor. La evidencia reciente ha aclarado, en parte, los requerimientos temporales de estos receptores en el crecimiento del tumor. Parece que la señalización VEGF es crítica en el crecimiento de tumor temprano y el bFGF es más importante a últimas fechas asociado con la expansión del tumor.

Los compuestos que pueden beneficiarse de los procesos de la invención incluyen los de las solicitudes de prioridad, así como los compuestos descritos en la WO 00/71129, que se incorporan en la presente por referencia en su totalidad.

BREVE DESCRIPCIÓN DE LA INVENCION

La presente invención proporciona un proceso para la

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preparación de ciertos compuestos de pirrolotriazina. El proceso de la invención proporciona una preparación útil, conveniente y mejorada de los derivados de pirrolotriazina que contienen un grupo hidroxilo enlazado directamente al anillo de pirrolotriazina.

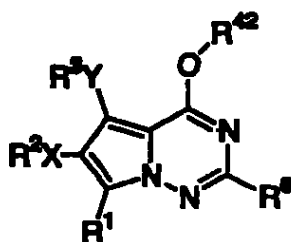
El proceso de la invención comprende, en una modalidad, las etapas de hacer reaccionar una pirrolotriazina sustituida con cloro con un anión de óxido para formar un éter; convertir el éster a un alcohol bencílico, re-arreglar de manera oxidante el alcohol para formar un fenol. El compuesto de hidroxilo se alquila subsecuentemente con un agente electrofílico para proporcionar un compuesto sustituido con fenoxi que se hidroliza para proporcionar una amida. Esta se convierte al compuesto final formando primero un cloroimidato y haciendo reaccionar éste con un agente de alquilación, tal como hidroxí fluoroindol en presencia de una base en un solvente polar, para proporcionar el compuesto final.

En una segunda modalidad, la invención proporciona un proceso para preparar la porción del fluoroindol de los compuestos usando un proceso nuevo y mejorado, que se somete a las preparaciones a gran escala y proporciona derivados de fluoroindol de alta calidad. Además, los derivados de fluoroindol preparados usando el proceso descrito en la presente son sólidos estables que son fáciles de aislar y tienen estabilidad a largo plazo, dando productos de mayor

calidad que los derivados de fluoroindol preparados usando los métodos alternativos.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención proporciona un proceso para la preparación de ciertos compuestos de pirrolotriazina de la fórmula:



(I)

sus enantiómeros, diastereómeros y sales farmacéuticamente aceptables, profármacos y solvatos de los mismos, que inhiben la actividad de la tirosina cinasa de los receptores del factor de crecimiento, tales como VEGFR-2. En la Fórmula I y a través de la especificación, los símbolos anteriores se definen como sigue:

X e Y se seleccionan independientemente de O, OCO, S, SO, SO₂, CO, CO₂, NR¹⁰, NR¹¹CO, NR¹²CONR¹³, NR¹⁴CO₂, NR¹⁵SO₂, NR¹⁶SO₂NR¹⁷, SO₂NR¹⁸, CONR¹⁹, halógeno, nitro, ciano o X ó Y están ausentes;

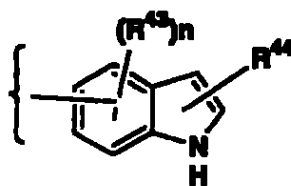
R¹ es hidrógeno;

R^2 y R^3 son independientemente hidrógeno, alquilo, alquilo sustituido, alqueno, alqueno sustituido, alquino, alquino sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, aralquilo, aralquilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido; con la condición de que cuando X es halo, nitro o ciano, R^2 está ausente, y, cuando Y es halo, nitro o ciano, R^3 está ausente;

R^6 es H;

R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} y R^{19} se seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo o heterociclo sustituido;

R^{42} es



$(R^{43})_n$ en donde n es igual a 0, 1 ó 2 y cada R^{43} se selecciona independientemente del grupo que consiste de hidrógeno, flúor, cloro y metilo; y

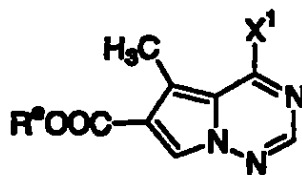
R^{44} es metilo o hidrógeno,
con la condición adicional de que:

a. R^2 no puede ser hidrógeno si X es SO, SO₂, NR¹³CO₂ o NR¹⁴SO₂; y

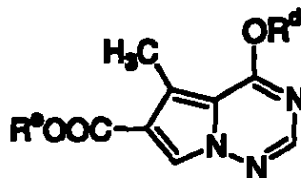
b. R^3 no puede ser hidrógeno si Y es SO, SO₂, NR¹³CO₂ o NR¹⁴SO₂.

El proceso de la invención comprende, en una modalidad, las etapas de:

a) convertir un compuesto de la fórmula



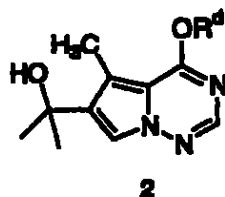
en donde R^e es alquilo inferior o arilo y X^1 es halógeno, a un compuesto 1 de la fórmula



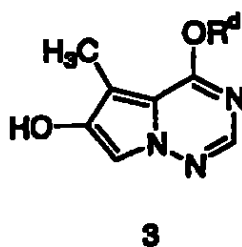
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en donde R^d es alquilo inferior, arilo, arilo sustituido, heteroarilo o heteroarilo sustituido mediante el tratamiento con un fenóxido o alcóxido,

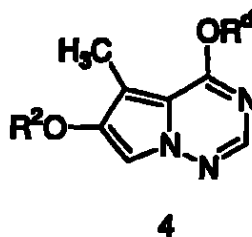
b) alquilar el Compuesto 1 para proporcionar el Compuesto 2 de la fórmula



c) tratar el Compuesto 2 con un peróxido en presencia de un ácido de Lewis, para proporcionar el Compuesto 3 de la fórmula

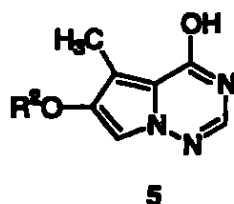


d) alquilar el grupo fenol en el compuesto 3 para proporcionar el Compuesto 4 de la fórmula



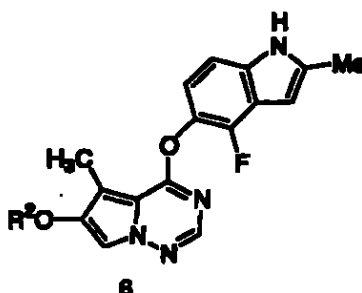
donde R² es bencilo o bencilo sustituido,

e) hidrolizar el Compuesto 4 para proporcionar el Compuesto 5 de la fórmula



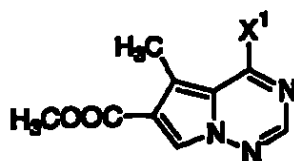
donde R^2 es bencilo o bencilo sustituido, y

f) convertir el Compuesto 5 al Compuesto 6 de la fórmula



convirtiendo primero el compuesto 5 a un cloroimidato y alquilando subsecuentemente el cloroimidato para proporcionar el Compuesto 6, en donde R^2 es bencilo. La desprotección del fenol está acompañada por el tratamiento con un donador de hidrógeno en presencia de un catalizador, para proporcionar el compuesto 6 donde R^2 es hidrógeno.

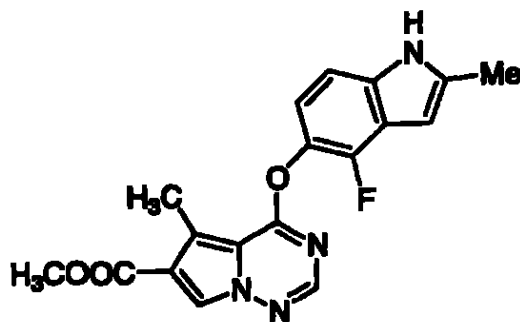
En una segunda modalidad de la invención, el compuesto iniciador de la fórmula



7

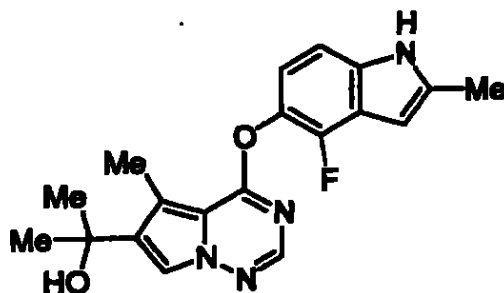
donde X_1 es halógeno;

se hace reaccionar con un nucleófilo para proporcionar el
Compuesto 8 de la fórmula



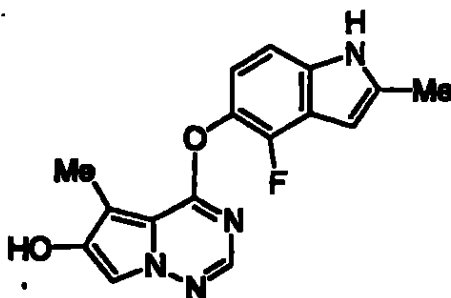
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que se trata con un agente de alquilación a una baja
temperatura, para proporcionar el Compuesto 9 de la fórmula



9

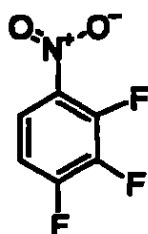
El Compuesto 9 después se trata con un peróxido en presencia de un ácido de Lewis para proporcionar el Compuesto 10 de la fórmula



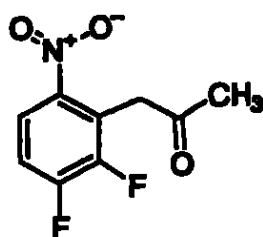
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En una modalidad adicional de la invención, la parte del fluoroindol puede prepararse como sigue:

a) hacer reaccionar un compuesto fluorado de la fórmula

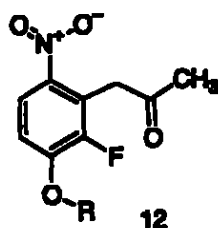


con un nucleófilo para proporcionar el Compuesto 11 de la fórmula.



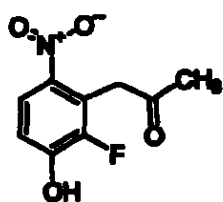
11

b) hacer reaccionar el Compuesto 11 con un anión de alcoxi para proporcionar el Compuesto 12 de la fórmula



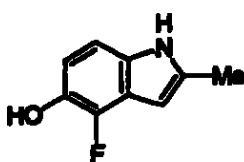
en donde R es un grupo protector,

c) desproteger el grupo alcoxi mediante tratamientos con reactivos desprotectores, para proporcionar el Compuesto 13 de la fórmula



y

d) ciclizar el Compuesto 13 bajo condiciones reductoras para proporcionar el Compuesto 14 de la fórmula



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En una modalidad preferida, la etapa 1 del esquema de reacción 1 involucró la conversión del compuesto a un éter mediante el tratamiento con un nucleófilo, tal como un anión fenóxido o alcóxido. De preferencia, el anión alcóxido es un anión de metóxido o etóxido.

Los agentes de alquilación preferidos en la etapa 2 del esquema de reacción 1 incluyen un haluro de alquil magnesio, es decir, bromuro de metil magnesio o cloruro de metil magnesio a baja temperatura, de aproximadamente -25°C a aproximadamente 25°C .

El compuesto 2 en la etapa 3 se trata preferentemente con un peróxido tal como peróxido de hidrógeno o perborato de sodio en presencia de un ácido de Lewis, tal como trifluoruro de boro, en un solvente orgánico tal como diclorometano (DCM), para proporcionar el compuesto 3. El compuesto 3 se alquila con un agente electrofílico tal como bromuro de bencilo o cloruro de bencilo en presencia de una base, tal como NaH a una temperatura de aproximadamente 0°C a aproximadamente 100°C .

El compuesto 4 se hidroliza mediante el tratamiento con un ácido, de preferencia HCl, acuoso a una temperatura elevada para proporcionar el Compuesto 5. El compuesto 5 se convierte finalmente al Compuesto 6 por medio del cloroimidato que se alquila subsecuentemente, de preferencia con hidroxí fluoroindol, en presencia de una base tal como

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47

carbonato de potasio o hidruro de sodio en un solvente polar, tal como dimetilformamida (DMF) o tolueno, de preferencia DMF. La desprotección bencílica se logra mediante el tratamiento con una fuente de hidrógeno, tal como formato de amonio en presencia de un catalizador tal como Paladio sobre carbono.

Las condiciones preferidas para la segunda modalidad incluyen en la etapa 1, el uso de un nucleófilo, tal como fluoroindol en presencia de una base tal como carbonato de potasio o hidruro de sodio, para tratar el Compuesto 7 para proporcionar el Compuesto 8. Esta reacción se lleva a cabo, de preferencia, en un solvente polar tal como DMF. La etapa 2 involucra tratar el Compuesto 8 con un agente de alquilación, tal como un haluro de alquil magnesio, es decir, bromuro de metil magnesio o cloruro de metil magnesio a baja temperatura, de aproximadamente -25°C a aproximadamente 25°C . en una modalidad preferida, la Etapa 3 involucra tratar el Compuesto 9 con un peróxido tal como peróxido de hidrógeno o perborato de sodio en presencia de un ácido de Lewis, tal como trifluoruro de boro a una temperatura de aproximadamente -25°C a aproximadamente 25°C , para proporcionar el Compuesto 10.

En la preparación de la cadena lateral de indol, el compuesto fluorado iniciador, en este caso, trifluoronitrobenceno, puede hacerse reaccionar con un

nucleófilo, tal como acetoacetato de etilo o terbutilacetoacetato, que es seguido por descarboxilación del grupo éster en presencia de un ácido o una base, de preferencia un ácido acuoso. En la Etapa 2, el Compuesto 11 se hace reaccionar con un anión de alcoxi, tal como metóxido de sodio o metanol en presencia de una base, tal como carbonato de potasio o la sal de sodio del alcohol bencílico, para proporcionar el Compuesto 12. El grupo alcoxi o benciloxi después se desprotege mediante el tratamiento con un reactivo desprotector, tal como cloruro de piridinio o bromuro de hidrógeno en ácido acético, para proporcionar el Compuesto 13. En la etapa final, el Compuesto 13 se cicliza bajo condiciones reductoras, usando de preferencia agentes de reducción, tales como ditionato de sodio o paladio sobre carbono en presencia de una fuente de hidrógeno, para proporcionar los compuestos de indol deseados.

La invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula I ó II y un vehículo farmacéuticamente aceptable.

La invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula I ó II en combinación con un vehículo farmacéuticamente aceptable y un agente anti-cáncer o citotóxico. En una modalidad preferida, el agente anti-cáncer o citotóxico se selecciona del grupo que consiste de linomida: inhibidores de la función $\alpha\beta$ de

integrina; angiostatina; razoxano; tamoxifen; toremifeno; raloxifeno; droloxifeno; yodoxifeno; acetato de megestrol; anastrozol; letrozol; borazol; exemestano; flutamida; nilutamida; bicalutamida; acetato de ciproterona; acetato de goserelina; leuprolida; finasterida; inhibidores de metaloproteinasa; inhibidores de la función del receptor del activador de plasminógeno de urocinasa; anticuerpos del factor de crecimiento; anticuerpos del receptor del factor de crecimiento, tales como Avastin® (bevacizumab) y Erbitux® (cetuximab); inhibidores de tirosina cinasa; inhibidores de serina/treonina cinasa; metotrexato; 5-fluorouracilo; purina; análogos de adenosina; citosina arabinosida; doxorubicina; daunomicina; epirubicina; idarubicina; mitomicina-C; dactinomicina; mitramicina; cisplatina; carboplatina; mostaza de nitrógeno, melfalan, clorambucil; busulfan; ciclofosfamida; ifosfamida nitrosoureas; tiotepa; vincristina; Taxol® (paclitaxel); Taxotere® (docetaxel); análogos de epotilona; análogos de discodermolida; análogos de eleuterobina; etoposida; teniposida; ambsacrina; topotecano; flavopiridoles; modificadores de la respuesta biológica e inhibidores de proteasoma, tal como Velcade® (bortezomib).

La invención también proporciona un método para inhibir la actividad de la proteína cinasa de los receptores del factor de crecimiento, que comprende administrar a una

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especie mamífera en necesidad del mismo, una cantidad de inhibición de la proteína cinasa terapéuticamente efectiva de un compuesto de fórmula I.

Adicionalmente, se describe un método para inhibir la actividad de la tirosina cinasa de por lo menos un receptor del factor de crecimiento, tal como que comprende administrar a una especie mamífera en necesidad del mismo, una cantidad terapéuticamente efectiva de un compuesto de fórmula I ó II. En una modalidad preferida, el receptor del factor de crecimiento se selecciona del grupo que consiste de VEGFR-2 y FGFR-1.

Finalmente, se describe un método para tratar una enfermedad proliferativa, que comprende administrar a una especie mamífera en necesidad del mismo, una cantidad terapéuticamente efectiva de un compuesto de fórmula I. En una modalidad preferida, la enfermedad proliferativa es cáncer.

Las siguientes son definiciones de los términos que pueden usarse en la presente especificación. La definición inicial proporcionada para un grupo o término en la presente, aplica para tal grupo o término a través de la presente especificación, individualmente o como parte de otro grupo, a menos que se indique lo contrario.

El término "alquilo" se refiere a grupos de hidrocarburos no sustituidos de cadena lineal o ramificada de

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1 a 20 átomos de carbono, de preferencia 1 a 7 átomos de carbono. La expresión "alquilo inferior" se refiere a grupos alquilo no sustituidos de 1 a 4 átomos de carbono.

El término "alquilo sustituido" se refiere a un grupo alquilo sustituido mediante, por ejemplo, uno a cuatro sustituyentes, tales como, halo, hidroxilo, alcoxi, oxo, alcanilo, arilo, alcanilo, amino, alquilamino, arilamino, aralquilamino, aminos disustituídos en las que los dos sustituyentes amino se seleccionan de alquilo, arilo o aralquilo; alcanilamino, aroilamino, aralcanilamino, alcanilamino sustituido, arilamino sustituido, aralcanilamino sustituido, tiol, alquiltio, ariltio, aralquiltio, alquiltionio, ariltionio, aralquiltionio, alquilsulfonilo, arilsulfonilo, aralquilsulfonilo, sulfonamido, por ejemplo, SO_2NH_2 , sulfonamido sustituido, nitro, ciano, carboxi, carbamilo, por ejemplo, CONH_2 , carbamilo sustituido, por ejemplo, CONH alquilo, CONH arilo, CONH aralquilo o los casos donde hay dos sustituyentes en el nitrógeno seleccionados de alquilo, arilo o aralquilo; alcoxicarbonilo, arilo, arilo sustituido, guanidino y heterociclos, tales como, indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares. Cuando se observa anteriormente que el sustituyente se sustituye adicionalmente, será con alquilo, alcoxi, arilo o aralquilo.

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

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

El término "aralquilo" se refiere a un grupo arilo enlazado directamente a través de un grupo alquilo, tal como bencilo.

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

El término "heteroarilo" se refiere a un grupo aromático, opcionalmente sustituido por ejemplo, que es un sistema de anillo de 4 a 7 miembros monocíclico, 7 a 11

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miembros bicíclico ó 10 a 15 miembros tricíclico, que tiene por lo menos un heteroátomo y por lo menos un anillo que contiene átomos de carbono, por ejemplo, piridina, tetrazol, indazol, indol.

El término "alquenilo" se refiere a grupos de hidrocarburos de cadena lineal o ramificada de 2 a 20 átomos de carbono, de preferencia 2 a 15 átomos de carbono, y más preferentemente 2 a 8 átomos de carbono, que tienen uno a cuatro enlaces dobles.

El término "alquenilo sustituido" se refiere a un grupo alquenilo sustituido mediante, por ejemplo, uno a dos sustituyentes, tales como, halo, hidroxí, alcoxi, alcanóilo, alcanóiloxi, amino, alquilamino, dialquilamino, alcanóilamino, tiol, alquiltio, alquiltiono, alquilsulfonilo, sulfonamido, nitro, ciano, carboxi, carbamilo, carbamilo sustituido, guanidino, indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares.

El término "alquinilo" se refiere a grupos de hidrocarburos de cadena lineal o ramificada de 2 a 20 átomos de carbono, de preferencia 2 a 15 átomos de carbono y más preferentemente 2 a 8 átomos de carbono, que tienen uno a cuatro enlaces triples.

El término "alquinilo sustituido" se refiere a un grupo alquinilo sustituido mediante, por ejemplo, un sustituyente,

tales como, halo, hidroxí, alcoxi, alcanóilo, alcanóiloxi, amino, alquílamo, dialquílamo, alcanóilamo, tiol, alquiltio, alquiltiono, alquilsulfonilo, sulfonamido, nitro, ciano, carboxi, carbamilo, carbamilo sustituido, guanidino y heterociclo, por ejemplo imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo y similares.

El término "cicloalquilo" se refiere a sistemas de anillos de hidrocarburos opcionalmente sustituidos, cíclicos saturados, que contienen de preferencia 1 a 3 anillos y 3 a 7 carbonos por anillo, que pueden ser fusionados además con un anillo carbocíclico C_3-C_7 no saturado. Ejemplos de estos grupos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecilo, ciclododecilo y adamantilo. Ejemplos de los sustituyentes incluyen uno o más grupos alquilo como se describió anteriormente, o uno o más de los grupos descritos anteriormente como sustituyentes alquilo.

Los términos "heterociclo", "heterocíclico" y "heterociclo" se refieren a un grupo cíclico opcionalmente sustituido, completamente saturado o no saturado, aromático o no aromático, por ejemplo, que es un sistema de anillo de 4 a 7 miembros monocíclico, 7 a 11 miembros bicíclico o 10 a 15 miembros tricíclico, que tiene por lo menos un heteroátomo en por lo menos un anillo que contiene átomos de carbono. Cada anillo del grupo heterocíclico que contiene un heteroátomo

X 55

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 también pueden oxidarse opcionalmente y los heteroátomos de nitrógeno también pueden cuaternizarse opcionalmente. El grupo heterocíclico puede enlazarse a cualquier heteroátomo o átomo de carbono.

Ejemplos de los grupos heterocíclicos monocíclicos incluyen pirrolidinilo, pirrolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahidrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxazepinilo, azepinilo, 4-piperidonilo, piridilo, N-oxo-piridilo, pirazinilo, pirimidinilo, piridazinilo, tetrahidropirranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, tiamorfolinilo sulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo, dioxanilo, isotiazolidinilo, tietanilo, tiiranilo, triazinilo y triazolilo y similares.

Ejemplos de los grupos heterocíclicos bicíclicos incluyen 2,3-dihidro-2-oxo-1H-indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, quinolinilo-N-óxido, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopirranilo, indolizininilo,

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benzofurilo, cromonilo, cumarinilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tales como furo[2,3-c]piridinilo, furo[3,1-b]piridinilo o furo[2,3-b]piridinilo), dihidroisoindolilo, dihidroquinazolinilo (tales como 3,4-dihidro-4-oxoquinazolinilo), bencisotiazolilo, bencisoxazolilo, benzodiazinilo, bencimidazolilo, benzofurazanilo, benzotiopiranilo, benzotriazolilo, benzpirazolilo, dihidrobenzofurilo, dihidrobenzotienilo, dihidrobenzotiopiranilo, dihidrobenzotiopiranilo sulfona, dihidrobenzopiranilo, indolinilo, indolilo, isocromanilo, isoindolinilo, naftiridinilo, ftalazinilo, piperonilo, purinilo, piridopiridilo, quinazolinilo, tetrahidroquinolinilo, tienofurilo, tienopiridilo, tienotienilo y similares.

Ejemplos de los sustituyentes incluyen uno o más grupos alquilo o aralquilo como se describió anteriormente o uno o más de los grupos descritos anteriormente como sustituyentes alquilo. También se incluyen heterociclos más pequeños, tales como, epóxidos y aziridinas.

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

Los compuestos de fórmula I pueden formar sales que también están dentro del alcance de esta invención. Se prefieren las sales farmacéuticamente aceptables (es decir,

X
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no tóxicas, fisiológicamente aceptables), aunque también son útiles otras sales, por ejemplo, en el aislamiento o purificación de los compuestos de esta invención.

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

Los compuestos de fórmula I pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. Tales sales incluyen las formadas con cloruro de hidrógeno, bromuro de hidrógeno, ácido metansulfónico, ácido sulfúrico, ácido acético, ácido trifluoroacético, ácido oxálico, ácido maleico, ácido bencensulfónico, ácido toluensulfónico y varios otros (por ejemplo, nitratos, fosfatos, boratos, tartratos, citratos, succinatos, benzoatos, ascorbatos, salicilatos y similares). Tales sales pueden formarse como se conoce por los experimentados en la técnica.

Además, pueden formarse zwitteriones ("sales internas").

Se contemplan todos los estereoisómeros de los compuestos de la presente invención, ya sea en mezcla o en la forma pura o sustancialmente pura. La definición de los compuestos de acuerdo con la invención abarca todos los

estereoisómeros posibles y sus mezclas. Muy particularmente abarca las formas racémicas y los isómeros ópticos aislados que tienen la actividad especificada. Las formas racémicas pueden resolverse por los métodos físicos, tales como, por ejemplo, destilación fraccionada, separación o cristalización de los derivados diastereoméricos o separación por 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 seguido de cristalización.

Los compuestos de fórmula I también pueden tener formas de profármacos. Cualquier compuesto que se convertirá in vivo para proporcionar el agente bioactivo (es decir, el compuesto para la fórmula I) es un profármaco dentro del alcance y espíritu de la invención.

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

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

b) A Textbook of Drug Design and Development, editado por Krosgaard-Larsen and H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs", editado por H. Bundgaard, p.

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113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992).

Debería entenderse además que los solvatos (por ejemplo, hidratos) de los compuestos de fórmula I, también están dentro del alcance de la presente invención. En general, los métodos de solvatación son conocidos en la técnica.

De esta manera, de acuerdo con un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo en la manufactura de un medicamento para el uso en la producción de un efecto antiangiogénico y/o reductor de la permeabilidad vascular, en un animal mamífero tal como un ser humano.

De acuerdo con una característica adicional de la invención, se proporciona un método para producir un antiangiogénico y/o efecto reductor de la permeabilidad vascular en un animal mamífero, tal como un ser humano, en necesidad de tal tratamiento, que comprende administrar al animal una cantidad efectiva de un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo como se definió en la presente anteriormente.

Los compuestos descritos en la presente también inhiben otros receptores de tirosina cinasa incluyendo HER1 y HER2 y por lo tanto, son útiles en el tratamiento de trastornos proliferativos, tales como psoriasis y cáncer. La cinasa del

receptor HER1 se ha mostrado que se expresa y activa en muchos tumores sólidos, que incluyen cáncer de pulmón de células no pequeñas, colorrectal y mama. De manera similar, la cinasa del receptor HER2 se ha mostrado que se sobreexpresa en cáncer de mama, ovario, pulmón y gástrico. Los anticuerpos monoclonales que sub-regulan la abundancia del receptor HER2 o inhiben la señalización por el receptor HER1 han mostrado eficacia anti-tumoral en los estudios preclínicos y clínicos. Por lo tanto, se espera que los inhibidores de las cinasas HER1 y HER2 tengan eficacia en el tratamiento de tumores que dependen de la señalización de cualquiera de los dos receptores. La capacidad de estos compuestos para inhibir HER1 aumenta adicionalmente su uso como agentes anti-angiogénicos. Ver los siguientes documentos y referencias citados en la presente: Cobleigh, M.A., Vogel, C.L., Tripathy, D., Robert, N.J., Scholl, S., Fehrenbacher, L., Wolter, J. M., Paton, V., Shak, S., Lieberman, G., and Slamon, D.J., "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease", *J. of Clin. Oncol.* 17(9), p. 2639-2648 (1999); Baselga, J., Pfister, D., Cooper, M.R., Cohen, R., Burtness, B., Bos, M., D'Andrea, G., Seidman, A., Norton, L., Gunnett, K., Falcey, J., Anderson, V., Waksal, H., and Mendelsohn, J., "Phase I

studies of anti-epidermal growth factor receptor chimeric antibody C225 alone and in combination with cisplatin", *J. Clin. Oncol.* 18(4), p. 904-911 (2000).

El tratamiento antiproliferativo, antiangiogénico y/o reductor de la permeabilidad vascular definido en la presente anteriormente, puede aplicarse como una sola terapia o puede involucrar, además de un compuesto de la invención, una o más de otras sustancias y/o tratamientos. Tal tratamiento conjunto puede lograrse por medio de la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. Los compuestos de esta invención también pueden ser útiles en combinación con los agentes anti-cáncer y citotóxicos conocidos y tratamientos incluyendo radiación. Si se formula como una dosis fijada, tales productos de combinación emplean los compuestos de esta invención dentro del intervalo de dosificación descrito a continuación y el otro agente farmacéuticamente activo dentro de su intervalo de dosificación aprobado. Los compuestos de fórmula I pueden usarse secuencialmente con los agentes anticáncer o citotóxicos conocidos y tratamiento, incluyendo radiación, cuando es inapropiada una formulación de combinación.

En el campo de la oncología médica, es práctica normal usar una combinación de diferentes formas de tratamiento para tratar cada paciente con cáncer. En la oncología médica, el o

los otros componentes de tal tratamiento conjunto, además del tratamiento antiproliferativo, antiangiogénico y/o reductor de la permeabilidad vascular definido en la presente anteriormente, puede ser: cirugía, radioterapia o quimioterapia. La quimioterapia puede cubrir tres categorías principales del agente terapéutico:

(i) agentes antiangiogénicos que trabajan por mecanismos diferentes de los definidos anteriormente (por ejemplo, linomida, inhibidores de la función $\alpha v \beta 3$ de integrina, angiostatina, razoxano);

(ii) agentes citostáticos, tales como antiestrógenos (por ejemplo, tamoxifen, toremifeno, raloxifeno, droloxifeno, yodoxifeno), progestogenos (por ejemplo, acetato de megestrol), inhibidores de aromataza (por ejemplo, anastrozol, letrozol, boraol, exemestano), antihormonas, antiprogestogenos, antiandrógenos (por ejemplo, flutamida, nilutamida, bicalutamida, acetato de ciproterona), agonistas y antagonistas de LHRH (por ejemplo, acetato de goserelina, leuprolida), inhibidores de testosterona 5 α -dihidrorreductasa (por ejemplo, finasterida), inhibidores de farnesiltransferasa, agentes anti-invasión (por ejemplo, inhibidores de metaloproteinasa, tales como marimastat e inhibidores de la función del receptor del activador de plasminógeno de urocina) e inhibidores de la función del factor de crecimiento (tales factores de crecimiento

incluyen, por ejemplo, EGF, FGF, factor de crecimiento derivados de plaquetas y factor de crecimiento de hepatocitos, tales inhibidores incluyen anticuerpos del factor de crecimiento, anticuerpos del receptor del factor de crecimiento tales como Avastin® (bevacizumab) y Erbitux® (cetuximab); inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa); y fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, como se usa en la oncología médica, tales como antimetabolitos (por ejemplo, antifolatos tipo metotrexato, fluoropirimidinas tipo 5-fluorouracilo, purina y análogos de adenosina, citosina arabinosida); antibióticos antitumorales intercalados (por ejemplo, antraciclinas tales como doxorubicina, daunomicina, epirubicina e idarubicina, mitomicina-C, dactinomicina, mitramicina); derivados de platino (por ejemplo, cisplatina, carboplatina); agentes de alquilación (por ejemplo, mostaza de nitrógeno, melfalan, clorambucil, busulfan, ciclofosfamida, ifosfamida, nitrosoureas, tiotepa; agentes antimitóticos (por ejemplo, alcaloides vinca, tales como vincristina y taxoides tal como Taxol® (paclitaxel), Taxotere® (docetaxel) y agentes microtúbulo más nuevos tales como análogos de epotilona, análogos de discodermolida y análogos de eleuterobina); inhibidores de topoisomerasa (por ejemplo, epipodofilotoxinas tales como etoposida y teniposida, amsacrina, topotecano);

inhibidores del ciclo celular (por ejemplo, flavopiridoles); modificadores de la respuesta biológica e inhibidores de proteasoma, tales como Velcade® (bortezomib).

Como se estableció anteriormente, los compuestos de fórmula I de la presente invención son de interés por sus efectos antiangiogénicos y/o reductores de la permeabilidad vascular. Tales compuestos de la invención se espera que sean útiles en un amplio intervalo de estados de enfermedades, que incluyen cáncer, diabetes, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, obesidad, nefropatías aguda y crónica ateroma, restenosis arterial, enfermedades autoinmunes, inflamación aguda y enfermedades oculares asociadas con proliferación de vasos de la retina, tal como retinopatía diabética.

Más específicamente, los compuestos de fórmula I son útiles en el tratamiento de una variedad de cánceres, que incluyen (pero no se limitan a) los siguientes:

- carcinoma, que incluye el de vejiga, mama, colon, riñón, hígado, pulmón, que incluye cáncer de pulmón de células pequeñas, esófago, vesícula biliar, ovario, páncreas, estómago, cerviz, tiroides, próstata y piel, incluyendo carcinoma de células escamosas;

- tumores hematopoyéticos de la línea linfoide, que incluyen leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células

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T, linfoma de Hodgkins, linfoma de no Hodgkins, linfoma de células cabellosas y linfoma de Burkett;

- tumores hematopoyéticos de la línea mieloide, que incluye leucemias mielógenas aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

- tumores de origen mesenquimatoso, que incluyen fibrosarcoma y rabdomiosarcoma;

- tumores del sistema nervioso central y periférico, que incluyen astrocitoma, neuroblastoma, glioma y schwannomas (neurilemoma); y

- otros tumores, que incluyen melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratocantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Debido al papel clave de las cinasas en la regulación de la proliferación celular en general, los inhibidores pueden actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de cualquier proceso de enfermedad que caracteriza a la proliferación celular anormal, por ejemplo, hiperplasia benigna de próstata, poliposis por adenomatosis familiar, neuro-fibromatosis, aterosclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis después de angioplastia o cirugía vascular, formación de cicatrices hipertróficas, enfermedad de intestino inflamatorio, rechazo de transplantes, choque

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endotóxico e infecciones por hongos.

Los compuestos de la fórmula I pueden inducir o inhibir la apoptosis. La respuesta apoptótica es aberrante en una variedad de enfermedades en el humano. Los compuestos de fórmula I, como moduladores de apoptosis, serán útiles en el tratamiento de cáncer (incluyendo, pero no se limitan a los tipos mencionados anteriormente), infecciones virales (incluyendo, pero no se limitan a virus del herpes, poxvirus, virus de Epstein-Barr, virus de Sindbis y adenovirus), prevención del desarrollo de SIDA en individuos infectados con VIH, enfermedades autoinmunes (que incluyen, pero no se limitan a lupus eritematoso sistémico, glomerulonefritis mediada autoinmune, artritis reumatoide, psoriasis, enfermedad de intestino inflamatorio y diabetes mellitus autoinmune), trastornos neurodegenerativos (que incluyen, pero no se limitan a enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal y degeneración cerebelar), síndromes mielodisplásicos, anemia aplásica, lesión isquémica asociada con infartos del miocardio, ataque y daño por reperfusión, arritmia, aterosclerosis, enfermedades del hígado inducidas por toxinas o relacionadas con el alcohol, enfermedades hematológicas (que incluyen, pero no se limitan a anemia crónica y anemia aplásica), enfermedades degenerativas del

67
fz

sistema musculoesquelético (que incluyen, pero no se limitan a osteoporosis y artritis), rinosinusitis sensible a aspirina, fibrosis quística, esclerosis múltiple, enfermedades del riñón y dolor por cáncer.

Los compuestos de la fórmula I son especialmente útiles en el tratamiento de tumores que tienen una alta incidencia de actividad de la tirosina cinasa, tales como tumores de colon, pulmón y pancreáticos. Mediante la administración de una composición (o una combinación) de los compuestos de esta invención, se reduce el desarrollo de tumores en un huésped mamífero.

Los compuestos de la fórmula I también pueden ser útiles en el tratamiento de enfermedades además del cáncer que puede asociarse con las trayectorias de la transducción de señal que operan a través de los receptores del factor de crecimiento, tales como VEGFR-2 y FGFR-1.

Los compuestos de esta invención pueden formularse con un vehículo o diluyente farmacéutico para la administración oral, intravenosa o subcutánea. La composición farmacéutica puede formularse de una manera clásica usando los vehículos sólidos o líquidos, los diluyentes y aditivos apropiados para el modo de administración deseado. Oralmente, los compuestos pueden administrarse en la forma de tabletas, cápsulas, gránulos, polvos y similares. Los compuestos también pueden administrarse como suspensiones usando los vehículos

apropiados para este modo de administración. Los compuestos pueden administrarse en un intervalo de dosificación de aproximadamente 0.05 a 300 mg/kg/día, de preferencia menos de 200 mg/kg/día, en una dosis simple o en 2 a 4 dosis divididas.

Métodos de Preparación

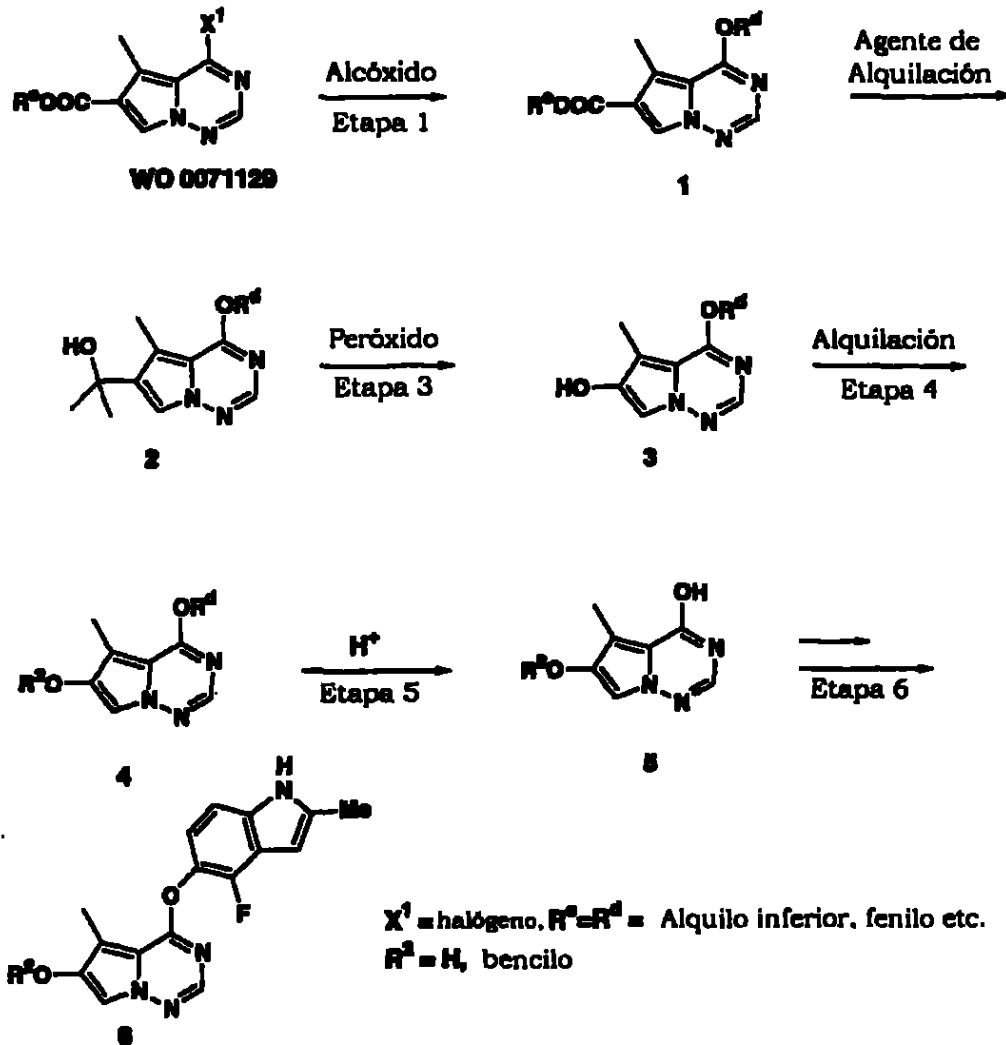
Algunos compuestos de la fórmula I pueden prepararse de acuerdo con los siguientes esquemas de reacción y el conocimiento de un experimentado en la técnica.

Todas las temperaturas están en grados Celsius (°C) a menos que se indique lo contrario. Las purificaciones por CLAR de Fase Inversa (FI) Preparativa se hicieron en columnas YMC S5 ODS de columnas de fase inversa (FI) C18 que eluyen con metanol acuoso al 90%, que contienen TFA al 0.1% como la solución amortiguadora y se monitorean a 220 nm. Para la CLAR analítica, se usó ácido fosfórico al 0.2% en lugar de TFA. Todos los compuestos sintetizados se caracterizaron mediante por lo menos RMN protónica y LC/EM. Durante la elaboración de las reacciones, el extracto orgánico se secó sobre sulfato de magnesio (MgSO_4), a menos que se mencione lo contrario.

Las siguientes abreviaciones se usan para los reactivos usados comúnmente. Et_2O ; éter dietílico, Na_2SO_4 ; sulfato de sodio; HCl ; ácido clorhídrico, NaOH ; hidróxido de sodio, NaCl ; cloruro de sodio, Pd/C ; paladio sobre carbono, K_2HPO_4 ; fosfato monoácido de potasio, K_2CO_3 ; carbonato de potasio,

NaHCO₃; bicarbonato de sodio, LiOH; hidróxido de litio, RT; temperatura ambiente, TFA; ácido trifluoroacético, h; hora.

Esquema de reacción 1



Etapa 1

Un compuesto de la Publicación WO 0071129 del PCT se convierte a un éter (eterificado) en la posición 4, por ejemplo, mediante el tratamiento con un anión de fenóxido o metóxido o etóxido.

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Etapas 2

El compuesto 1 después puede tratarse con un agente de alquilación tal como bromuro de metil magnesio o cloruro de metil magnesio, a temperaturas bajas, para proporcionar el compuesto 2.

Etapas 3

El compuesto 2 después puede tratarse con un peróxido, tal como peróxido de hidrógeno o perborato de sodio en presencia de un ácido de Lewis, tal como trifluoruro de boro, a baja temperatura, para proporcionar el compuesto 3.

Etapas 4

La alquilación del grupo fenol en el compuesto 3 con un agente electrofílico, tal como bromuro de bencilo, en presencia de una base, tal como NaH, de 0°C a 80°C, proporciona el compuesto 4.

Etapas 5

La hidrólisis del compuesto 4 de este esquema de reacción se logra mediante el tratamiento con un ácido, tal como HCl acuoso, a una temperatura elevada, para proporcionar el compuesto 5.

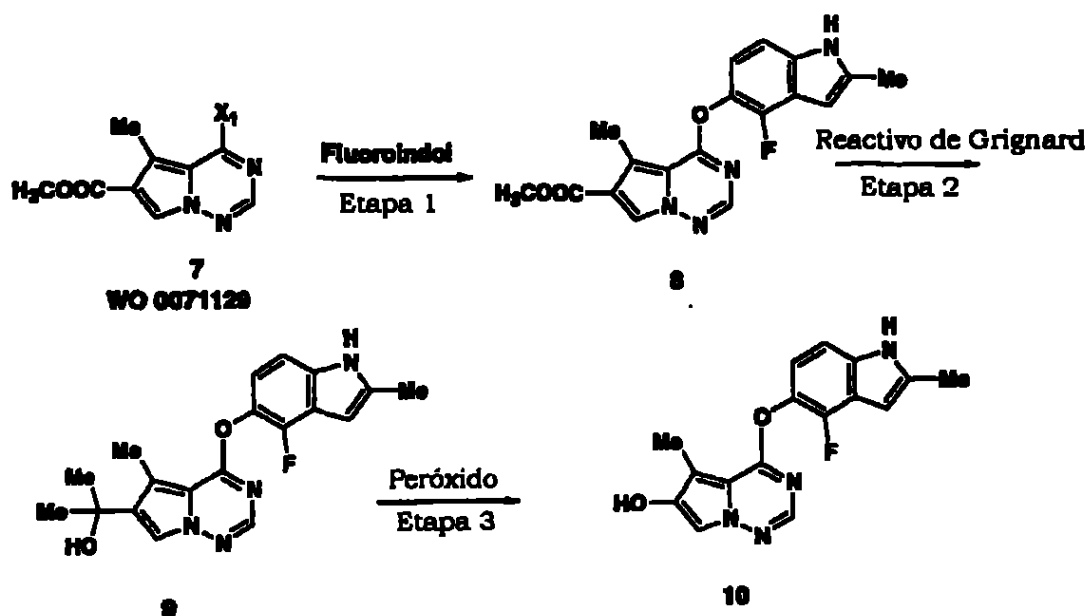
Etapas 6

El compuesto 5 de este esquema de reacción se convierte al compuesto 6 convirtiéndose primero al cloroimidato como se describe anteriormente, seguido de alquilación del cloroimidato resultante con un hidroxí fluorindol en

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presencia de una base, tal como carbonato de potasio en un solvente polar tal como dimetilformamida, para proporcionar el compuesto 6 protegido.

Esquema de reacción 2



Etapa 1

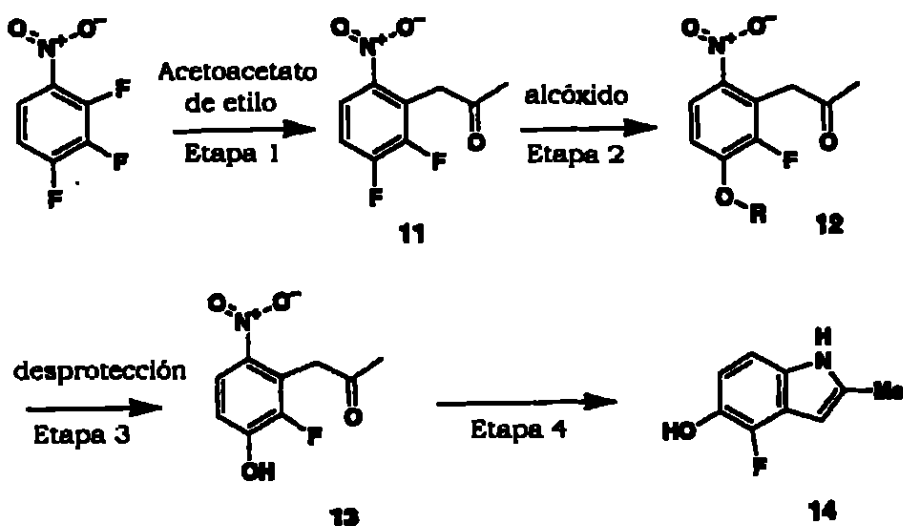
Un compuesto de la Publicación WO 0071129 del PCT, en donde X_1 es halógeno, tal como cloro, puede tratarse con un nucleófilo tal como fluoroindol en presencia de una base, tal como carbonato de potasio en un solvente polar, tal como dimetilformamida para proporcionar el compuesto 8.

Etapa 2

El compuesto 8 después puede tratarse con un agente de alquilación tal como bromuro de metil magnesio o cloruro de metil magnesio, a bajas temperaturas, para proporcionar el compuesto 9.

72
73**Etapas 3**

El compuesto 9 después puede tratarse con un peróxido, tal como peróxido de hidrógeno o perborato de sodio en presencia de un ácido de Lewis, tal como trifluoruro de boro, a baja temperatura, para proporcionar el compuesto fenólico 10.

Esquema de reacción3**Etapas 1**

Un compuesto fluorado, tal como trifluoro nitrobenzeno puede hacerse reaccionar con un nucleófilo tal como acetoacetato de etilo seguido de descarboxilación del grupo éster en presencia de un ácido o una base, para dar el compuesto 11.

Etapas 2

El compuesto 11 después puede hacerse reaccionar con un anión alcoxi, tal como metóxido de sodio o sal de sodio de alcohol bencílico para dar el compuesto 12.

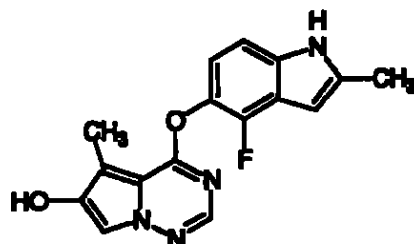
73
74**Etapas 3**

La desprotección del grupo alcoxi del Compuesto 12 de este esquema de reacción después puede realizarse mediante el tratamiento con reactivos como cloruro de piridinio o bromuro de hidrógeno en ácido acético para dar el compuesto 13.

Etapas 4

El compuesto 13 después puede ciclizarse bajo condiciones reductoras, tal como ditionito de sodio o paladio sobre carbono en presencia de hidrógeno para dar los derivados de indol de la fórmula 14.

El compuesto 12 puede convertirse directamente al compuesto 14 mediante el tratamiento con paladio sobre carbono en presencia de una fuente de hidrógeno, tal como formato de amonio.

Ejemplo 1

4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

A. Etil éster del ácido 4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico

Una mezcla de etil éster del ácido 4-hidroxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico (60.0 g, 271.2 mmol, para la preparación ver WO 0071129), oxicloruro de fósforo (30.3 mL, 325.4 mmol) y diisopropiletil amina (37.7 mL, 217 mmol) en tolueno (800 mL) se calentó a reflujo bajo argón durante 18 h y después se enfrió a temperatura ambiente. La mezcla se concentró en el rotavapor y el residuo se diluyó con diclorometano (1000 mL) y solución de bicarbonato de sodio frío (300 mL). La mezcla resultante se agitó a temperatura ambiente durante 10 min. La capa orgánica separada se lavó con salmuera fría (300 mL), se secó, y se concentró in vacuo. El material crudo se purificó por cromatografía en gel de sílice eluyendo con diclorometano, para proporcionar el compuesto deseado (64.8 g, 99%) como un sólido amarillo.

B. Etil éster del ácido 4-etoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico

A una solución del compuesto A de este ejemplo (23 g, 96 mmol) en tetrahidrofurano (0.6 L) bajo argón a 0°C, se adicionó etóxido de sodio en etanol (21% p/p, 43 mL, 115.2 mmol) gota a gota durante 20 min. La reacción se agitó a 0°C durante 1 h, se diluyó con acetato de etilo y se lavó con solución de cloruro de amonio y salmuera. La capa orgánica se secó, se concentró y el residuo se purificó por cromatografía en gel de sílice eluyendo con diclorometano seguido de acetato de etilo al 50% en hexanos, para proporcionar el

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compuesto deseado (23.5 g, 98%) como un sólido blanco. LC/EM; $(M+H)^+ = 250.17$.

C. 2-(4-Etoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-il)-propan-2-ol

A una solución del compuesto B de este ejemplo en THF (2.5 L) a 0°C se adicionó lentamente bromuro de metil magnesio (3M en Et₂O, 360 mL, 1.08 mol) con un embudo de adición. La mezcla se dejó calentar a temperatura ambiente, después de lo cual se continuó la agitación durante 4 h. La reacción se apagó con solución de cloruro de amonio y se extrajo con acetato de etilo. La capa orgánica se lavó con solución de cloruro de sodio y se secó, para proporcionar el compuesto deseado (78 g, 100%) como un sólido amarillo. LC/EM; $(M+H)^+ = 236.1$.

D. 4-Etoxi-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

Una mezcla de peróxido de hidrógeno (30%, 10.3 mL, 178.5 mmol) y dietil eterato de trifluoruro de boro (271.4 mL, 2.14 mol) se agitó a 0°C durante 30 min. Después se enfrió a -20°C y se adicionó una solución del Compuesto C de este ejemplo (30 g, 129.5 mmol) en diclorometano (1.45 L) a -15°C. La mezcla de reacción alcanzó -3°C, y después se enfrió a -40°C. A esta mezcla se adicionó una solución saturada de sulfito de sodio con agitación. La mezcla resultante se extrajo con acetato de etilo, se secó y se concentró in vacuo para proporcionar el Compuesto D (26 g, 76%). LC/EM; $(M+H)^+ = 194.2$.

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E. 6-Benciloxi-4-etoxi-5-metilpirrolo[2,1-f][1,2,4]triazina

Una mezcla del compuesto D de este ejemplo (1 g, 5.2 mmol), bromuro de bencilo (0.62 mL, 5.2 mmol) y carbonato de potasio (2.1 g, 15.5 mmol) en dimetilformamida (10 mL) se agitó a temperatura ambiente durante 12 h. La reacción se diluyó con acetato de etilo y se lavó con agua, solución de cloruro de litio al 10% y salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró in vacuo para dar el Compuesto E (1 g) como un sólido amarillo que se usó sin purificación adicional para la siguiente etapa.

F. 6-Benciloxi-5-metilpirrolo[2,1-f][1,2,4]triazin-4-ol

El compuesto E de este ejemplo (90 g, crudo) en HCl 1N (600 mL) y etanol (800 mL) se calentó a reflujo durante 4 h. Un precipitado sólido que se colectó por filtración, se lavó con un solvente mezclado (agua/etanol/metanol = 4/4/2) y se secó para dar un sólido casi blanco, que se lavó con diclorometano, para proporcionar el Compuesto F (65 g) como un sólido blanco. LC/EM; $(\text{M}+\text{H})^+ = 256.2$.

G. 6-Benciloxi-4-cloro-5-metilpirrolo[2,1-f][1,2,4]triazina

Una mezcla del compuesto F de este ejemplo (10 g, 39.2 mmol), oxicloruro de fósforo (4.4 mL, 47.1 mmol) y diisopropiletil amina (5.5 mL, 31.4 mmol) en tolueno (150 mL) se agitó a 85°C durante 2 h y después se adicionó más oxicloruro de fósforo (1.1 mL, 11.8 mmol). Después de 2 h, se adicionó más oxicloruro de fósforo (1.1 mL, 11.8 mmol). La

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mezcla de reacción se agitó continuamente a 85°C durante 1 h y después se concentró. El residuo se disolvió en diclorometano, se lavó con solución de bicarbonato de sodio frío, se secó y se concentró in vacuo. El material crudo se purificó por cromatografía en gel de sílice eluyendo con diclorometano, para proporcionar el Compuesto G (9.9 g, 93%) como un sólido amarillo.

H. 6-Benciloxi-4-(4-fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazina

Una solución de 4-fluoro-2-metil-1H-indol-5-ol (6.47 g, 39.2 mmol, Ejemplo 2) en dimetilformamida (100 mL) se desgasificó con argón y después se enfrió a -20°C. Se adicionó hidruro de sodio (60% en aceite, 1.57 g, 39.2 mmol) en una porción. La mezcla de reacción se dejó calentar a 0°C con agitación durante 30 min, se enfrió nuevamente a -20°C y se adicionó en una porción una solución del Compuesto G de este ejemplo en dimetilformamida (100 mL). La reacción se calentó a temperatura ambiente. Después de 30 min, la mezcla se acidificó con HCl 1N (200 mL), se diluyó con acetato de etilo (1.8 L) y se lavó con solución de cloruro de litio al 10% (0.4 L x 2), solución de NaOH 1N (0.3 L x 2), amortiguador (pH = 2, 200 mL) y solución de NaCl (0.4 L). La capa orgánica se secó y se concentró in vacuo para proporcionar el Compuesto H (15 g, 95%) como un sólido de color canela: LC/EM; (M+H)⁺ = 403.1.

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I. 4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

Una mezcla del compuesto H de este ejemplo (15 g, 37.3 mmol), formato de amonio (12 g, 190 mmol) y Pd/C (10%, 1.5 g) en dimetilformamida (100 mL) se agitó a temperatura ambiente durante 2 h. La mezcla se filtró a través de Celite® y el filtrado se diluyó con acetato de etilo y se lavó sucesivamente con solución de cloruro de litio al 10% (2X), solución de bicarbonato de sodio al 5% (2X) y salmuera. La capa orgánica se secó (Na₂SO₄) y se concentró *in vacuo* para dar un sólido café claro, que se lavó con diclorometano para proporcionar el compuesto de título (7.8 g, 64%) como un sólido casi blanco. EM: [M+H]⁺ = 313.2. ¹HRMN (CDCl₃): δ 2.44 (s, 3H), 2.51 (s, 3H), 6.31 (s, 1H), 6.95 (dd, 1H), 7.07 (d, 1H, J = 8.8 Hz), 7.38 (s, 1H), 7.78 (s, 1H).

El ejemplo 1 también puede prepararse mediante la ruta alternativa descrita a continuación.

A-1. Etil éster del ácido 4-cloro-5-metil-pirrolo[2,1-f][1,2,4]triazin-6-carboxílico

Un reactor de 10 L se cargó con etil éster del ácido 4-hidroxi-5-metil-pirrolo[2,1-f][1,2,4]triazin-6-carboxílico (155.1 g, 0.7 mol) y tolueno (2.7 L). Después se adicionó oxicloruro de fósforo (128.8 g, 78 mL, 0.84 mol) seguido de la adición de diisopropiletilamina (94.2 g, 127 mL, 0.7 mol). La mezcla de reacción se agitó durante 5 min a temperatura

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ambiente y después se calentó a reflujo durante 20 h. Los análisis de CLAR indicaron la desaparición completa del material iniciador. La mezcla de reacción después se enfrió a 0°C y se adicionó una solución de K₂HPO₄ frío (527 g en 2.4 L de agua) a una velocidad para mantener la temperatura interna de la mezcla de reacción debajo de 5°C. El pH final de la mezcla fue de 8. La mezcla después se agitó entre 0°C a 5°C durante 20 min y después a temperatura ambiente durante 1 h. La fase orgánica se separó y se lavó con solución de K₂HPO₄ (85 g en 405 mL de agua) y agua (345 mL) y después se filtró y se concentró in vacuo hasta que comenzaron a precipitar sólidos amarillos. Se adicionó dimetilformamida (1 L) y el tolueno restante se removió in vacuo (temperatura del baño = 38°C, presión = 9 Torr). Después de la concentración, se observó por CLAR aproximadamente 4% de tolueno.

J. Etil éster del ácido 4-(4-fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-carboxílico

El residuo de la etapa A-1 anterior se transfirió a un reactor de 10 L y se adicionó dimetilformamida (1.1 L) seguido de K₂CO₃ (276 g, 2.1 mol) y 4-fluoro-2-metil-1H-indol-5-ol (109.5 g, 0.7 mol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y después se enfrió a 0°C. Se adicionaron agua (2.0 L) y acetato de etilo (2 L) a una velocidad como para mantener la temperatura interna debajo de 20°C. Las fases después se separaron y la fase acuosa se

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extrajo con acetato de etilo (2 L). Los extractos orgánicos combinados después se lavaron con agua (2 L), LiCl acuoso al 10% (2 L) y agua (2 L). Después se adicionó tolueno (1 L) y los extractos orgánicos se concentraron *in vacuo*. Se adicionó más tolueno (500 mL) y la mezcla se volvió a concentrar *in vacuo*. LC/EM; (M+H)⁺ = 369.4. ¹H RMN (CDCl₃): δ 1.41 (t, 3H, J = 7.15 Hz), 2.45 (s, 3H), 2.87 (s, 3H), 4.39 (q, 2H, J = 7.15 Hz), 6.34 (s, 1H), 6.98 (dd, 1H), 7.08 (d, 1H, J = 8.25 Hz), 7.90 (s, 1H), 8.15 (s, 1H).

K. 2-[4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metil-pirrol-2,1-f][1,2,4]triazin-6-il]-propan-2-ol

El residuo de la etapa anterior (etapa J) se transfirió a un reactor de 10 L y se adicionó suficiente tolueno para proporcionar un volumen de reacción total de 1.1 L. Después se adicionó THF (1.1 L) seguido por la adición de LiCl (140 g) y la mezcla de reacción se enfrió a 0°C. Después se adicionó bromuro de metil magnesio [1.4 M en tolueno, THF (75:25), 2.1 L, 2.8 mol] a una velocidad para mantener una temperatura interna debajo de 5°C. El tiempo de adición total fue de aproximadamente 2 h. La mezcla de reacción se agitó a 0°C durante 2 h adicionales y después se calentó a 15°C durante 3 h, tiempo en el cual se observó aún 5% del material iniciador por CLAR. La mezcla de reacción después se volvió a enfriar a 5°C y se adicionó 100 mL adicionales de bromuro de metilmagnesio y la mezcla se agitó durante 1.5 h adicionales. Después se adicionaron acetato de etilo (1.5 L y una solución de NH₄Cl al 15% (3.2 L) para mantener una temperatura

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interna por debajo de 5°C. Las capas después se separaron y la fase acuosa se extrajo con acetato de etilo (2 L). Las capas orgánicas combinadas se lavaron con NH₄Cl al 15% (2 x 2 L) y agua (2 x 2L) y después se concentraron *in vacuo*, para proporcionar el producto deseado como un sólido amarillo amorfo. El producto crudo se disolvió en diclorometano (5 L) usando un baño de agua (T=37°C) para ayudar a la disolución. La solución después se pasó a través de una almohadilla corta de gel de sílice (400 g) y la almohadilla se lavó con diclorometano (7 L) y acetato de etilo al 5%/diclorometano (1.2 L). El filtrado se evaporó para producir un sólido casi blanco al que se adicionó acetato de etilo (1.2 L). La suspensión resultante se transfirió a un reactor de 10 L y se obtuvo una solución clara después de la agitación durante 2 h a 50°C. La solución después se enfrió a temperatura ambiente y precipitó un sólido blanco. Después se adicionó heptano (2.6 L) y la mezcla se agitó a temperatura ambiente durante 20 h. Los sólidos resultantes se filtraron, se lavaron con heptano (1 L) y se secaron bajo presión reducida a 50°C durante 24 h. Se obtuvo 2-[4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-il]-propan-2-ol como un sólido blanco (186 g, 75% durante 3 etapas). LC/EM; (M+H)⁺ = 355.4.

I.1. 4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol

A una solución de BF₃·OEt₂ (120 mL, 0.948 mol) en diclorometano (200 mL) a 0°C se adicionó H₂O₂ (solución acuosa

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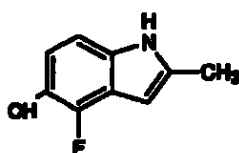
al 50%, 4.6 mL, 0.079 mol). La mezcla de reacción se agitó a 0°C durante 30 min y después se enfrió a -20°C. En un matraz separado, 2-[4-(4-fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-il]-propan-2-ol de la etapa anterior (20 g, 0.0564 mol) se disolvió en diclorometano (400 mL) usando calor indirecto hasta lograr la disolución completa. Esta solución después se adicionó rápidamente mediante una cánula (tiempo de adición = 20 min) a la solución de peróxido. La temperatura de reacción durante la adición estuvo entre -15°C y -25°C. Después de que se completó la adición, la temperatura de reacción se elevó a -15°C y se mantuvo a esta temperatura durante 40 minutos adicionales. La mezcla de reacción se apagó mediante la adición de Na₂SO₃ (200 mL, solución acuosa al 20%) y etanolamina (solución acuosa al 33%, 300 mL). Ambos reactivos se adicionaron a una velocidad para mantener la temperatura interna por debajo de 0°C. El baño de enfriamiento se removió y la mezcla de reacción se agitó durante 2 h y después se vertió en un embudo de separación. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (100 mL). Las capas orgánicas combinadas se lavaron con ácido cítrico acuoso al 5% (100 mL), NaHCO₃ acuoso al 10% (100 mL), agua (2 x 100 mL) y salmuera (100 mL) y después se secaron, se filtraron y se concentraron *in vacuo*, para proporcionar una espuma anaranjada. El material crudo se cargó en una columna

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Florisil® usando tetrahidrofurano como el solvente cargado y la columna se eluyó con acetato de etilo al 30%/heptano. Las fracciones que contienen el producto deseado se colectaron y se concentraron *in vacuo* y después se recrystalizaron con acetato de etilo/heptano. Los sólidos se colectaron y se lavaron con heptano para proporcionar (9.1 g, 52%) del producto deseado como un sólido casi blanco. El filtrado se concentró *in vacuo* y se purificó en gel de sílice usando acetato de etilo al 40%/heptano como el eluyente, para proporcionar 2.5 g adicionales (14%) del producto deseado. El rendimiento total de 4-(4-fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-ol fue de (11.6 g, 66%).

CLAR de fase inversa: 3.75 min (columna YMC S5 ODS de 4.6 x 50 mm, metanol acuoso al 10-90% durante 4 minutos que contiene ácido fosfórico al 0.2%, 4 mL/min, monitoreando a 220 nm). LC/EM; (M+H)⁺ = 313.2.

Ejemplo 2



4-Fluoro-2-metil-1H-indol-5-ol

A. 1-(2,3-Difluoro-6-nitrofenil)-propan-2-ona

Un reactor de 10 litros se cargó con ter-butóxido de potasio (570.6 g, 5.082 mol) y tetrahidrofurano (2 L). Se

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inició la agitación por arriba y la suspensión resultante se enfrió a 11°C, antes se adicionó acetoacetato de etilo (668 mL, 5.082 mol). La adición del acetoacetato de etilo requirió 1 h y se observó una exoterma. La velocidad de adición se controló de modo que la temperatura interna del reactor no excediera 25°C. La mezcla resultante llegó a ser homogénea y fue de color amarillo pálido. Después de que se completó la adición, la mezcla de reacción se enfrió entre 10°C y 15°C y después se adicionó gota a gota 1,2,3-trifluoronitrobenceno (260 mL, 600 g, 2.259 mol) como una solución en tetrahidrofurano (1 L). La adición requirió 35 min y se observó una exoterma. La velocidad de adición se controló de modo que no excediera una temperatura interna de 21°C. Después de que se completó la adición, la mezcla de reacción café resultante se calentó a RT y se agitó durante 2.5 h, tiempo en el cual, el análisis de LC indicó 100% de conversión sin trazas de 1,2,3-trifluoronitrobenceno restante. La mezcla de reacción se volvió a enfriar a 15°C y se adicionaron lentamente 3 L de HCl 1N durante 15 min y la solución café llegó a ser, por lo general, una solución amarillo claro. El pH de la fase acuosa fue de ~ pH 4. La mezcla se extrajo con acetato de etilo (2 x 1 L) y los extractos orgánicos combinados se lavaron con salmuera (1 L) y se concentraron in vacuo para proporcionar un aceite anaranjado.

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El aceite obtenido se cargó en un reactor de 10 L y se disolvió en ácido acético glacial (1 L). Después se adicionó ácido sulfúrico (1 L, concentrado) y se observó una evolución vigorosa además de una ligera exoterma. La agitación mecánica se inició y la mezcla de reacción se calentó a 70°C durante 3 h, después de este tiempo el análisis de LC indicó 100% de conversión. La mezcla de reacción se enfrió entre 15°C a 20°C y se adicionó acetato de etilo (3 L) seguido de la adición de agua (6 L). No se observó interfase visible. Se separaron siete litros de fase acuosa y después se extrajo con acetato de etilo (2 x 2 L). En este momento, se observó una interfase visible. Los extractos orgánicos combinados se lavaron con NaOH 1 N (6 x 1 L) (el pH de la fase acuosa fue de 6.6) y salmuera (3 x 1 L). Los extractos orgánicos cafés se concentraron bajo presión reducida (temperatura del baño 35°C, 35 torr) durante ~ 10 h, para proporcionar 569 g del compuesto deseado como un aceite café crudo que fue 82% AP por CLAR.

El acetato de etilo residual fue de 3% por GC. KF: 0.25%. ¹H y ¹³C RMN igualaron los datos reportados. Impureza principal: regioisómero para.

B. Una mezcla de 1-(2,3-difluoro-6-nitrofenil)-propan-2-ona (183 g) y carbonato de potasio (100 g) en metanol (1 L) se calentó a reflujo durante 3 h. La mezcla de reacción después se enfrió y se concentró *in vacuo* para remover la mayoría del

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metanol. El residuo se diluyó con acetato de etilo (1 L), se filtró y se lavó con agua. La fase acuosa separada se neutralizó con HCl 2N y se extrajo con acetato de etilo (2 x 500 mL). La capa orgánica combinada se lavó con salmuera, se secó (Na_2SO_4) y se concentró *in vacuo* para dar un sólido café. El sólido se trituró con éter dietílico y se filtró para proporcionar 1-(2-fluoro-3-metoxi-6-nitrofenil)-propan-2-ona (121 g, 71%) como un sólido amarillo. LC/EM; $(\text{M}+\text{H})^+ = 228.2$.

C. Una mezcla de 1-(2-fluoro-3-metoxi-6-nitrofenil)-propan-2-ona de la etapa anterior (454 mg, 21 mmol) y cloruro de piridinio (0.9 g, 7.8 mmol) se agitó a 180°C durante 75 min. La reacción se enfrió a temperatura ambiente, se diluyó con HCl 1N (3 mL) y acetato de etilo (10 mL) y se filtró. El filtrado se lavó con salmuera (2x), se secó y se concentró *in vacuo* para dar 1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona (410 mg, 96%) como un sólido gris, que se usó sin purificación adicional para la siguiente etapa. LC/EM; $(\text{M}+\text{H})^+ = 214$. $^1\text{HRMN}$ (CDCl_3): δ 2.37 (s, 3H), 4.22 (s, 2H), 6.95 (dd, 1H), 7.95 (d, 1H, $J = 9.35$ Hz).

D. 1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona de la etapa anterior (50 g, 0.234 mol) se adicionó a un matraz de fondo redondo de 2 litros. Se adicionó agua (1 L) y la suspensión amarilla se agitó a RT. Se adicionó ditionito de sodio (225 g, 5.5 eq) en una porción y la mezcla de reacción se agitó y se mantuvo <30°C hasta que el análisis de CLAR

2X

indicó que no permaneció material iniciador (típicamente menor de 1 hora). Una vez que se completó, la mezcla de reacción se enfrió a 0°C y el producto sólido de color anaranjado se colectó por filtración a vacío. El producto húmedo se secó a <50°C bajo vacío local, para proporcionar 4-fluoro-2-metil-1H-indol-5-ol (31.4 g, 81% de rendimiento) que se aisló como un polvo cristalino de color canela. El material tuvo una pureza por CLAR >99.8. ¹H RMN (CDCl₃, 400 MHz): δ 7.8 (s, 1H), 6.9-6.7 (m, 2H), 6.2 (s, 1H), 4.7 (s, 1H), 2.4 (s, 3H). ¹³C RMN (CDCl₃, 100 MHz) δ 145.7, 143.4, 137.5, 136.7, 134.4, 120.1, 112.7, 106.8, 95.4, 13.3.

También, la 1-(2,3-difluoro-6-nitrofenil)-propan-2-ona puede convertirse al compuesto de título mediante una ruta alternativa como se describe a continuación.

E. 1-(3-Benciloxi-2-fluoro-6-nitro-fenil)-propan-2-ona

A una solución de 1-(2,3-difluoro-6-nitrofenil)-propan-2-ona (2.5 g, 82% de pureza por análisis CLAR, 9.54 mmol) se adicionaron alcohol bencílico (2.5 mL) y LiOH·H₂O (1.07 g, 25.58 mmol). La mezcla de reacción después se calentó a 100-110°C y se agitó durante 4 horas hasta que el análisis CLAR indicó que se completó la reacción. Después del enfriamiento a RT, la mezcla de reacción se diluyó con diclorometano (18 mL) y se neutralizó a pH 6-7 con HCl 1N. Las capas se separaron y la fase orgánica se lavó con salmuera y se colectó. Con agitación, se adicionó heptano (30-25 mL) a la

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solución orgánica tras lo cual se inició la cristalización. La suspensión resultante se enfrió a 0-5°C y se agitó durante 1 h adicional. La suspensión después se filtró y la torta de filtrado se lavó con heptano. Los sólidos amarillo-café después se secaron in vacuo a 50°C durante 12-15 h, para proporcionar el compuesto deseado (1.6 g) que fue 95% puro por análisis CLAR. Método CLAR: Columna: YMC Pack Cyano 3 μ m, 4.6 x 50 mm, Solvente A: TFA al 0.05% en MeOH:Agua (20:80), Solvente B: TFA al 0.05% en MeOH:agua (20:80), Longitud de onda: 254 nm, Velocidad de Flujo: 3 mL/min. Tiempo de gradiente: 3 min. %B final: 100 inicial, Retención: 0.5 min. %B Inicial: 0. Tiempos de retención típicos: SM, 1.2 min; Producto 2.2-2.3 min.

F. 4-Fluoro-2-metil-1H-indol-5-ol

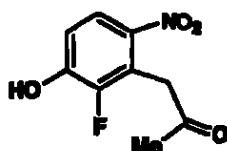
A una solución del compuesto E de la etapa anterior (20.00 g, 66.03.30 mmol) en metanol bajo una atmósfera de nitrógeno (300 mL) a temperatura ambiente en ausencia de luz, se adicionaron 10% de Pd/C (2.0 g) y formato de amonio (60.0 g, 0.95 mol). La mezcla de reacción se agitó durante 3.5 h y después se diluyó con acetato de etilo (200 mL) y se filtró a través de una almohadilla de Celite®/gel de sílice. El residuo después se purificó por cualquiera de los siguientes métodos:

Después de la concentración in vacuo, el residuo resultante se purificó por cromatografía, eluyendo con

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acetato de etilo al 30%/hexanos, para proporcionar (7.32 g, 67%) del compuesto deseado como un sólido blanco después de la titulación con diclorometano/hexanos. Después de la concentración *in vacuo*, el residuo se disolvió en diclorometano y se pasó a través de una almohadilla de gel de sílice lavando con diclorometano. El filtrado se concentró *in vacuo*, para proporcionar (6.66 g, 61%) del compuesto de título como un sólido blanco.

El compuesto E de este ejemplo también puede convertirse a 1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona mediante los siguientes dos métodos alternativos.



1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona

Método G-1: A una solución de 1-(3-benciloxi-2-fluoro-6-nitrofenil)-propan-2-ona (3.03 g, 10 mmol) en anhídrido acético (5 mL) y ácido acético (5 mL) a temperatura ambiente, se adicionó ácido bromhídrico (solución acuosa al 48%, 3 mL). Después de la adición, la reacción se calentó a 100°C durante 30 min y después se enfrió a temperatura ambiente. A esta mezcla se adicionó 10 mL de hexanos con agitación. La solución se decantó y se concentró. El residuo se diluyó con acetato de etilo (50 mL) y se lavó con salmuera (3 x 20 mL).

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La capa orgánica se secó y se concentró *in vacuo* para proporcionar 1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona (1.7 g, 80%) como un sólido café, que se usó en la siguiente etapa sin purificación adicional. LC/EM; $(M+H)^+ = 213.2$.

Método G-2: Una mezcla de 1-(3-benciloxi-2-fluoro-6-nitrofenil)-propan-2-ona (65.0 g, 0.214 mol) y cloruro de piridinio (60.74 g, 0.526 mol) se agitó a 180°C durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con HCl 3N (100 mL) y acetato de etilo (500 mL) y se filtró. La capa acuosa se extrajo con acetato de etilo (2X) y las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron a través de una almohadilla de gel de sílice y se concentraron *in vacuo*. El residuo se decoloró con carbón natural en metanol, se filtró y se concentró *in vacuo*, para proporcionar 1-(2-fluoro-3-hidroxi-6-nitrofenil)-propan-2-ona (37 g, 81%) como un sólido café. LC/EM; $(M+H)^+ = 213.2$.

Alternativamente, puede ciclizarse 1-(3-benciloxi-2-fluoro-6-nitrofenil)-propan-2-ona a 5-benciloxi-4-fluoro-2-metil-1H-indol como se describe a continuación, que después se puede ser desbencilado como se describió anteriormente.

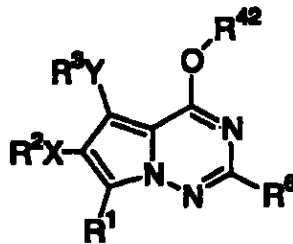
H. Una mezcla de 1-(3-benciloxi-2-fluoro-6-nitrofenil)-propan-2-ona (9.09 g, 30 mmol) y níquel Raney (~5 g) en metanol (100 mL) se calentó a 40°C y después se adicionó gota a gota una solución de hidrazina en metanol (15 mL) con

a1
41

agitación vigorosa durante un periodo de 30 min. Después de someter a reflujo durante 1 h, la mezcla de reacción se enfrió a temperatura ambiente, se filtró a través de Celite y se concentró. El material crudo se pasó a través de una almohadilla de gel de sílice eluyendo con diclorometano y se concentró *in vacuo* para proporcionar 5-benciloxi-4-fluoro-2-metil-1H-indol (6.1 g, 80%) como un aceite amarillento. LC/EM; (M+H)⁺ = 256.3⁺.

REIVINDICACIONES

1. Un proceso para preparar un compuesto de fórmula (I)



(I)

caracterizado porque

X e Y se seleccionan independientemente de O, OCO, S, SO, SO₂, CO, CO₂, NR¹⁰, NR¹¹CO, NR¹²CONR¹³, NR¹⁴CO₂, NR¹⁵SO₂, NR¹⁶SO₂NR¹⁷, SO₂NR¹⁸, CONR¹⁹, halógeno, nitro, ciano o X ó Y están ausentes;

R¹ es hidrógeno;

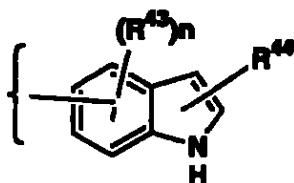
R² y R³ son independientemente hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, heterociclo, heterociclo sustituido, aralquilo, aralquilo sustituido, heteroarilo, heteroarilo sustituido, heterocicloalquilo o heterocicloalquilo sustituido; con la condición de que cuando X es halo, nitro o ciano, R² está ausente, y, cuando Y es halo, nitro o ciano, R³ está ausente;

R⁶ es H;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ y R¹⁹ se

seleccionan independientemente del grupo que consiste de hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterociclo o heterociclo sustituido;

R^{42} es



$(R^{43})_n$ en donde n es igual a 0, 1 ó 2 y cada R^{43} se selecciona independientemente del grupo que consiste de hidrógeno, flúor, cloro y metilo; y

R^{44} es metilo o hidrógeno,

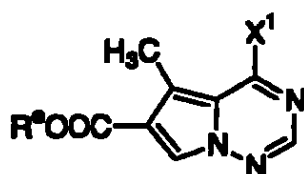
con la condición adicional de que:

a. R^2 no puede ser hidrógeno si X es SO , SO_2 , $NR^{13}CO_2$ o $NR^{14}SO_2$; y

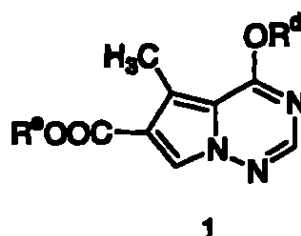
b. R^3 no puede ser hidrógeno si Y es SO , SO_2 , $NR^{13}CO_2$ o $NR^{14}SO_2$;

o un enantiómero, diastereómero o sal farmacéuticamente aceptable, profármaco o solvato del mismo, que comprende las etapas de:

a) convertir un compuesto de la fórmula

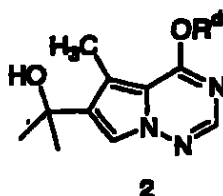
94
y

en donde R^e es alquilo inferior o arilo y X^1 es halógeno, a un compuesto 1 de la fórmula



en donde R^d es alquilo inferior, arilo, arilo sustituido, heteroarilo o heteroarilo sustituido mediante el tratamiento con un fenóxido o alcóxido,

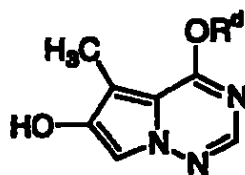
b) alquilar el Compuesto 1 para proporcionar el Compuesto 2 de la fórmula



c) tratar el Compuesto 2 con un peróxido en presencia de un ácido de Lewis, para proporcionar el Compuesto 3 de la

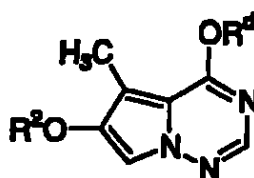
as
~~11~~

fórmula



3

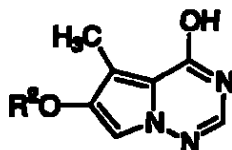
d) alquilar el grupo fenol en el compuesto 3 para proporcionar el Compuesto 4 de la fórmula



4

donde R² es bencilo o bencilo sustituido,

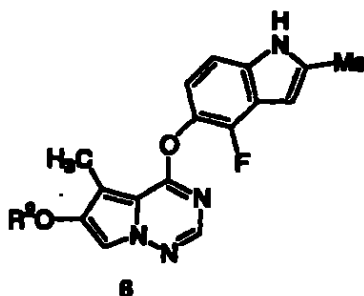
e) hidrolizar el Compuesto 4 para proporcionar el Compuesto 5 de la fórmula



5

donde R² es bencilo o bencilo sustituido, y

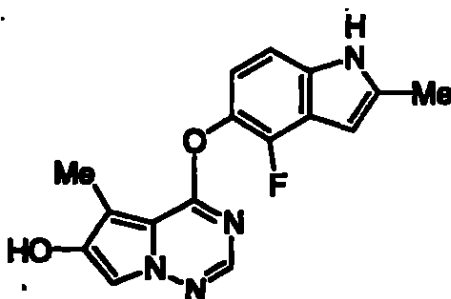
f) convertir el Compuesto 5 al Compuesto 6 de la fórmula

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4/8

convirtiendo primero el compuesto 5 a un cloroimidato y alquilando subsecuentemente el cloroimidato para proporcionar el Compuesto 6, en donde R^2 es bencilo y desprotegiendo el fenol mediante el tratamiento con un donador de hidrógeno en presencia de un catalizador, para proporcionar el compuesto 6 donde R^2 es hidrógeno.

2. El proceso de conformidad con la reivindicación 1, caracterizado porque en la etapa c), se usa peróxido de hidrógeno en presencia de un ácido de Lewis para convertir el alcohol bencílico al fenol.

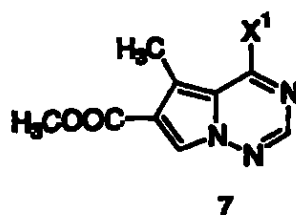
3. Un proceso para preparar un compuesto de la fórmula



97
~~47~~

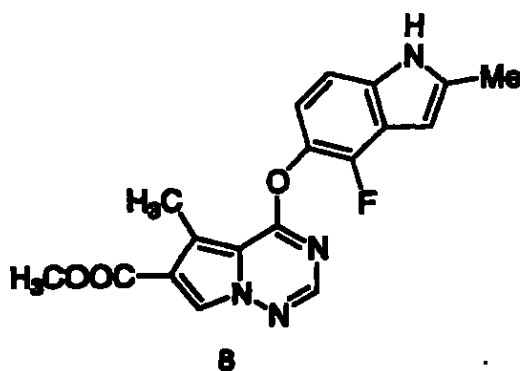
caracterizado porque comprende las etapas de:

a) hacer reaccionar un compuesto de la fórmula

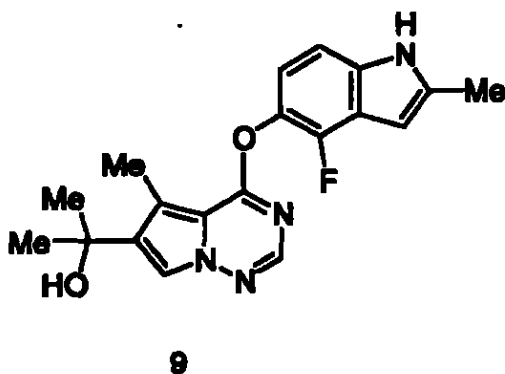


donde X₁ es halógeno;

con un nucleófilo para proporcionar el Compuesto 8 de la fórmula



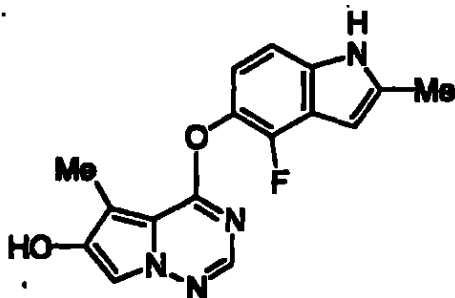
b) tratar el Compuesto 8 con un agente de alquilación a una baja temperatura, para proporcionar el Compuesto 9 de la fórmula



y

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c) tratar el Compuesto 9 con un peróxido en presencia de un ácido de Lewis para proporcionar el Compuesto 10 de la fórmula



10

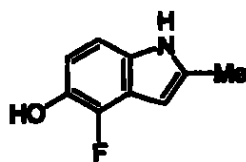
4. El proceso de conformidad con la reivindicación 3, caracterizado porque el agente de alquilación en la etapa (b) es un haluro de alquil magnesio.

5. El proceso de conformidad con la reivindicación 4, caracterizado porque el haluro de alquil magnesio es bromuro de metil magnesio o cloruro de metil magnesio.

6. El proceso de conformidad con la reivindicación 4, caracterizado porque el peróxido usado en la etapa c) es peróxido de hidrógeno o perborato de sodio.

7. El proceso de conformidad con la reivindicación 4, caracterizado porque el ácido de Lewis usado en la etapa c) es trifluoruro de boro.

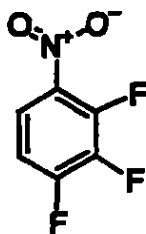
8. Un proceso para preparar un compuesto de fórmula



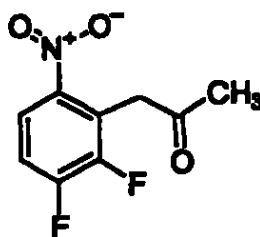
14

caracterizado porque comprende las etapas de:

a) hacer reaccionar un compuesto fluorado de la fórmula

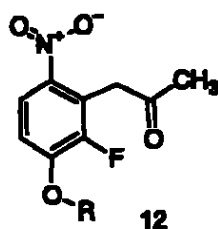


b) con un nucleófilo para proporcionar el Compuesto 11 de la fórmula



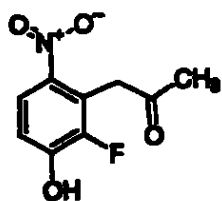
11

c) hacer reaccionar el Compuesto 11 con un anión de alcoxi para proporcionar el Compuesto 12 de la fórmula

108
100

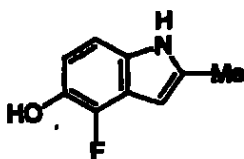
en donde R es un grupo protector,

d) desproteger el grupo alcoxi mediante tratamientos con reactivos desprotectores, para proporcionar el Compuesto 13 de la fórmula



y

e) ciclizar el Compuesto 13 bajo condiciones reductoras para proporcionar el Compuesto 14 de la fórmula



9. El proceso de conformidad con la reivindicación 8, caracterizado porque la reducción en la etapa (e) usa

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ditionito de sodio en agua o una mezcla de agua y un solvente orgánico tal como THF.

10. El proceso de conformidad con la reivindicación 8, caracterizado porque la reducción en la etapa (d) usa cloruro de piridinio o yoduro de piridinio o bromuro de hidrógeno.

11. Una composición farmacéutica, caracterizada porque comprende por lo menos uno o más compuestos de conformidad con la reivindicación 1 en combinación con un vehículo farmacéuticamente aceptable y por lo menos un agente anti-cáncer o citotóxico adicional.

12. Un método para producir un efecto antiangiogénico, caracterizado porque comprende administrar a una especie mamífera en necesidad del mismo, una cantidad que produce el efecto antiangiogénico de por lo menos un compuesto elaborado mediante el proceso de conformidad con la reivindicación 1.

13. Un método para producir un efecto reductor de la permeabilidad vascular, caracterizado porque comprende administrar a una especie mamífera en necesidad del mismo, una cantidad efectiva que reduce la permeabilidad vascular de por lo menos un compuesto elaborado mediante el proceso de conformidad con la reivindicación 1.

14. Un método para inhibir la actividad de la proteína cinasa de los receptores del factor de crecimiento, caracterizado porque comprende administrar a una especie mamífera en necesidad del mismo, una cantidad efectiva para

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inhibir la protefna cinasa de por lo menos un compuesto elaborado mediante el proceso de conformidad con la reivindicación 1.

15. Un método para inhibir la actividad de la tirosina cinasa de los receptores del factor de crecimiento, caracterizado porque comprende administrar a una especie mamífera en necesidad del mismo, una cantidad efectiva para inhibir la tirosina cinasa de por lo menos un compuesto elaborado mediante el proceso de conformidad con la reivindicación 1.

16. Un método para tratar las enfermedades asociadas con las trayectorias de transducción de señal que operan a través de los receptores del factor de crecimiento, caracterizado porque comprende administrar a una especie mamífera en necesidad del mismo, una cantidad terapéuticamente efectiva de por lo menos un compuesto elaborado mediante el proceso de conformidad con la reivindicación 1.

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RESUMEN DE LA INVENCION

La presente invención se refiere a un proceso para preparar ciertos compuestos de pirrolotriazina de la fórmula (I) y sales farmacéuticamente aceptables de los mismos. Los compuestos de la fórmula (I) inhiben la actividad de la tirosina cinasa de los receptores del factor de crecimiento, tales como VEGFR-2 y FGFR-1, por lo que los hacen útiles como agentes anti-cáncer. Los compuestos de la fórmula I también son útiles para el tratamiento de otras enfermedades asociadas con las trayectorias de transducción de señal que operan a través de los receptores del factor de crecimiento.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

LD0339-WO-PCT
PCT
Col

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference LD0339 PCT		Date of Mailing (day/month/year) 23 JUL 2004
International application No. PCT/US03/22755		REPLY DUE within 1 month/days from the above date of mailing ✓
International filing date (day/month/year) 21 July 2003 (21.07.2003)	Priority date (day/month/year) 19 July 2002 (19.07.2002)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): C07D 487/04; A61K 31/53; A61P 13/08, 29/00, 37/00 and US Cl.: 544/183; 514/243		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.3(d).

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

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

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **19 November 2004 (19.11.2004)**

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (703) 308-1234
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Form PCT/IPEA/408 (cover sheet)(July 1998)

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BMS PATENT LAW

JUL 26 2004

WRITTEN OPINION

Internat. application No. 105
PCT/US03/22735

I. Basis of the opinion

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

- ☒ the international application as originally filed
- ☒ the description:
pages 1-38, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the claims:
pages 39-47, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

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

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

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

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

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

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

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

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

WRITTEN OPINION

International application No.
PCT/US03/22755

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

1. STATEMENT

Novelty (N)	Claims 1-16	YES
	Claims NONE	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-16	NO
Industrial Applicability (IA)	Claims 1-16	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-16 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach the instant process, composition and method of use embraced in the claims 1-16.

Claims 1-16 lack an inventive step under PCT Article 33(3) as being obvious over WO 02/40486. WO 02/40486 teaches several pyrrolotriazine compounds and which include a process for making embraced in the instant claims. See formula I and note the definition of various variable groups. Note Z can be oxygen as required by the instant claims. See Schemes 1-14 on pages 25-38 for process of making and examples 1-152 shown on pages 38-88. WO 02/40486 does not show examples of compounds wherein Z is O as required by the instant claims. However, WO 02/40486 teaches equivalency of exemplified compounds with those claimed in the definition of various variable groups of compound of formula I and the process schemes 1-14. Thus it would be obvious to one trained in the art at the time of the invention to make variously substituted pyrrolotriazine including instant pyrrolotriazine using the processes taught by pyrrolotriazine in view of equivalency teaching taught by the reference.

Claims 1-16 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry for making pharmaceuticals useful for treating cancer.

QAC237

WRITTEN OPINION

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107
International application No.
PCT/US03/22735

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

TIME LIMIT:

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

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

De la
AUTORIDAD DE EXAMEN PRELIMINAR INTERNACIONAL

Para:
ELLIOTT KORSEN
BRISTOL-MYERS SQUIBB COMPANY
POST BOX 4000
PRINCETON, NJ 08543-4000

PCT
OPINIÓN ESCRITA
(PCT Regla 66)

Fecha de envío 23 de julio de 2004
(día/mes/año)

Referencia de archivo del Solicitante o mandatario LD0339 PCT	RESPUESTA DEBIDA dentro de 2 meses/días a partir de la fecha de envío anterior
--	---

Solicitud internacional No. PCT/US03/22755	Fecha de presentación internacional (día/mes/año) 21 de julio de 2003 (21.07.2003)	Fecha de prioridad (día/mes/año) 19 de julio de 2002 (19.07.2002)
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Clasificación de patente internacional (IPC) o clasificación nacional e IPC
IPC(7): C07D 487/04; A61K 31/53; A61P 13/08, 29/00, 37/00 y US Cl.; 544/183; 514/243

Solicitante
BRISTOL-MYERS SQUIBB COMPANY

1. Esta opinión escrita es la **primera** formulada por esta Autoridad de Examen Preliminar Internacional.
2. Esta opinión contiene indicaciones que se refieren a los siguientes puntos:

- I ☒ Bases de la opinión
- II ☐ Prioridad
- III ☐ No establecimiento de opinión con respecto a novedad, paso inventivo y aplicabilidad industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Declaración razonada bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial, citas y explicaciones que soportan tal declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones en la solicitud internacional

3. Se invita al solicitante en la presente a responder a esta opinión.

Cuándo? Ver el tiempo límite indicado arriba.

Cómo? Presentando una respuesta escrita, acompañada, cuando sea apropiado, mediante enmiendas, de acuerdo con la Regla 66.3. Para la forma y el idioma de las enmiendas, ver las Reglas 66.8 y 66.9.

También: Para una oportunidad adicional de presentar las enmiendas, ver Regla 66.4. Para la obligación del examinador de considerar a las enmiendas y/o argumentos, ver Regla 66.4bis.

Para una comunicación adicional con el examinador, ver Regla 66.6.

Si no se presenta respuesta, el reporte de examen preliminar internacional se establecerá sobre la base de esta opinión.

4. La fecha final mediante la cual el reporte de examen preliminar internacional debe establecerse de acuerdo con la Regla 69.2 es: ~~08 de agosto de 2004 (08.08.2004)~~ **14 NOV 2004**

Nombre y dirección de correspondencia de la ISA/US Comisionado de Patentes y Marcas Registradas Mail Stop PCT, Attn: ISA/US Comisionado de patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimil No. (703) 305-3230	Oficial autorizado: Venkataraman Balasubramanian Tel. No. (703) 308-1236
--	---

Forma PCT/IPEA/408 (portada) (julio de 1998)

I. Base de la opinión

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

☒ la solicitud internacional como se presentó originalmente.☒ la descripción:

páginas 1-38, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del

☒ las reivindicaciones:

páginas 39-47, como se presentó originalmente

páginas NINGUNA, como se enmendó (junto con cualquier declaración) bajo el Artículo 19

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del

☒ los dibujos

páginas NINGUNA, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del

☐ La parte del listado de secuencias de la descripción:

páginas NINGUNA, como se presentó originalmente

páginas NINGUNA, presentado con la demanda

páginas NINGUNA, presentado con la carta del

2. Con respecto al idioma, todos los elementos mercados arriba estuvieron disponibles o se presentaron a esta Autoridad en el idioma en el que se presentó la solicitud internacional, a menos que se indique lo contrario bajo este punto.

Estos elementos estuvieron disponibles o se presentaron a esta Autoridad en el siguiente idioma: , que es:

☐ el idioma de una traducción presentada para los propósitos de la búsqueda internacional (bajo la Regla 23.1(b)).☐ el idioma de publicación de la solicitud internacional (bajo la Regla 48.3(b)).☐ el idioma de una traducción presentada para los propósitos del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia nucleótida y/o de aminoácido descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.☐ presentado con la solicitud internacional en la forma legible por computadora.☐ presentado subsecuentemente a esta Autoridad en forma escrita.☐ presentado subsecuentemente a esta Autoridad en la forma legible por computadora.☐ Se ha proporcionado la declaración de que el listado de secuencias escrito presentado subsecuentemente no va más allá de la descripción en la solicitud internacional como se presenta.☐ Se ha proporcionado la declaración de que la información registrada en la forma legible por computadora es idéntica al listado de secuencias escrito.4. ☒ Las enmiendas han resultado en la cancelación de:☒ La descripción, páginas: NINGUNA☒ Las reivindicaciones, Nos.: NINGUNO☒ Los dibujos, hojas: NINGUNA5. ☐ Esta opinión se ha establecido como si (algunas de) las enmiendas no se hubieran realizado, porque se han considerado que van más allá de la descripción como se presentó (Regla 70.2(c)).*"Las hojas de reemplazamiento que se han presentado a la Oficina de recepción en respuesta a una invitación bajo el Artículo 14 se refieren en este reporte como "presentado originalmente".*

Forma PCT/IPEA/408 (Cuadro I) (julio de 1998)

V. Declaración razonada bajo la Regla 66.2(a)(ii) con respecto a novedad, paso inventivo o aplicabilidad industrial; citas y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Reivindicaciones SI:	1-16
	Reivindicaciones NO:	NINGUNA
Paso Inventivo (PI)	Reivindicaciones SI:	NINGUNA
	Reivindicaciones NO:	1-16
Aplicabilidad industrial (AI)	Reivindicaciones SI:	1-16
	Reivindicaciones NO:	NINGUNA

2. Citas y Explicaciones:

Las reivindicaciones 1-16 satisfacen los criterios establecidos en el Artículo 33(2)-(3) del PCT, porque la técnica anterior no muestra el presente proceso, composición y método de uso abarcado en las reivindicaciones 1-16.

Las reivindicaciones 1-16 carecen de un paso inventivo bajo el Artículo 33(3) del PCT como es obvio en WO 02/40486. La WO 02/40486 muestra diferentes compuestos de pirrolotriazina y que incluyen un proceso para hacer la elaboración incluida en las presentes reivindicaciones. Ver la fórmula I y observar la definición de varios grupos variables. Observar que Z puede ser oxígeno como se requiere por las presentes reivindicaciones. Ver los Esquemas 1-14 en las páginas 25-38 para el proceso de elaboración y los ejemplos 1-152 mostrados en las páginas 38-88. La WO 02/40486 no muestra ejemplos de los compuestos en donde Z es O como se requiere por las presentes reivindicaciones. Sin embargo, la WO 02/40486 muestra la equivalencia de los compuestos ejemplificados con los reivindicados en la definición de los diferentes grupos variables del compuesto de la fórmula I y los esquemas del proceso 1-14. De esta manera, habría sido obvio para

un experimentado en la técnica en el momento de la invención, hacer diferentes pirrolotriazinas sustituidas incluyendo ~~la~~ presente pirrolotriazina usando los procesos mostrados por la pirrolotriazina desde el punto de vista de la equivalencia mostrada por referencia.

Las reivindicaciones 1-16 satisfacen los criterios establecidos en el Artículo 33(4) del PCT y de esta manera, tienen aplicabilidad industrial porque el asunto relacionado reivindicado puede formularse o usarse en la industria para la elaboración de fármacos útiles para el tratamiento de cáncer.

Cuadro suplementario

(para ser usado cuando el espacio en cualquiera de los cuadros anteriores no sea suficiente)

TIEMPO LÍMITE

El tiempo límite establecido para la respuesta a una Opinión Escrita no puede excederse, 37 CFR 1.484(d). Cualquier respuesta recibida después de la expiración del tiempo límite establecido en la Opinión Escrita no se considerará en la preparación del Reporte de Examen Preliminar Internacional.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

RECEIVED
ELI LILLY PATENT LAW
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000
MAY 27 2004
Docketed Item **DADD**
Due Date **10/25/04**
Attorney **EK**

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

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

Applicant's or agent's file reference LD0339 PCT		Date of mailing (day/month/year) 25 MAY 2004
IMPORTANT NOTIFICATION		
International application No. PCT/US03/22755	International filing date (day/month/year) 21 Jul 2003	Priority date (day/month/year) 19 Jul 2002
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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

05 Feb 2004

2. That date of receipt is:

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

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

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

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

Name and mailing address of the IPEA/ Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 703-305-3230	Authorized officer Latrice Russell Telephone No. 703-306-5829
--	--

Form PCT/IPEA/402 (July 1998)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

INVITATION TO CORRECT
DEFECTS IN THE DEMAND

(PCT Rule 60.1)

To:

ELLIOTT KORSEN
BRISTOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

Date of mailing
(day/month/year)

25 MAY 2004

Applicant's or agent's file reference

LD0338 PCT

REPLY DUE

within ONE MONTH from
the above date of mailing.
See also below.

International application No.

PCT/US03/22755

International filing date
(day/month/year)

21 Jul 2003

Applicant

BRISTOL-MYERS SQUIBB COMPANY

The applicant is hereby invited within the time limit indicated above to correct the following defects which this International Preliminary Examining Authority has found in the demand for international preliminary examination:

1. ☐ It does not contain the election of at least one Contracting State bound by Chapter II (Rules 53.2(a)(iv) and 53.7).
2. ☐ It does not permit identification of the international application to which it relates (Rule 60.1(b)).
3. ☐ It does not contain the required petition (Rules 53.2(a)(i) and 53.3).
4. ☐ It does not contain the required indications concerning the agent as specified in the Annex (Rules 53.2(a)(ii) and 53.5).
5. ☐ It does not contain the required indications concerning the international application as specified in the Annex (Rules 53.2(a)(iii) and 53.6).
6. ☐ It is not submitted in the required language which is: _____ (Rule 55.1).
7. ☐ It is not made on the printed form (Rule 53.1(a)).
8. ☐ It is presented as a computer print-out the particulars of which do not comply with the Administrative Instructions (Rule 53.1(a)).
9. ☒ It does not contain the required indications concerning the applicant as specified in the Annex (Rules 53.2(a)(ii) and 53.4).
10. ☐ It does not contain the required signature as specified in the Annex (Rules 53.2(b) and 53.8).

Effect of the date of receipt of the corrections on the date of receipt of the demand:

- (i) If the defects noted under items 1 and 2 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the date when the corrections are received (Rule 60.1(b)). If that date is later than the expiration of 19 months from the priority date, entry into the national phase before the elected Offices will NOT be postponed until the expiration of 30 months from the priority date.
- (ii) If the defects noted under items 3 to 10 are corrected within the time limit indicated above, the demand shall be considered as if it had been received on the actual filing date (Rule 60.1(b)).

Effect of failure to correct the defects within the time limit indicated above:

- (i) In the case of defects noted under items 1 to 8, this Authority will declare that the demand is considered as if it had not been submitted.
- (ii) In the case of defects noted under items 9 and 10, this Authority will declare that the election(s) of the State(s) concerned in (are) considered as if it (they) had not been made.

A copy of this invitation has been sent to the International Bureau.

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

Authorized officer
Latrice Russell

Facsimile No. 703-305-3230

Telephone No. 703-306-5829

Form PCT/IPEA/404 (July 1998)

ANNEX TO
FORM PCT/IPEA/404

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✓
International application No.
PCT/US03/22755

Continuation of item 4: As to indications concerning the agent (Rule 4.4), the demand:

- a. ☐ does not properly indicate the agent's name (specify):
- b. ☐ does not indicate the agent's address.
- c. ☐ does not properly indicate the agent's address (specify):

Continuation of item 5: As to indications concerning the international application, the demand does not indicate:

- a. ☐ the international filing date.
- b. ☐ the international application number.
- c. ☐ the name of the receiving Office, where the international application number was not known to the applicant at the time the demand was filed.
- d. ☐ the title of the invention.

Continuation of item 9: As to indications concerning the applicant (Rules 4.4 and 4.5), the demand:

- ✓ a. ☒ does not indicate all the applicants for the elected States.
- b. ☐ does not properly indicate the applicant's name (specify):
- c. ☐ does not indicate the applicant's address.
- d. ☐ does not properly indicate the applicant's address (specify):
- e. ☐ does not indicate the applicant's nationality.
- f. ☐ does not indicate the applicant's residence.

Continuation of item 10: As to requirements concerning signature (Rules 4.15 and 90.4), the demand:

- a. ☐ is not signed.
- b. ☐ is not signed by all the applicants for the elected States.
- c. ☐ is not accompanied by the statement referred to in the check list in Box No. VI of the demand explaining the lack of the signature of an applicant for the election of the United States of America.
- d. ☐ is signed by what appears to be an agent/common representative but
 - ☐ the demand is not accompanied by a power of attorney appointing him.
 - ☐ the power of attorney accompanying the demand is not signed by all the applicants for the elected States.

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H/O

Docket No. LD0339 PCT

New Int'l. Application No. based on USSN 60/397,256 Filed: 19 July 2002, et al.

Documents enclosed: Application, General Power of Attorney, copy of Certification;
PCT Easy Request, Diskette with Request and Abstract

Express mail mailing label number EV 001830675 US

Date of Deposit July 21, 2003

I hereby certify that this paper or fee is being deposited with the United States
Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to the Assistant Commissioner for
Patents, Box PCT, Washington, D.C. 20231.

Maria Castaldo

(Typed or printed name of person mailing paper or fee)

Maria Castaldo

(Signature of person mailing paper or fee)

EV001830675US

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

PCT MAR 01 2004

NOTIFICATION OF RESULTS OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION
Attorney
(PCT Rule 44.1)

Date of Mailing
(day/month/year)

24 FEB 2004

Applicant's or agent's file reference
LD339 PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US03/22755

International filing date
(day/month/year)

21 July 2003 (21.07.2003)

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

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

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

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

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

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

4. Reminders

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

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

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

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

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1430
Alexandria, Virginia 22313-1430
Facsimile No. (703)305-3230

Authorized officer
Venkatarayan Balasubramanian
Telephone No. (703)308-1235

Form PCT/ISA/220 (April 2002)

(See notes on accompanying sheet)

PCT REQUEST

Original (for SUBMISSION) - printed on 21.07.2003 08:49:00 AM

LD339 PCT

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)
0-5	Petition The undersigned requests that the present International application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	LD339 PCT
I	Title of invention	PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Princelaine Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	BHIDE, Rajeev
III-1-5	Address:	22 Hawthorne Dr. Princeton Junction, NJ 08550 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

PCT REQUEST

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III-2	Applicant and/or inventor	applicant and inventor
III-2-1	This person is:	US only
III-2-2	Applicant for	FAN, Junying
III-2-4	Name (LAST, First)	5 Ryan Ct.
III-2-5	Address:	Monmouth Junction, NJ 08852
		United States of America
III-2-6	State of nationality	CN
III-2-7	State of residence	US
III-3	Applicant and/or inventor	applicant and inventor
III-3-1	This person is:	US only
III-3-2	Applicant for	PARLANTI, Luca
III-3-4	Name (LAST, First)	114 Cascade Ct.
III-3-5	Address:	Apt.# 7
		Princeton, NJ 08540
		United States of America
III-3-6	State of nationality	IT
III-3-7	State of residence	US
III-4	Applicant and/or inventor	applicant and inventor
III-4-1	This person is:	US only
III-4-2	Applicant for	BARBOSA, Stephanie
III-4-4	Name (LAST, First)	2 Big Top Dr.
III-4-5	Address:	Lambertville, NJ 08530
		United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or inventor	applicant and inventor
III-5-1	This person is:	US only
III-5-2	Applicant for	QIAN, Ligang
III-5-4	Name (LAST, First)	11 Coventry Ln.
III-5-5	Address:	Hopewell, NJ 08525
		United States of America
III-5-6	State of nationality	US
III-5-7	State of residence	US

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LD338 PCT

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III-6	Applicant and/or inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	CAI, Zhen-Wei
III-6-5	Address:	36 Hills Dr. Belle Mead, NJ 08502 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US
III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	GIBSON, Francis, S.
III-7-5	Address:	24 Shara Lane Pennington, NJ 08534 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	KORSEN, Elliott
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-4741
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	32,705

PCT REQUEST

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IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GIBBONS, Maureen(44,121); ALGIERI, Aldo(31,697); BABAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); PATEL, Rena(41,412); DAVIS, Stephen(26,693); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); PEIST, Kenneth(45,006); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); VANATTEN, Mary, K.(39,408); GOLIAN, Paul, D.(42,591); LAMERDIN, John(44,858); DUNCAN, Laurelee(44,096); WARREN, Volles(33,810); BAXAM, Deanna(45,266)
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

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V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 16 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	19 July 2002 (19.07.2002)
VI-1-2	Number	60/397,256
VI-1-3	Country	US
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	13 February 2003 (13.02.2003)
VI-2-2	Number	60/447,213
VI-2-3	Country	US
VI-3	Priority claim of earlier national application	
VI-3-1	Filing date	18 July 2003 (18.07.2003)
VI-3-2	Number	
VI-3-3	Country	US
VI-4	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2, VI-3
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

PCT REQUEST

Original (for SUBMISSION) - printed on 21.07.2003 08:49:00 AM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	38	-
IX-3	Claims	9	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	54	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EA5Y diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the International application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	KORSEN, Elliott	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported International application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported International application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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2/2

0	Solo para uso de la Oficina de Recepción	
0-1	Solicitud Internacional No.	
0-2	Fecha de Presentación Internacional	
0-3	Nombre de la Oficina de Recepción y "Solicitud Internacional PCT"	
0-4	Forma - PCT/RO/101 PCT Petitorio	
0-4-1	Uso preparado	PCT-EASY Versión 2.92 (actualizado 01.04.2003)
0-5	Petición El abajo firmante requiere que la presente solicitud internacional sea procesada de acuerdo con el Tratado de Cooperación de Patentes	
0-6	Oficina de Recepción (especificada por el solicitante)	Oficina de patentes y marcas registradas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo del solicitante o mandatario	LD339 PCT
I	Título de la invención	PROCESO PARA LA PREPARACIÓN DE CIERTOS COMPUESTOS DE PIRROLOTRIAZINA
II	Solicitante	
II-1	Esta persona es:	Sólo solicitante
II-2	Solicitante para	Todos los Estados designados excepto US
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América
II-6	Estado de nacionalidad	US
II-7	Estado de residencia	US
II-8	No. de teléfono	609-252-4000
II-9	No. de facsímil	609-252-4526
III-1	Solicitante e/o inventor	
III-1-1	Esta persona es:	Solicitante e inventor
III-1-2	Solicitante para	Sólo US
III-1-4	Nombre (APELLIDO, Nombre)	BHIDE, Rajeev
III-1-5	Dirección:	22 Hawthorne Dr. Princeton Junction, NJ 08550 Estados Unidos de América
III-1-6	Estado de nacionalidad	US
III-1-7	Estado de residencia	US

III-2	Solicitante e/o inventor	
III-2-1	Esta persona es:	Solicitante e inventor
III-2-2	Solicitante para	Sólo US
III-2-4	Nombre (APELLIDO, Nombre)	FAN, Junying
III-2-5	Dirección:	5 Ryan Ct. Monmouth Junction, NJ 08852 Estados Unidos de América
III-2-6	Estado de nacionalidad	CN
III-2-7	Estado de residencia	US
III-3	Solicitante e/o inventor	
III-3-1	Esta persona es:	Solicitante e inventor
III-3-2	Solicitante para	Sólo US
III-3-4	Nombre (APELLIDO, Nombre)	PARLANTI, Luca
III-3-5	Dirección:	114 Cascade Ct. Apt. # 7 Princeton, NJ 08540 Estados Unidos de América
III-3-6	Estado de nacionalidad	IT
III-3-7	Estado de residencia	US
III-4	Solicitante e/o inventor	
III-4-1	Esta persona es:	Solicitante e inventor
III-4-2	Solicitante para	Sólo US
III-4-4	Nombre (APELLIDO, Nombre)	BARBOSA, Stephanie
III-4-5	Dirección:	2 Big Top Dr. Lambertville, NJ 08530 Estados Unidos de América
III-4-6	Estado de nacionalidad	US
III-4-7	Estado de residencia	US
III-5	Solicitante e/o inventor	
III-5-1	Esta persona es:	Solicitante e inventor
III-5-2	Solicitante para	Sólo US
III-5-4	Nombre (APELLIDO, Nombre)	QIAN, Ligang
III-5-5	Dirección:	11 Coventry Ln. Hopewell, NJ 08525 Estados Unidos de América
III-5-6	Estado de nacionalidad	US
III-5-7	Estado de residencia	US

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III-6	Solicitante e/o inventor	
III-6-1	Esta persona es:	Solicitante e inventor
III-6-2	Solicitante para	Sólo US
III-6-4	Nombre (APELLIDO, Nombre)	CAI, Zhen-Wei
III-6-5	Dirección:	36 Hills Dr. Belle Mead, NJ 08502 Estados Unidos de América
III-6-6	Estado de nacionalidad	US
III-6-7	Estado de residencia	US
III-7	Solicitante e/o inventor	
III-7-1	Esta persona es:	Solicitante e inventor
III-7-2	Solicitante para	Sólo US
III-7-4	Nombre (APELLIDO, Nombre)	GIBSON, Francis, S.
III-7-5	Dirección:	24 Shara Lane Pennington, NJ 08534 Estados Unidos de América
III-7-6	Estado de nacionalidad	US
III-7-7	Estado de residencia	US
IV-1	Mandatario o representante común; o dirección para correspondencia La persona identificada abajo es aquí/ha sido designada para actuar en nombre del solicitante(s) antes de las Autoridades internacionales competentes como:	Mandatario
IV-1-1	Nombre (APELLIDO, Nombre)	KORSEN, Elliott
IV-1-2	Dirección	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	609-252-4741
IV-1-4	Facsimil No.	609-252-4526
IV-1-5	Registro del mandatario no.	32,705

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IV-2	Mandatario(s) adicional(es)	Mandatario(s) adicional(es) con la misma dirección que el mandatario nombrado al principio
IV-2-1	Nombre(s)	GIBBONS, Maureen (44,121); ALGIERI, Aldo (31,697); BARAJKO, Suzanne (32,880); BUCHHOLZ, Briana (39,123); D'AMICO, Stephen (46,652); KLEIN, Christopher (34,363); LANGE, Keith (44,201); MAKUJINA, Shah (41,174); PATEL, Rena (41,412); DAVIS, Stephen (26,693); RODNEY, Burton (22,076); RYAN, Richard (30,491); SHER, Audrey (39,024); PEIST, Kenneth (45,006); O'BRIEN, Maureen (42,043); BELFIELD, Jing (45,194); VANATTEN, Mary, K. (39,408); GOLIAN, Paul, D. (42,591); LAMERDIN, John (44,858); DUNCAN, Laurelee (44,096); WARREN, Volles (33,810); BAXAM, Deanna (45,266)
V	Designación de Estados	
V-1	Patente regional (otros tipos de protección o tratamiento, si existen, se especifican entre paréntesis después de la designación(es) referidas)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro Estado que sea un Estado de Contratación del protocolo Harare y del PCT EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro Estado que sea un Estado de Contratación de la Convención de Patente Europea y del PCT EP: AT BE BG CH & LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR y cualquier otro Estado que sea un Estado de Contratación de la Convención de Patente Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro Estado que sea un Estado miembro de OAPI y un Estado de Contratación del PCT
V-2	Patente Nacional (otros tipos de protección o tratamiento, si existiera, se especifican entre paréntesis después de la designación(s))	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH&LI, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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V-5	Declaración de Designación Preventiva. Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace bajo la Regla 4.9(b) todas las designaciones que serían permitidas bajo el PCT, excepto cualquier designación(es) del Estado(s) indicados bajo el punto V-6 posterior. El solicitante declara que las designaciones adicionales se someten a confirmación y que cualquier designación que no sea confirmada antes de la expiración de 15 meses a partir de la fecha de prioridad, va a considerarse como eliminada por el solicitante en la expiración de tal tiempo límite.	
V-6	Exclusión(es) de las designaciones preventivas	NINGUNA
VI-1	Reivindicación de prioridad de la solicitud nacional previa	
VI-1-1	Fecha de presentación	19 de julio de 2002 (19.07.2002)
VI-1-2	Número	60/397,256
VI-1-3	País	US
VI-2	Reivindicación de prioridad de la solicitud nacional previa	
VI-2-1	Fecha de presentación	13 de febrero de 2003 (13.02.2003)
VI-2-2	Número	60/447,213
VI-2-3	País	US
VI-3	Reivindicación de prioridad de la solicitud nacional previa	
VI-3-1	Fecha de presentación	18 de julio de 2003 (18.07.2003)
VI-3-2	Número	
VI-3-3	País	US
VI-4	Solicitud del documento de prioridad La Oficina de recepción se requiere para preparar y transmitir a la Oficina Internacional una copia certificada de las Solicitudes previas identificadas anteriormente como punto(s):	VI-1, VI-2, VI-3
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina de marcas y patentes de los Estados Unidos (USPTO) (ISA/US)

VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para identidad del inventor	-	
VIII-2	Declaración como derecho del solicitante, como en la fecha de presentación internacional, de solicitar y otorgarse una patente	-	
VIII-3	Declaración como derecho del solicitante, como en la fecha de presentación internacional, de reivindicar la prioridad de la solicitud previa	-	
VIII-4	Declaración del Inventor (solo para los propósitos de la designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones no perjudiciales o excepciones de carencia de novedad	-	
IX	Lista de Verificación	Número de hojas	Archivos electrónicos anexos
IX-1	Petitorio (incluyendo hojas de declaración)	6	
IX-2	Descripción	38	
IX-3	Reivindicaciones	9	
IX-4	Resumen	1	EZABST00.TXT
IX-5	Dibujos	0	-
IX-7	TOTAL	54	
	Puntos Anexos	Documento(s) en papel	Archivos electrónicos anexos
IX-8	Hoja de cálculo de honorarios	√	-
IX-9	Poder del abogado original separado	√	-
IX-17	PCT-EASY disquete	-	Disquete
IX-18	Otro (especificado):	Certificación	-
IX-19	Figura de los dibujos que debería acompañar al resumen		
IX-20	Idioma de presentación de la solicitud internacional	Inglés	
X-1	Firma del solicitante, mandatario o representante común	(rúbrica)	
X-1-1	Nombre (APELLIDOS)	KORSEN, Elliott	
PARA USO SOLAMENTE DE LA OFICINA DE RECEPCIÓN			
10-1	Fecha de la recepción actual de la solicitud internacional pretendida		

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2A

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PCT PETITORIO Original (para PRESENTACIÓN) - impreso el 21.07.2003 08:19:00 AM

10-2	Dibujos:	
10-2-1	Recibidos:	
10-2-2	No recibidos:	
10-3	Fecha corregida de la recepción actual debido al final, pero los papeles recibidos a tiempo o dibujos que completan la solicitud internacional pretendida	
10-4	Fecha de recepción a tiempo de las correcciones requeridas bajo el Artículo 11(2) del PCT	
10-5	Autoridad de búsqueda internacional	ISA/US
10-6	Transmisión de la copia de búsqueda retrasada hasta que la tarifa de búsqueda sea pagada	
PARA USO SOLAMENTE DE LA OFICINA INTERNACIONAL		
11-1	Fecha de recepción de la copia de registro por la Oficina internacional	

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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 21.07.2003 08:48:00 AM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only		
0-1	International Application No.		
0-2	Date stamp of the receiving Office		
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)	
0-9	Applicant's or agent's file reference	LD339 PCT	
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.	
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)
12-1	Transmittal fee T	⇒	240
12-2-1	Search fee S	⇒	700
12-2-2	International search to be carried out by	US	
12-3	International fee		
	Basic fee		
	(first 30 sheets) b1	476	
12-4	Remaining sheets	24	
12-5	Additional amount (X)	12	
12-6	Total additional amount b2	288	
12-7	b1 + b2 = B	764	
12-8	Designation fees		
	Number of designations contained in international application	97	
12-9	Number of designation fees payable (maximum 5)	5	
12-10	Amount of designation fee (X)	104	
12-11	Total designation fees D	520	
12-12	PCT-EASY fee reduction R	-148	
12-13	Total international fee (B+D-R) I	⇒	1,136
12-14	Fee for priority document		
	Number of priority documents requested	3	
12-15	Fee per document (X)	20	
12-16	Total priority document fee P	⇒	60
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	2,136
12-19	Mode of payment	authorization to charge deposit account	
12-20	Deposit account instructions		
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)	
12-20-1	Authorization to charge the total fees indicated above.	✓	

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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 21.07.2003 08:49:00 AM

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19-3880
12-22	Date	21 July 2003 (21.07.2003)
12-23	Name and signature	KORSEN, Elliott 

VALIDATION LOG AND REMARKS

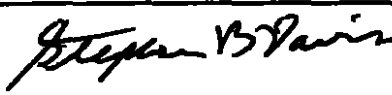
13-1-1	Applicant remarks	chemical structure
13-2-4	Validation messages Priority	Yellow! Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify.
		Yellow Priority 3: Application No. is missing
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
13-2-10	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

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PCT POWER OF ATTORNEY

Printed on 14.07.2003 12:55:37 PM

LD339 PCT

0-1	PCT Power of Attorney (for an International application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.04.2003)
1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	KORSEN, Elliott; GIBBONS, Maureen; ALGIERI, Aldo; BABAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; PATEL, Rena; DAVIS, Stephen; RODNEY, Burton; RYAN, Richard; SHER, Audrey; PEIST, Kenneth; O'BRIEN, Maureen; BELFIELD, Jing; VANATTEN, Mary, K.; GOLIAN, Paul, D.; LAMERDIN, John; DUNCAN, Laurelee; WARREN, Volles; BAXAM, Deanna Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	In connection with the International application identified below:	
1-4-1	Title of the invention	PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE COMPOUNDS
1-4-2	Applicant's or agent's file reference	LD339 PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	
2-1	Signature of applicant	
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Stephen B. Davis
2-1-3	Capacity	Senior Patent Counsel
3	Date	14 July 2003 (14.07.2003)

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PCT

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Original (for SUBMISSION) - printed on 21.07.2003 08:49:00 AM

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

Yellow!	Priority
Yellow	Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify. Priority 3: Application No. is missing
Green?	Contents
	The international application contains no drawings. Please verify.
Green?	Payment
	Please ensure that you have a valid deposit account with the receiving Office selected.
Green?	Annotate
	All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Before submitting the international Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and Item 12-23 of the Annex to the Request form have been signed;
- all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the international Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

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X 3 3

PCT

LD339 PCT

Original (for SUBMISSION) - printed on 21.07.2003 08:49:00 AM

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the International application)

VALIDATION LOG

Yellow! Yellow	Priority Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify. Priority 3: Application No. is missing
Green?	Comments The international application contains no drawings. Please verify.
Green?	Payment Please ensure that you have a valid deposit account with the receiving Office selected.
Green?	Annotate All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form and item 12-23 of the Annex to the Request form have been signed;
- all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

From the INTERNATIONAL BUREAU

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

(PCT Rule 47.1(c), first sentence)

To:

KORSEN, Elliott
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE**RECEIVED
BMS PATENT LAW**

FEB 10 2004

Docketed Item _____

Due Date _____

Attorney **EK**

Date of mailing (day/month/year)

29 January 2004 (29.01.2004)

Applicant's or agent's file reference

PCT/US2003/022755

IMPORTANT NOTICE

International application No.

PCT/US2003/022755

International filing date (day/month/year)

21 July 2003 (21.07.2003)

Priority date (day/month/year)

19 July 2002 (19.07.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

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

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

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

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

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

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 29 January 2004 (29.01.2004) under No. WO 2004/009542

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

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

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

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

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

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

Authorized officer

Gijsbertus Beijer - Carlos Roy

Facsimile No.(41-22) 740.14.35

Telephone No.(41-22) 338.91.11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LD339 PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/230) as well as, where applicable, item 5 below.
International application No. PCT/US03/22755	International filing date (day/month/year) 21 July 2003 (21.07.2003)	(Earliest) Priority Date (day/month/year) 19 July 2002 (19.07.2002)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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

This international search report consists of a total of 2 sheets.



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

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/22755

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 487/04; A61K 31/53; A61P 13/08, 29/00, 37/00
US CL : 544/183; 514/243

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/183; 514/243

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 40486 A2 (BRISTOL-MYERS SQUIBB COMPANY) 23 May 2002 (23.05.2002). See entire document especially pages 64-77, examples 61-125.	1-16

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

☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

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

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

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

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

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

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

"A" document number of the same patent family

Date of the actual completion of the international search

29 January 2004 (29.01.2004)

Date of mailing of the international search report

24 FEB 2004
Authorized officer
Venkateswarar, Ramesh Kumar
Telephone No. (703)308-1235

Name and mailing address of the ISA/US

Mall Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Form PCT/ISA/210 (second sheet) (July 1998)

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia de archivo del solicitante o apoderado : LD339 PCT	PARA UNA ACCION ADICIONAL.	Véase la Notificación de transmisión del reporte de examen preliminar internacional (Forma PCT/ISA/220)
No. de solicitud internacional : PCT/US03/22755	Fecha de presentación internacional (día/mes/año) : 21 de julio de 2003 (21.07.2003)	Fecha de prioridad (día/mes/año) : 19 de julio de 2002 (19.07.2002)
Solicitante: BRISTOL-MYERS SQUIBB COMPANY		

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

Este reporte de búsqueda internacional consiste de un total de 2 Hojas.

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

1. Base del reporte

a. Con respecto al idioma, la búsqueda internacional se lleva a cabo con base en la solicitud internacional en el idioma en que se presentó, salvo que se indique lo contrario conforme a este inciso.

☐ la búsqueda internacional se realizó con base en la traducción de la solicitud internacional proporcionada a esta autoridad (Regla 23.1(b)).

b. Con respecto a cualquier secuencia de aminoácidos y/o nucleótidos descritos en la solicitud internacional, la búsqueda internacional se llevó a cabo con base en el listado de secuencias.

☐ contenido en la solicitud internacional en forma escrita

☐ presentado junto con la solicitud internacional en forma legible en computadora

☐ proporcionado subsecuentemente a esta Autoridad en forma escrita.

☐ proporcionado subsecuentemente a esta Autoridad en la forma legible por computadora.

☐ Se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada subsecuentemente no va más allá de la descripción en la solicitud internacional como se presentó.

☐ Se ha proporcionado la declaración de que la información registrada en la forma legible por computadora es idéntica a la lista de secuencias escrita.

2. ☐ Se encontró que ciertas reivindicaciones eran inescrutables (Véase bloque I).

3. ☐ Se carece de unidad de la invención (Véase bloque II).

4. Con respecto al título ☒ el texto está aprobado como se presentó por el solicitante.

☐ el texto ha sido establecido por esta Autoridad para leerse como sigue:

5. Con respecto al resumen,

☒ el texto está aprobado como se presentó por el solicitante.

☐ el texto ha sido establecido, de acuerdo a la Regla 38.2(b), por esta Autoridad como aparece en el Bloque III. El solicitante puede, en el término de un mes a partir de la fecha de envío de este Reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

6. La figura de los dibujos a ser publicada con el extracto es:

Figura No. ☐ Como se sugiere por el solicitante.

☐ Ninguna de las figuras

☐ Debido a que el solicitante no sugirió ninguna.

☐ Debido a que esta figura caracteriza mejor la invención.

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US03/22755

A. CLASIFICACION DEL TEMA

IPC (7): C07D 487/04, A61K 31/53; A61P 13/08, 29/00, 37/00
US CL: 544/183; 514/243
De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
U.S.: 544/183; 514/243

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

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
CAS ONLINE, EAST

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
Y	WO 02 40486 A2 (BRISTOL-MYERS SQUIBB COMPANY) 23 de mayo de 2002 (23.05.2002). Ver el documento completo, especialmente las páginas 64-77, ejemplo 61-125.	1-16

☐ Documentos adicionales se listan en la continuación del bloque C ☐ Véase familia de patentes anexa.

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.
"E" documento anterior publicado en o después de la fecha de presentación internacional.
"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)
"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.
"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.
"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.
"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional
29 de enero de 2004 (29.01.2004)

Fecha de envío del reporte de búsqueda internacional
24 de febrero de 2004

Nombre y dirección de correspondencia de la ISA/US
Comisionado de Patentes y Marcas Registradas
Mail Stop PCT, Attn: ISA/US
Comisionado de patentes
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimil No. (703) 305-3230

Funcionario Autorizado
Venkataraman Belasubramanian
Teléfono no. (703) 308-1235

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

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

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

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

Where not to file the amendments ?

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

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

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

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

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

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

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

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Docket No. LD0339PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

International Application No.: PCT/US03/22755
International Filing Date: 21 July 2003
Priority Date: 19 July 2002
Applicant: Bristol-Myers Squibb Company

For: PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE
COMPOUNDS

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

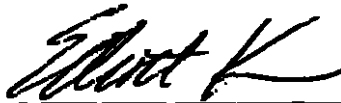
RESPONSE TO INVITATION TO CORRECT DEFECTS IN DEMAND

SIR:

In response to Annex 9(a) of the Invitation to Correct Defects in the Demand for the above noted international application, applicant encloses herewith the substitute Form PCT/IPEA/401 (continuation sheet), pages 2 and 2A, containing the remainder of the inventors, Zhen-Wei Cai and Francis S. Gibson, which were erroneously omitted when submitted on February 4, 2004.

No fee is believed due. However, in the event a fee is due it is requested that the payment be charged to Deposit Account 19-3880.

Respectfully submitted,



Elliott Korsen
Reg. No. 32,705
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
(609) 252- 4741

Express Mail mailing label number, EV 306636031 US

Date of Deposit 6/10/04

I hereby certify that this paper correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Carrie A. Shaw

(Typed or printed name of person mailing paper or fee)


(Signature of Person mailing paper or fee)

144
142

Sheet No. 2.

International application No.
PCT/US03/22755

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.)

PARLANTI, Luca
114 Cascade Ct.
Apt. #7
Princeton, NJ 08540
UNITED STATES OF AMERICA

State (that is, country) of nationality:
IT

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.)

BARBOSA, Stephanie
2 Big Top Dr.
Lambertville, NJ 08530
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.)

QIAN, Ligang
11 Coventry Ln.
Hopewell, NJ 08525
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.)

CAI, Zhen-Wei
36 Hills Drive
Belle Meade, NJ 08502
United States of America

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

☒ Further applicants are indicated on another continuation sheet.

SUBSTITUTE

145
1/13

Sheet No. 2A

International application No.
PCT/US03/22755

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.)*

GIBSON, Francis, S.
24 Shara Lane
Pennington, NJ 08534
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.)*

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:

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.



EV 306636031 US

Mailing Label
Label 7-7 June 2002



UNITED STATES POSTAL SERVICE

Post Office To Addressee

ORIGIN (POSTAL USE ONLY)				DELIVERY (POSTAL USE ONLY)			
PO ZIP Code	Day of Delivery ☐ Next ☐ Second		Flat Rate Envelope ☐	Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature	
Date In Mo. Day Year	☐ 10 Noon ☐ 6 PM		Postage	Delivery Attempt	Time ☐ AM ☐ PM	Employee Signature	
Time In ☐ AM ☐ PM	Military		Return Receipt Fee	Mo. Day	Time ☐ AM ☐ PM	Employee Signature	
Weight	NET Alpha Country Code		ODD Fee	Delivery State	Time ☐ AM ☐ PM	Employee Signature	
No Delivery ☐ Weekend ☐ Holiday	Acceptance Clerk Initials		Insurance Fee	Postage and Fees Due to Addressee			
Total Postage & Fees							
METHOD OF PAYMENT Express Mail Computer Post. No. X085205				Post Office Agency, Post. No. or Post Office Name, No.			
FROM: (PLEASE PRINT) STEPHEN DAVIS BRISTOL-MYERS SQUIBB CO PO BOX 4000 PRINCETON NJ 08543-4000				TO: (PLEASE PRINT) MAIL STOP PCT COMMISSIONER FOR PATENTS PO BOX 1450 ALEXANDRIA VA 22313-1450			

FOR PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.com

527-1000 F:02 F:23

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~~145~~

Case No.: LD0339 PCT

Application No.: PCT/US03/22755

Mailing Date: 6/10/04

Express Mail No.: EV 306631031 US

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

☐ Appin. Filing Papers

☐ Transmittal Fee:

☐ Search Fee:

☐ Basic Fee:

☐ Designation Fee:

☐ Priority Document Fee:

☒ Response to Invitation To
Correct Defects in Demand

PATENT COOPERATION TREATY

LD0339-WO-PCT

COR

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

RECEIVED

BMS PATENT LAW

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

AUG 16 2004

Due Date

Attorney

IMPORTANT INFORMATION

Date of mailing (day/month/year)

06 August 2004 (06.08.2004)

Applicant's or agent's file reference

LD339 PCT

International application No.

PCT/US2003/022755

International filing date (day/month/year)

21 July 2003 (21.07.2003)

Priority date (day/month/year)

19 July 2002 (19.07.2002)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

National : BG, CA, CN, CZ, DE, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NI, NZ, OM, PG, PH, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the International application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the International preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

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

Facsimile No. (41-22) 338.70.10

Authorized officer:

Françoise HENNEQUIN (Fax 338 7010)

Telephone No. (41-22) 338 8935

PATENT COOPERATION TREATY

149
~~LD0339-110-PCT~~
CON

From the INTERNATIONAL BUREAU

PCT

RECEIVED
BMS PATENT LAW

MAY 25 2004

Docketed Item _____
Due Date _____
Attorney EK

To:

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/22755

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 487/04; A61K 31/53; A61P 13/08, 29/00, 37/00

US CL : 544/183; 514/243

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/183; 514/243

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, RAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 40486 A2 (BRISTOL-MYERS SQUIBB COMPANY) 23 May 2002 (23.05.2002). See entire document especially pages 64-77, examples 61-125.	1-16

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

☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

"L" document which may show doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (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 documents published after the international filing date or priority date and not in conflict with the application (as 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 number of the same patent family

Date of the actual completion of the international search

29 January 2004 (29.01.2004)

Date of mailing of the international search report

24 FEB 2004

Name and mailing address of the ISA/US

Mali Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Venkataraman Ramakrishnaiah

Telephone No. (703)308-1235

151 8
TH

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 IPBA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference LD0339 PCT
International application No. PCT/US03/22755	International filing date (day/month/year) 21 July 2003	(Earliest) Priority date (day/month/year) 19 July 2002
Title of invention PROCESS FOR PREPARING CERTAIN PYRROLOTRIAZINE COMPOUNDS		
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. 609-252-4741
		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.) BHIDE, Rajeev 22 Hawthorne Dr. Princeton, NJ 08550 UNITED STATES OF AMERICA		
State (that is, country) of nationality: US		State (that is, country) of residence: US
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) FAN, Junying 5 Ryan Ct. Monmouth Junction, NJ 08852 UNITED STATES OF AMERICA		
State (that is, country) of nationality: CN		State (that is, country) of residence: US
☒ Further applicants are indicated on a continuation sheet.		

152
152

Sheet No. 2.

International application No.
PCT/US03/22755

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.)*
PARLANTI, Luca
114 Cascade Ct.
Apt. #7
Princeton, NJ 08540
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:
IT

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.)*
BARBOSA, Stephanie
2 Big Top Dr.
Lambertville, NJ 08530
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.)*
QIAN, Ligang
11 Coventry Ln.
Hopewell, NJ 08525
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.)*

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.)KORSEN, Elliott
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.

609-252-4741

Facsimile No.

609-252-4526

Teleprinter No.

Agent's registration No. with the Office

32,705

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description

☒

as originally filed

☐

as amended under Article 34

the claims

☒

as originally filed

☐

as amended under Article 19 (together with any accompanying statement)

☐

as amended under Article 34

the drawings

☒

as originally filed

☐

as amended under Article 34

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

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

Language for the purposes of international preliminary examination: English

☒

which is the language in which the international application was filed.

☐

which is the language of a translation furnished for the purposes of international search.

☐

which is the language of publication of the international application.

☐

which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

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

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

Sheet No. 4.

International application No.
PCT/US03/22755

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. ☐ sequences 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 Date: February 4, 2004
Elliott Korsen

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:

155
13

PCT Demand Chapter II

Int'l. Application No. PCT/US03/22755
Docket No. LD0339 PCT

Express mail mailing label number EV 306636204 US

Date of Deposit 02/05/04
I hereby certify that this paper or fee is being deposited with the United States
Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to the Commissioner for
Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Carrie A. Shaw
(Typed or printed name of person mailing paper or fee)
Carrie A. Shaw
(Signature of person mailing paper or fee)

THIS PATENT IS

PCT/US03/22755

PATENT COOPERATION TREATY LD0339-WO-PCT

DEC 03 2003

From the INTERNATIONAL BUREAU

Registered Item

Due Date

Attorney

**NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT**

(PCT Administrative Instructions, Section 411)

To:

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

Date of mailing (day/month/year)

24 November 2003 (24.11.03)

Applicant's or agent's file reference

LD0339-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US03/22755

International filing date (day/month/year)

21 July 2003 (21.07.03)

International publication date (day/month/year)

Not yet published

Priority date (day/month/year)

19 July 2002 (19.07.02)

Applicant

BRISTOL-MYERS SQUIBB COMPANY et al

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 July 2002 (19.07.02)	60/397,256	US	08 Sept 2003 (08.09.03)
13 Febr 2003 (13.02.03)	60/447,213	US	09 Sept 2003 (09.09.03)
18 July 2003 (18.07.03)	10/622,280	US	12 Nove 2003 (12.11.03)

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

Facsimile No. (41-22) 338 70 10

Authorized officer

Jean-Marie MCADAMS (Fax 338 70 10)

Telephone No. (41-22) 338 88 13

157

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No.	For International Preliminary Examining Authority use only	
Applicant's or agent's file reference LD0339 PCT	Date stamp of the IPEA	
Applicant Bristol-Myers Squibb Company		
CALCULATION OF PRESCRIBED FEES		
1. Preliminary examination fee	750.00	P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	172.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	922.00	
	TOTAL	
MODE OF PAYMENT		
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	
☐ cheque	☐ revenue stamps	
☐ postal money order	☐ coupons	
☐ bank draft	☐ other (specify):	
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)		
☒ Authorization to charge the total fees indicated above.	IPEA/US	
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: 19-3880	
	Date: February 4, 2004	
	Name: Elliott Kersen	
	Signature: Elliott Kersen	

158 10
157

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko
Stephen B. Davis
John M. Kilcoyne
Christopher Klein
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 8th day of APRIL 2003.


John L. McGoldrick
Executive Vice President
and General Counsel


Secretary

159
PCT/US03/22755

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

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

Date of mailing (day/month/year) 03 October 2003 (03.10.03)	
Applicant's or agent's file reference LD339 PCT	IMPORTANT NOTIFICATION
International application No. PCT/US03/22755	International filing date (day/month/year) 21 July 2003 (21.07.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 July 2002 (19.07.02)
Applicant BRISTOL-MYERS SQUIBB COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 July 2002 (19.07.02)	60/397,256	US	08 Sept 2003 (08.09.03)
13 Febr 2003 (13.02.03)	60/447,213	US	09 Sept 2003 (09.09.03)

RECEIVED
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OCT 23 2003

Uncketed Item

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

Facsimile No. (41-22) 938 70 10

Authorized officer

Farid-ABBOU

Telephone No. (41-22) 938 8189

160 11
11

#3885

Case No.: LD0339 PCT

Application No.: PCT/US03/22755

Mailing Date: 02/05/04

Express Mail No.: EV 306636204

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

☐ Appln. Filing Papers

☐ Transmittal Fee:

☐ Search Fee:

☐ Basic Fee:

☐ Designation Fee:

☐ Priority Document Fee:

☒ Demand

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161



Mailing Label
Label 1-4 June 1992



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FROM: (PLEASE PRINT) STEPHEN DAVIS BRISTOL-MYERS SQUIBB CO PO BOX 4000 PRINCETON NJ 08543-4000			TO: (PLEASE PRINT) MAIL STOP PCT COMMISSIONER FOR PATENTS PO BOX 1450 ALEXANDRIA VA 22313-1450		
LD0339 PCT EK					

FOR PICKUP OR TRACKING CALL 1-800-222-1611 www.usps.com



~~XX~~



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22312-1450
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE RECD	ATTY. DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
10/622,280	07/18/2003	1624	880	LD0339 NP		18	3

23914

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

CONFIRMATION NO. 4608 ✓

UPDATED FILING RECEIPT



0C00000011658793

Date Mailed: 01/09/2004 ✓

Receipt is acknowledged of this regular 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 Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Rajeev S. Bhide, Princeton Junction, NJ; ✓
Junying Fan, Monmouth Junction, NJ; ✓
Luca Parlanti, Princeton, NJ; ✓
Stephanie Barbosa, Lambertville, NJ; ✓
Ligang Qian, Hopewell, NJ; ✓
Zhen-Wai Cai, Belle Mead, NJ; ✓
Francis S. Gibson, Pennington, NJ; ✓

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BMS PATENT LAW

JAN 12 2004

Docketed Item Updated F.R.Due Date PPD-4/22/04Attorney (K)

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/397,256 07/19/2002 ✓
and claims benefit of 60/447,213 02/13/2003 ✓

Foreign Applications

If Required, Foreign Filing License Granted: 08/30/2003 ✓

Projected Publication Date: 04/22/2004 ✓

Non-Publication Request: No

Early Publication Request: No

Title

Process for preparing certain pyrrolotriazine compounds ✓

Preliminary Class

544

**LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15**

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 8 months from the filing date of the application. If 8 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).

164 13
The present invention relates to a process for preparing certain pyrimidine compounds of the following structure:

Structure and pharmaceutically acceptable salts thereof. The formula I compounds inhibit the tyrosine kinase activity of growth factor receptors such as VEGFR-2 and FGFR-1, thereby making them useful as anti-cancer agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

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EV 001830675 US



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Time In ☐ AM ☐ PM	11 AM ☐ 2 PM ☐	Return Receipt Fee \$		NO DELIVERY ☐ Insured ☐ Registered ☐			
Weight	1st Alpha Country Code	COG Fee	Insurance Fee	NO DELIVERY ☐ Insured ☐ Registered ☐			
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EXPRESS MAIL ONLY Express Mail Corporate Acct. No. X085205				Postnet Agency Acct. No. or Postnet Station Acct. No.			
FROM: (PLEASE PRINT) STEPHEN B. DAVIS MARLA MATHIAS BRISTOL-MYERS SQUIBB CO PO BOX 4000 PRINCETON NJ 08543-4000 ELLIOTT KORSER PCT- LD339				TO: (PLEASE PRINT) USPTO ASSISTANT COMMISSIONER FOR PATENTS BOX PCT APPLICATION WASHINGTON DC 20231-9999 ALEXANDRIA, VA 22313-1450			
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Label 11-F August 2000

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166

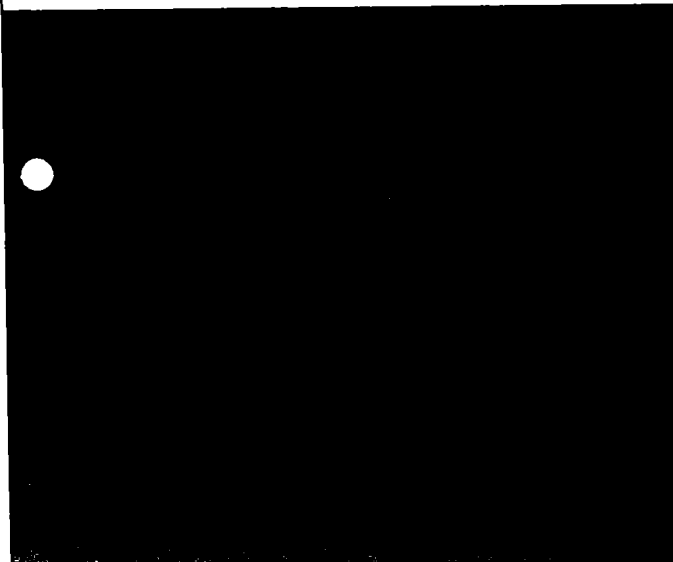
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ELLIOTT KORSEN D3
PATENT DEPARTMENT
BRISTOL-MYERS SQUIBB COMPANY
PO BOX 4000
PRINCETON NJ 08543-5179



167

Case No.: _____

Application No.: LD339 - USSN # to be Assigned

Mailing Date: 21 July 2003

Express Mail No.: EV 001830675 US

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

☐ Appln. Filing Papers

☒ Transmittal Fee: 240

☐ Search Fee: 700

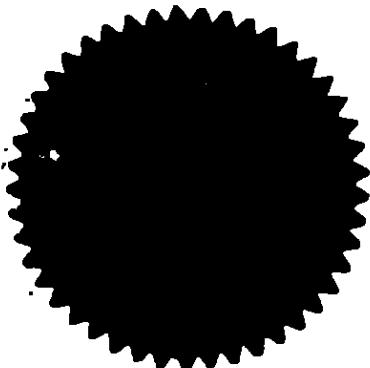
☐ Basic Fee: 476

☐ Designation Fee: 520

☐ Priority Document Fee: 60

168
166

STATE OF NEW JERSEY. } ss.
County of Mercer



I, CATHERINE DICOSTANZO, Clerk of the County of Mercer,

Do Hereby Certify that *Diene P. Bortone*
Esq., whose name is subscribed to the acknowledgment, proof or affidavit of
the annexed instrument, and thereon written, is and was at the time of
taking the same, a Notary Public in and for said State,
dwelling in said County, commissioned and sworn and duly authorized by
the laws thereof to take the proofs and acknowledgments of deeds or other
instruments of writing, and affidavits to be recorded in said State, and that I
am well acquainted with the handwriting of said official, and verily believe
that the signature is genuine.
Further Certify that impression of Seal of Notaries Public not required by
law be filed in my office.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of
said County and Courts, at Trenton this *15th* day of

April A.D. nineteen hundred and *twenty one*
Catherine D. Costanzo Mercer County Clerk.





Brigard & Castro

SANTA FE DE BOGOTÁ - COLOMBIA

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PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) BRISTOL-MYERS SQUIBB COMPANY,

domiciliado(s) en

domiciled in
Princeton, New Jersey, USA

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and records of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el recargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm deal, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

and signed in Princeton, New Jersey, USA.

en

de

de 19

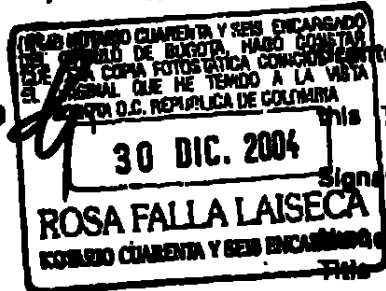
this 14th

day of April 1999

Firma

Nombre

Cargo



Signature

BRISTOL-MYERS SQUIBB COMPANY

Stephen B. Davis
Stephen B. Davis
Associate Counsel Patents

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante
está autorizado por dicha compañía para conferir este
poder; que el sello estampado por él al pie de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de
en fecha

y que quien confiere el presente poder es su
representante.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los
fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION ANTE CONSUL COLOMBIANO ES
REQUERIDA.

On this 14th day of April of 1998
personally appeared before me

Stephen B. Davis
to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

Associate Counsel Patents
of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired,
that deponent is authorized by said Company to confer
this Power of Attorney: that the seal affixed hereunto
by the deponent in the name and on behalf of said
Corporation is the corporate seal thereof; and that the
purpose for which this instrument is granted is included
within the corporate purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Delaware
under date of November 13, 1989

and that he (she) who grants the present power of
attorney is its Representative.

Diane C. Bartram

Diane C. Bartram Public Notary (Seal)
Notary Public of New Jersey
My Commission Expires March 9, 2000

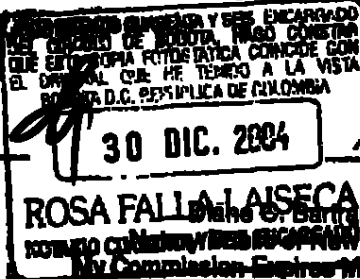
**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this 14th day of April of 1999
personally appeared before me

Stephen B. Davis

who is(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed.

Notary Public (Seal)



LEGALIZATION BEFORE COLOMBIAN CONSUL IS REQUIRED.

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167**EL SUSCRITO CONSUL DE COLOMBIA****VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS****CERTIFICA**

Que el Señor (a), **CATHERINE Dicostanzo Clerck** del condado de Mercer estado de New Jersey, autenticó la firma de la notario(a) publico(a) sr (a). **DIANE C. BARTRAN** del estado de New Jersey, Estados Unidos de América y quien ejercia las funciones antes expresadas, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales;

Que la notario(a) antes citada autenticó la firma del señor **STEPHEN B. DAVIS-** quien actua en calidad de Asesor de Patentes de la Compañia **BRISTOL-MEYERS SQUIBB COMPANY** sociedad que existe y esta legalmente organizada bajo las leyes del estado de Delaware U.S.A



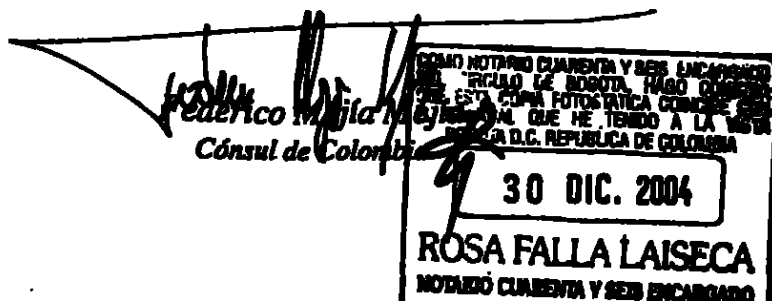
Que ha tenido a la vista los documentos probatorios de los hechos citados y constatados por el notario público y el County Clerck del estado de New Jersey, los cuales forman parte integral del presente documento.

Se expide la presente certificación en cumplimiento de los artículos 259 del Código de Procedimiento Civil y 480 del Código de Comercio y a solicitud del interesado el 20 de Abril de 1999.

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO ADJUNTO.

PAGADO IMPUESTO DE TIMBRE Y DERECHOS CONSULARES.

VALOR CINCUENTA Y SIETE DOLARES US\$57.00 RECIBO No. 200283



172
172

TRADUCCION OFICIAL No. 260/99 de las Legalizaciones que se encuentran a continuación de un Poder otorgado por BRISTOL-MYERS SQUIBB COMPANY, una sociedad domiciliada en Princenton, New Jersey, Estados Unidos de América al doctor RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sellan con el Sello del Traductor al mismo tiempo que la presente.-

ANEXOS: El Poder arriba mencionado, Certificaciones Notariales, Certificación de las Firmas Notariales, Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

Diane C. Bartram (firmado)

Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

Diane C. Bartram (firmado)

Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

Diane C. Bartram (firmado)

Notario Público

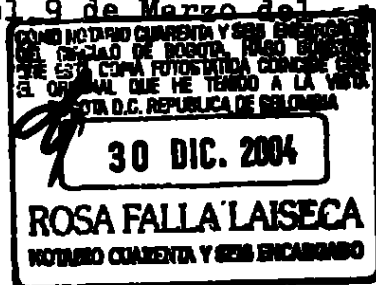
HAY UN SELLO QUE DICE:

Diane C. Bartram

Notario Público de New Jersey

Mi Comisión Expira el 9 de Marzo del
año 2000

1000 NADA DE LA VAREZ
NOTARIO PUBLICO



173
f7

+++++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

+++++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

+++++

Diane C. Bartram (firmado)
Notario Público

HAY UN SELLO QUE DICE:

Diane C. Bartram
Notario Público de New Jersey
Mi Comisión Expira el 9 de Marzo del
año 2000

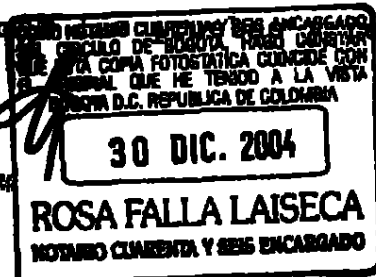
+++++

ESTADO DE NEW JERSEY
Condado de Mercer

Yo, CATHERINE DiCOSTANZO, Escribano del Condado de Mercer,

Por Medio del Presente Certifico que Diane C. Bartram, cuyo nombre está suscrito al reconocimiento, prueba o declaración jurada del instrumento anexo, y en éste escrito, es y era en el momento de tomar el mismo, un Notario Público en y para dicho Estado, residente en dicho Condado, comisionado y juramentado y debidamente autorizado por las leyes de éste para tomar el mismo.

W. M. MARQUEZ ALVAREZ
FOTOCOPIADO Y VERIFICADO



cimientos de escrituras u otros instrumentos escritos, y declaraciones juradas para ser registrados en dicho Estado, y que estoy familiarizado con la caligrafía de dicho funcionario, y de veras creo que la firma es genuina.

Además Certifico que la impresión del Sello de Notarios Públicos no está requerida por la ley para ser presentada en mi oficina.

En Testimonio de lo Cual, he firmado el presente de mi puño y letra y fijado el sello de dichos Condado y Tribunales, en Tranton este día 15 de Abril del A.D. de mil novecientos noventa y nueve.

Catherine DiConstanzo (fdo.) Escribano del Condado de Mercer.

SELLO EN RELIEVE.

+++++
EN ESPAÑOL: La Certificación del Consulado General de Colombia en New York, Estado de New York, Estados Unidos de América bajo el número 200283 de fecha 20 de Abril de 1999; Autenticación hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 044498 de fecha 29 de Abril de 1999.

(Pagado Impuesto de Timbre y Derechos Consulares por valor de \$57.00 Dólares).

+++++
ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS ADJUNTOS.

ALVARO ALVAREZ
INTERPRETE OFICIAL
P.O. BOX 1000000, NEW YORK

Resolución número 1876 del Ministerio de Justicia.

Fecha: Mayo 3 de 1999.

JEFE DELEGACIONES
SANTAFE DE BOGOTA D.C.
60 MAY - 4 AM 11:09
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES
EXTERIORES
1029201
30 DIC. 2004
ROSA FALLA LAISECA
NOTARIO CUARENTA Y SEIS ENCARGADO



ORGANIZACIÓN ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

175
GAVIRI A
[Firma]

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo
Serial 5562241

Datos de la oficina de registro									
Clase de oficina:	Registraduría	Notaría	☒	Consulado	Corregimiento	Imp. de Policía	Código	9795	
País: Colombia - Departamento: Cundinamarca - Municipio: Bogotá D.C. - Corregimiento: sin Inspección de Policía									
COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32.									

Datos del inscrito	
Apellidos y nombres completos	
CASTRO DUQUE RAMIRO	
Inscripción de Identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción		
Lugar de la Defunción: País: Colombia - Departamento: Cundinamarca - Municipio: Bogotá D.C.		
Fecha de la defunción	Hora	Número de certificado de defunción
Año: 2004 Mes: 10 Día: 30 04:10 PM		A- 2094375.
Preparación de muerte		
Lugar en que ocurrió la defunción		
Fecha de la postmorte		
Documento presentado		
Autopsia judicial	Certificado Médico	☒
Nombre y cargo del declarante		
ANDRES DIAZ CAMPOS - R.M. No. 79982662		

Datos del denunciante	
Apellidos y nombres completos	
EDGAR DAVID REGINO II.	
Documento de Identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	<i>[Firma]</i>

Primer testigo	
Apellidos y nombres completos	
Documento de Identificación (Clase y número)	
Firma	

Segundo testigo	
Apellidos y nombres completos	
Documento de Identificación (Clase y número)	
Firma	

Fecha de inscripción	Nombre y cargo del funcionario que declara	
Año: 2004 Mes: 10 Día: 02	BLANCA CHOTA GONZALEZ RESTREPO NOTARIA DE	

PADRES: ALFONSO CASTRO		ESPACIO PARA NOTAS
MERCEDES DUQUE		

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

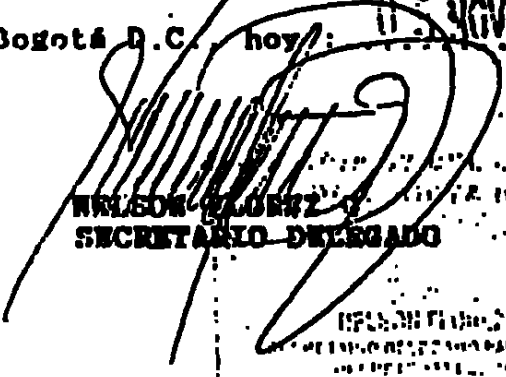
Germán Eleázar Moreno L.

Notario

174
COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO, QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: 556224
que expido en la ciudad de Bogotá D.C. hoy: 11 AGO. 2004


WILSON FLORENT
SECRETARIO DELEGADO

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()

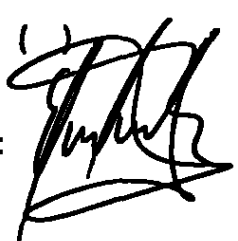
COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable:



Fecha: Radicación : 85001141 00000000
Fecha (MM): 2005-01-07 16:54:54
Trámite : 011 PCT-PATENT 379 FASE NACT 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Extracto publicación
Folios 276 al 281

177
182



Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a)
HECTOR GOMEZ MEJIA
Apoderado(a)
BRISTOL – MYERS SQUIBB COMPANY

Oficio-Nº **12031**

ASUNTO:

Radicación N°	05-1141
Solicitud internacional	PCT/US2003/022755
Fecha inicio fase nacional	19/02/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- El solicitante deberá anexar la traducción de las modificaciones realizadas al capítulo reivindicatorio de la solicitud, lo anterior de acuerdo con la información publicada por la oficina europea y que corresponde al trámite en fase internacional de la misma.
- El solicitante deberá anexar la traducción del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante establecido, de acuerdo con la regla 4.17 51 bis PCT. (Art. 26-k) Decisión 486). Folios 51-53.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,

12 FEB 2005
202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Commutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia