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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 **EXPEDIENTE No** 04-43611

54 **TITULO** IDAZOLILPIRROLOTRIAZINAS MODIFICADAS C5

51 **CLASIFICACION INTERNACIONAL** A61K31/4196, A61K31/416

71 **SOLICITANTE** BRISTOL MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY ESTADOS UNIDOS DE AMERICA

74 **APODERADO** RAMIRO CASTRO DUQUE

22 **SANTAFE DE BOGOTA D C** 12/05/2004

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Oficina de Comunicaciones

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Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04043611 00000000 Folios: 181
Fecha (AMD): 2004-05-12 18:55:12
Tramite : 811 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 provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Harold Mastalerz, Guifen Zhang, James G. Tarrant, Gregory D. Vite Dirección: 70 Robin Lane, Guilford, CT 06437, US; 883 Durham Rd, Wallingford, CT 06492, US; 156 Handy Rd, Hamden, CT 06518, US; 28 Continental Lane, Titusville, NJ 08560, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/US2002/36528 Fecha 12-11-2002
Publicación Internacional No. WO 2003/042172 A3 Fecha 22-05-2003

6 Título (54): IDAZOLILPIRROLOTRIAZINAS MODIFICADAS C5

7 Clasificación Internacional (51) C07D A61K 31/4196 ; A61K 31/416.

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	14-11-2001	60/333.014

9 Comprobante de pago No.: 04-29.660 [illegible] Fecha: 10-05-2004

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

10 ANEXOS

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

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170322 de Bogotá T.P. 103 del C.S.J.

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

NIT : 900176089-2

SUPERINTENDENCIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 04 - 29,660
FECHA : ABRIL 14 DE 2004

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21740204	14/04/2004	7,050,000.00

C O N C E P T O

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

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2003 (22.05.2003)

PCT

(10) International Publication Number
WO 2003/042172 A3

(51) International Patent Classification[7]: C07D 403/12, 401/14, A61K 31/53, A61P 35/00

(21) International Application Number: PCT/US2002/036528

(22) International Filing Date: 12 November 2002 (12.11.2002)

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(26) Publication Language: English

(30) Priority Data:
60/333,014 14 November 2001 (14.11.2001) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MASTALERZ, Harold [CA/US]; 70 Robin Lane, Guilford, CT 06437 (US). ZHANG, Guifen [CN/US]; 883 Durham Rd, Wallingford, CT 06492 (US). TARRANT, James, G. [US/US]; 156 Handy Rd, Hamden, CT 06518 (US). VITE, Gregory, D. [US/US]; 28 Continental Lane, Titusville, NJ 08560 (US).

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

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

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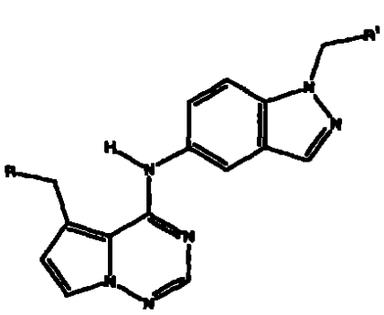
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/042172 A3

(54) Title: C-5 MODIFIED INDAZOLYLPYRROLOTRIAZINES



(I)

(57) Abstract: The present invention provides compounds of formula I and pharmaceutically acceptable salts thereof. The formula I compounds inhibit tyrosine kinase activity of growth factor receptors such as HER1, HER2 and HER4 thereby making them useful as antiproliferative agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/36528

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 403/12,401/14; A61K 31/53; A61P 35/00
US CL : 514/183; 544/243
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. : 514/243; 544/183

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/071129 A1 (BRISTOL-MYERS SQUIBB COMPANY), 30 November 2000 (30.11.00), Examples 71, 138, and 140-143.	1-13
A	FRY, D.W. Chapter 16. Recent Advances in Tyrosine Kinase Inhibitors. Ann. Rep. Med. Chem., 1996, Vol. 31, pages 151-160.	1-13

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 February 2003 (09.02.2003)	29 JUL 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Thomas McKenzie Telephone No. (703) 308-1235

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

Published:
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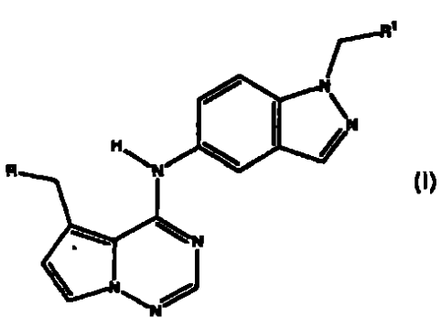
(54) Title: C-5 MODIFIED INDAZOLYLPYRROLOTRIAZINES

WO 03/042172 A2



(I)

(57) Abstract: The present invention provides compounds of formula I and pharmaceutically acceptable salts thereof. The formula I compounds inhibit tyrosine kinase activity of growth factor receptors such as HER1, HER2 and HER4 thereby making them useful as antiproliferative agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

C-5 Modified Indazolylpyrrolotriazines

Field of the Invention

This invention relates to compounds that inhibit the tyrosine kinase activity of growth factor receptors such as HER1, HER2, and HER4 thereby making them useful as anti-cancer agents. The compounds are also useful in the treatment of diseases, other than cancer, which are associated with signal transduction pathways operating through growth factor receptors such as HER1, HER2 and HER4.

Background of the Invention

Receptor tyrosine kinases (RTKs) are important in the transmission of 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.

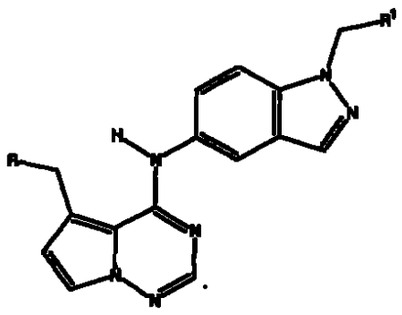
The human epidermal growth factor receptor (HER) family consists of four distinct receptor tyrosine kinases referred to HER1, HER2, HER3, and HER4. These kinases are also referred to as erbB1, erbB2, etc. HER1 is also commonly referred to as the epidermal growth factor (EGF) receptor. With the exception of HER3, these receptors have intrinsic protein kinase activity that is specific for tyrosine residues of phosphoacceptor proteins. The HER kinases are expressed in most epithelial cells as well as tumor cells of epithelial origin. They are also often expressed in tumor cells of mesenchymal origin such as sarcomas or rhabdomyosarcomas. RTKs such as HER1 and HER2 are involved in cell proliferation and are associated with diseases such as psoriasis and cancer. Disruption of signal transduction by inhibition of these kinases would have an antiproliferative and therapeutic effect.

The enzymatic activity of receptor tyrosine kinases can be stimulated by either overexpression, or by ligand-mediated dimerization. The formation of homodimers as well as heterodimers has been demonstrated for the HER receptor family. An example of homodimerization is the dimerization of HER1 (EGF receptor) by one of the EGF family of ligands (which includes EGF, transforming growth factor alpha, betacellulin, heparin-binding EGF, and epiregulin).

Heterodimerization among the four HER receptor kinases can be promoted by binding to members of the heregulin (also referred to neuregulin) family of ligands. Such heterodimerization as involving HER2 and HER3, or a HER3/HER4 combination, results in a significant stimulation of the tyrosine kinase activity of the receptor dimers even though one of the receptors (HER3) is enzymatically inert. The kinase activity of HER2 has been shown to be activated also by virtue of overexpression of the receptor alone in a variety of cell types. Activation of receptor homodimers and heterodimers results in phosphorylation of tyrosine residues on the receptors and on other intracellular proteins. This is followed by the activation of intracellular signaling pathways such as those involving the microtubule associated protein kinase (MAP kinase) and the phosphatidylinositol 3-kinase (PI3 kinase). Activation of these pathways have been shown to lead to cell proliferation and the inhibition of apoptosis. Inhibition of HER kinase signaling has been shown to inhibit cell proliferation and survival.

Summary

The compounds of the invention inhibit the tyrosine kinase activity of growth factor receptors such as HER1, HER2, and HER4 and as such, can be used to treat diseases that are associated with signal transduction pathways operating through growth factor receptors. For example the compounds of the instant invention can be used as antiproliferatives and anticancer agents. More specifically, the invention comprises a compound of formula I



I

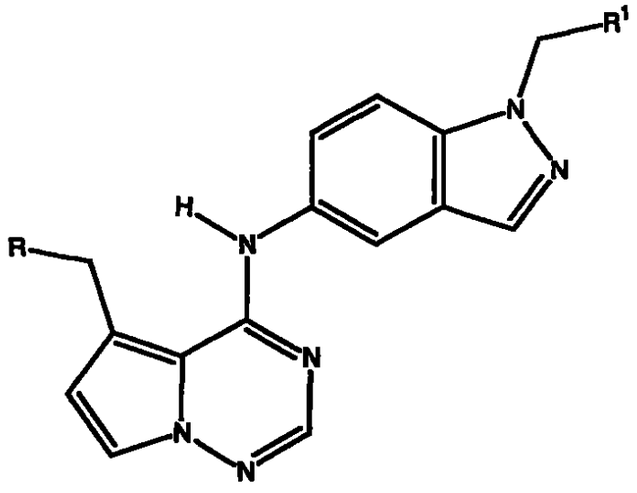
its enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein R is selected from the group consisting of SR^2, SOR^2, SO_2R^2, OR^2, and NR^3R^4; R^1 is selected from the group consisting of aryl, substituted aryl, heterocyclo, and substituted heterocyclo; R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, heterocyclo, and substituted heterocyclo; R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo; or R^2 and R^3 may together form an optionally substituted monocyclic 4-8 membered saturated or unsaturated carbocyclic or heterocyclic ring, or an optionally substituted bicyclic 7 –12 membered saturated or unsaturated carbocyclic or heterocyclic ring.

Also provided for is a method for treating proliferative diseases, comprising administering to a warm-blooded species in need thereof, a therapeutically effective amount of a compound of formula I.

Description

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

In accordance with the present invention, compounds of formula I



I

their enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof inhibit the tyrosine kinase activity of growth factor receptors such as HER2. In formula I and throughout the specification, the above symbols are defined as follows:

R is selected from SR^2, SOR^2, SO_2R^2, OR^2, NR^3R^4;

R^1 is aryl, substituted aryl, heterocyclo, substituted heterocyclo;

R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, heterocyclo, substituted heterocyclo;

R^3 and R^4 are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, or substituted heterocyclo or R^2 and R^3 may together form an optionally substituted monocyclic 4-8 membered saturated or unsaturated carbocyclic or heterocyclic ring, or an optionally substituted bicyclic 7 –12 membered saturated or unsaturated carbocyclic or heterocyclic ring;

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

The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

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, heterocyclo, e.g., indolyl,

imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl and the like, and substituted heterocyclo. 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.

The term "aralkyl" refers to an aryl or a substituted 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, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, aralkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, alkanoyl, alkanoyloxy, aryloxy, aralkyloxy, amino, alkylamino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by hydroxy, halo, alkyl, alkoxy, alkenyl, alkynyl, aryl or aralkyl.

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.

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

The term "substituted alkenyl" refers to an alkenyl group substituted by, for example, one to two substituents, such as, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, 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 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, 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.

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 C_3-C_7 carbocylic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary 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 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 quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, homopiperazinyl, 2-oxohomopiperazinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl,

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

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

The term "carbocyclic ring" refers to stable, saturated or partially unsaturated monocyclic hydrocarbon rings of 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "optionally substituted" as it refers to "carbocyclic ring" herein indicates that the carbocyclic ring may be substituted at one or more substitutable ring positions by one or more groups independently selected from alkyl (preferably lower alkyl), alkoxy (preferably lower alkoxy), nitro, monoalkylamino (preferably a lower alkylamino), dialkylamino (preferably a di[lower]alkylamino), cyano, halo, haloalkyl (preferably trifluoromethyl), alkanoyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkyl amido (preferably lower alkyl amido), alkoxyalkyl (preferably a lower alkoxy[lower]alkyl), alkoxycarbonyl (preferably a lower alkoxycarbonyl), alkylcarbonyloxy (preferably a lower alkylcarbonyloxy) and aryl (preferably phenyl), said aryl being optionally substituted by halo, lower alkyl and lower alkoxy groups.

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.

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

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

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

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It 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 the formula I may also have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (i.e., the compound for formulas I) is a prodrug within the scope and spirit of the invention.

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

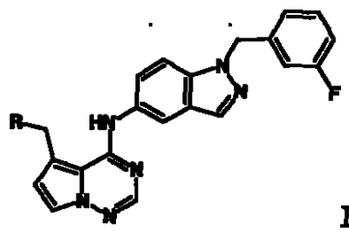
a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol.42, p. 309-396, edited by K. Widder, et al. (Acamedic Press, 1985);

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

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.

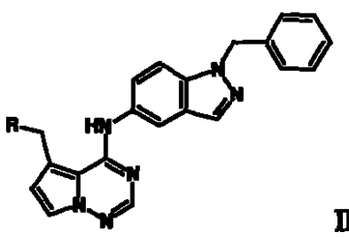
In a preferred embodiment, the invention comprises a compound of formula II,



II,

its enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein R is the same as previously defined above.

In yet another preferred embodiment, the invention comprises a compound of formula III

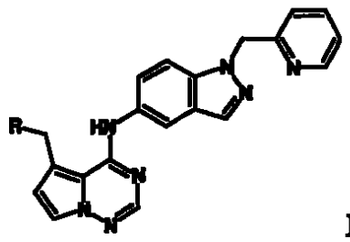


III,

its enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein R is the same as previously defined above

In still yet another embodiment, the invention comprises a compound a

formula IV,



IV,

its enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein R is the same as previously defined above.

Use and Utility

The present invention is based on the discovery that certain pyrrolotriazines are inhibitors of protein kinases. More specifically, pyrrolotriazines such as those described in this invention inhibit the protein tyrosine kinase activity of members of the HER family of receptors. These inhibitors will be useful in the treatment of proliferative diseases that are dependent on signaling by one or more of these receptors. Such diseases include psoriasis, rheumatoid arthritis, and solid tumors of the lung, head and neck, breast, colon, ovary, and prostate. The invention relates to a pharmaceutical composition of compound of formula I, or pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier in the treatment of hyperproliferative disorder in mammal. In particular, the said pharmaceutical composition is expected to inhibit the growth of those primary and recurrent solid tumors which are associated with HER1 (EGF receptor) and HER2, especially those tumors which are significantly dependent on HER1 or HER2 for their growth and spread, including for example, cancers of the bladder, squamous cell, head, colorectal, oesophageal, gynecological (such as ovarian), pancreas, breast, prostate, vulva, skin, brain, genitourinary tract, lymphatic system (such as thyroid), stomach, larynx and lung. In another embodiment, the compounds of the present invention are also useful in the treatment of noncancerous disorders such as psoriasis and rheumatoid arthritis.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiproliferative effect in

a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiproliferative effect in a warm-blooded 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.

By virtue of their ability to inhibit HER1,HER2, and HER4 kinases, compounds of the present invention can be used for the treatment of proliferative diseases, including psoriasis and cancer. The HER1 receptor kinase has been shown to be expressed and activated in many solid tumors including head and neck, prostate, 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 effficacy in preclincal 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. In addition, these compounds will have efficacy in inhibiting tumors that rely on HER receptor heterodimer signaling. These compounds are expected to have efficacy either as single agent or in combination (simultaneous or sequentially) with other chemotherapeutic agens such as Taxol, adriamycin, and cisplatin. Since HER1 and HER2 signaling has been shown to regulate expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and interleukin 8 (IL8), these compounds are expected to have anti-tumor efficacy resulting from the inhibition of angiogenesis in addition to the inhibition of tumor cell proliferation and survival. The HER2 receptor has been shown to be involved in the hyperproliferation of synovial cells in rheumatoid arthritis, and may contribute to the angiogenic component of that inflammatory disease state. The inhibitors described in this invention are therefore expected to have efficacy in the treatment of rheumatoid arthritis. 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: Schlessinger J. , "Cell signaling by receptor tyrosine kinases", *Cell* 103(2), p. 211-225 (2000); 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. 904-914 (2000); Satoh, K., Kikuchi, S., Sekimata, M., Kabuyama, Y., Homma, M. K., and Homma Y., "Involvement of ErbB-2 in rheumatoid synovial cell growth", *Arthritis Rheum.* 44(2), p. 260-265 (2001).

The antiproliferative 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 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 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, razoxin);

(ii) cytostatic agents such as antiestrogens (for example tamoxifen,

toremifen, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, borazole, exemestane), anti-neoplastic harmonal agents , antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example gosereline acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), farnesyltransferase inhibitors, anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of other growth factor function, (such growth factors include for example FGF, platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, 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 like 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, thiotephan); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere and newer microbtubule agents such as epothilone analogs, discodermolide analogs, and eleutherobin analogs); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan); cell cycle inhibitors (for example flavopyridols); and biological response modifiers.

As stated above, the formula I compounds of the present invention are of interest for their antiproliferative effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, psoriasis, and

rheumatoid arthritis.

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;

-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, and osteosarcoma.

Due to the key role of kinases in the regulation of cellular proliferation in general, inhibitors could 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, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation and inflammatory bowel disease

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 HER1 (EGF receptor), HER2, or HER4.

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 be administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Biological assays

HER1, HER2 or HER4 Kinase assays:

Compounds of interest were assayed in a kinase buffer that contained 20 mM Tris.HCl, pH 7.5, 10 mM $MnCl_2$, 0.5 mM dithiothreitol, bovine serum albumin at 0.1 mg/ml, poly(glu/tyr, 4:1) at 0.1 mg/ml, 1 μM ATP, and 4 μCi/ml [γ-^{33}P]ATP. Poly(glu/tyr, 4:1) is a synthetic polymer that serves as a phosphoryl acceptor and is purchased from Sigma Chemicals. The kinase reaction is initiated by the addition of enzyme and the reaction mixtures were incubated at 26 °C for 1 h. The reaction is terminated by the addition of EDTA to 50 mM and proteins are precipitated by the addition of trichloroacetic acid to 5%. The precipitated proteins are recovered by filtration onto Packard Unifilter plates and the amount of radioactivity incorporated is measured in a Topcount scintillation counter.

For the preparation of recombinant HER1 and HER4, the cytoplasmic sequences of the receptors were expressed in insect cells as GST fusion proteins, which were purified by affinity chromatography. The cytoplasmic sequence of HER2 was subcloned into the baculovirus expression vector pBlueBac4 (Invitrogen) and was expressed as an untagged protein in insect cells. The recombinant protein was partially purified by ion-exchange chromatography.

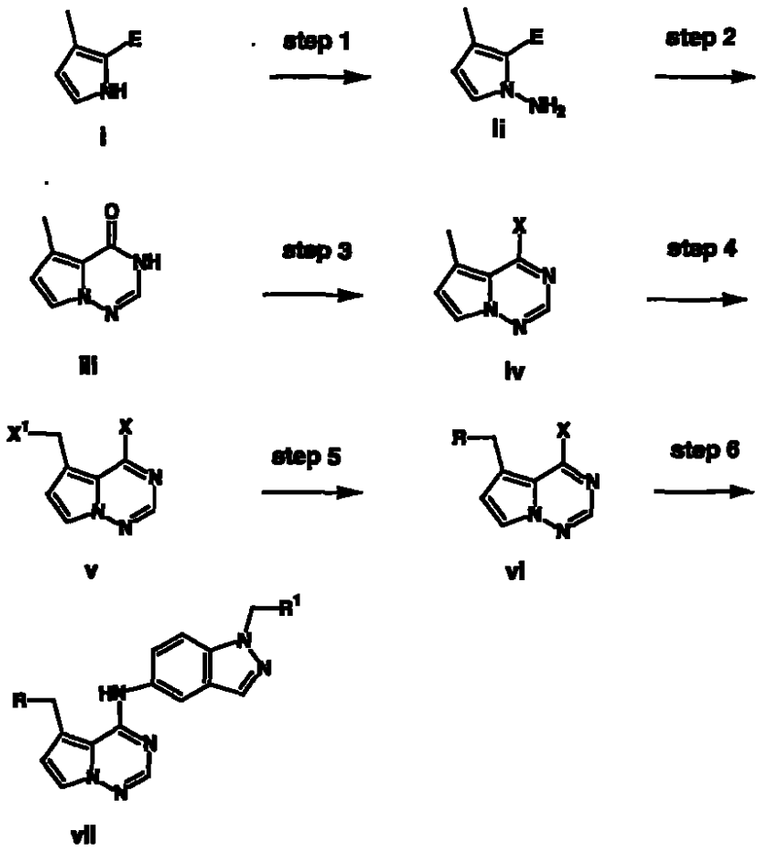
The instant compounds inhibit HER1, HER2, and HER4 kinases with IC_{50} values between 0.001 25 μM. Preferred compounds have IC_{50} values between 0.001 – 5.0 μM. More preferred compounds have IC_{50} values between 0.001 – 1.0 μM. Most preferred compounds have IC_{50} values between 0.001 – 0.1 μM.

A HERG potassium channel assay may be used to screen compounds for HERG activity (see Caballero R, et al., *Direct Effects of Candesartan and Eprosartan on Human Cloned Potassium Channels Involved in Cardiac Repolarization*, Molecular Pharmacology, Vol. 59, No. 4, pp. 825-36, 2001). Accordingly, preferred compounds have lower HERG assay activity.

Methods of Preparation

Certain compounds of formula I may generally be prepared according to the following schemes and the knowledge of one skilled in the art. Supplemental preparation information may also be found in co-pending US patent application serial number 09/573,829 filed May 18, 2000 and international application published under the Patent Cooperation Treaty (PCT), International Publication Number WO 00/71129, both herein incorporated by reference.

Scheme 1



wherein E is an ester group and X and X^1 are halogen

Step 1

The first step of Scheme 1 is accomplished by treatment of a 3-methyl-1H-pyrrole-2-carboxylic acid ester i (T. D. Lash et al., J. Heterocyclic Chem., 1991, 28, 1671) with a base such as potassium t-butoxide or sodium hydride in an anhydrous solvent such as THF or DMF followed by an aminating reagent, such as O-(2,4-dinitro-phenyl)-hydroxylamine (T. Sheradsky, J. Heterocyclic Chem., 1967, 4, 413) or chloramine (I. P. Sword, J. Chem. Soc. C, 1971, 820) to give the pyrrolylamine ii.

Step 2

The pyrrolylamine ii is heated with excess formamide to give the pyrrolotriazinone iii.

Step 3

Compound iii is converted to a 4-halo-pyrrolotriazine iv by heating with the appropriate phosphorus oxyhalide, e.g., the 4-chloro-pyrrolotriazine is obtained by

heating iii with phosphorus oxychloride.

Step 4

Halogenation of the 5-methyl group of iv is affected by treatment with a halogenating agent such as a N-bromosuccinimide or sulfuryl chloride. The reaction is performed under an inert atmosphere such as N_2 in the presence of a catalyst such as dibenzoyl peroxide or 2,2'-azobisisobutyronitrile, or irradiation and gives the 4-halo-5-halomethyl-pyrrolotriazine v.

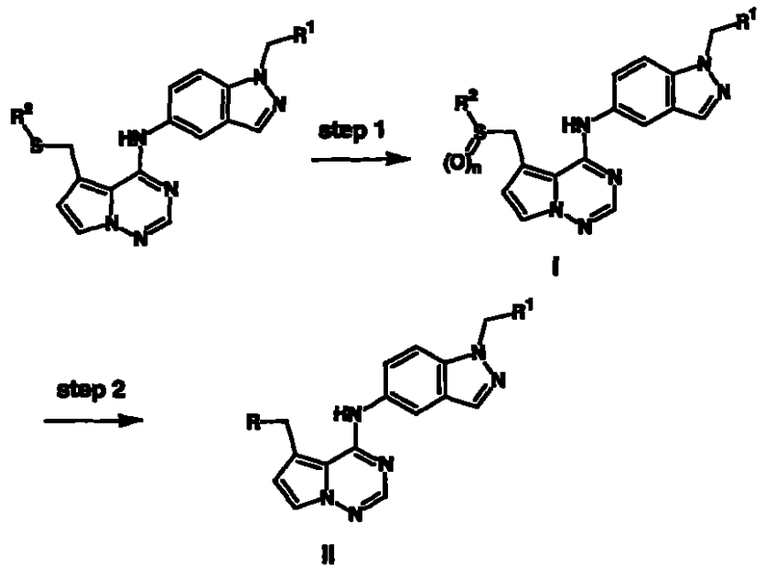
Step 5

Treatment of v with a thiol, a thiocarboxylic acid, water, an alcohol, a carboxylic acid, a primary or a secondary amine in the presence of a base such as $NaHCO_3$ or triethylamine in a solvent such as acetonitrile affords intermediate vi in Scheme 1.

Step 6

Treatment of vi with a 5-amino-indazole derivative at room temperature in the presence of a base such as $NaHCO_3$ or triethylamine in a solvent such as acetonitrile gives the final product vii. Heating vi with a 5-amino-indazole derivative in the absence of base also affords also affords vii.

Scheme 2



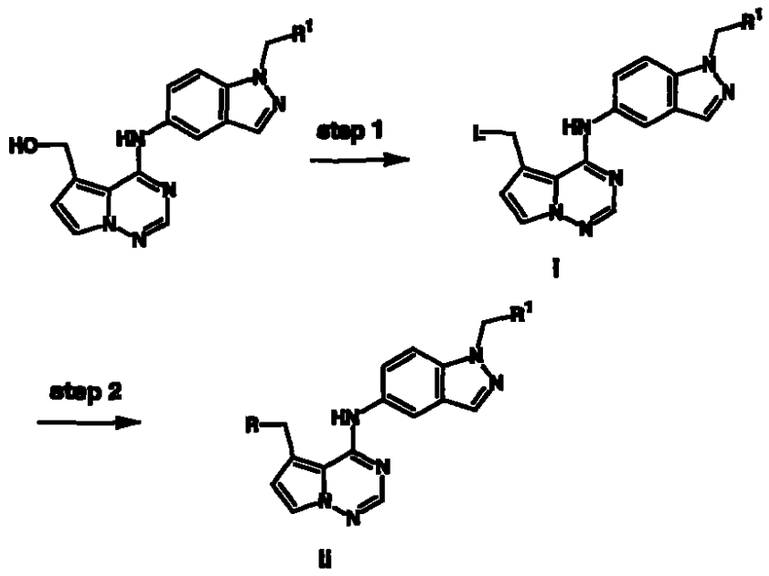
Step 1

Compound vii ($R = SR^2$) of **Scheme 1** can be oxidized to the sulfoxide, **i** (n =1), or the sulfone, **i** (n = 2), of **Scheme 2** by treatment with the appropriate amount of an oxidizing agent such as *m*-chloroperbenzoic acid.

Step 2

The 5-aminomethyl derivative **ii** is obtained by heating the sulfoxide **i** (n = 1) or the sulfone (n = 2) in the presence of an excess of an alcohol or a primary or secondary amine.

Scheme 3



wherein L = leaving group

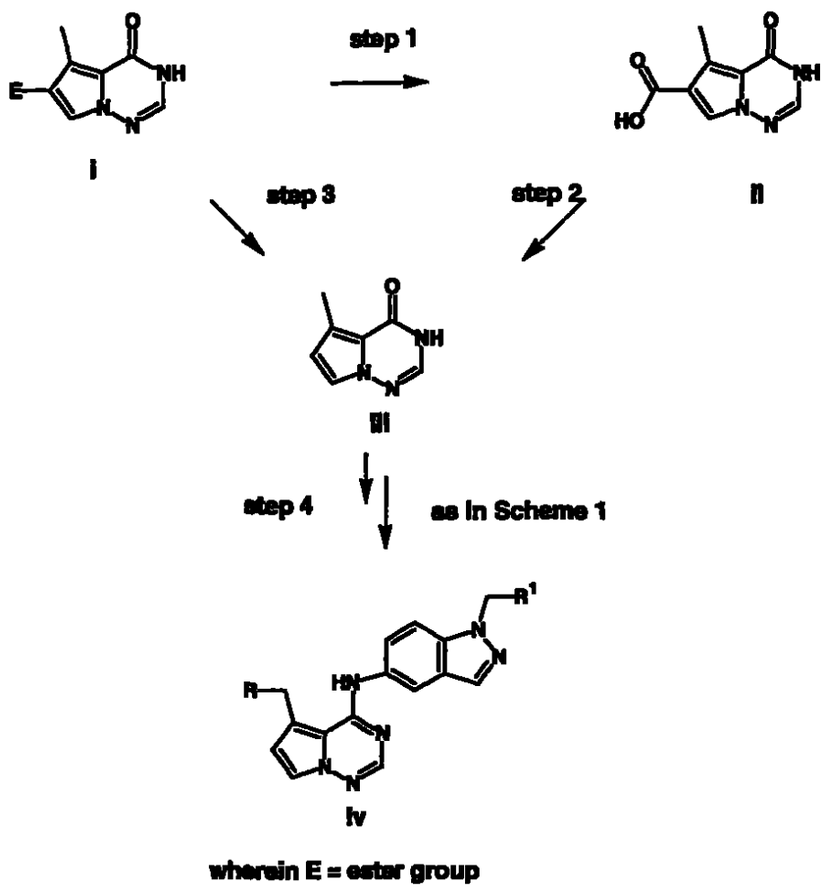
Step 1

The alcohol group in compound vii (R = OH) of **Scheme 1** can be converted to a leaving group as in compound i of **Scheme 3**. A variety of leaving groups can be introduced, e.g, treatment with thionyl chloride gives the chloride i (L = Cl), treatment with methanesulfonic anhydride and diisopropylethylamine gives the methanesulfonate i (L = OSO_2Me), esterification with acetic anhydride in the presence of diisopropylethylamine gives the acetate i (L = OAc).

Step 2

For very reactive leaving groups such as chloride or sulfonate, i is converted directly into compound ii of **Scheme 3** by reaction with an alcohol or a primary or secondary amine in the presence of a base such as diisopropylethylamine without the isolation of i. For less reactive leaving groups such as carboxylates, i is heated with alcohols or a primary or secondary amines in the presence of a base such as diisopropylethylamine to give ii.

Scheme 4



Step 1

The 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ester i (see WO 00/71129, herein incorporated by reference)can be saponified by treatment with a base such as an aqueous solution of LiOH and then acidified by treatment with an acid such as HCl to give the carboxylic acid ii of Scheme 4.

Step 2

The carboxylic acid ii is decarboxylated to give the 6H-pyrrolotriazin-4-one iii. This can be accomplished under a variety of conditions, for example, by heating a mixture of ii in 85% H_3PO_4 at 110 °C.

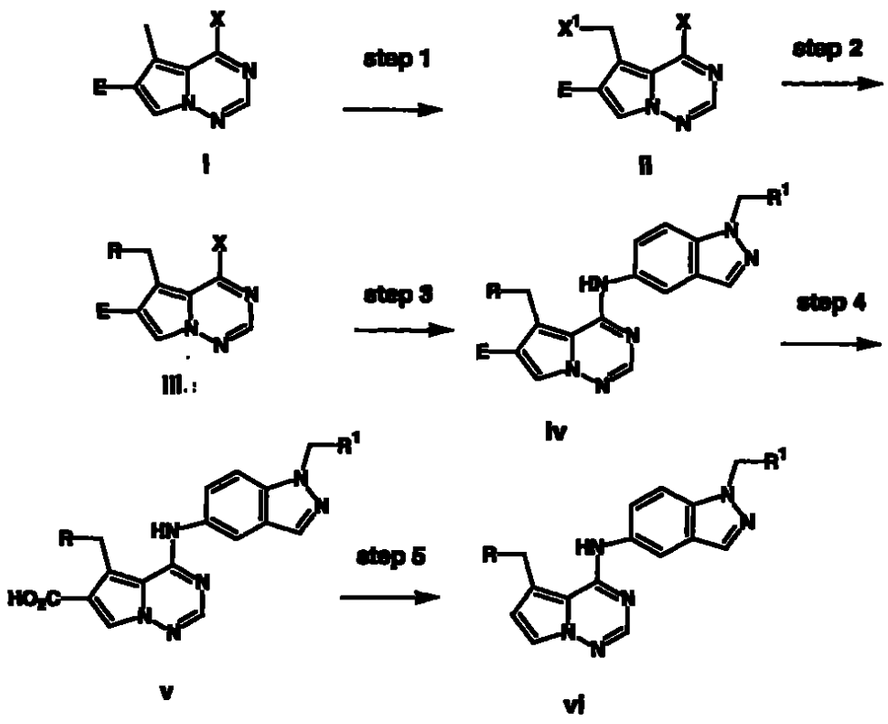
Step 3

The ester i can be converted directly into iii, for example, by heating a mixture of 1 in 85% H_3PO_4 at 110 °C.

Step 4

The 6H-pyrrolotriazin-4-one iii can be converted into iv as outlined in Scheme 1.

Scheme 5



wherein E is an ester group and X and X^1 are halogen

Step1

Halogenation of the 5-methyl group of 4-halo-5-methyl-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid ester i (see WO 00/71129, herein incorporated by reference) can be effected by treatment of i with a halogenating agent such as a N-bromosuccinimide or sulfuryl chloride. The reaction is performed under an inert atmosphere such as N_2 in the presence of a catalyst such dibenzoyl peroxide or 2,2'-azobisisobutyronitrile, or irradiation and gives the 4-halo-5-halomethyl-pyrrolotriazine ii of Scheme 5.

Step 2

Treatment of **ii** with a thiol, an alcohol, a primary or a secondary amine in the presence of a base such as $NaHCO_3$ or triethylamine in a solvent such as acetonitrile affords intermediate **iii**.

Step 3

Treatment of **iii** with a substituted 5-amino-indazole derivative in the presence of a base such as $NaHCO_3$ or triethylamine in a solvent such as acetonitrile gives **iv**.

Step 4

The ester **iv** can be saponified by treatment with a base such as an aqueous solution of LiOH and then acidified by treatment with an acid such as HCl to give the carboxylic acid **v** of **Scheme 5**.

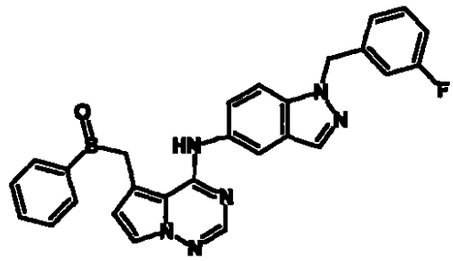
Step 5

The carboxylic acid **v** of **Scheme 5** is decarboxylated by heating to give the final product **vi**.

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

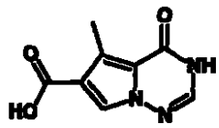
The invention will now be further described by the following working examples(s), which are preferred embodiments of the invention. All temperatures are in degrees Celsius (^{o}C) unless otherwise indicated. "HPLC Ret Time" is the HPLC retention time that was obtained under the following conditions: column type and length, gradient time [unless otherwise indicated, all gradients started with 100% solvent A (10% MeOH, 90% H_2O, *0.1% TFA*) and ended with 100% solvent B (90% MeOH, 10% H_2O, *0.1% TFA*)], flow rate (mL/min). UV detection was always conducted at 220 nM. These examples are illustrative rather than limiting and it is to be understood that there may be other embodiments that fall within the spirit and scope of the invention as defined by the claims appended hereto.

Example 1



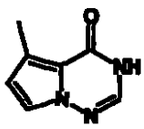
(5-Benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

A. Preparation of 5-Methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid



A solution of LiOH (25 gm, 10 equiv) in water (416 mL) was added to a solution of 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester (23.0 gm, 0.104 mol) in a mixture of THF (1.2 L) and MeOH (0.4 L). This was heated at 65 °C for 20 h and then concentrated in vacuo to about 200 mL. Water (400 mL) was added and the pH was adjusted to 4 using conc. aqueous HCl. The precipitate was collected, washed with water, and dried to give the acid (18.2 gm, 90%). ^{1}H NMR (MeOH-D_4) δ 2.67 (s, 3H), 7.63 (s, 1H), 7.84 (s, 1H). HPLC Ret Time: 0.97 min (YMC C18 S5, 4.6 x 50 mm column, 3 min gradient, 4 mL/min).

B. Preparation of 5-Methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one



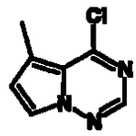
Procedure I: A suspension of 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid (18.1 gm, 93.7 mmole) in 85% aq. H_3PO_4 (250 mL) was heated at 110 °C for 3.5 h. After cooling to RT, ice water (500 mL) was added and the precipitate was collected, washed with water, and dried. This afforded 5.8 gm of the product as a brown solid. An additional 4.1 gm (total of 9.9 gm, 71%) of

product was obtain by extraction of the filtrate with DCM (4 x 500 mL), drying (Na_2SO_4), and removal of the solvent. ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 6.35 (d, 1H, J = 3 Hz), 7.31 (d, 1H, J = 3 Hz), 7.42 (s, 1H), 9.52 (br s, 1H); HPLC Ret Time: 1.17 min (YMC C18 S5, 4.6 x 50 mm column, 3 min gradient, 4 mL/min).

Procedure II: A suspension of 5-methyl-4-oxo-3,4-dihydro-pyrrolo[2,1-f][1,2,4]triazine-6-carboxylic acid methyl ester (5.81 gm, 0.028 mol) in 85% aq. H_3PO_4 (60 mL) was heated at 110 °C for 6 h. After cooling to RT, ice (120 gm) was added and the precipitate was collected, washed with water and dried to afforded the product (3.47 gm, 83%).

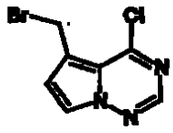
Procedure III: A solution of 3-methyl-1H-pyrrole-2-carboxylic acid methyl ester (4.59 gm, 33 mmole) in dry DMF (100 mL) was added slowly to an ice cooled suspension of NaH (1.72 gm, 60% dispersion in oil, 1.3 equiv) in dry DMF (300 mL). After 30 min, O-(2,4-dinitro-phenyl)-hydroxylamine (1.53 gm, 1.1 equiv) was added in one portion and the reaction was left stirring in the ice bath for 1 hr. After 0.5 hr it was removed from the bath and diluted with brine. This was extracted with EtOAc (3 times) and the combined extracts were dried (Na_2SO_4) and the solvents were removed. The residue was chromatographed on a silica gel column (gradient elution with hexane containing 5 to 20% EtOAc) to give 1-amino-3-methyl-1H-pyrrole-2-carboxylic acid methyl ester (2.96 gm, 58%) as a yellow solid. ^1H NMR (MeOH-D_4) δ 2.25 (s, 3H), 3.81 (s, 3H), 5.83 (d, 1H, J = 2 Hz), 6.82 (d, 1H, J = 2 Hz); MS: 155 $(M+H)^+$; HPLC Ret Time: 0.97 min (YMC Exterra ODS S7 3.0 x 50 mm, 2 min gradient, 5 mL/min). A mixture of this 1-amino-pyrrole (2.96 gm, 19.2 mmole) in formamide (30 mL) was heated at 165 °C for 10 hr. After cooling to RT, this was diluted with cold water and the precipitate was collected, washed with cold water followed by a mixture of Et2O and hexane (6:4). This gave 5-methyl-3H-pyrrolo[2,1-f][1,2,4]triazin-4-one (1.83 gm, 64%) as a brown solid.

C. Preparation of 4-Chloro-5-methyl-pyrrolo[2,1-f][1,2,4]triazine



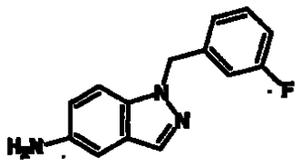
A suspension of of 5-methyl-3*H*-pyrrolo[2,1-f][1,2,4]triazin-4-one (2.57 gm, 17.2 mmole) in $POCl_3$ (28 mL) was heated at 100 °C for 40 min. The excess reagent was removed under vacuum and the residue was dissolved in DCM (300 mL). This was washed with water, dried (Na_2SO_4), and the solvent removed. Flash chromatography on silica gel using DCM as eluent afforded the product as a yellow solid (2.38 gm, 82%). 1HNMR (CDCl3): δ 2.63 (s, 3H), 6.74 (d, 1H, J = 2 Hz), 7.74 (d, 1H, J = 2 Hz), 8.05 (s, 1H).

D. Preparation of 5-Bromomethyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine



A solution of 4-chloro-5-methyl-pyrrolo[2,1-f][1,2,4]triazine (2.32 gm, 14.0 mmole) in CCl_4 (140 mL) was sparged with N_2 for 20 min. N-bromosuccinimide (2.60 gm, 1.05 equiv) and benzoyl peroxide (60 mg) were added and the mixture was heated at reflux for 1 hr. After cooling to RT, the succinimide was removed by filtration. The solvent was removed from the filtrate and the residue was quickly chromatographed on a short silica gel column using DCM as the eluent. This afforded the 5-bromomethyl compound as a yellow solid (2.49 gm, 74%). ^1H NMR ($CDCl_3$): δ 4.96 (s, 2H), 7.03 (d, 1H, J = 3 Hz), 7.80 (d, 1H, J = 3 Hz), 8.21 (s, 1H).

E. Preparation of 1-(3-Fluoro-benzyl)-1H-indazol-5-ylamine



A mixture of 5-nitro-1H-indazole (8.15 gm, 50 mmole), m-fluoro-benzyl chloride (7.95 gm, 1.1 equiv), K_2CO_3 (7.59 gm, 1.1 equiv), and KI (8.47 gm, 1.02 equiv) in dry

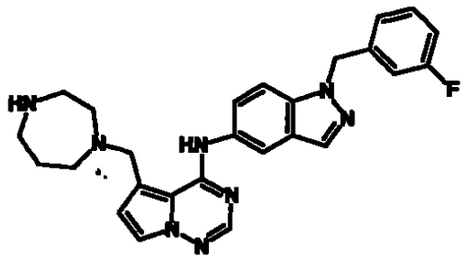
DMF (75 mL) was heated at 70 °C overnight. After cooling to RT, water (75 mL) was slowly added to give a precipitate that consisted of about a one to one mixture of isomers [HPLC Ret Time: 1.92 (1-substitued isomer vs. 2.03 (2-substituted isomer) YMC C18 S5 4.6 x 50 mm, 3 min gradient, 4 mL/min]. This was collected by filtration and washed with water. The solid was crystallized twice from acetone/water to afford the desired 1-(3-fluoro-benzyl)-5-nitro-1H-indazole (4.47 gm, 33%). A suspension of this material (3.00 gm, 11.1) and 10% Pd/C (3.00 gm) in EtOH (21 mL) was kept under an H_2 atmosphere (balloon) for 24 hr. The catalyst was removed by filtration and the solvent was evaporated to leave the product as a solid (2.4 gm, 90%). ^{1}H NMR ($CDCl_3$): δ 3.61 (br s, 2H), 5.52 (s, 2H), 6.81 – 7.85 (m, 7H), 7.85 (s, 1H); MS: 242 $(M+H)^+$; HPLC Ret Time: 1.03 min (YMC Xterra ODS S7, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

F. Preparation of (5-Benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

A solution of 5-bromomethyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine (850 mg, 3.46 mmole) in DCM (30 mL) was sparged with N_2 for 0.5 hr and then placed in a –20 °C bath. Thiophenol (384 µL, 1.0 equiv) and diisopropylethylamine (605 µL, 1.0 equiv) were added and the reaction was kept at –20 °C for 3hr. After warming to RT, the reaction mixture was washed with water, dried (Na_2SO_4), and the solvent was removed. 1,2-Dichloroethane (10 mL), n-butanol (10mL) and 1-(3-fluoro-benzyl)-1H-indazol-5-ylamine (750 mg, 0.9 equiv) were added to the residue and this mixture was heated at 85 °C for 2.5 hr. The solvents were removed and the residue was taken up in DCM, washed with sat. aq $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent followed by chromatography on silica gel using DCM containing 0 to 2% MeOH as eluent afforded [1-(3-fluoro-benzyl)-1H-indazol-5-yl]-(5-phenylsulfanylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine (957 mg, 58%) as a foam. ^{1}H NMR ($CDCl_3$) δ 4.48 (s, 2H), 5.59 (s, 2H), 6.53 (d, 1H, J = 3Hz), 6.8 – 7.0 (m, 3H), 7.2 – 7.6 (m, 9H), 7.95 (s, 1H), 8.06 (s, 1H), 8.15 (d, 1H, J = 2 Hz), 8.88 (br s, 1H); MS: 481 $(M+H)^+$; HPLC Ret Time: 1.87 min (YMC S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min). This was dissolved in chloroform (25 mL),

cooled in an ice bath and m-chloro-perbenzoic acid (500 mg, 57 to 80%, 1 equiv) was added in small portions over 15 min. After 1 hr., the reaction was washed with 10% aqueous $NaHSO_3$ solution, sat. aq. $NaHCO_3$ solution (three times) and dried (Na_2SO_4). Removal of the solvent left the product as a foam (957 mg, 95%). ^1H NMR ($CDCl_3$) δ 4.28 (d, 1H, J = 14 Hz), 4.53 (d, 1H, J = 14 Hz), 5.60 (s, 2H), 6.13 (d, 1H, J = 3 Hz), 6.8 – 7.6 (m, 11H), 7.71 (dd, 1H, J = 2, 9 Hz), 7.98 (s, 1H), 8.05 (s, 1H), 8.14 (d, 1H, J = 2 Hz); MS: 497 $(M+H)^+$; HPLC Ret Time: 1.67 min (YMC S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

Example 2

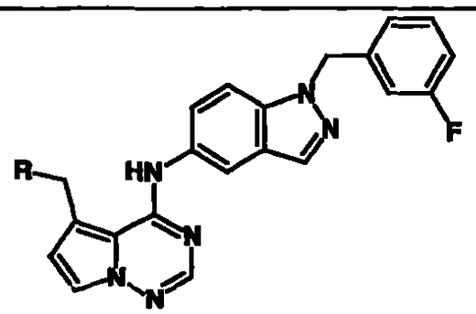


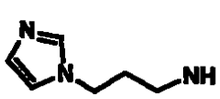
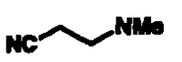
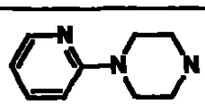
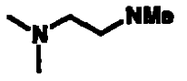
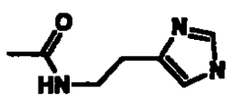
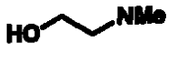
(5-[1,4]Diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

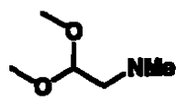
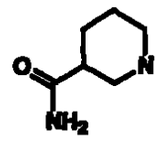
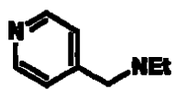
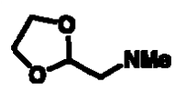
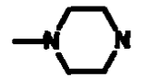
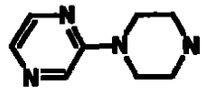
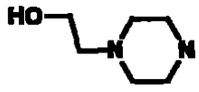
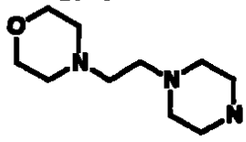
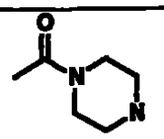
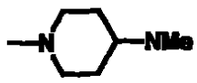
A mixture of (5-benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (50 mg, 0.101 mmole) and homopiperazine (300 mg, 30 equiv) in a sealed tube was heated at 135 °C overnight. The reaction mixture was taken up in DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate eluted with DCM containing 5% MeOH) afforded the title compound as a foam (39 mg, 82%). ^1H NMR ($CDCl_3$) δ 1.85 (m, 2H), 2.96 (m, 8H), 3.91 (s, 2H), 5.58 (s, 2H), 6.50 (d, 1H, J = 3 Hz), 6.8 – 7.6 (m, 7H), 7.89 (s, 1H), 8.05 (d,1H, J = 1 Hz), 8.11 (d, 1H, J = 2 Hz); MS: 471 $(M+H)^+$; HPLC Ret Time: 1.09 min (YMC Xterra ODS S7, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

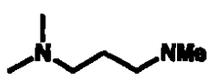
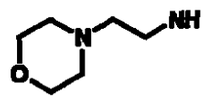
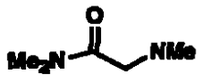
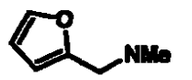
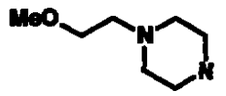
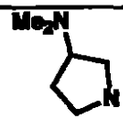
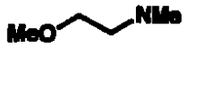
Examples 3 to 73

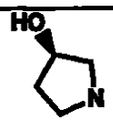
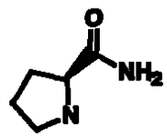
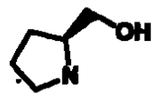
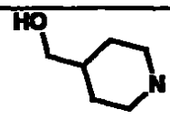
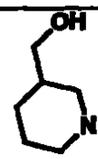
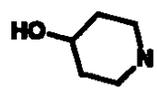
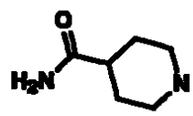
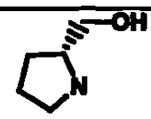
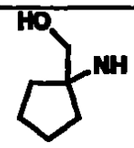
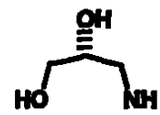
The follow examples were prepared in the same manner as Example 2.

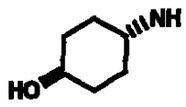
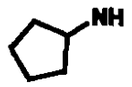
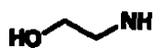
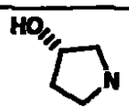
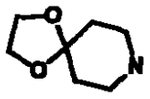
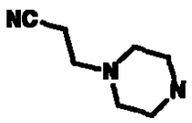
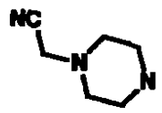
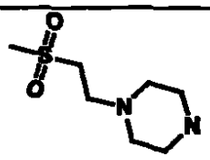
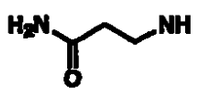


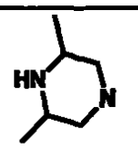
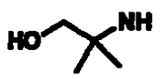
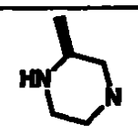
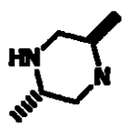
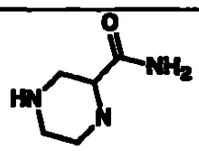
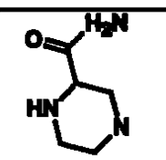
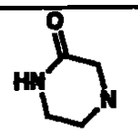
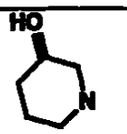
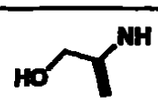
Ex.	R	Compound Name	HPLC Ret Time (min)
3		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-imidazol-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine	1.21
4		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[(3-imidazol-1-yl-propylamino)-methyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine	1.12
5		{1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-{[(2-cyano-ethyl)-methyl-amino]-methyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine	1.29
6		{1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-pyridin-2-yl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.17
7		N-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-N, N',N'-trimethyl-ethane-1,2-diamine	1.17
8		N-[2-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl} -1H-imidazol-4-yl)-ethyl]-acetamide	1.22
9		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-methyl -amino)-ethanol	1.20

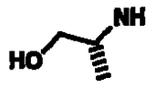
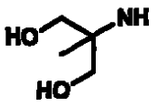
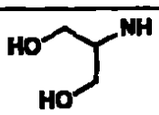
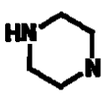
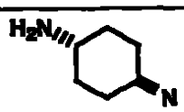
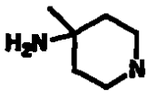
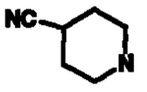
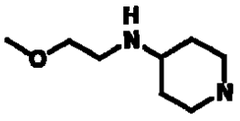
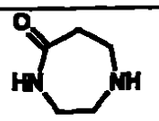
10		(5-{[(2,2-Dimethoxy-ethyl)-methyl-amino]-methyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.32
11		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-3-carboxylic acid amide	1.23
12		{5-[(Ethyl-pyridin-4-ylmethyl-amino)-methyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-[1-(3-fluoro-benzyl) -1H-indazol-5-yl]-amine	1.29
13		{5-[([1,3]Dioxolan-2-ylmethyl-methyl-amino)-methyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.30
14		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-methyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4] triazin-4-yl]-amine	1.14
15		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-ylmethyl)-pyrrolo [2,1-f][1,2,4]triazin-4-yl]-amine	1.35
16		2-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-1-yl)-ethanol	1.12
17		2-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-1-yl)-ethanol	1.12
18		1-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-1-yl)-ethanone	1.22
19		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-{[methyl-(1-methyl-piperidin-4-yl)-amino]-methyl}-pyrrolo [2,1-f][1,2,4]triazin-4-yl)-amine	0.97*

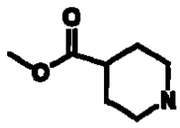
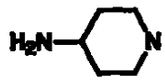
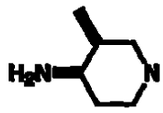
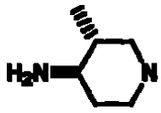
20		N-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-N, N',N'-trimethyl-propane-1,3-diamine	0.95*
21		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[(2-morpholin-4-yl-ethylamino)-methyl]-pyrrolo[2,1-f] [1,2,4]triazin-4-yl}-amine	1.13
22		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[(3-morpholin-4-yl-propylamino)-methyl]-pyrrolo[2,1-f] [1,2,4]triazin-4-yl}-amine	1.11
23		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-methyl -amino)-N,N-dimethyl-acetamide	1.19
24		[5-(2,5-Dihydro-pyrrol-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.32
25		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[(furan-2-ylmethyl-methyl-amino)-methyl]-pyrrolo[2,1-f] [1,2,4]triazin-4-yl}-amine	1.46
26		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methoxy-ethyl)-piperazin-1-ylmethyl]-pyrrolo[2,1f][1,2,4]triazin-4-yl}-amine	1.23
27		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-pyrrolidin-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine	1.31
28	 racemic	[5-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.21
29		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine	1.20*

30		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1f][1,2,4]triazin-5-ylmethyl}-(3R)-pyrrolidin-3-ol	1.10*
31		N-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-N,N'-dimethyl-ethane-1,2-diamine	0.98*
32		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(2S)-pyrrolidine-2-carboxylic acid amide	1.11*
33		(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(2S)-pyrrolidin-2-yl)-methanol	1.11*
34		(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-methanol	1.26
35	 racemic	(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-3-yl)-methanol	1.28
36		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ol	1.10*
37		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carboxylic acid amide	1.24
38		(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(2R)-pyrrolidin-2-yl)-methanol	1.11*
39		[1-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-cyclopentyl]-methanol	1.43
40		(2R)-3-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propane-1,2-diol	1.25

41		Trans-4-({4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-cyclohexanol	1.30
42		(5-Cyclopentylaminomethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.46
43		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-ethanol	1.24
44		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino}-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(3S)-pyrrolidin-3-ol	1.27
45		[5-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.35
46		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-cyano-ethyl)-piperazin-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine	1.01*
47		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-cyanomethyl-cyclohexylmethyl)-pyrrolo[2,1-f] [1,2,4]triazin-4-yl]-amine	1.30
48		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methanesulfonyl-ethyl)-piperazin-1-ylmethyl]-pyrrolo [2,1-f][1,2,4]triazin-4-yl}-amine	1.22
49		3-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propionamide	1.26

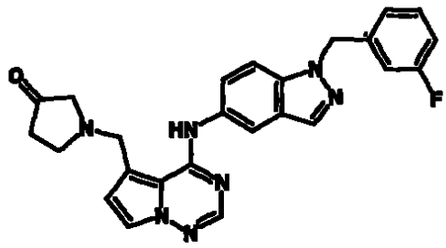
50	 diastereomeric mixture	[5-(3,5-Dimethyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.06*
51		[5-(2,5-Diaza-bicyclo[2.2.1]hept-2-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.17
52		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propan-2-ol	1.35
53		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-((3S)-3-methyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.02*
54		[5-(Trans-2,5-dimethyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.27
55	 racemic	1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazine-2-carboxylic acid amide	1.07
56	 racemic	4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazine-2-carboxylic acid amide	1.17
57		4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-2-one	1.24
58		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(3R)-piperidin-3-ol	1.29
59		(2S)-2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-	1.26

		propan-1-ol	
60		(2R)-2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propan-1-ol	1.26
61		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-2-methyl-propane-1,3-diol	1.25
62		2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propane-1,3-diol	1.21
63		[1-(3-Fluoro-benzyl)-1*H*-indazol]-5-yl]-(5-piperazin-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)amine	1.02
64		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(thiomorpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.92
65		N-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-transcyclohexane-1,4-diamine	1.09**
66		[5-(4-Amino-4-methyl-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	0.99*
67		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperid ine-4-carbonitrile	1.28
68		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methoxy-ethylamino)-piperidin-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine	1.30
69		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-5-one	2.05***

70		1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carboxylic acid methyl ester	1.41
71		[5-(4-Amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.03*
72		(±)-[5-(*cis*-4-Amino-3-methyl-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.08*
73		(±)-[5-(*trans*-4-Amino-3-methyl-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.31

Unless otherwise indicated, HPLC Retention Times were determined using a YMC Xterra ODS S7 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min. HPLC Retention Times marked with a "*" were determined using a YMC S7 C18 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min, with "**" were determined using a YMC ODS-A S7 C18 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min, and those with "***" were determined using a YMC ODS-A C18 S5 4.6 x 33 mm column with a 4 minute gradient time and a flow rate of 4 mL/min

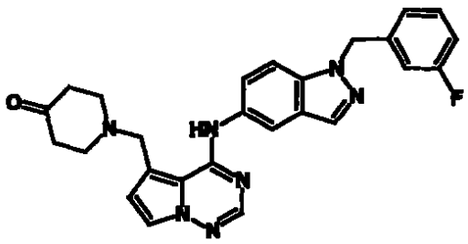
Example 74



1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-pyrrolidin-3-one

Tetrapropylammonium perruthenate (3.2 mg, 0.1 equiv) was added to a stirred suspension of 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1f][1,2,4]triazin-5-ylmethyl}-(3R)-pyrrolidin-3-ol (42 mg, 0.092 mmole), N-methylmorpholine N-oxide (16 mg, 1.5 equiv), and dried, powdered 4A molecular sieves (100 mg) in dry DCM under N_2. After 0.75 hr, the dark green suspension was filtered through a short pad of silica gel using ethyl acetate as eluent. Removal of the solvent from the fractions containing the product followed by radial chromatography (2 mm silica gel plate employing gradient elution with mixtures of hexane containing 30 to 50% EtOAc) afforded the title compound as an oil (26 mg, 61%). MS: 456. $(M+H)^+$; HPLC Ret Time: 1.28 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

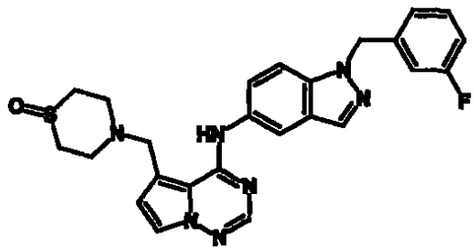
Example 75



1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-one

A solution of [5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (54 mg, 0.105 mmole) in a mixture of THF (1 mL) and 1 N aq. HCl (1 mL) containing 16 drops of conc. HCl was left stirring a RT for 7 days. The reaction was diluted with DCM and neutralized with sat. aq. $NaHCO_3$ solution. After drying (Na_2SO_4), the solvent was removed to leave the title compound as an oil (19 mg, 39 %). MS: 488 $(M+H_2O+H)^+$; HPLC Ret Time: 2.35 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 5 min gradient (component B was varied from 20 to 60%), 5 mL/min).

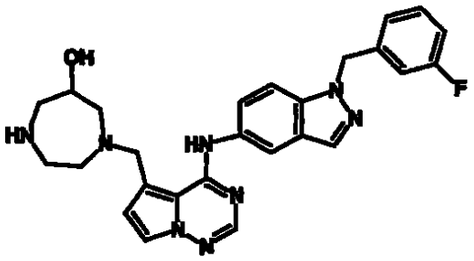
Example 76



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(1-oxo-1λ⁴-thiomorpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

A solution of [1-(3-fluoro-benzyl)-1H-indazol-5-yl]-[5-(thiomorpholin-4-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine (46 mg, 0.096 mmole) in chloroform (2 mL) was cooled in an ice bath and m-chloroperbenzoic acid (26 mg, 65 %, 1 equiv) was added in portions over 12 min. After 1 hr, the reaction was then diluted with chloroform, washed with 6 % aq. $NaHSO_3$ solution, sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). The solvent was removed and purification by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 5 % MeOH) afforded the title compound as an oil (13 mg, 27 %). MS: 490 $(M+H)^+$; HPLC Ret Time: 1.62 min (YMC S5 C18, 4.60 x 50 mm column, 3 min gradient, 4 mL/min).

Example 77



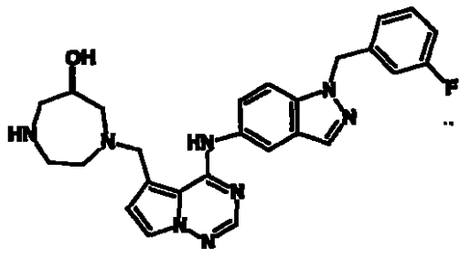
(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(±)-[1,4]diazepan-6-ol

A mixture of (5-benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (397 mg, 0.8 mmole) and [1,4]diazepan-6-ol (417 mg, 4.5 equiv, Saari et al., J. Org. Chem., 1971, 36, 1711) in dry DMSO (1.5 mL) in a sealed tube was heated at 140°C for 11 hr. This was diluted with DCM (150 ml), washed with water and dried (Na_2SO_4). Removal of the solvent followed by

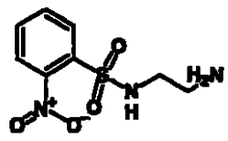
radial chromatography (4 mm silica gel plate; gradient elution with DCM containing 0 to 3 of a 2N NH_3 solution in MeOH) gave the title compound as a solid (242 mg, 62%), MS: 487 $(M+H)^+$; HPLC Ret Time: 0.96 min (Xterra S7 3.0 x 50 mm S7 C18 column, 2 min gradient, 5 ml/min).

The racemic material could be separated on a Chiralpak AD 4.6 x 250 mm column, eluting with 0.05% diethylamine in EtOH for 25 min with a flow rate of 0.7 mL/min) The *S* and R enantiomers had retention times of 16.20 and 18.90 min respectively. The R enantiomer was synthesized as outlined below.

Examples 78



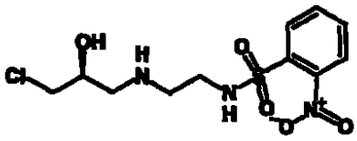
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(6R)-[1,4]diazepan-6-ol



A. Preparation of N-(2-Amino-ethyl)-2-nitro-benzenesulfonamide

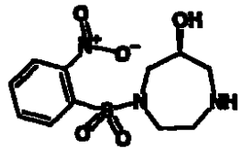
A solution of ethylene diamine (268 mL, 20 equiv) in DCM (400 mL) was added to an ice-cooled solution of o-nitrobenzene sulfonyl chloride (44.4 gm, 0.2 mole) in DCM (200 mL) over 1 hr. Concentration on the rotary evaporator left an oil which was partitioned between DCM and sat. aq. Na_2CO_3 solution. The aqueous phase was backextracted with DCM and the combined organic phases were dried (Na_2SO_4). Removal of the solvents followed by silica gel chromatography (step gradient elution with DCM containing 0, 5, 10, 20, 30% MeOH) affored the title compound as an oil

(37.2 gm, 76%). ^{1}H NMR ($CDCl_3 + D_2O$) δ 2.82 (t, 2H, J = 5.1 Hz), 3.10 (t, 2H, J = 5.1 Hz), 7.73 (m, 2H), 7.83 (m, 1H), 8.11 (m, 1H); MS: 246 (M+H)+; HPLC Ret Time: 0.39 min (YMC Xterra 3.0 x 50 mm S7 C18 column, 3 min gradient, 4 mL/min).



B. Preparation of N-[2-({2S}-3-Chloro-2-hydroxy-propylamino)-ethyl]-2-nitro-benzenesulfonamide

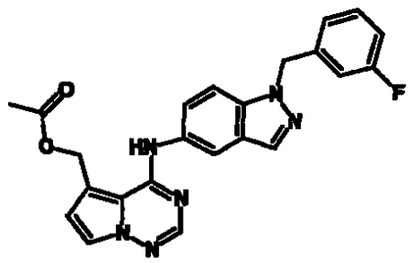
S-(+)-epichlorohydrin (5.92 mL, 0.5 equiv) was added to a suspension of N-(2-amino-ethyl)-2-nitro-benzenesulfonamide (37.2 gm, 0.152 mole) and $MgSO_4$ (9.1 gm, 0.5 equiv) in dry MeOH (38 mL) at RT. After 8 hr, the solid was removed by filtration. The filtrate was concentrated and partitioned between DCM and water. The organic phase was separated, dried (Na_2SO_4) and the solvent was removed. Silica gel chromatorgraphy (step gradient elution with DCM containing 0, 1, 1.5, 2, 2.5, 3% MeOH) afforded the title compound as an oil (20.73 gm, 81%). ^{1}H NMR ($CDCl_3$ + D_2O) δ 2.59 – 2.76 (m, 2H), 2,80 (t, 2H, J = 5.4 Hz), 3.17 (t, 2H, J = 5.4 Hz), 3.53 (d, 2H, J = 5.7 Hz), 3.79 (m, 1H), 7.74 (m, 2H), 7.85 (m, 1H), 8.13 (m, 1H); MS: 338 ($M+H^+$); HPLC Ret Time: 0.67 min (YMC Xterra 3.0 x 50 mm S7 C18 column, 3 min gradient, 4 mL/min).



C. Preparation of 1-(2-Nitro-benzenesulfonyl)-(6S)-[1,4]diazepan-6-ol

A suspension of N-[2-({2S}-3-chloro-2-hydroxy-propylamino)-ethyl]-2-nitro-benzenesulfonamide (20.73 gm, 61.4 mmole) and Cs_2CO_3 (73 gm, 3 equiv) in dry acetonitrile (600 mL) under a N_2 atmosphere was heated at 60 °C for 6.5 hr. The solid was removed by filtration and then the solvent was removed from the filtrate. The residue was partitioned between DCM (400 mL) and water (100 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed. Silica gel chromatography

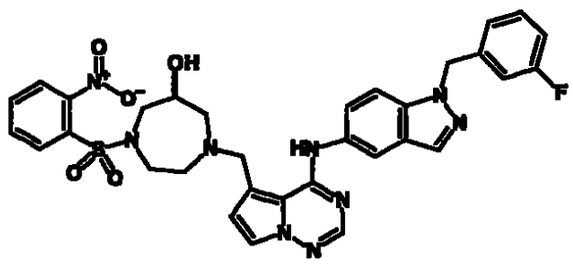
(step gradient elution with DCM containing: 0, 1, 2, 3, 4% MeOH) afforded the title compound as an oil (5.68 gm, 31%). ^{1}H NMR ($CDCl_3 + D_2O$) δ 2.3 (br. s, 2H), 2,85 (m, 4H), 3.09 (m, 4H), 7.68 (m, 3H), 8.00 (m, 1H); MS: 302 ($M+H^+$); HPLC Ret Time: 0.56 min (YMC Xterra 3.0 x 50 mm S7 C18 column, 3 min gradient, 4 mL/min).



D. Preparation of Acetic acid 4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethylester

A solution of crude 5-bromomethyl-chloropyrrolo[2,1-f][1,2,4]triazine (15.3 gm, 0.062 mole) in EtOAc (300 mL) and cooled in an ice bath under a N_2 atmosphere and acetic acid (17.8 mL, 5 equiv) followed by diisopropylethylamine (54.3 mL, 5 equiv.) were added. The reaction vessel was removed from the bath and stirred for 18 hours at RT. The precipitate was removed by filtration and the resulting filtrate was diluted with hexane (250 mL). This was washed with water (2 x 125 mL), saturated NaCl solution (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give a viscous brown oil which solidify on standing. A sample of pure acetic acid 4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl ester was obtained by silica gel chromatography (gradient elution with 0 to 30% EtOAc in hexane) as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$,) δ 2.09 (s, 3H), 5.48 (s, 2H), 7.00 (d, J = 2.7 Hz, 1H), 7.80 (d, J = 2.7 Hz, 1H), 8.18 (s, 1H), 7.80 (d, J = 2.7 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 5.48 (s, 2H), 2.09 (s, 3H). The crude acetic acid 4-chloro-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl ester was then dissolved in acetonitrile (300 mL) and treated with sodium bicarbonate (26.2 gm, 5 equiv.) and (18.1 gm, 1.2 equiv.). After stirring at RT for 20 hr, the mixture was concentrated *in vacuo* and dissolved in DCM (500 mL). This was washed with 100 mL water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a dark colored solid. This was crystallized from acetonitrile to give 10 g

of the title compound. The mother liquor was chromatographed on silica gel eluting with 70% hexane/EtOAc to give another 8 gm of pure material (overall yield, 67%): ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 5.42 (s, 2H), 5.59 (s, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.98 – 6.90 (bm, 2H), 7.35 – 7.22 (bm, 3H), 7.56 (d, J = 2.6 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 8.06 (s, 1H), 8.17 (s, 1H), 9.42 (s, 1H); MS: 431(M + H$^+$); HPLC Ret Time = 2.59 min (YMC Xterra 4.5 x 50 mm S7 C18 column, 3 min gradient, 4 mL/min).



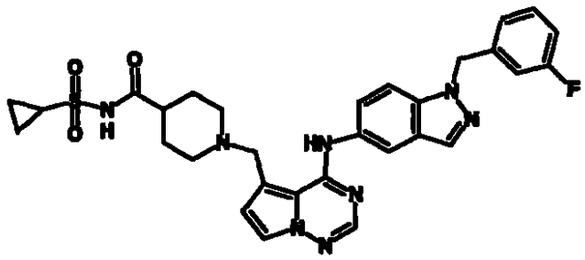
E. Preparation of 1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-4-(2-nitro-benzenesulfonyl)-(6S)-[1,4]diazepan-6-ol

A mixture of acetic acid 4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl ester (860 mg, 2 mmole), 1-(2-nitro-benzenesulfonyl)-[1,4]diazepan-6R-ol (602mg, 2 mmole) and diisopropylethylamine (0.522 mL, 3 mmole, 1.5 equiv.) in dry acetonitrile (4 ml) in a pressure vessel was heated at 102 °C for 17 hours. After removal of the solvent, the residue was taken up in DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by silica gel chromatography (gradient elution with DCM containing 0 to 2% 2M NH_3 in MeOH) afforded the title compound as a solid (1.14g, 85%). ^{1}H NMR ($CDCl_3$) δ 2.87 – 3.08 (m, 5H), 3.36 – 3.60 (m, 4H), 3.97 – 4.05(m, 3H), 5.52 (s, 2H), 6.51 (d, 1H, J = 2.5Hz), 6.82 (m, 1H), 6.91-6.96 (m, 2H), 7.21-7.25 (m,1H), 7.25 – 7.31 (m, 1H), 7.44 (d, 1H, J = 3.0 Hz), 7.47-7.49 (m,1H), 7.58 – 7.66 (m, 3H), 7.85 (s, 1H), 7.91 (d, 1H, J = 1.5 Hz), 7.98 (d, 1H, J = 1.0 Hz), 8.03 (d, 1H, J = 1.5 Hz), 11.02 (s, 1H). MS: 672 (M+H$^+$); HPLC Ret Time: 1.37 min (Gradient Time = 2 min, Flow Rate = 5 ml/min, Xterra C18 S7, 3.0 x 50 mm C18 S7 column).

F. Preparation of 1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(6R)-[1,4]diazepan-6-ol

Benzenethiol (54 mg, 2 equiv) was added to a suspension of 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1f][1,2,4]triazin-5-ylmethyl}-4-(2-niro-benzenesulfonyl)-(6S)-[1,4]diazepan-6-ol (164 mg, 0.244 mmole) and K_2CO_3 (168 mg, 1.22 mmole, 5 equiv.) in 2.5 ml of anhydrous DMF under nitrogen. After stirring at RT for 50 min, the solid was removed by filtration. The filtrate was concentrated and partitioned between DCM and water. Ther organic phase was dried (Na_2SO_4) and the solvent removed. Radial chromatography (2 mm silica gel plate, gradient elution with 0 to 5% 2M NH_3 in MeOH) afforded the title compound as a solid (109 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 2.69 – 2.77 (m, 2H), 2.84 – 3.03 (m, 6H), 3.78 – 3.81 (m, 1H), 3.90 (d, 1H, J = 13.4 Hz), 3.96 (d, 1H, J = 13.4 Hz), 5.55 (s, 2H), 6.48 (d, 1H, J = 2.5 Hz), 6.86 – 6.88 (m, 1H), 6.92 – 6.98 (m, 2H), 7.23 – 7.27 (m, 1H), 7.32 – 7.33 (m, 1H), 7.44 (d, 1H, 2.5 Hz), 7.54 – 7.56 (m, 1H), 7.86 (s, 1H), 8.02 (d, 1H, J = 1.0 Hz), 8.04 (d, 1H, J = 2.0 Hz), 11.54 (s, 1H). MS: 487 $(M+H)^+$; HPLC Ret Time: 18.86 min (Chiralpak AD 4.6 x 250 mm column, eluting with 0.05% diethylamine in EtOH for 25 min with a flow rate of 0.7 mL/min).

Example 79



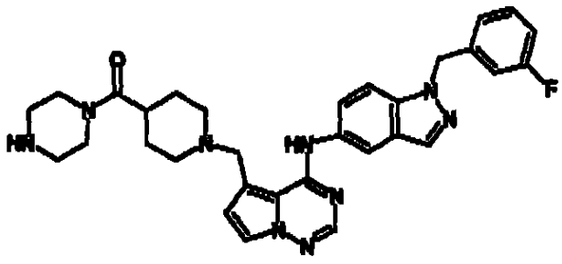
Cyclopropanesulfonic acid (1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carbonyl)-amide

Aqueous NaOH (2.1 mL, 1.0 N) was added to a solution of 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carboxylic acid methyl ester (352 mg, 0.686 mmole) in a mixture of MeOH (0.2 ml) and THF (0.2 ml) at 0°C . After stirring at 0 °C for 1 hour, the reaction mixture was

allowed to warm to RT and left stirring overnight. Aqueous HCl (2.1 ml, 1.0 N) was added dropwise and the reaction was extracted with DCM. The organic extracts were dried (Na_2SO_4) and the solvents were removed to leave 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carboxylic acid, as a solid (329 mg, purity 84% by LCMS) which was used as such.

A solution of the crude acid (100 mg, 0.168 mmole) in THF (2 ml) was added dropwise to a solution of 1,1'-carbonyldiimidazole (33 mg, 0.2 mmole) in THF (0.3 ml) and this was heated at reflux for 30 min. After cooling to RT, cyclopropylsulfonamide (82 mg, 0.67 mmole, 4 equiv.) was added followed by a solution of DBU (50 uL, 0.336 mmole, 2 equiv.) in THF (0.2 ml). The reaction was stirred for 18 hr, diluted with EtOAc (120 ml), washed with pH 4.0 buffer (9 mL), brine (5 mL) and dried (Na_2SO_4). Removal the solvent followed by radial chromatography (2 mm silica gel plate gradient elution with DCM containing 1 to 5% MeOH) afforded the title compound as a solid (58 mg, 57%). ^1H NMR ($CDCl_3$) δ 0.98-1.00 (m, 2H), 1.22-1.27 (m, 2H), 1.84-1.92 (m, 4H), 2.03-2.16 (m, 2H), 2.24-2.32 (m, 1H), 2.83-2.92 (m, 1H), 3.08-3.11 (m, 2H), 3.74 (s, 2H), 5.54 (s, 2H), 6.46 (d, 1H, J = 2.5 Hz), 6.81-6.97 (m, 3H), 7.20-7.27 (m, 1H), 7.36-7.51 (m, 3H), 7.84 (s, 1H), 8.06 (s, 2H), 11.82 (bs, 1H). MS: 603.7 ($M+H^+$); HPLC Ret Time: 1.21 min (Gradient Time = 2 min, Flow Rate = 5 ml/min, Xterra 3.0 x 50 mm S7 C18 column).

Example 80

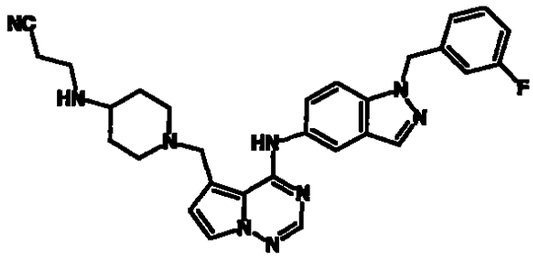


(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-piperazin-1-yl-methanone

A mixture of crude 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carboxylic acid (75 mg, 0.15 mmole), EDC

(72 mg, 0.376 mmole), and DMAP (37 mg, 0.3 mmole) in dry DCM (1 mL) was stirred at RT for 0.5 hr. Piperazine (104 mg, 1.2 mmole) was added and, after 64 hr, the reaction was diluted with DCM, washed with water and dried (Na_2SO_4). Removal of solvent followed by radial chromatography (1 mm silica gel plate, gradient elution with DCM containing 1 to 5% MeOH) afforded the title compound as a solid (11mg, 13 %). ^1H NMR ($CDCl_3$) δ 1.67-1.80 (m, 4H), 1.96-2.09 (m, 2H), 2.15-2.18 (m, 1H), 2.58-2.65 (m, 1H), 2.82-2.86 (m, 4H), 3.17-3.20 (m, 2H), 3.43-3.48 (m, 2H), 3.57-3.62 (m, 2H), 3.77 (s, 2H), 5.57 (s, 2H), 6.48 (d, 1H, J = 2.5 Hz), 6.83-6.88 (m, 1H), 6.90-6.97 (m, 2H), 7.21-7.29 (m, 1H), 7.36-7.39 (m, 1H), 7.44 (d, 1H, J = 2.7 Hz), 7.55-7.58 (m, 1H), 7.89 (s, 1H), 8.08 (s, 1H), 8.18 (d, 1H, J = 1.5 Hz), 11.87 (br, 1H). MS: 568.67 ($M+H^+$); HPLC Ret Time: 1.03 min (Gradient Time = 2 min, Flow Rate = 5 ml/min, Xterra 3.0 x 50 mm S7 C18 column).

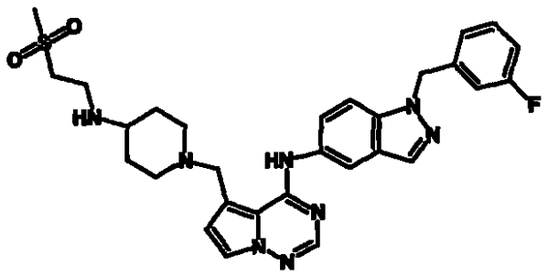
Example 81



3-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ylamino)-propionitrile

Acrylonitrile (0.2 mL, 30 equiv.) was added to a solution of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.1 mmole) in MeOH (3 mL) at RT. Removal the solvent followed by radial chromatography (1 mm silica gel plate, gradient elution with DCM containing 0 to 2% MeOH) afforded 40 mg (76%) of the title compound as a solid. MS: 524 $(M+H)^+$; HPLC Ret Time: 0.99 min (Xterra 3.0 x 50 mm S7 C18 column, 2min gradient, 5 mL/min).

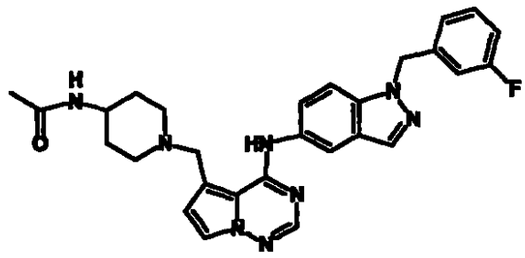
Example 82



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methanesulfonyl-ethylamino)-piperidin-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine

Methyl vinyl sulfone (0.011 mL, 0.1 mmole) was added to a solution of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.1 mmole) in MeOH (3 mL) at RT. After stirring overnight, the title compound title compound (54 mg, 94 %) was collected by filtration washed with MeOH and dried. MS: 577 $(M+H)^+$; HPLC Ret Time: 0.98 min (Xterra 3.0 x 50 mm S7 C18 column, 2min gradient, 5 ml/min).

Example 83

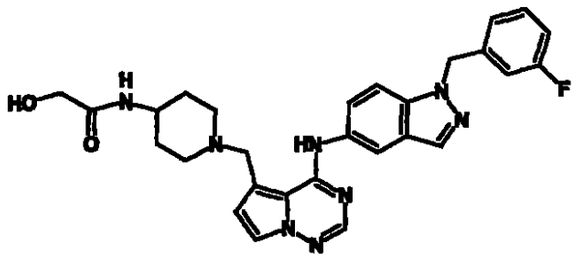


N-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-acetamide

Acetic anhydride (25 uL, 2.3 equiv.) was added to a mixture of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-ind azol-5-yl]-amine (47 mg, 0.1 mmole) and K_2CO_3 (21 mg 0.15 mmole) in MeOH (3 mL) at 0° C under nitrogen. After 1 h, the reaction was removed from the ice bath and the mixture was left stirred at RT overnight. The solvent was removed and the residue was taken up in DCM, washed with water and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate, gradient elution

with DCM containing 0 to 3% MeOH) afforded the title compound as a solid (41 mg, 80%). MS: 513 $(M+H)^+$; HPLC Ret Time: 1.12 min (Xterra 3.0 x 50 mm S7 C18 column, 2min gradient, 5 mL/min).

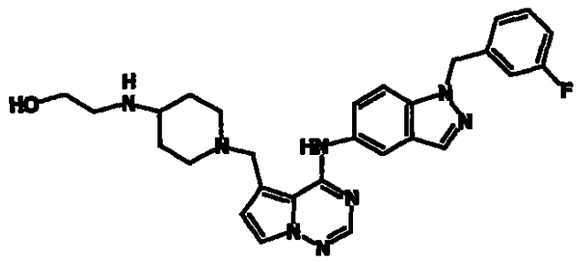
Example 84



N-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-2-hydroxy-acetamide

Acetoxyacetyl chloride (46 mg, 2 equiv) was added dropwise to a solution of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.1 mmole) (80 mg, 0.17 mmole) and triethylamine (71 µL, 3 equiv.) in dry DCM (3 mL) at 0 °C under nitrogen. After stirring at 0 °C for 3hr and at RT for 1hr, it was diluted with DCM, washed with water and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate, gradient elution with DCM containing 0 to 2% MeOH) afforded acetic acid (1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ylcarbamoyl)-methyl ester as a solid (73 mg, 75%). A solution of this ester in THF (0.4 mL) was treated with aq. NaOH (1N, 0.38 mL, 3 equiv.). After 2 hr at RT it was diluted with DCM, washed with water and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 3% MeOH) afforded the title compound as a solid (47 mg, 70%). MS: 529 $(M+H)^+$; HPLC Ret Time: 1.37 min (YMC Xterra ODS S7 3.0 x 50 mm column, 2min gradient, 5 ml/min).

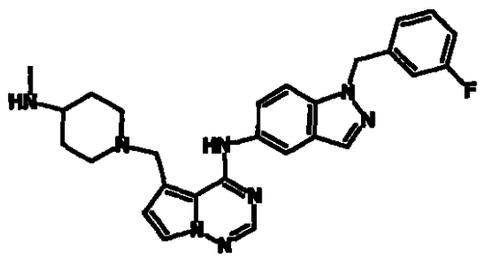
Example 85



2-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ylamino)-ethanol

A mixture of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (188 mg, 0.4 mmole) and [1,3]dioxolan-2-one (352 mg, 10 equiv) in a sealed tube was heated at 100 °C for 3.5 h. The title compound was isolated by radial chromatography (2 mm silica gel plate, gradient elution with DCM containing 0 to 3% MeOH) afforded the title compound as a solid (43 mg, 21%); MS: 515 ($M+H^+$); HPLC Ret Time: 1.29 min (YMC Xterra ODS S7 3.0 x 50 mm column, 2min gradient, 5 ml/min).

Example 86

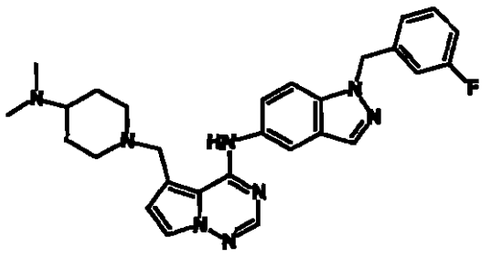


[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-methylamino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

A mixture of (5-benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (200 mg, 0.4 mmole) and 4-amino-piperidine (1.2 g, 30 equiv.) in a vial was placed in microwave reactor (Personal Chemistry's Smith Creator) and irradiated at 150°C for 20 min. Ethyl formate (3 ml) was added to above mixture and irradiation was continued at 135°C for 30 min. Concentration of the reaction mixture followed by preparative HPLC purification afforded N-(1-{4-[1-(3-

fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-formamide (71 mg, 36%). This was dissolved in dry THF (0.3 ml) and added dropwise to a stirred solution of $LiAlH_4$ (1M in ether, 0.57 ml, 4 equiv.). Water (0.5 mL) was slowly added after 20 hr and the title compound (16 mg, 23%) was isolated by preparative HPLC. MS: 485 $(M+H)^+$; HPLC Ret Time: 1.02min (Xterra 3.0 x 50 mm S7 C18 column, 2min gradient, 5 ml/min).

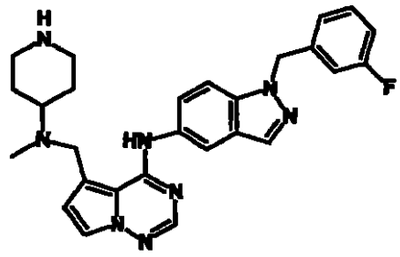
Example 87



[5-(4-Dimethylamino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

Sodium cyanoborohydride (5 mg, 2 equiv.) was added to a solution of [5-(4-amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (20 mg, 0.042 mmole), acetic acid (3 uL), and 37% formaldehyde (7 uL, 2 equiv.) in DCM (0.3 ml) at 0 °C. After 0.5 h, the reaction was removed from the ice-bath and, after an additional 4h, was diluted with DCM and made alkaline with saturated $NaCO_3$ solution. The organic layer was dried (Na_2SO_4) and the solvent was removed. The title compound (4 mg, 8%) was isolated by preparative HPLC. MS: 499 $(M+H)^+$; HPLC Ret Time: 1.04 min (YMC ODS-A C18 S7 3.0 x 50 mm column, 2min gradient, 5 ml/min).

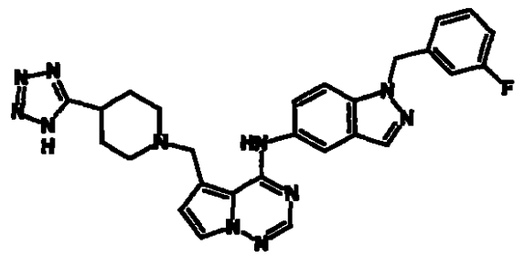
Example 88



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[(methyl-piperidin-4-yl-amino)-methyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine

Similarly, 4-({4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-piperidin-1-carboxylic acid *tert*-butyl ester was convertet to 4-({4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-methylamino)-piperidin-1-carboxylic acid *tert*-butyl ester which was treated with TFA at 0°C for 1h to give the title compound as a solid (overall yield 37%). MS: 485 $(M+H)^+$; HPLC Ret Time: 0.95 min (YMC 3.0 x 50 mm S7 C18 column, 2min gradient, 5 ml/min).

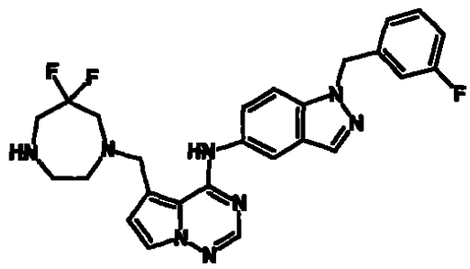
Example 89



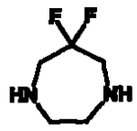
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(1H-tetrazol-5-yl)-piperidin-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine

A mixture of 1-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-4-carbonitrile (145 mg, 0.3 mmole), sodium azide (59 mg, 3 equiv.) and ammonium chloride (48 mg, 3 equiv.) in DMF (0.6 mL) in a sealed vial was stirred at 100°C for 20 h. The reaction mixture was cooled to RT, diluted with DCM, washed with water, and dried (Na_2SO_4). Removal the solvent followed by radial chromatography (2 mm silica gel plate, gradient elution with DCM containing 2 to 7% 2 M NH_3 in MeOH) afforded the title compound as a solid (38 mg, 24%) ; MS: 524 $(M+H^+)$; HPLC Ret Time: 1.13 min (Xterra 3.0 x 50 mm S7 C18 column, 2min gradient, 5 ml/min).

Example 90



[5-(6,6-Difluoro-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine



A. Preparation of 6,6-Difluoro-[1,4]diazepane

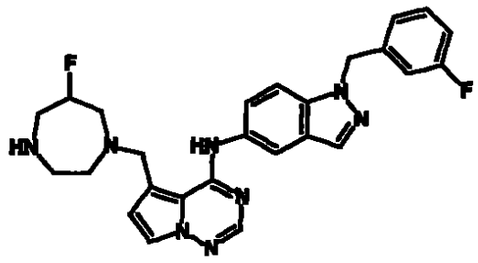
Tertrapropylammonium perruthenate (0.75 gm, 0.05 equiv) was added to a stirred suspension of 1,4-bis-(toluene-4-sulfonyl)-[1,4]diazepan-6-ol (13 gm, 30.7 mmoles, Saari et al., J. Org. Chem., 1971, 36, 1711), N-methylmorpholine N-oxide (5.38 gm, 1.5 equiv) and crushed 4 A molecular sieves (20 gm) in dry DCM (100 mL). After 1.5 hr, this was poured onto a short column of silica gel and eluted with a mixture of 10% EtOAc in DCM to give 1,4-bis-(toluene-4-sulfonyl)-[1,4]diazepan-6-one (8.9 gm, 60%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 6H), 3.71 (s, 4H), 3.91 (s, 4H), 7.32 (d, 4H, J = 8.1 Hz), 7.65 (d, 4H, J = 8.1 Hz). A solution of this ketone (8.9 gm, 21.1 mmole) in dry DCM was cooled in an acetone/dry ice bath and DAST (8.4 mL, 3 equiv) was added over 5 min. The reaction was allowed to warm to RT and, after 20 hr, it was cooled in an ice bath and water was added dropwise to decompose the excess reagent. The pH of the aqueous phase was adjusted to 10 with aq. NaOH solution and additional DCM (300 mL) was added. The organic phase was separated, dried (Na2SO4) and the solvent removed. The residue was crystallized from acetone/water to give 6,6-difluoro-1,4-bis-(toluene-4-sulfonyl)-[1,4]diazepane (6.47 gm, 69%) as fluffy white crystals: ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 6H), 3.41 (s, 4H), 3.68 (t, 4H, J = 12.3 Hz), 7.33 (d, 4H, J = 8.0 Hz), 7.64 (d, 4H, J = 8.0 Hz). A solution of the difluoride (3.41 gm, 7.75 mmole) and phenol (2.9 gm, 4 equiv) in a 30% solution of HBr in HOAc (50 mL) was heated at 60 oC for 6 hr. The reaction was

concentrated and the residue was suspended in ethanol to deposit the bis-HBr salt of 6,6-difluoro-[1,4]diazepane as a tan solid (1.82 gm, 79). This salt (600 mg, 2.04 mmole) was suspended in MeOH (10 mL) and aq. NaOH (0.41 mL, 10 N, 2 equiv) was added with stirring. The resulting solution was eluted through a Varian Mega Bond Elut SCX cartridge followed by 10 mL of MeOH. 6,6-Difluoro-[1,4]diazepane was eluted off the SCX cartridge with 50 mL of 2 N solution of NH3 in MeOH. Removal of the solvents left it as an oil (211 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 4H), 3.21 (t, 4H, J = 13.9 Hz)

B. Preparation of [5-(6,6-Difluoro-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

A solution of methanesulfonic anhydride (114 mg, 3.2 equiv.) in DCM (0.6 mL) was added to a solution of {4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-yl}-methanol (78 mg, 2 mmole) in dry DCM (1.4 mL) at 0 °C under nitrogen followed by triethylamine (0.140 mL, 5 equiv.). After stirring at 0 °C for 1hr, 6,6-difluoro-[1,4]diazepane (82 mg, 3 equiv.) and 1,2 dichloroethane (2 mL) were added. The reaction mixture was transferred to a microwave reactor (Personal Chemistry's Smith Creator) and irradiated at 65 °C for 50 min. Removal of the solvent followed by preparative HPLC afforded the title compound as a solid (29 mg, 29 %). MS: 507 ($M+H^+$); HPLC Ret Time: 1.47 min (YMC Xterra ODS S7 3.0 x 50 mm column, 2min gradient, 5 ml/min).

Example 91

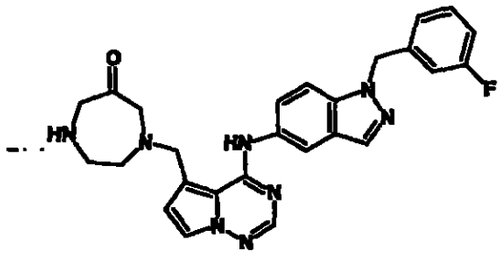


(±)-[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(6-fluoro-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

Following the above coupling procedure with 6-fluoro-[1,4]diazepane (Ziegler et al.,

J. Med. Chem., 1990, 33, 142) gave the title compound as a solid (yield 26%). MS: 489 $(M+H)^+$; HPLC Ret Time: 1.33 min (YMC Xterra ODS S7 3.0 x 50 mm column, 2min gradient, 5 ml/min).

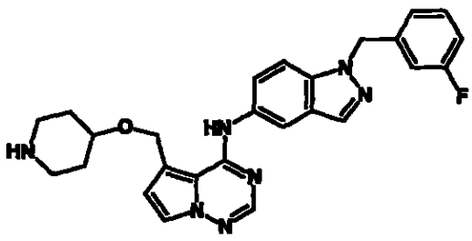
Example 92



1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-6-one

Oxidation of 4-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-6-hydroxy-[1,4]diazepane-1-carboxylic acid tert-butyl ester as described for **Example 74** gave 4-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-6-oxo-[1,4]diazepane-1-carboxylic acid tert-butyl ester which was deprotected with TFA to afford the title compound as a solid (overall yield 61%). MS: 485 $(M+H)^+$; HPLC Ret Time: 1.01 min (Xterra S7 3.0 x 50 mm S7 C18 column, 2min gradient, 5 ml/min).

Example 93



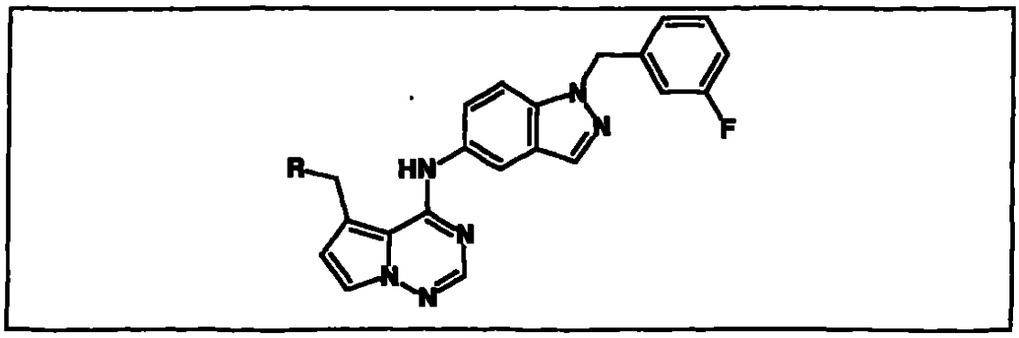
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-4-yloxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

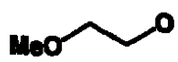
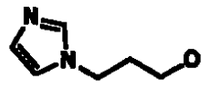
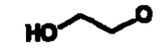
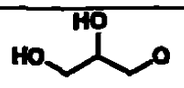
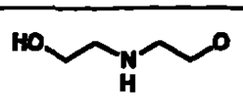
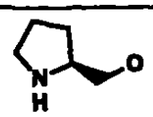
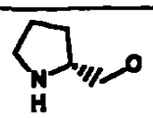
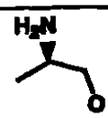
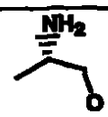
A suspension of 5-bromomethyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine (61 mg, 0.25 mmole), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 10 equiv) and $NaHCO_3$ (42 mg, 2 equiv) in dry CH_3CN (0.5 mL) under N_2 was left stirring at

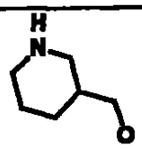
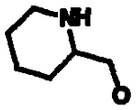
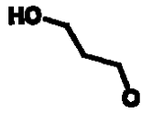
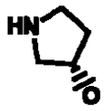
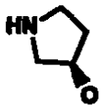
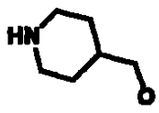
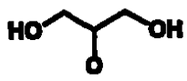
RT for 3 days. 1-(3-Fluoro-benzyl)-1H-indazol-5-ylamine (54 mg, 0.9 equiv) and additional $NaHCO_3$ (42 mg, 2 equiv) were added and the reaction was left stirring overnight. The reaction was diluted with DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2mm silica gel plate, gradient elution with DCM containing 0 to 3% MeOH) afforded 4-{4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethoxy}-piperidine-1-carboxylic acid tert-butyl ester as a foam (47 mg, 33%). This was treated with a mixture of DCM (1.5 mL) and TFA (1 mL) for 40 min and then the solvents were removed. The residue was taken up in DCM, washed with sat. aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 *mm* silica gel plate, gradient elution with DCM containing 0 to 5 % MeOH) afforded the pure amine (11 mg, 29%) as an oil. ^1H NMR ($CDCl_3$) δ 1.1 – 1.3 (m, 2H), 1.7 – 1.9 (m, 4H), 2.5 –2.6 (m, 2H), 3.0 – 3.1 (m, 2H), 3.44 (d, 2H, $J = 7$ Hz), 4.85 (s, 2H), 5.59 (s, 2H), 6.55 (d, 1H, $J = 2$ Hz), 6.8 – 7.0 (m, 3H), 7.2 – 7.5 (m, 4H), 7.97 (s, 1H), 8.05 (s, 1H), 8.20 (d, 1H, $J = 2$ Hz), 9.70 (s, 1H); MS: 486 $(M+H)^+$; HPLC Ret Time: 1.35 min (YMC S7 C18, 3.0 x 50 mm, 2 min gradient, 5 mL/min.

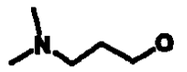
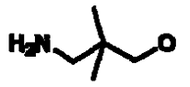
Examples 94 to 116

The follow ether analogs were prepared using the procedure described for Example 93. When the starting alcohol did not carry a Boc protecting group, the deprotection step was omitted. Alcohols that that carried a primary or secondary amino group were first converted to their N-Boc derivative using di-tert-butyl dicarbonate according to general literature procedures (T. Greene and P. Wuts, Protective Groups in Organic Synthesis, 3rd edition).



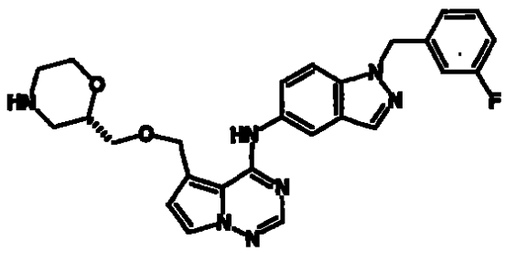
Ex.	R	Compound Name	HPLC Ret Time (min)
94		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(2-methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.33*
95	MeO	[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-methoxymethyl-pyrrolo [2,1-f][1,2,4]triazin-4-yl)-amine	2.18**
96		[5-(2-Dimethylamino-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.24
97		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(3-imidazol-1-yl-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.33
98		2-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-ethanol	1.4
99	 racemic	3-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-propane-1,2-diol	1.33
100		2-(2-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-ethylamino)-ethanol	1.25
101		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(2S)-pyrrolidin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.27
102		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(2R)-pyrrolidin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.27
103		[5-{(2R)2-Amino-propoxymethyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.33
104		[5-{(2S)-2-Amino-propoxymethyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.33

105		[5-(2-Amino-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.29
106	 racemic	[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-3-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.34
107	 racemic	[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.38
108		3-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-propan-1-ol	2.15**
109		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-{(3S)-pyrrolidin-3-yloxymethyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.24*
110		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-{(3R)-pyrrolidin-3-yloxymethyl}-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.24*
111		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-4-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	1.35*
112		2-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-propane-1,3-diol	1.41

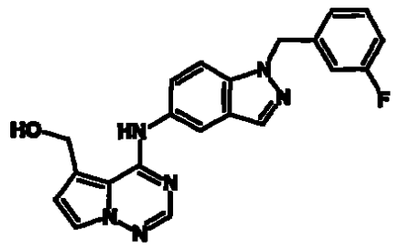
113		[5-(3-Dimethylamino-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.95***
114		[5-(4-Amino-butoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.84****
115		[5-(3-Amino-2,2-dimethyl-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	2.12***
116		[5-(4-Amino-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.98***

Unless otherwise indicated, HPLC Retention Times were determined using a YMC Xterra ODS S7 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min. HPLC Retention Times marked with a "*" were determined using a YMC C18 SF 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min; with a "**" were determined using using a YMC C18 SF 4.6 x 50 mm column with a 3 minute gradient time and a flow rate of 4 mL/min; with a "***" on a YMC Xterra C18 S5 4.6 x 50 mm column with a 3 min gradient time and a flow rate of 4 mL/ min, with; with a "****" on a YMC Xterra C18 S5 3.0 x 50 mm column with a 3 min gradient and a flow rate of 4 mL/min.

Example 117



([1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-({2S}-morpholin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine



A. Preparation of {4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-yl}-methanol

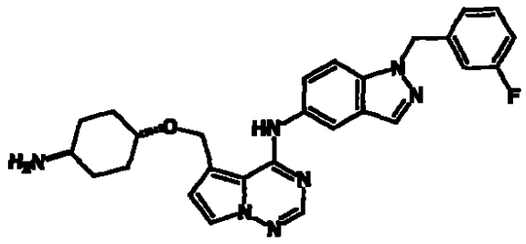
A mixture of crude 5-bromomethyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine (3.69 gm, 0.015 moles and $NaHCO_3$ (2.51 gm, 2 equiv) in a mixture of acetonitrile (50 mL) and water (5 mL) was stirred under a N_2 atmosphere for 3 days. This was treated with Na_2SO_4 and then with 1-(3-flurobenzyl)-1H-indazol-5-ylamine (3.24 gm, 0.90 equiv) and $NaHCO_3$ (1 gm) and left stirring for 18 hr at RT. The reaction was filtered and the filter cake was washed with DCM (100 mL). The filtrate was concentrated and silica gel chromatography (elution with 30% EtOAc in hexane) of the residue gave the title compound as a tan solid (3.78 gm, 65% yield): ^1H NMR ($CDCl_3$) δ 3.03 (t, J = 5.9 Hz, 1H), 4.98 (d, J = 5.7 Hz, 2H), 5.55 (s, 2H), 6.76 (d, J = 2.7 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.98 – 6.90 (m, 3H), 7.43 (d, J = 2.5 Hz, 1H), 7.51 (dd, J = 2.1, 8.8 Hz, 1H), 7.96 (s, 1H), 8.03 (s, 1H), 8.22 (s, 1H), 9.91 (s, 1H); MS: (M+H+); HPLC Ret Time: 2.38 min (YMC C18 S5, 3.0 x 50 mm, 4 min gradient, 4 mL/min.

B. Preparation of ([1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-({2S}-morpholin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

Thionyl chloride (18 μL, 1.1 equiv) was added to a solution of {4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-yl}-methanol (80 mg,

0.205 mmole) in dry DCM (4 mL) at RT. After 12 min, (2S)-2-hydroxymethyl-morpholine-4-carboxylic acid tert-butyl ester (65.3 mg, 1.5 equiv, H. Yanagisawa et al., Heterocycles, 1993, 35, 105.) was added followed by DIPEA (39.5 μL, 1.1 equiv). After 72 hr at RT, the solvent was removed and silica gel chromatography of the residue (gradient elution with 0 to 50% EtOAc in hexane) afforded 2-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxymethyl}-morpholine-4-carboxylic acid tert-butyl ester (60 mg, 50% yield); MS: 588 $(M+H)^+$; HPLC Ret Time: 2.69 min (Xterra C18 S5, 3.0 x 50 mm, 3 min gradient, 4 mL/min. A solution of this material in DCM (2 mL) was cooled to 0°C and treated with TFA (1 mL). After 90 min, the solvents were removed and the residue was dissolved in DCM. This was washed with saturated $NaHCO_3$ solution and the organic phase was dried (Na_2SO_4) and the solvents removed. Purification by preparative HPLC and then radial chromatography (1 mm silica gel plate, gradient elution with 0 to 3% NH_3 (2N in MeOH) in DCM gave the title compound (30 mg, 60% yield): ^1H-NMR ($CDCl_3$) δ 2.84 – 2.58 (m, 4H), 3.65 – 3.35 (m, 4H) 3.65 – 3.35 (m, 4H), 4.87 (s, 2H), 5.58 (s, 2H), 6.54 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 9.5 Hz, 1H), 6.98 – 6.90 (m, 2H), 7.32 – 7.20 (m, 3H), 7.48 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 1.8, 8.8 Hz, 1H), 7.94 (s, 1H), 8.19 (s, 1H), 9.58 (s, 1H); MS: 488 $(M+H)^+$; HPLC Ret Time: 1.65 min (Xterra C18 S5, 3.0 x 50 mm, 3 min gradient, 4 mL/min).

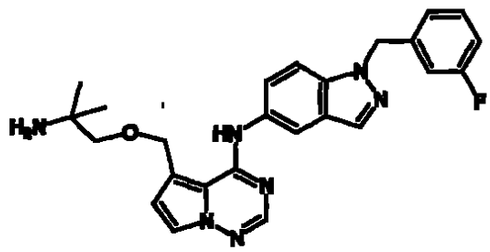
Example 118



[trans-5-(4-Amino-cyclohexyloxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

The title compound was prepared from (trans-4-hydroxy-cyclohexyl)-carbamic acid tert-butyl ester in a similar manner: MS: 486 $(M+H)^+$; HPLC Ret Time: 2.13 min (Xterra C18 S5, 4.6 x 50 mm, 3 min gradient, 4 mL/min).

Example 119

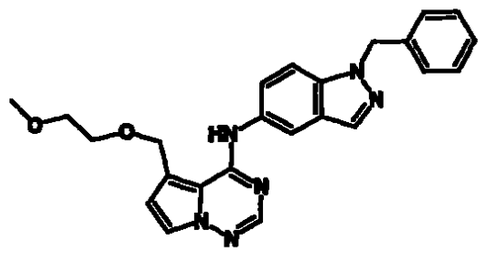


[5-(2-Amino-2-methyl-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

A mixture of acetic acid 4-[1-(3-fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethylester (100 mg, 0.24 mmol), (2-hydroxy-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester 156 mg, 3 equiv) and DIPEA (62 µL, 1.5 equiv) in dry acetonitrile (0.2 mL) in a vial was placed in a microwave reactor (Personal Chemistry's Smith Creator) and irradiated for 10 min at 109°C. The solvent was removed and the residue was taken up in dry DCM (3mL) and cooled to 0°C. TFA (3 mL) was added and after 1.5 hr, the solvents were removed. The residue was partitioned between DCM and saturated $NaHCO_3$ solution. The organic phase was dried (Na_2SO_4) and the solvent was removed. Purification by radial chromatography (1 mm silica gel plate, gradient elution with 0 to 5 % MeOH in DCM) gave the title compound (13 mg, 12% yield): MS: 460 (M+H)+; HPLC Ret Time: 1.34 min, YMC Xterra ODS S7 3.0 x 50 mm, 2 min gradient , 5 mL/min).

Example 120

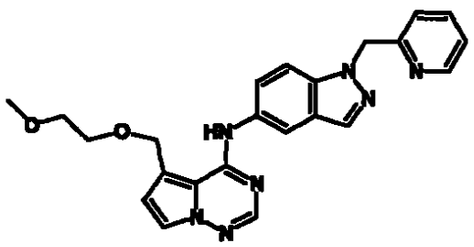
(1-Benzyl-1H-indazol-5-yl)-[5-(2-methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine



A suspension of 5-bromomethyl-4-chloro-pyrrolo[2,1-f][1,2,4]triazine (50 mg, 0.202 mmole and $NaHCO_3$ (75 mg, 4.4 equiv) in 2-methoxyethanol (1.0 mL) under N_2 was

left stirring at RT for 6 hr. The reaction was diluted with DCM, extracted with water and dried (Na_2SO_4). Removal of the solvent left 4-chloro-5-(2-methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazine (41 mg, 84%) as an oil. ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H), 3.67 (m, 4H), 4.96 (s, 2H), 7.05 (d, 1H, J = 3 Hz), 7.82 (d, 1H, J = 3 Hz), 8.16 (s, 1H). A suspension of 4-chloro-5-(2-methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazine (5 mg, 0.020 mmole), $NaHCO_3$ (3 mg, 2 equiv) and 1-benzyl-1H-indazol-5-ylamine (4.5 mg, 1 equiv, prepared in the same manner as 1-(3-fluoro-benzyl)-1H-indazol-5-ylamine but using benzyl chloride) in dry CH_3CN (0.5 mL) was left stirring at RT for 2 hr. The reaction was diluted with DCM, washed with water and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (1 mm silica gel plate, gradient elution with DCM containing 0 to 1% MeOH) afforded the product as and oil (1.8 mg, 21%). ^1H NMR ($CDCl_3$) δ 3.16 (s, 3H), 3.63 (m, 4H), 4.83 (s, 2H), 5.53 (s, 2H), 6.48 (d, 1H, J = 3 Hz), 7.1 – 7.5 (m, 8H), 7.88 s, 1H), 7.96 (s, 1H), 8.11 (s, 1H), 9.56 (s, 1H); MS: 429 $(M+H)^+$; HPLC Ret Time: 2.58 min (YMC C18 S5, 4.6 x 50 mm, 3 min gradient (starting with 0% solvent B and ending with 70% solvent B), 4 mL/min.

Example 121

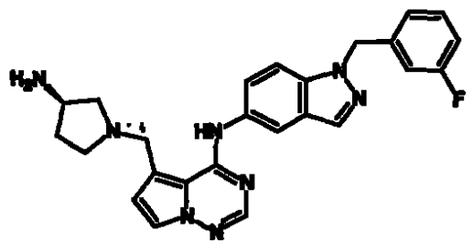


[5-(2-Methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-(1-pyridin-2-ylmethyl-1H-indazol-5-yl)-amine

A suspension of 4-chloro-5-(2-methoxy-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazine (24 mg, 0.099 mmole), $NaHCO_3$ (42 mg, 5 equiv) and 1-pyridin-2-ylmethyl-1H-indazol-5-ylamine (22 mg, 1 equiv, prepared in the same manner as 1-(3-fluoro-benzyl)-1H-indazol-5-ylamine but using 2-picolyl chloride) in dry CH_3CN (1 mL) was

left stirring at RT for 1 hr. The reaction was diluted with DCM, washed with water and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (1 mm silica gel plate, gradient elution with DCM containing 0 to 1% MeOH) afforded the product as and oil (4.8 mg, 11%). ^1H NMR ($CDCl_3$) δ 3.26 (s, 3H), 3.76 (m, 4H), 4.90 (s, 2H), 5.75 (s, 2H), 6.56 (d, 1H, J = 3 Hz), 6.83 (d, 1H, J = 5 Hz), 7.18 (m, 1H), 7.40 (d, 1H, J = 5 Hz), 7.49 (d, 1H, J = 2 Hz), 7.56 (m, 2H), 7.96 (s, 1H), 8.07 (s, 1H), 8.22 (d, 1H, J = 1 Hz), 8.59 (m, 1H), 9.65 (s, 1H); MS: 429 (M+H)+; HPLC Ret Time: 1.30 min (YMC ODS-A C18 S7, 3.0 x 50 mm, 2 min gradient (starting with 0% solvent B and ending with 70% solvent B), 5 mL/min.

Example 122

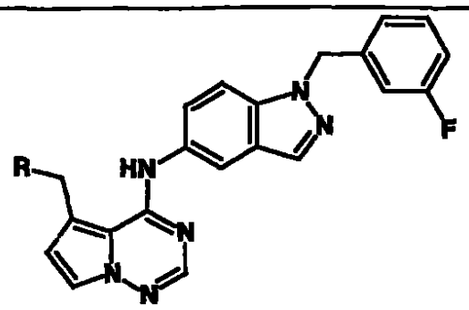


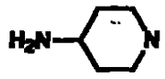
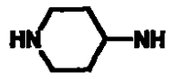
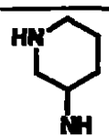
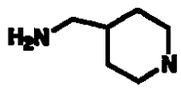
{5-[(3R)-3-Amino-pyrrolidin-1-ylmethy]-pyrrolo[2,1-*f*][1,2,4]triazin-4-yl}-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine

A mixture of (5-benzenesulfinylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (100 mg, 0.20 mmole) and (3R)-3-(N-tert-butoxycarbonylamino)pyrrolidine; (380 mg, 10 equiv) in a sealed tube was heated at 130 °C for 35 hr. The reaction mixture was taken up in DCM, washed water and dried (Na_2SO_4). After removal of the solvent the residue was taken up in DCM (1.5 mL) and TFA (1 mL) was added. The solvents were removed and the residue was dissolved in DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 1 to 5% MeOH) to afforded the title compound as an oil (13 mg, 14%). ^1H NMR ($CDCl_3$) δ 1.49 (br s, 2H), 1.66 (m, 1H), 2.29 (m, 1H), 2.43 (m, 1H), 3.69 (m, 1H), 3.87 (d, 1H, J = 13.5 Hz), 3.96 (d, 1H, J = 13.5 Hz), 5.58 (s, 2H), 6.49 (d, 1H, J = 3 Hz), 6.8 – 7.6 (m, 7H), 7.92 (s, 1H), 8.04 (s, 1H), 8.26 (d, 1H, J = 2 Hz); MS: 457 $(M+H)^+$; HPLC Ret Time: 1.15 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

Examples 123 to 127

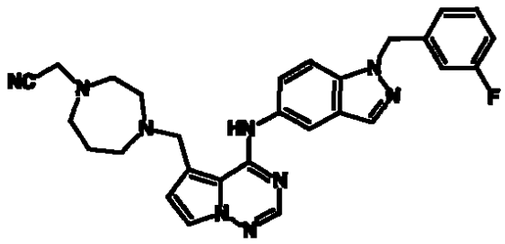
The follow examples were prepared in the same manner as **Example 122.**



Ex.	R	Compound Name	HPLC Ret Time (min)
123		[5-(4-Amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.03
124		[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-4-ylaminomethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	0.98
125		[5-((3R)-3-Amino-pyrrolidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.15*
126		(+)-[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-3-ylaminomethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine	0.97*
127		[5-(4-Aminomethyl-piperidin-1ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine	1.53**

Unless otherwise indicated, HPLC Retention Times were determined using a YMC S7 C18 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min. HPLC Retention Times marked with a "*" were determined using a YMC S7 C18 3.0 x 50 mm column with a 2 minute gradient time and a flow rate of 5 mL/min; with a "**" were determined using using a YMC ODS-A C18 S7 3.0 x 50 mm column with a 3 minute gradient time and a flow rate of 4 mL/min.

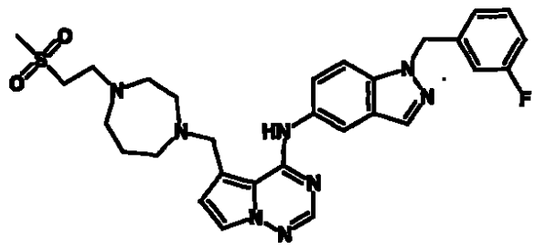
Example 128



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-cyanomethyl-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine

Bromoacetonitrile (0.028 mL, 4 equiv) was added to an ice cooled solution of 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.10 mmole) and TEA (0.055 mL, 4 equiv) in DCM (3 mL). This was left stirring for 1 hr and then removed from the ice bath. After standing overnight, the reaction was diluted with DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 1% MeOH) afforded the title compound as an oil (49 mg, 95%). MS: 510 $(M+H)^+$; HPLC Ret Time: 1.17 min (YMC S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

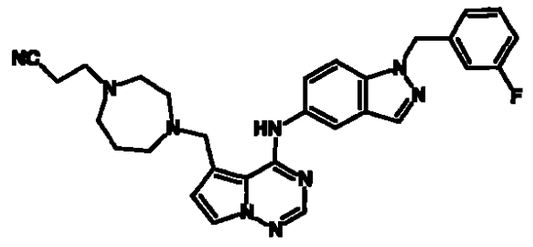
Example 129



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methanesulfonyl-ethyl)-[1,4]diazepan-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine

Methyl vinyl sulfone (0.042 mL, 4 equiv) was added to a solution of 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.10 mmole) in DCM (3 mL). After stirring overnight, the solvent was removed and purification by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 1% MeOH) afforded the title compound as an oil (54 mg, 93%).); MS: 577 $(M+H)^+$; HPLC Ret Time: 1.08 min (YMC S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

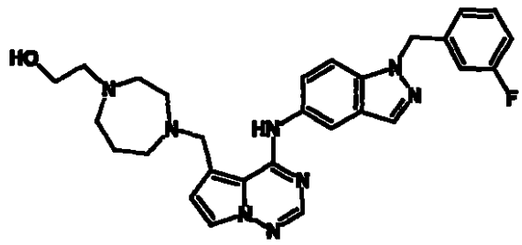
Example 130



[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-cyano-ethyl)-[1,4]diazepan-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine

Acrylonitrile (0.302 mL, 45 equiv) was added in 3 portions over 2 days to a solution of 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.10 mmole) in DCM (3 mL) at RT. The solvent was removed and purification by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 1% MeOH) afforded the title compound as an oil (34 mg, 64%).); MS: 524 $(M+H)^+$; HPLC Ret Time: 1.08 min (YMC S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

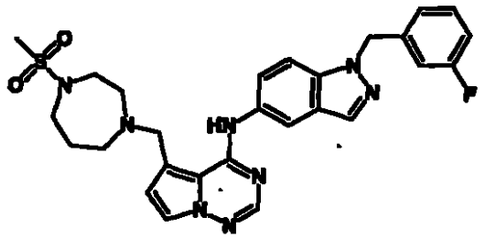
Example 131



2-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-*f*][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-1-yl)-ethanol

A mixture of 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.10 mmole), 2-bromoethanol (0.019 mL, 1.5 equiv) and K_2CO_3 (35 mg, 2.5 equiv) in CH_3CN (2.5 mL) was heated at reflux overnight. The reaction was then diluted with DCM, washed with water and dried (Na_2SO_4). The solvent was removed and purification by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 5 % MeOH) afforded the title compound as an oil (21 mg, 41%). MS: 515 $(M+H)^+$; HPLC Ret Time: 1.15 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

Example 132

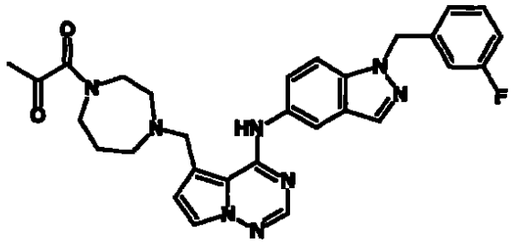


[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-methanesulfonyl-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-*f*][1,2,4]triazin-4-yl]-amine

Methanesulfonyl chloride (0.034 mL, 4 equiv) was added to an ice an ice cooled solution of 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (35 mg, 0.074 mmole) and TEA (0.041 mL, 4 equiv) in DCM (2.5 mL). This was left stirring for 1 hr and then removed from the ice bath. After standing overnight, the reaction was diluted with DCM, washed with water, and dried (Na_2SO_4). Removal of the solvent followed by radial chromatography (2 mm silica gel plate employing gradient elution with DCM containing 0 to 2% MeOH)

afforded the title compound as an oil (22 mg, 54%).); MS: 549 $(M+H)^+$; HPLC Ret Time: 1.26 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

Example 133



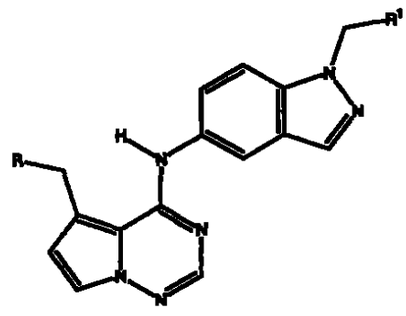
1-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-1-yl)-propane-1,2-dione

A solution of pyruvic acid (0.008 mL, 1 equiv) and 5-[1,4]diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine (47 mg, 0.10 mmole) in EtOAc (3 mL) was cooled to -16 °C and a solution of dicyclohexylcarbodiimide (22 mg, 1.1 equiv) in EtOAc (0.5 mL) was added. This was allowed to slowly warm to RT and was left stirring overnight. The reaction was filtered and the solvent was removed from the filtrate. Radial chromatography of the residue (2 mm silica gel plate employing gradient elution with DCM containing 0 to 2% MeOH) afforded the title compound as an oil (8 mg, 14%). MS: 541 $(M+H)^+$; HPLC Ret Time: 1.27 min (YMC Xterra ODS S7 C18, 3.0 x 50 mm column, 2 min gradient, 5 mL/min).

Claims

What is claimed is:

1. A compound of formula I



I

its enantiomers, diastereomers, and pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

R is selected from the group consisting of SR^2, SOR^2, SO_2R^2, OR^2, and NR^3R^4;

R^1 is selected from the group consisting of aryl, substituted aryl, heterocyclo, and substituted heterocyclo;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, aralkyl, heterocyclo, and substituted heterocyclo;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, and substituted heterocyclo; or R^2 and R^3 may together form an optionally substituted monocyclic 4-8 membered saturated or unsaturated carbocyclic or heterocyclic ring, or an optionally substituted bicyclic 7 to12 membered saturated or unsaturated carbocyclic or heterocyclic ring.

2. The compound according to claim 1 wherein R^1 is selected from the group consisting of benzene, fluoro substituted benzene and pyridine.

3. The compound according to claim 2 wherein R^1 is a fluoro substituted benzene.

4. The compound according to claim 3 wherein R is an ether.

5. The compound according to claim 1 selected from the group consisting of: (5-[1,4]Diazepan-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-(5-imidazol-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)-amine;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidine-3-carboxylic acid amide;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-methyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
2-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-1-yl)-ethanol;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1f][1,2,4]triazin-5-ylmethyl}-(3R)-pyrrolidin-3-ol;
(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-yl)-methanol;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ol;
(2R)-3-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propane-1,2-diol;
2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-ethanol;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(3S)-pyrrolidin-3-ol;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-cyanomethyl-cyclohexylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
[5-(3,5-Dimethyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-((3S)-3-methyl-piperazin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-

ylmethyl}-piperazine-2-carboxylic acid amide;
4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperazin-2-one;
2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-2-methyl-propane-1,3-diol;
2-({4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-amino)-propane-1,3-diol;
[1-(3-Fluoro-benzyl)-1H-indazol]-5-yl]-(5-piperazin-1-ylmethyl-pyrrolo[2,1-f][1,2,4]triazin-4-yl)amine;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-{5-[4-(2-methoxy-ethylamino)-piperidin-1-ylmethyl]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-amine;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-5-one;
[5-(4-Amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
(+)-[5-(cis-4-Amino-3-methyl-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
(+)-[5-(trans-4-Amino-3-methyl-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-one;
(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(+)-[1,4]diazepan-6-ol;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-(6R)-[1,4]diazepan-6-ol;
2-(1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-piperidin-4-ylamino)-ethanol;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(4-methylamino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
[5-(6,6-Difluoro-[1,4]diazepan-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
(+)-[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(6-fluoro-[1,4]diazepan-1-ylmethyl)-

pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
1-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-6-one;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-4-yloxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
2-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-ethanol;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-3-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
3-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-propane-1,2-diol;
[5-(4-Amino-butoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[5-(4-Amino-propoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
([1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-({2S}-morpholin-2-ylmethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
[trans-5-(4-Amino-cyclohexyloxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[5-(2-Amino-ethoxymethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
3-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethoxy}-propan-1-ol;
{5-[(3R)-3-Amino-pyrrolidin-1-ylmethy]-pyrrolo[2,1-f][1,2,4]triazin-4-yl}-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[5-(4-Amino-piperidin-1-ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-fluoro-benzyl)-1H-indazol-5-yl]-amine;
[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-4-ylaminomethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
(+)-[1-(3-Fluoro-benzyl)-1H-indazol-5-yl]-[5-(piperidin-3-ylaminomethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-amine;
[5-(4-Aminomethyl-piperidin-1ylmethyl)-pyrrolo[2,1-f][1,2,4]triazin-4-yl]-[1-(3-

fluoro-benzyl)-1H-indazol-5-yl]-amine;
2-(4-{4-[1-(3-Fluoro-benzyl)-1H-indazol-5-ylamino]-pyrrolo[2,1-f][1,2,4]triazin-5-ylmethyl}-[1,4]diazepan-1-yl)-ethanol;

6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier and at least one other anti-cancer or cytotoxic agent formulated as a fixed dose.

8. The pharmaceutical composition of claim 7 wherein said anti-cancer or cytotoxic agent is selected from the group consisting of: tamoxifen, toremifen, raloxifene, droloxifene, iodoxyfene, megestrol acetate, anastrozole, letrazole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotephan, vincristine, taxol, taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan and an epothilone.

9. A method for treating a proliferative disease, comprising administering to a warm-blooded species in need thereof, a therapeutically effective amount of a compound of claim 1.

10. The method of claim 9 wherein the proliferative disease is selected from the group consisting of cancer, psoriasis and rheumatoid arthritis.

11. The method of claim 10 wherein the proliferative disease is cancer.

12. The method of claim 11 further comprising administering to a warm-blooded species in need thereof, a therapeutically effective amount of at least one other anti-cancer or cytotoxic agent in combination with a compound of claim 1.

13. The method of claim 12 wherein said anti-cancer or cytotoxic agent is selected from the group consisting of: tamoxifen, toremifen, raloxifene, droloxifene, iodoxyfene, megestrol acetate, anastrozole, letrazole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotephan, vincristine, taxol, taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan and an epothilone.

14. A method of modulating receptor tyrosine kinase activity which comprises administering to a warm blooded species in need thereof, an effective amount of a compound of claim 1.

15. The method of claim 14 wherein said receptor tyrosine kinase is selected from the group consisting of HER1, HER2 and HER4.

16. A method for treating diseases associated with signal transduction pathways operating through growth factor receptors, which comprises administering to a warm-blooded species in need thereof a therapeutically effective amount of a compound of claim 1.

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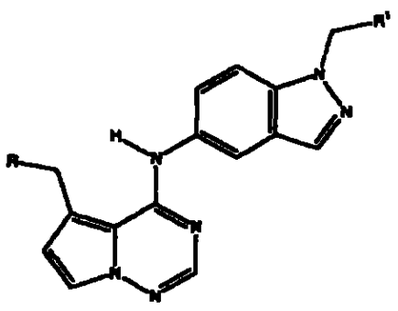
(54) Título: INDAZOLILPIRROLOTRIAZINAS MODIFICADAS C-5



(I)

(57) Extracto: La presente invención proporciona compuestos de fórmula I y sales farmacéuticamente aceptables de los mismos. Los compuestos de fórmula I inhiben la actividad tirosina cinasa de receptores de factor de crecimiento tales como HER1, HER2 y HER4 haciéndolos así útiles como agentes antiproliferantes. Los compuestos de fórmula I son asimismo útiles para el tratamiento de otras enfermedades asociadas con vías de transducción de señales mediante a través de receptores de crecimiento.

Indazolilpirrolotriazinas Modificadas C-5

Campo de la Invención

Esta invención se relaciona con compuestos que inhiben la actividad tirosina cinasa de receptores de factor de crecimiento tales como HER1, HER2, y HER4, haciéndolos de esta manera útiles como agentes anti-cáncer. Los compuestos son también útiles en el tratamiento de enfermedades, distintas del cáncer, que están asociadas con vías de transducción de señales que operan a través de receptores de factor de crecimiento tales como HER1, HER2 y HER4.

Antecedentes de la Invención

Las tirosina cinasas de receptor (RTKs) son importantes en la transmisión de señales bioquímicas a través de la membrana de plasma de las células. Estas moléculas transmembrana constan característicamente de un dominio fijación-ligando extracelular conectado a través de un segmento la membrana de plasma a un dominio tirosina cinasa intracelular.

La familia de receptor de factor de crecimiento epidérmico (HER) se compone de cuatro diferentes tirosina cinasas de receptor conocidas como HER1, HER2, HER3, y HER4. Estas cinasas se conocen también como erbB1, erbB2, etc. Asimismo HER1 se conoce comúnmente como el receptor de factor de crecimiento epidérmico (EGF). Con la excepción de HER3, estos receptores poseen actividad proteína cinasa intrínseca que es específica para residuos de tirosina de proteínas de fosfoaceptor. Las cinasas HER se expresan en la mayoría de las células epiteliales, así como las células tumorales de origen epitelial. Igualmente se expresan a menudo en células tumorales de origen mesenquimatoso tales como sarcomas o rabdomiosarcomas. RTKs tales como HER1 y HER2 están implicadas en la proliferación celular y están asociadas con enfermedades tales como psoriasis y cáncer. La alteración de transducción de señales por inhibición de estas cinasas tendría un efecto antiproliferante y terapéutico.

La actividad enzimática de tirosina cinasas de receptor puede

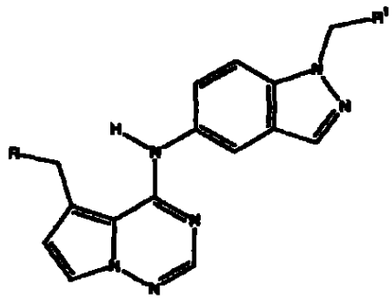
estimularse ya sea por sobreexpresión, o por dimerización mediada por ligando. La formación de homodímeros así como heterodímeros ha sido demostrada para la familia de receptor HER. Un ejemplo de homodimerización es la dimerización de HER1 (receptor de EGF) por una de la familia EGF de ligandos (que incluye EGF, factor de crecimiento alfa transformante, betacelulina, EFG de fijación de heparina, y epiregulina).

La heterodimerización entre las cuatro cinasas de receptor HER puede promoverse mediante fijación a miembros de la familia heregulina (también conocida como neuregulina) de ligandos. Tal heterodimerización, al implicar una combinación HER2 y HER3, o HER3/HER4, resulta en una estimulación importante de la actividad tirosina cinasa de los dímeros de receptor incluso aunque uno de los receptores (HER3) es enzimáticamente inerte. Se ha demostrado que la actividad cinasa de HER2 se activa también en virtud de la sobreexpresión del receptor solo en una variedad de tipos de células. La activación de homodímeros de receptor y heterodímeros resulta en la fosforilación de residuos de tirosina en los receptores y en otras proteínas intracelulares. Ésta es seguida por la activación de vías de señalización intracelular tales como aquellas que implican la proteína cinasa asociada con microtúbulos (cinasa MAP) y la fosfatidilinositol 3-cinasa (cinasa PI3). Se ha demostrado que la activación de estas vías conduce a proliferación celular y a la inhibición de apoptosis. Se ha demostrado que la inhibición de la señalización de la cinasa HER inhibe la proliferación y la supervivencia celular.

Sumario

Los compuestos de la invención inhiben la actividad tirosina cinasa de receptores de factor de crecimiento tales como HER1, HER2, y HER4 y como tales, pueden usarse para tratar enfermedades que están asociadas con vías de transducción de señales que operan a través de receptores de factor de crecimiento. Por ejemplo los compuestos de la presente invención

pueden usarse como antiproliferantes y agentes anticáncer. Más específicamente, la invención comprende un compuesto de fórmula I



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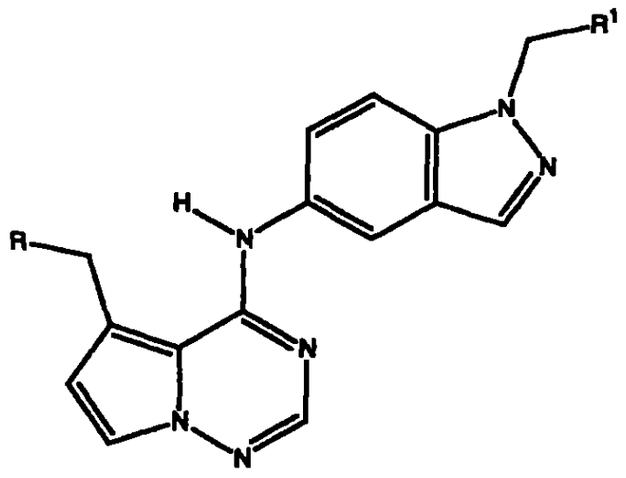
sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables, profármacos y solvatos del mismo, en donde R se selecciona del grupo conformado por SR^2, SOR^2, SO_2R^2, OR^2, y NR^3R^4; R^1 se selecciona del grupo conformado por arilo, arilo sustituido, heterociclo, y heterociclo sustituido; R^2 se selecciona del grupo conformado por hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, aralalquilo, heterociclo, y heterociclo sustituido; R^3 y R^4 se seleccionan independientemente del grupo conformado por hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido; o R^2 y R^3 pueden formar conjuntamente un anillo carbocíclico o heterocíclico, saturado o insaturado, de 4-8 miembros, monocíclico opcionalmente sustituido, o un anillo carbocíclico o heterocíclico, saturado o insaturado, de 7-12 miembros, bicíclico opcionalmente sustituido.

Se hace posible igualmente un método para tratar enfermedades proliferanttes, que comprende administrar a una especie de sangre caliente, necesitada de él, una cantidad terapéuticamente efectiva de un compuesto de fórmula I.

Descripción

La presente invención hace posibles compuestos de fórmula I, composiciones farmacéuticas que emplean tales compuestos y métodos de

usar tales compuestos. De acuerdo con la presente invención, compuestos de fórmula I



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sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables, profármacos y solvatos de los mismos inhiben la actividad tirosina cinasa de receptores de factor de crecimiento tales como HER2. En fórmula I y de principio a fin de la especificación, los símbolos anteriores se definen como sigue:

R se selecciona de SR^2, SOR^2, SO_2R^2, OR^2, NR^3R^4;

R^1 es arilo, arilo sustituido, heterociclo, heterociclo sustituido;

R^2 es hidrógeno, alquilo, alquilo sustituido arilo, arilo sustituido, aralalquilo, heterociclo, heterociclo sustituido;

R^3 y R^4 son independientemente hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, o heterociclo sustituido o R^2 y R^3 pueden formar conjuntamente un anillo carbocíclico o heterocíclico, saturado o insaturado, de 4-8 miembros, monocíclico opcionalmente sustituido, o un anillo carbocíclico o heterocíclico, saturado o insaturado, de 7-12 miembros, bicíclico opcionalmente sustituido;

Listadas más abajo se encuentran definiciones de varios términos usados para describir esta invención. Estas definiciones se aplican a los términos tal como ellos se emplean de comienzo a fin de esta

especificación, a menos que se limite en otra forma en casos específicos, ya sea individualmente o como parte de un grupo más amplio.

El término "alquilo" se refiere grupos hidrocarburos no sustituidos, de cadena recta o ramificada, de 1 a 20 átomos de carbono, preferiblemente 1 a 7 átomos de carbono. La expresión "alquilo inferior" se refiere a grupos alquilo no sustituidos de 1 a 4 átomos de carbono.

El término "alquilo sustituido" se refiere a un grupo alquilo sustituido por, por ejemplo, uno a cuatro sustituyentes, tales como, halo, hidroxi, alcoxi, oxo, alcanoilo, ariloxi, alcanoiloxi, amino, alquilamino, arilamino, aralquilamino, aminas disustituidas en las cuales los 2 sustituyentes amino se seleccionan de alquilo, arilo o aralquilo; alcanoilamino, aroilamino, aralcanoilamino, alcanoilamino sustituido, arilamino sustituido, aralcanoilamino sustituido, tiol, alquiltio, ariltio, aralquiltio, alquiltiono, ariltiono, aralquiltiono, alquilsulfonilo, arilsulfonilo, aralquilsulfonilo, sulfonamido, por ejemplo SO_2NH_2, sulfonamido sustituido, nitro, ciano, carboxi, carbamilo, por ejemplo $CONH_2$, carbamilo sustituido por ejemplo CONHalquilo, CONHarilo, CONHaralquilo o casos en donde hay dos sustituyentes en el nitrógeno seleccionados de alquilo, arilo o aralquilo; alcoxicarbonilo, arilo, arilo sustituido, guanidino, heterociclo, por ejemplo, indolilo, imidazolilo, furilo, tienilo, tiazolilo, pirrolidilo, piridilo, pirimidilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, homopiperazinilo y similares, y heterociclo sustituido. Donde, como ya se anotó, el sustituyente se sustituye adicionalmente, éste será con alquilo, alcoxi, arilo o aralquilo.

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

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

El término "aralquilo" se refiere a un grupo arilo o arilo sustituido enlazado directamente mediante un grupo alquilo, tal como bencilo.

El término "arilo sustituido" se refiere a un grupo arilo sustituido por, por ejemplo, uno a cuatro sustituyentes tales como alquilo, alquilo sustituido alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, aralalquilo, halo, trifluorometoxi, trifluorometilo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, ariloxi, aralquiloxi, amino, alquilamino, arilamino, aralquilamino, dialquilamino, alcanoilamino, tiol, alquiltio, ureido, nitro, ciano, carboxi, carboxialquilo, carbamilo, alcoxicarbonilo, alquiltiono, ariltiono, arilsulfonilamina, ácido sulfónico, alquisulfonilo, sulfonamido, ariloxi y similares. El sustituyente puede sustituirse adicionalmente por hidroxi, halo, alquilo, alcoxi, alquenilo, alquinilo, arilo o aralquilo.

El término "heteroarilo" se refiere a un grupo aromático opcionalmente sustituido, por ejemplo, que es un sistema de anillo monocíclico de 4 a 7 miembros, bicíclico de 7 a 11 miembros, o tricíclico de 10 a 15 miembros, que tiene por lo menos un heteroátomo y por lo menos un átomo de carbono que contiene un anillo, por ejemplo, piridina, tetrazol, indazol.

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

El término "alquenilo sustituido " se refiere a un grupo alquenilo sustituido por, por ejemplo, uno a dos sustituyentes, tales como, halo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, amino, alquilamino, dialquilamino, alcanoilamino, 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 hidrocarburos de cadena recta o ramificada de 2 a 20 átomos de carbono, preferiblemente 2 a 15 átomos de carbono, y muy preferiblemente 2 a 8 átomos de carbono, que tienen uno a cuatro enlaces triples.

El término "alquinilo sustituido" se refiere a un grupo alquinilo sustituido por, por ejemplo, un sustituyente, tal como, halo, hidroxi, alcoxi, alcanoilo, alcanoiloxi, amino, alquilamino, dialquilamino, alcanoilamino, 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 anillo hidrocarburo cíclico saturado, opcionalmente sustituido, que contienen preferiblemente 1 a 3 anillos y 3 a 7 carbonos por anillo, el cual puede sustituirse adicionalmente con un anillo carbocíclico C_3-C_7 insaturado. Grupos ejemplares incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, cicloctilo, ciclodecilo, ciclododecilo, y adamantilo. Sustituyentes ejemplares incluyen uno o más grupos alquilo como se describe anteriormente, o uno o más grupos descritos anteriormente como sustituyentes alquilo.

Los términos "heterociclo", "heterocíclico" y "heterociclo" se refieren a un grupo cíclico aromático o no aromático, completamente saturado o insaturado, opcionalmente sustituido, por ejemplo, que es un sistema de anillo monocíclico de 4 a 7 miembros, bicíclico de 7 a 11 miembros, o tricíclico de 10 a 15 miembros, el cual tiene por lo menos un heteroátomo en por lo menos anillo que contiene un átomo de carbono. Cada anillo del grupo heterocíclico que contiene un heteroátomo puede tener 1, 2 ó 3 heteroátomos seleccionados de átomos de nitrógeno, átomos de oxígeno y átomos de azufre, donde los heteroátomos de nitrógeno y azufre pueden, además, oxidarse de manera opcional y los heteroátomos de nitrógeno pueden asimismo cuaternizarse opcionalmente. El grupo heterocíclcio puede unirse a cualquier heteroátomo o átomo de carbono.

Grupos heterocíclicos monocíclicos ejemplares incluyen pirrolidinilo, pirrolilo, indolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo,

isotiazolidinilo, furilo, tetrahidrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, homopiperazinilo, 2-oxohomopiperazinilo, 2-oxopirrolidinilo, 2-oxazepinilo, azepinilo, 4-piperidonilo, piridilo, N-oxo-piridilo, pirazinilo, pirimidinilo, piridazinilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, sulfota de tiamorfolinilo, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo, dioxanilo, isotiazolidinilo, tietanilo, tiiranilo, triazinilo, y triazolilo, y similares.

Grupos heterocíclicos bicíclicos ejemplares incluyen 2,3-dihidro-2-oxo-1H-indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, quinolinil-N-óxido, tetrahidroisoquinolinilo, isoquinolinilo, benzimidazolilo, benzopiranilo, indolizinilo, benzofurilo, cromonilo, coumarinilo, cinnolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tal como furo[2,3-c]piridinilo, furo[3,1-b]piridinilo] o furo[2,3-b]piridinilo), dihidroisoindolilo, dihidroquinazolinilo (tal como 3,4-dihidro-4-oxo-quinazolinilo), benzisotiazolilo, benzisoxazolilo, benzodiazinilo, benzofurazanilo, benzotiopiranilo, benzotriazolilo, benzpirazolilo, dihidrobenzofurilo, dihidrobenzotienilo, dihidrobenzotiopiranilo, dihidrobenzotiopiranilo sulfona, dihidrobenzopiranilo, indolinilo, indazolilo, isocromanilo, isoindolinilo, naftiridinilo, ftalazinilo, piperonilo, purinilo, piridopiridilo, quinazolinilo, tetrahidroquinolinilo, tienofurilo, tienopiridilo, tienotienilo, y similares.

Sustituyentes ejemplares incluyen uno o más grupos alquilo o aralquilo como se describe anteriormente o uno o más grupos descritos anteriormente como sustituyentes alquilo. Se incluyen igualmente heterociclos más pequeños, tales como, epóxidos y aziridinas.

El término "anillo carbocíclico" se refiere a anillos hidrocarburos monocíclicos estables, saturados o parcialmente insaturados de 3 a 7 átomos de carbono tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. El término "opcionalmente sustituido", en la medida en que se refiera aquí a un "anillo carbocíclico" indica que el anillo carbocíclico

puede sustituirse, en una o más posiciones de anillo sustituibles, por uno o más grupos seleccionados independientemente de alquilo (preferiblemente alquilo inferior), alcoxi (preferiblemente alcoxi inferior), nitro, monoalquilamino (preferiblemente un alquilamino inferior), dialquilamino (preferiblemente un di[inferior]alquilamino), ciano, halo, haloalquilo (preferiblemente trifluorometilo), alcanoilo, aminocarbonilo, monoalquilaminocarbonilo, dialquilaminocarbonilo, alquilamido (preferiblemente alquilamido inferior), alcoxialquilo (preferiblemente un inferior alcoxi[inferior]alquilo), alcoxicarbonilo (preferiblemente un alcoxicarbonilo inferior), alquilcarboniloxi (preferiblemente un alquilcarboniloxi inferior) y arilo (preferiblemente fenilo), siendo dicho arilo opcionalmente sustituido por grupos halo, alquilo inferior y alcoxi inferior.

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

Los compuestos de fórmula I pueden formar sales que se encuentran igualmente dentro del ámbito de esta invención. Se prefieren sales farmacéuticamente aceptables (es decir, atóxicas, fisiológicamente aceptables), aunque también son útiles otras sales, por ejemplo, en aislar o purificar 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 expertos en el arte.

Los compuestos para fórmula I pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. Tales sales incluyen aquellas formadas con cloruro de hidrógeno, bromuro de hidrógeno, ácido metanosulfónico, ácido sulfúrico, ácido acético, ácido trifluoroacético, ácido oxálico, ácido maleico, ácido bencenosulfónico, ácido toluenosulfónico y varios más (por ejemplo, nitratos, fosfatos, boratos, tartratos, citratos, succinatos, benzoatos, ascorbatos, salicilatos y similares). Tales sales pueden formarse como se conoce por los expertos en el arte.

Adicionalmente, pueden formarse iones dipolares ("sales internas ").

Se contemplan todos los estereoisómeros de los compuestos de la presente invención, ya sea en mezcla o en forma pura o sustancialmente pura. La definición de compuestos de acuerdo con la invención abarca todos los estereoisómeros posibles y sus mezclas. Muy particularmente comprende las formas racémicas y los isómeros ópticos aislados que tienen la actividad especificada. Las formas racémicas pueden resolverse por métodos físicos, tales como, por ejemplo, cristalización fraccional, separación o cristalización de derivados diastereoméricos o separación por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos a partir de métodos convencionales, tales como, por ejemplo, formación de sal con un ácido óptimamente activo seguido por cristalización.

Los compuestos de la fórmula I pueden tener igualmente formas de profármaco. Cualquier compuesto que se convierta *in vivo* para proporcionar el agente bioactivo (es decir, el compuesto para fórmulas I) es un profármaco dentro del ámbito y espíritu de la invención.

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

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

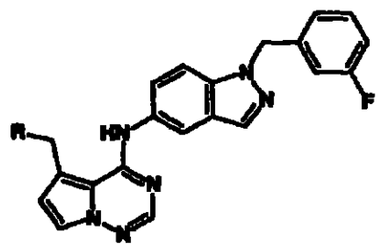
b) A Textbook of Drug Design and Development, editado por Krosgaard-Larsen y H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs," por H. Bundgaard, páginas 113-191 (1991);

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

Además debe entenderse que solvatos (por ejemplo, hidratos) de los compuestos de fórmula I se encuentran también dentro del ámbito de la presente invención. Métodos de solvatación son conocidos por lo general

en el arte.

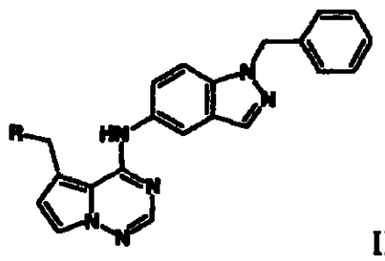
En una incorporación preferida, la invención comprende un compuesto de fórmula II,



II,

sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables, profármacos y solvatos del mismo, en donde R el mismo es como ya se definió previamente.

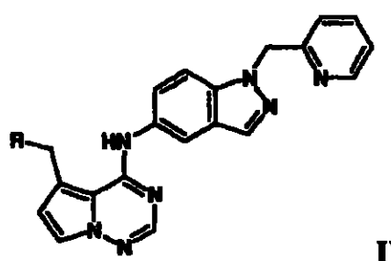
En todavía otra incorporación preferida, la invención comprende un compuesto de fórmula III



III,

sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables, profármacos y solvatos del mismo, en donde R el mismo es como ya se definió previamente.

En aún otra incorporación, la invención comprende a compuesto de fórmula IV,



IV,

sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables,

profármacos y solvatos del mismo, en donde R el mismo es como ya se definió previamente.

Uso y Utilidad

La presente invención se basa en el descubrimiento de que ciertas pirrolotriazinas son inhibidores de proteína cinasas. Más específicamente, pirrolotriazinas tales como aquellas descritas en esta invención inhiben la actividad de proteína tirosina cinasa de miembros de la familia HER de receptores. Estos inhibidores serán útiles en el tratamiento de enfermedades proliferantes que son dependientes de la señalización por uno o más de estos receptores. Tales enfermedades incluyen psoriasis, artritis reumatoide, y tumores sólidos del pulmón, cabeza y cuello, mama, colon, ovario, y próstata. La invención se relaciona con una composición farmacéutica de compuesto de fórmula I, o sal farmacéuticamente aceptable o hidrato del mismo, y un trasportador farmacéuticamente aceptable en el tratamiento de un trastorno hiperproliferante en un mamífero. En particular, se espera que dicha composición farmacéutica inhiba el crecimiento de aquellos tumores sólidos primarios y recurrentes que están asociados con HER1 (receptor EGF) y HER2, especialmente aquellos tumores que son significativamente dependientes de HER1 ó HER2 en cuanto a su crecimiento y difusión, incluidos por ejemplo, cánceres de la vejiga, célula escamosa, cabeza, colorrectal, esofágico, ginecológico (tal como ovárico), páncreas, mama, próstata, vulva, piel, cerebro, tracto genitourinario, sistema linfático (tal como tiroides), estómago, laringe y pulmón. En otra incorporación, los compuestos de la presente invención son asimismo útiles en el tratamiento de trastornos no cancerosos tales como psoriasis y artritis reumatoide.

Por lo tanto, de acuerdo con un aspecto más de la invención se provee el uso de un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo en la manufactura de un medicamento para uso en la producción de un efecto antiproliferante en un animal de sangre caliente tal como un ser humano.

De acuerdo con una característica adicional de la invención se provee un método para producir un efecto antiproliferante en un animal de sangre caliente, tal como un ser humano, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo como se define aquí anteriormente.

En virtud de su capacidad de inhibir cinasas HER1, HER2, y HER4, los compuestos de la presente invención pueden usarse para el tratamiento de enfermedades proliferantes, incluidas psoriasis y cáncer. Se ha demostrado que la cinasa de receptor HER1 se expresa y activa en muchos tumores sólidos incluidos cáncer de cabeza y cuello, próstata, pulmonar amicrocítico, colorrectal, y de mama. Similarmente, se ha comprobado que la cinasa de receptor HER2 se sobreexpresa en cáncer de mama, ovárico, pulmonar y gástrico. Los anticuerpos monoclonales, que regulan por disminución la abundancia del receptor de HER2 o inhiben la señalización por el receptor HER1, han tenido eficacia anti-tumoral en estudios preclínicos y clínicos. Se espera en consecuencia 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. Además, estos compuestos tendrán eficacia en inhibir tumores que se basan en señalización de heterodímero de receptor HER. Se espera que estos compuestos tengan eficacia ya sea como agente único o en combinación (simultánea o secuencialmente) con otros agentes quimioterapéuticos tales como taxol, adriamicina, y cisplatino. Puesto que se ha demostrado que la señalización de HER1 y HER2 regula la expresión de factores angiogénicos tales como factor de crecimiento del endotelio vascular (VEGF) e interleucina 8 (IL8), se espera que estos compuestos tengan eficacia anti-tumoral resultante de la inhibición de angiogénesis además de la inhibición de proliferación celular tumoral y supervivencia. Se ha comprobado que el receptor HER2 está implicado en la hiperproliferación de células sinoviales en artritis reumatoide, y puede contribuir al componente angiogénico de tal estado patológico inflamatorio. En consecuencia, se espera que los

inhibidores descritos en esta invención tengan eficacia en el tratamiento de artritis reumatoide. La capacidad de estos compuestos de inhibir HER1 se añade además a su uso como agentes anti-angiogénicos. Véanse los siguientes documentos y referencias citadas en ellos: Schlessinger J., "Cell signaling by receptor tyrosine kinases", *Cell* 103(2), p. 211-225 (2000); Cobleigh, M. A., Vogel, C. L., Tripati, 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., "Fase 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); Satoh, K., Kikuchi, S., Sekimata, M., Kabuyama, Y., Homma, M. K., and Homma Y., "Involvement of ErbB-2 in rheumatoid synovial cell growth", *Arthritis Rheum.* 44(2), p. 260-265 (2001).

El tratamiento antiproliferante definido aquí puede aplicarse por lo tanto como terapia única 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. Igualmente los compuestos de esta invención pueden ser útiles en combinación con agentes anti-cáncer y citotóxicos conocidos y tratamientos, incluida radiación. Si se formulan como una dosis fija, tales productos de combinación emplean los compuestos de esta invención dentro del rango de administración descrito más adelante y el otro agente farmacéuticamente activo dentro de su rango aprobado de administración. Compuestos de fórmula I pueden usarse secuencialmente con agentes anti-

cáncer o citotóxicos conocidos y tratamiento, incluida radiación cuando una formulación de combinación es inapropiada.

En el campo de la oncología médica constituye una práctica normal usar una combinación de diferentes formas de tratamiento para tratar cada paciente con cáncer. En la oncología médica los demás componente(s) de tal tratamiento conjunto, además del tratamiento antiproliferante definido aquí antes, puede ser: cirugía, radioterapia o quimioterapia. Tal quimioterapia puede abarcar tres categorías principales de agente terapéutico:

(i) agentes antiangiogénicos que actúan por mecanismos diferentes de los definidos anteriormente en el texto (por ejemplo, linomide, inhibidores de la función αvβ3 integrina, angiostatina, razoxin);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno, yodoxifeno), progestógenos (por ejemplo acetato de megestrol), inhibidores de aromatasa (por ejemplo anastrozol, letrazol, borazol, exemestane), agentes anti-neoplásicos hormonales, antiprogestógenos, antiandrógenos (por ejemplo flutamida, nilutamida, bicalutamida, acetato de ciproterona), agonistas de LHRH y antagonistas (por ejemplo acetato de goserelina, luprolide), inhibidores de testosterona 5α-dihidrorreductasa (por ejemplo finasteride), inhibidores de farnesiltransferasa, agentes anti-invasión (por ejemplo inhibidores de metaloproteinasa como marimastat e inhibidores la función de receptor activador de plaminógeno tipo urocinasa) e inhibidores de otra función de factor de crecimiento, (tales factores de crecimiento incluyen por ejemplo FGF, factor de crecimiento derivado de plaquetas y factor de crecimiento de hepatocitos; tales inhibidores incluyen anticuerpos de factor de crecimiento, anticuerpos de receptor de factor de crecimiento, inhibidores de tirosina cinasa e inhibidores de serina/treonina

cinasa); y

(iii) fármacos antiproliferantes/antineoplásicos y combinaciones de los mismos, como se emplean en la oncología médica, tales como antimetabolitos (por ejemplo antifolatos como metotrexate, fluoropirimidinas como 5-fluorouracil, análogos de purina y adenosina, citarabina); antibióticos antitumorales intercaladores (por ejemplo antraciclinas como doxorubicina, daunomicina, epirubicina e idarubicina, mitomicina-C, dactinomicina, mitramicina); derivados de platino (por ejemplo cisplatino, carboplatino); agentes alquilantes (por ejemplo mostaza nitrogenada, melfalan, clorambucil, busulfan, ciclofosfamida, ifosfamida nitrosoureas, tiotefan); agentes antimitóticos (por ejemplo vinca alcaloides como vincristina y taxoides como taxol, taxotere y agentes microtúbulos más nuevos tales como análogos de epotilona, análogos de discodermolide, y análogos de eleuterobina); inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecan); inhibidores del ciclo celular (por ejemplo flavopiridoles); y modificadores de respuesta biológica.

Como ya se indicó antes, los compuestos de fórmula I de la presente invención son de interés por sus efectos antiproliferantes. Se espera que tales compuestos de la invención sean útiles en un amplio rango de estados patológicos incluidos cáncer, psoriasis, artritis reumatoide.

Más específicamente, los compuestos de fórmula I son útiles en el tratamiento de una variedad de cánceres, incluidos (pero no limitados a) los siguientes:

- carcinoma, incluidos los de vejiga, mama, colon, riñón, hígado, pulmón, incluidos cáncer pulmonar microcítico, de esófago, vesícula biliar, ovario, páncreas, estómago, cérvix, tiroides, próstata, y piel, incluido carcinoma de células escamosas;

- tumores de origen mesenquimatoso, incluidos fibrosarcoma y rabdomiosarcoma;

- tumores del sistema nervioso central y periférico, incluidos astrocitoma, neuroblastoma, glioma y schwannomas; y

- otros tumores, incluidos melanoma, seminoma, teratocarcinoma y osteosarcoma.

Debido al papel clave de las cinasas en la regulación de la proliferación celular en general, los inhibidores podrían actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de cualquier proceso patológico que exhibe proliferación celular anormal, por ejemplo, hiperplasia de próstata benigna, poliposis de adenomatosis familiar, neuro-fibromatosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis a consecuencia de angioplastia o cirugía vascular, formación de heridas hipertróficas y enfermedad intestinal inflamatoria.

Los compuestos de fórmula I son especialmente útiles en el tratamiento de tumores que tienen una elevada incidencia de actividad 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 anfitrión mamífero.

Los compuestos de fórmula I pueden también ser útiles en el tratamiento de enfermedades distintas del cáncer que pueden estar asociadas con vías de transducción de señales que operan a través de receptores de factor de crecimiento tales como HER1 (receptor de EGF), HER2, o HER4.

Los compuestos de esta invención pueden formularse con un vehículo farmacéutico o diluyente para administración oral, intravenosa o subcutánea. La composición farmacéutica puede formularse en una manera clásica usando vehículos sólidos o líquidos, diluyentes y aditivos apropiados al modo deseado de administración. Oralmente, los compuestos

pueden administrarse en la forma de tabletas, cápsulas, gránulos, polvos y similares. Los compuestos pueden administrarse en un rango de administración de alrededor de 0.05 a 200 mg/kg/día, preferiblemente menos de 100 mg/kg/día, en una dosis única o en 2 a 4 dosis divididas.

Estudios Biológicos

Estudios de Cinasa HER1, HER2 o HER4:

Se analizaron compuestos de interés en un tampón de cinasa que contenía 20 mM Tris.HCl, pH 7.5, 10 mM $MnCl_2$, 0.5 mM ditiotreitol, albúmina de suero bobino a 0.1 mg/ml, poly(glu/tyr, 4:1) a 0.1 mg/ml, 1 μM ATP, y 4 μCi/ml [γ-^{33}P]ATP. Poly(glu/tyr, 4:1) es un polímero sintético que sirve como un aceptor fosforilo y se adquiere de Sigma Chemicals. La reacción de cinasa se inicia por la adición de enzima y las mezclas de reacción se incubaron a 26 °C durante 1 hora. La reacción se termina por la adición de EDTA a 50 mM y las proteínas se precipitan por la adición de ácido tricloroacético a 5%. Las proteínas precipitadas se recuperan por filtración sobre placas Packard Unifilter y se mide la cantidad de radioactividad incorporada en un contador de centelleo Topcount.

Para la preparación de HER1 y HER4 recombinante, la secuencias citoplásmicas de los receptores se expresaron en células de insecto como proteínas de fusión GST, las cuales se purificaron por cromatografía de afinidad. La secuencia citoplásmica de HER2 se subclonó en el vector de expresión de baculovirus pBlueBac4 (Invitrogen) y se expresó como una proteína no marcada en células de insecto. La proteína recombinante se purificó parcialmente por cromatografía de intercambio de iones.

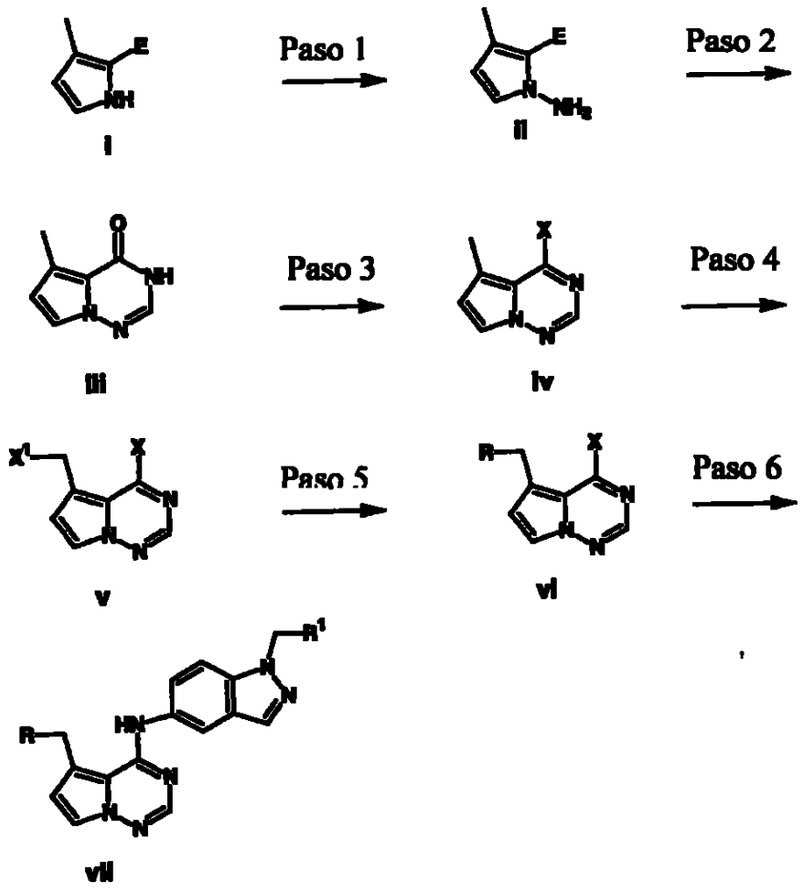
Los presentes compuestos inhiben las cinasas HER1, HER2 y HER4 con valores IC_{50} entre 0.001 25 μM. Compuestos preferidos tienen valores IC_{50} entre 0.001 - 5.0 μM. Compuestos más preferidos tienen valores IC_{50} entre 0.001 - 1.0 μM. Compuestos muy preferidos tienen valores IC_{50} entre 0.001 - 0.1 μM.

Un estudio de canal de potasio HERG puede usarse para tamizar compuestos con respecto a actividad HERG (véase Caballero R, y colaboradores, *Direct Effects of Candesartan and Eprosartan on Human Cloned Potassium Channels Involved in Cardiac Repolarization,* Molecular Farmacology, Vol. 59, No. 4, pp. 825-36, 2001). En consecuencia, los compuestos preferidos tienen actividad de estudio HERG más baja.

Métodos de Preparación

Ciertos compuestos de fórmula I pueden prepararse generalmente de acuerdo con los siguientes esquemas y el conocimiento de un experto en el arte. Información suplementaria puede encontrarse también en la solicitud co-pendiente de patente de los Estados Unidos número de serie 09/573,829 presentada el 18 de mayo de 2000 y la solicitud internacional publicada bajo el Tratado de Cooperación en Materia de Patentes (PCT, por sus siglas en inglés), Publicación Internacional Número WO 00/71129, ambas incorporadas aquí por referencia.

Esquema 1



en donde E es un grupo éster y X y X^1 son halógeno

Paso 1

El primer paso de **Esquema 1** se realiza mediante el tratamiento de un éster de ácido 3-metil-1H-pirrol-2-carboxílico **i** (T. D. Lash y colaboradores, J. Heterocyclic Chem., 1991, 28, 1671) con una base tal como t-butóxido de potasio o hidruro de sodio en un solvente anhidro tal como THF o DMF seguido por un reactivo aminante, tal como O-(2,4-dinitro-fenil)-hidroxilamina (T. Sheradsky, J. Heterocyclic Chem., 1967,4, 413) o cloramina (I. P. Sword, J. Chem. Soc. C, 1971, 820) para producir la pirrolilamina **ii.**

Paso 2

La pirrolilamina **ii** se calienta con exceso de formamida para producir la pirrolotriazinona **iii.**

Paso 3

Compuesto **iii** se convierte en una 4-halo-pirrolotriazina **iv**

calentando con el axihalogenuro de fósforo apropiado, por ejemplo, la 4-cloro-pirrolotriazina se obtiene calentando iii con oxicloruro de fósforo.

Paso 4

La halogenación del grupo 5-metilo de iv se afecta por el tratamiento con un agente halogenante tal como una N-bromosuccinimida o cloruro de sulfurilo. La reacción se lleva a cabo bajo una atmósfera inerte tal como N_2 en la presencia de un catalizador tal como peróxido de dibenzoilo o 2,2'-azobisisobutironitrilo, o irradiación y produce la 4-halo-5-halometil-pirrolotriazina v.

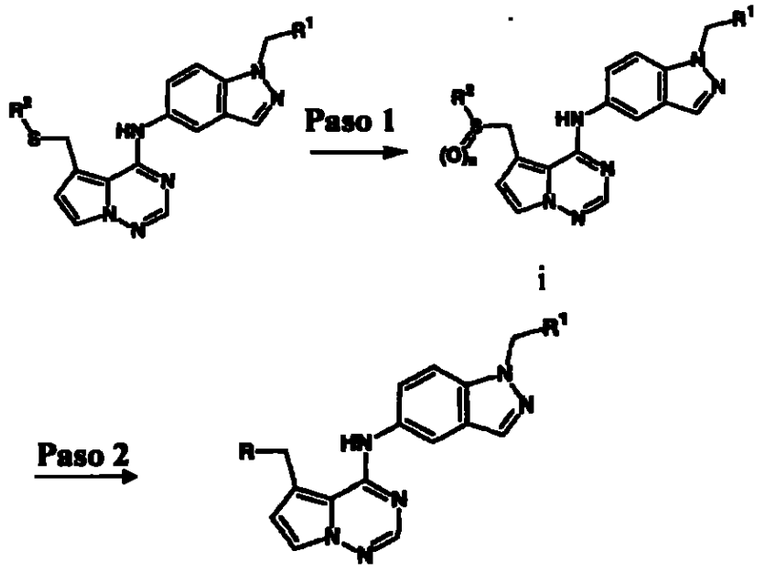
Paso 5

El tratamiento de v con un tiol, un ácido tiocarboxílico, agua, un alcohol, un ácido carboxílico, una amina primaria o secundaria en la presencia de una base tal como $NaHCO_3$ o trietilamina en un solvente tal como acetonitrilo proporciona el intermediato vi en **Esquema 1.**

Paso 6

El tratamiento de vi con un derivado de 5-amino-indazol a temperatura ambiente en la presencia de una base tal como $NaHCO_3$ o trietilamina en un solvente tal como acetonitrilo produce el producto final vii. Calentando vi con un derivado de 5-amino-indazol en la ausencia de una proporciona igualmente vii.

Esquema 2



i

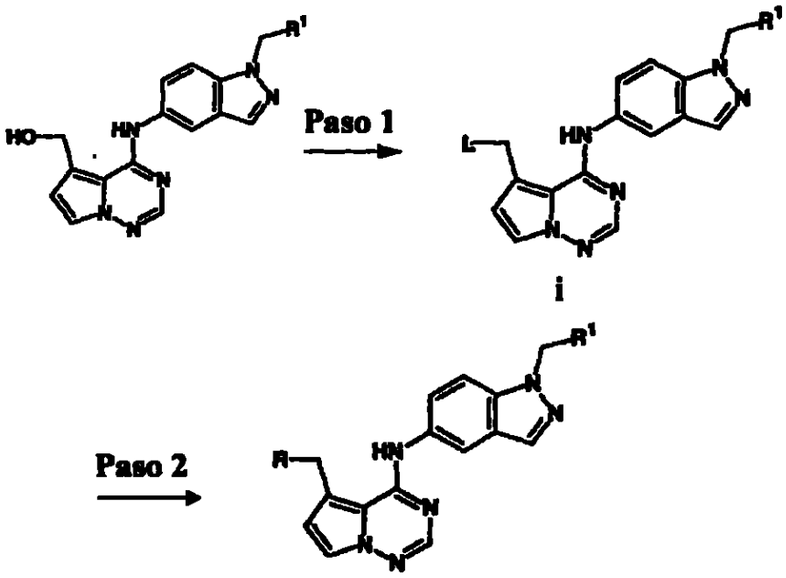
Paso 1

Compuesto vii (R = SR^2) de **Esquema 1** puede oxidarse al sulfóxido, i (n =1), o la sulfona, i (n = 2), de **Esquema 2** por tratamiento con la cantidad apropiada de u agente oxidante tal como ácido m-cloroperbenzoico.

Paso 2

El derivado 5-aminometilo ii se obtiene calentando el sulfóxido i (n = 1) o la sulfona (n = 2) en la presencia de un exceso de un alcohol o una amina primaria o secundaria.

Esquema 3



i

en donde L = grupo saliente

Paso 1

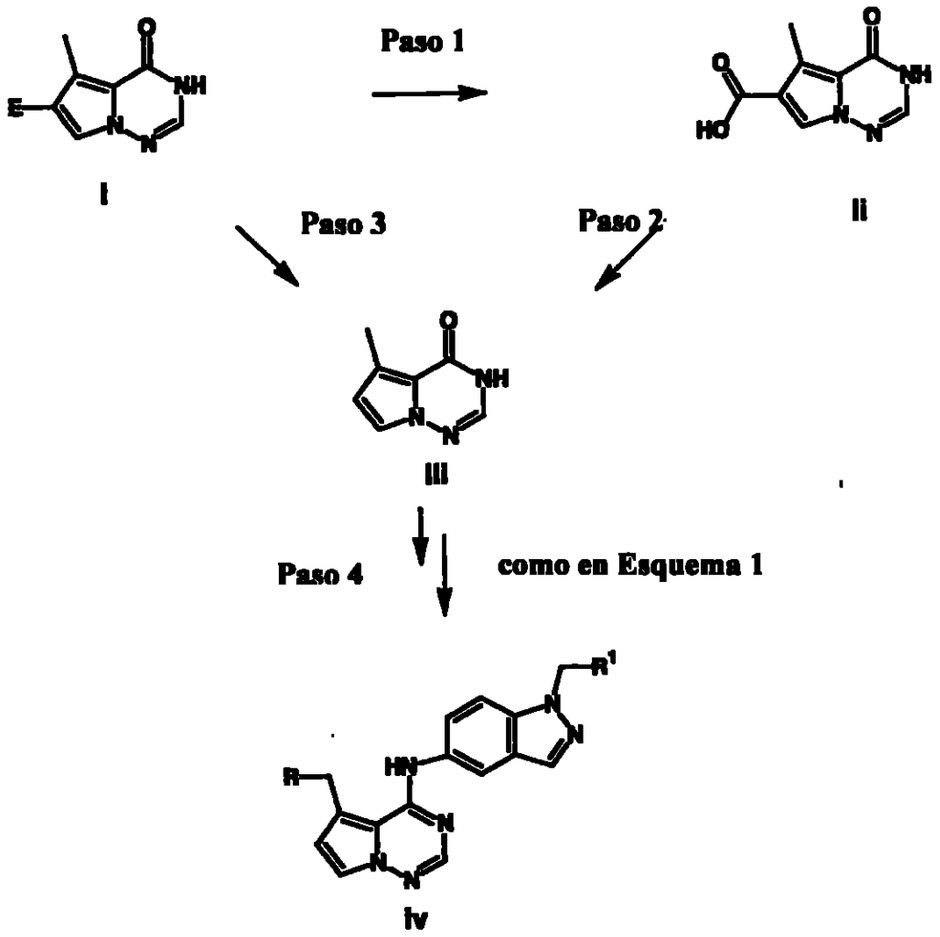
El grupo alcohol en compuesto vii (R = OH) de **Esquema 1** puede convertirse en un grupo saliente como en compuesto i de **Esquema 3**. Puede introducirse una variedad de grupos salientes, por ejemplo, tratamiento con cloruro de tionilo produce el cloruro i (L = Cl); tratamiento con anhídrido metanosulfónico y diisopropiletilamina produce el metanosulfonato i (L = OSO_2Me); esterificación con anhídrido acético en la presencia de diisopropiletilamina produce el acetato i (L = OAc).

Paso 2

Para grupos salientes muy reactivos tales como cloruro o sulfonato, i

se convierte directamente en compuesto **ii** de **Esquema 3** por reacción con un alcohol o una amina primaria o secundaria en la presencia de una base tal como diisopropiletilamina sin el aislamiento de **i**. Para grupos salientes menos reactivos tales como carboxilatos, **i** se calienta con alcoholes o aminas primarias o secundarias en la presencia de una base tal como diisopropiletilamina para producir **ii**.

Esquema 4



en donde E = grupo éster

Paso 1

El éster de ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazino-6-carboxílico **i** (véase WO 00/71129, incorporada aquí por referencia) puede saponificarse por tratamiento con una base tal como una solución acuosa de LiOH y luego acidificarse por tratamiento con un ácido

tal como HCl para producir el ácido carboxílico ii de **Esquema 4.**

Paso 2

El ácido carboxílico ii se decarboxila para producir la 6H-pirrolotriazin-4-ona iii. Esto puede realizarse bajo una variedad de condiciones, por ejemplo, calentando una mezcla de ii en 85% H_3PO_4 a 110 °C.

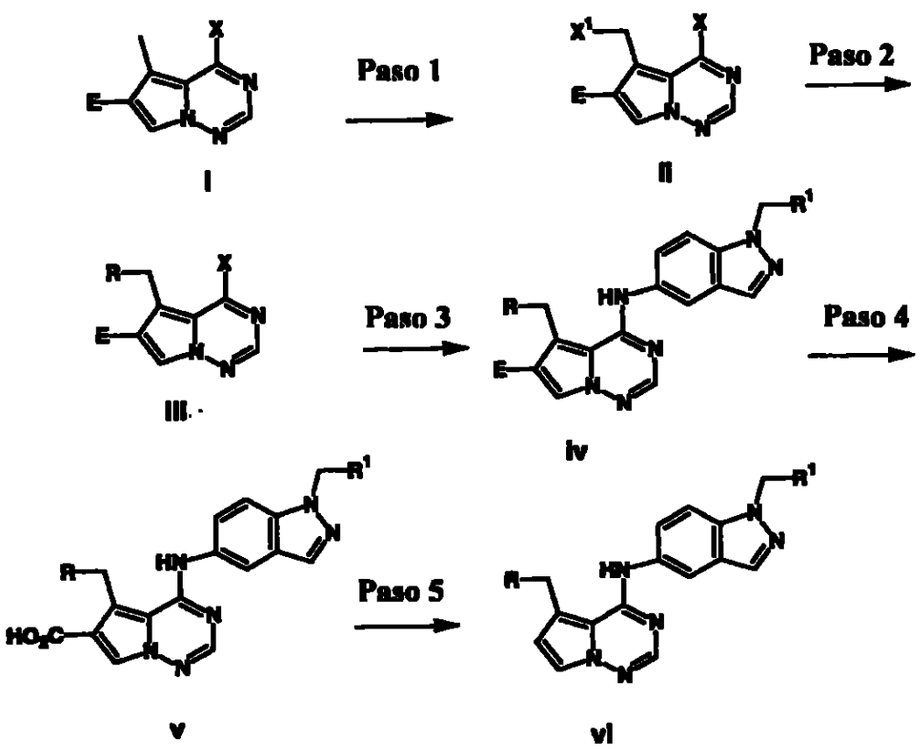
Paso 3

El éster i puede convertirse directamente a iii, por ejemplo, calentando una mezcla de i en 85% H_3PO_4 a 110°C.

Paso 4

La 6H-pirrolotriazin-4-ona iii puede convertirse en iv según lo descrito en **Esquema 1.**

Esquema 5



en donde E es un grupo éster y X y X^1 son halógeno

Paso 1

La halogenación del grupo 5-metilo del éster del ácido 4-halo-5-metil-pirrolo[2,1-f][1,2,4]triazino-6-carboxílico **i** (véase WO 00/71129, incorporada aquí por referencia) puede efectuarse por el tratamiento de **i** con un agente halogenante tal como una N-bromosuccinimida o cloruro de sulfurilo. La reacción se lleva a cabo bajo una atmósfera inerte tal como N_2 en la presencia de un catalizador tal como peróxido de dibenzoilo o 2,2'-azobisisobutironitrilo, o irradiación y produce la 4-halo-5-halometil-pirrolotriazina **ii** de **Esquema 5.**

Paso 2

Tratamiento de **ii** con un tiol, un alcohol, una amina primaria o secundaria en la presencia de una base tal como $NaHCO_3$ o trietilamina en un solvente tal como acetonitrilo produce el intermedio **iii.**

Paso 3

Tratamiento de **iii** con un derivado 5-amino-indazol sustituido en la presencia de una base tal como $NaHCO_3$ o trietilamina en un solvente tal como acetonitrilo produce **iv.**

Paso 4

El éster **iv** puede saponificarse por tratamiento con una base tal como una solución acuosa de LiOH y luego acidificarse por tratamiento con un ácido tal como HCl para producir el ácido carboxílico **v** de **Esquema 5.**

Paso 5

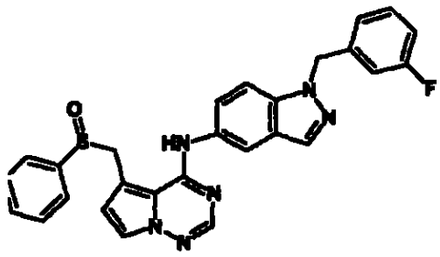
El ácido carboxílico **v** de **Esquema 5** se decarboxila calentando para producir el producto final **vi.**

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

La invención se describirá ahora con más detalle por los siguientes ejemplos(s) de trabajo, que son incorporaciones preferidas de la invención. Todas las temperaturas están en grados Celsius (°C) a menos que se indique

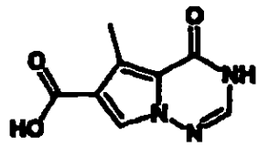
lo contrario. "Tiempo de Retención HPLC" es el tiempo de retención HPLC que se obtuvo bajo las siguientes condiciones: longitud y tipo de columna, tiempo de gradiente [a menos que se indique lo contrario, todas las gradientes se inician con 100% solvente A (10% MeOH, 90% H_2O, ***0.1% TFA***) y se terminan con 100% solvente B (90% MeOH, 10% H_2O, ***0.1% TFA***)], caudal (mL/min). La detección con UV se condujo siempre a 220 nM. Estos ejemplos son ilustrativos más que limitantes, y tiene que entenderse que puede haber otras incorporaciones que caen dentro del espíritu y el ámbito de la invención como se define en las reivindicaciones anexas a este documento.

Ejemplo 1



(5-Bencenosulfinilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

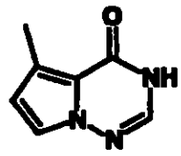
A. Preparación de ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4] triazino-6-carboxílico



Una solución de Li OH (25 gm, 10 equiv) en agua (416 mL) se agregó a una solución de éster metílico de ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazino-6-carboxílico (23.0 gm, 0.104 mol) en una mezcla de THF (1.2 L) y MeOH (0.4 L). Esto se calentó a 65 °C durante 20 horas y luego se concentró in vacuo a alrededor de 200 mL. Se agregó

agua (400 mL) y se ajusto el pH a 4 usando HCl acuoso concentrado. El precipitado se recogió, se lavó con agua, y se secó para producir el ácido (18.2 gm, 90%). ^{1}H NMR (MeOH-D_4) δ 2.67 (s, 3H), 7.63 (s, 1H), 7.84 (s, 1H). Tiempo de Retención HPLC: 0.97 min (columna YMC C18 S5, 4.6 x 50 mm, gradiente 3 min, 4 mL/min).

B. Preparación de 5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona



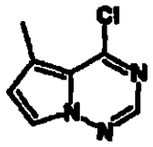
Procedimiento I: Una suspensión de ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazino-6-carboxílico (18.1 gm, 93.7 mmoles) en 85% aq. H_3PO_4 (250 mL) se calentó a 110 °C durante 3.5 horas. Después de enfriar a temperatura ambiente, se agregó agua helada (500 mL) y el precipitado se recogió, se lavó con agua, y se secó. Esto proporcionó 5.8 gm del producto como un sólido marrón. Se obtuvieron 4.1 gm adicionales (total de 9.9 gm, 71%) de producto por extracción del filtrado con DCM (4 x 500 mL), secamiento (Na_2SO_4), y el retiro del solvente. ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 6.35 (d, 1H, J = 3 Hz), 7.31 (d, 1H, J = 3 Hz), 7.42 (s, 1H), 9.52 (br s, 1H); tiempo de retención HPLC: 1.17 min (columna YMC C18 S5, 4.6 x 50 mm, gradiente 3 min, 4 mL/min).

Procedimiento II: Una suspensión de éster metílico de ácido 5-metil-4-oxo-3,4-dihidro-pirrolo[2,1-f][1,2,4]triazino-6-carboxílico (5.81 gm, 0.028 mol) en 85% aq. H_3PO_4 (60 mL) se calentó a 110 °C durante 6 horas. Después de enfriar a temperatura ambiente, se agregó hielo (120 gm) y el precipitado se recogió, se lavó con agua y se secó para proporcionar el producto (3.47 gm, 83%).

Procedimiento III: Una solución de éster metílico de ácido 3-metil-1H-pirrol-2-carboxílico (4.59 gm, 33 mmoles) en DMF seco (100 mL) se

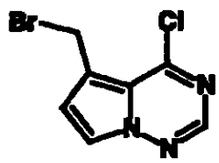
agregó lentamente a una suspensión enfriada con hielote NaH (1.72 gm, 60% dispersión en aceite, 1.3 equiv) en DMF seco (300 mL). Luego de 30 minutos, se agregó O-(2,4-dinitro-fenil)-hidroxilamina (1.53 gm, 1.1 equiv) en una porción y la reacción se dejó agitando en el baño helado durante 1 hora. Después de 0.5 hora se retiró del baño y se diluyó con salmuera. Esto se extrajo con EtOAc (3 veces) y los extractos combinados se secaron (Na_2SO4) y los solventes se retiraron. El residuo se cromatografió en una columna de gel de sílice (elución de gradiente con hexano que contenía 5 a 20% EtOAc) para producir éster metílico de ácido 1-amino-3-metil-1H-pirrol-2-carboxílico (2.96 gm, 58%) como un sólido amarillo. ^{1}H NMR (MeOH-D_4) δ 2.25 (s, 3H), 3.81 (s, 3H), 5.83 (d, 1H, J = 2 Hz), 6.82 (d, 1H, J = 2 Hz); MS: 155 $(M+H)^+$; tiempo de retención HPLC: 0.97 min (YMC Exterra ODS S7 3.0 x 50 mm, gradiente 2 min, 5 mL/min). Una mezcla de este 1-amino-pirrol (2.96 gm, 19.2 mmoles) en formamida (30 mL) se calentó a 165 °C durante 10 horas. Después de enfriar a temperatura ambiente, esto se diluyó con agua fría y el precipitado se recogió, se lavó con agua fría seguido por una mezcla de Et2O y hexano (6:4). Esto produjo 5-metil-3H-pirrolo[2,1-f][1,2,4]triazin-4-ona (1.83 gm, 64%) como un sólido marrón.

C. Preparación de 4-cloro-5-metil-pirrolo[2,1-f][1,2,4]triazina



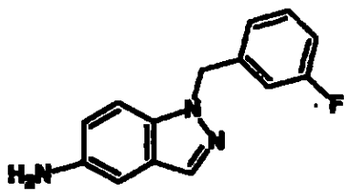
Una suspensión de 5-metil-3*H*-pirrolo[2,1-f][1,2,4]triazin-4-ona (2.57 gm, 17.2 mmoles) en $POCl_3$ (28 mL) se calentó a 100 °C durante 40 minutos. El reactivo en exceso se retiró bajo vacío y el residuo se disolvió en DCM (300 mL). Esto se lavó con agua, se secó (Na_2SO_4), y se retiró el solvente. Cromatografía de destello en gel de sílice usando DCM como eluyente proporcionó el producto como un sólido amarillo (2.38 gm, 82%). ^{1}HNMR ($CDCl_3$): δ 2.63 (s, 3H), 6.74 (d, 1H, J = 2 Hz), 7.74 (d, 1H, J = 2 Hz), 8.05 (s, 1H).

D. Preparación de 5-bromometil-4-cloro-pirrolo[2,1-fl[1,2,4] triazina



Una solución de 4-cloro-5-metil-pirrolo[2,1-f][1,2,4]triazina (2.32 gm, 14.0 mmoles) en CCl_4 (140 mL) se roció con N_2 durante 20 minutos. Se agregaron N-bromosuccinimida (2.60 gm, 1.05 equiv) y peróxido de benzoilo (60 mg) y la mezcla se calentó a reflujo durante 1 hora. Después de enfriar a temperatura ambiente, la succinimida se retiró por filtración. El solvente se retiró del filtrado y el residuo se cromatografió rápidamente en una columna corta de gel de sílice usando DCM como el eluyente. Esto proporcionó el compuesto 5-bromometilo como un sólido amarillo (2.49 gm, 74%). ^{1}H NMR ($CDCl_3$): δ 4.96 (s, 2H), 7.03 (d, 1H, J = 3 Hz), 7.80 (d, 1H, J = 3 Hz), 8.21 (s, 1H).

E. Preparación de 1-(3-fluoro-bencil)-1H-indazol-5-ilamina



Una mezcla de 5-nitro-1H-indazol (8.15 gm, 50 mmoles), cloruro de m-fluoro-bencilo (7.95 gm, 1.1 equiv), K_2CO_3 (7.59 gm, 1.1 equiv), y KI (8.47 gm, 1.02 equiv) en DMF seco (75 mL) se calentó a 70 °C durante la noche. Después de enfriar a temperatura ambiente, se agregó agua (75 mL) lentamente para producir un precipitado que consistía de una mezcla alrededor de 1:1 de isómeros [Tiempo de Retención HPLC: 1.92 (isómero 1-sustituido vs. 2.03 (isómero 2-sustituido) YMC C18 S5 4.6 x 50 mm, gradiente 3 min, 4 mL/min]. Esto se recogió por filtración y se lavó con agua. El sólido se cristalizó dos veces de acetona/agua para proporcionar el 1-(3-fluoro-bencil)-5-nitro-1H-indazol deseado (4.47 gm, 33%). Una suspensión de este material (3.00 gm, 11.1) y 10% Pd/C (3.00 gm) en EtOH

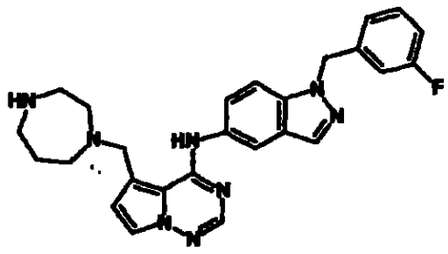
(21 mL) se mantuvo bajo una atmósfera H_2 (balón) durante 24 horas. El catalizador se retiró por filtración y el solvente se evaporó para dejar el producto como un sólido (2.4 gm. 90%). ^{1}H NMR ($CDCl_3$): δ 3.61 (br s, 2H), 5.52 (s, 2H), 6.81 - 7.85 (m, 7H), 7.85 (s, 1H); MS: 242 $(M+H)^+$; tiempo de retención HPLC: 1.03 min (columna YMC Xterra ODS S7, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

F. Preparación de (5-bencenosulfinilmetil-pirrolo[2,1-f][1-2,4] triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

Una solución de 5-bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina (850 mg, 3.46 mmoles) en DCM (30 mL) se roció con N_2 durante 0.5 hora y luego se puso en un baño a -20 °C. Se agregaron tiofenol (384 µL, 1.0 equiv) y diisopropiletilamina (605 µL, 1.0 equiv) y la reacción se mantuvo a -20 °C durante 3 horas. Después de calentar a temperatura ambiente, la mezcla de reacción se lavó con agua, se secó (Na_2SO_4), y el solvente se retiró. Se agregaron 1,2-dicloroetano (10 mL), n-butanol (10mL) y 1-(3-fluoro-bencil)-1H-indazol-5-ilamina (750 mg, 0.9 equiv) al residuo y esta mezcla se calentó a 85 °C durante 2.5 horas. Los solventes se retiraron y el residuo se tomó en DCM, se lavó con solución de $NaHCO_3$ acuoso saturado y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía en gel de sílice usando DCM que contenía 0 a 2% MeOH como eluyente proporcionó [1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-fenilsulfanilmetil-pirrolo[2,1-f] [1,2,4]triazin-4-il)-amina (957 mg, 58%) como una espuma. ^{1}H NMR ($CDCl_3$) δ 4.48 (s, 2H), 5.59 (s, 2H), 6.53 (d, 1H, J = 3Hz), 6.8 - 7.0 (m, 3H), 7.2 - 7.6 (m, 9H), 7.95 (s, 1H), 8.06 (s, 1H), 8.15 (d, 1H, J = 2 Hz), 8.88 (br s, 1H); MS: 481 $(M+H)^+$; tiempo de retención HPLC: 1.87 min (columna YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min). Esto se disolvió en cloroformo (25 mL), se enfrió en un baño helado y se agregó ácido m-cloro-perbenzoico (500 mg, 57 a 80%, 1 equiv) en pequeñas porciones durante 15 min. Después de 1 hora, la reacción se lavó con solución de $NaHSO_3$ acuoso al 10%, solución de $NaHCO_3$ acuoso

saturado (tres veces) y se secó (Na_2SO_4). El retiro del solvente dejó el producto como una espuma (957 mg, 95%). ^1H NMR ($CDCl_3$) δ 4.28 (d, 1H, J = 14 Hz), 4.53 (d, 1H, J = 14 Hz), 5.60 (s, 2H), 6.13 (d, 1H, J = 3 Hz), 6.8 - 7.6 (m, 11H), 7.71 (dd, 1H, J = 2,9 Hz), 7.98 (s, 1H), 8.05 (s, 1H), 8.14 (d, 1H, J = 2 Hz); MS: 497 $(M+H)^+$; tiempo de retención HPLC: 1.67 min (columna YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Ejemplo 2

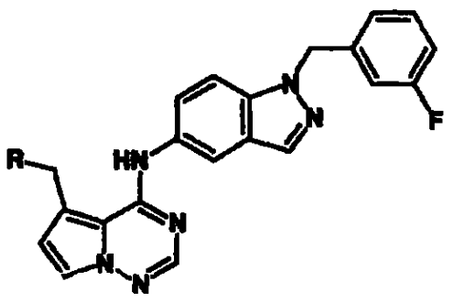


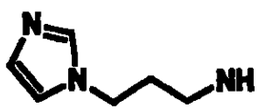
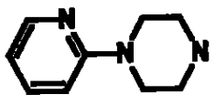
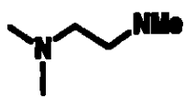
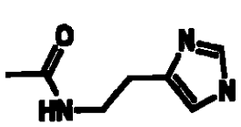
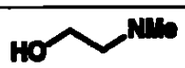
(5-[1,4]Diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

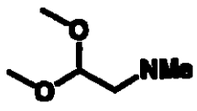
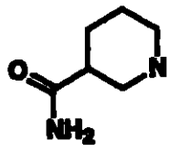
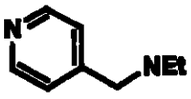
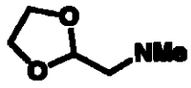
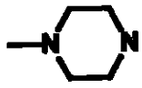
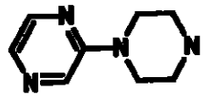
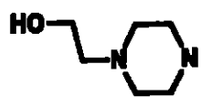
Una mezcla de (5-bencenosulfinilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (50 mg, 0.101 mmoles) y homopiperazina (300 mg, 30 equiv) en un tubo sellado se calentó a 135 °C durante la noche. La mezcla de reacción se tomó en DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm eluido con DCM que contenía 5% MeOH) proporcionó el compuesto del título como una espuma (39 mg, 82%). ^1H NMR ($CDCl_3$) δ 1.85 (m, 2H), 2.96 (m, 8H), 3.91 (s, 2H), 5.58 (s, 2H), 6.50 (d, 1H, J = 3 Hz), 6.8-7.6 (m, 7H), 7.89 (s, 1H), 8.05 (d,1H, J = 1 Hz), 8.11 (d, 1H, J = 2 Hz); MS: 471 $(M+H)^+$; tiempo de retención HPLC: 1.09 min (columna YMC Xterra ODS S7, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

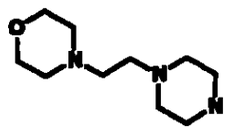
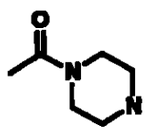
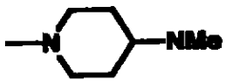
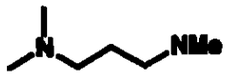
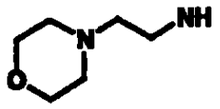
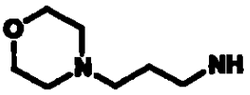
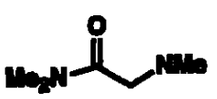
Ejemplos 3 a 73

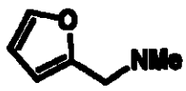
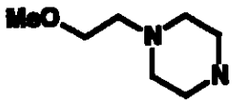
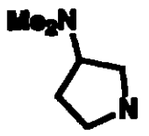
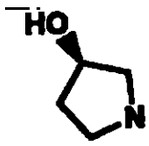
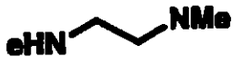
Los siguientes ejemplos se prepararon en la misma manera que **Ejemplo 2.**

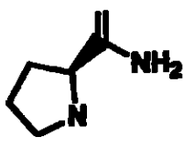
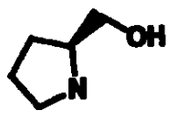
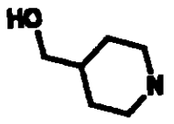
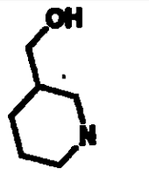
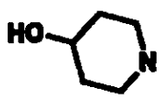
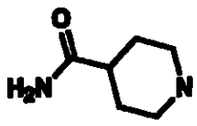
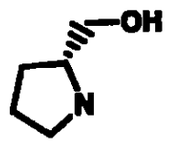
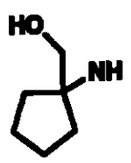


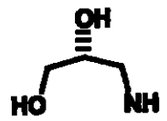
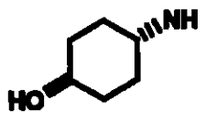
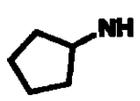
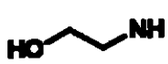
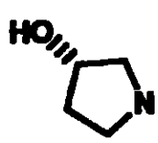
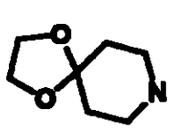
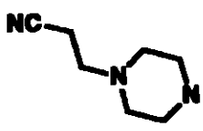
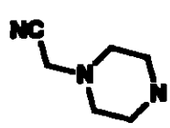
Ej.	R	Nombre del Compuesto	Tiempo Ret. HPLC (min)
3		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-imidazol-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-amina	1.21
4		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[(3-imidazol-1-il-propilamino)-metil]-pirrolo [2,1-f][1,2,4]triazin-4-il}-amina	1.12
5		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-{[(2-ciano-etil)-metil-amino]-metil}-pirrolo [2,1-f][1,2,4]triazin-4-il)-amina	1.29
6		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-piridin-2-il-piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-amina	1.17
7		N-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4] triazin-5-ilmetil}-N, N',N'-trimetil-etano-1,2-diamina	1.17
8		N-[2-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo [2,1-f][1,2,4]triazin-5-ilmetil}-1H-imidazol-4-il)-etil]-acetamida	1.22
9		2-({4-[1-(3-fluoro-bencil)-1H-	1.20

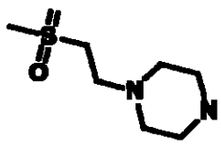
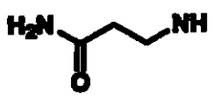
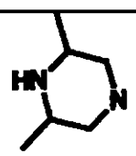
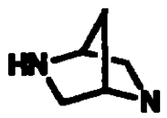
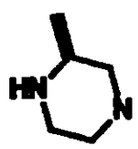
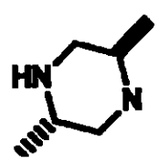
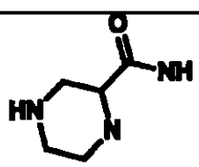
		indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-metil -amino)-etanol	
10		(5-{[(2,2-dimetoxi-etil)-metil-amino]-metil} - pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.32
11		amida de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidino-3-carboxílico	1.23
12		{5-[(etil-piridin-4-ilmetil-amino)-metil]-pirrolo[2,1-f] [1,2,4]triazin-4-il}-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.29
13		{5-[([1,3]dioxolan-2-ilmetil-metil-amino)-metil]-pirrolo [2,1-f][1,2,4]triazin-4-il}-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.30
14		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-metil-piperazin-1 - ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-amina	1.14
15		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(2,3,5,6-tetrahidro-[1,2']bipirazinil-4-ilmetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-amina	1.35
16		2-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} -	1.12

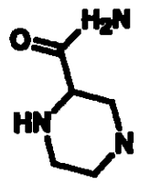
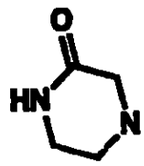
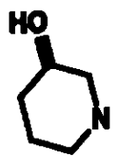
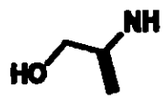
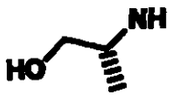
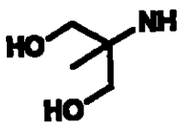
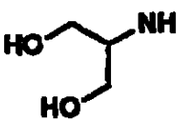
		piperazin-1-il)-etanol	
17		2-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil} - piperazin-1-il)-etanol	1.12
18		1-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}- piperazin-1-il)-etanona	1.22
19		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-{[metil-(1-metil-piperidin-4-il)-amino]-metil} - pirrolo [2,1-f][1,2,4]triazin-4-il)-amina	0.97*
20		N-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-N, N',N'-trimetil-propano-1,3-diamina	0.95*
21		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[(2-morfolin-4-il-etilamino)-metil]-pirrolo[2,1-f][1,2,4] triazin-4-il}-amina	1.13
22		[1-(3-fluoro-bencil)-1H-indazol - 5-il]-{5-[(3-morfolin-4-il-propilamino)-metil]-pirrolo [2,1-f][1,2,4] triazin-4-il}-amina	1.11
23		2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-metil - amino)-N,N-dimetil-acetamida	1.19
24		[5-(2,5-dihidro-pirrol-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-	1.32

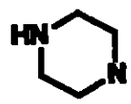
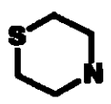
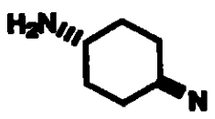
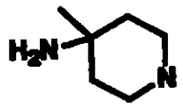
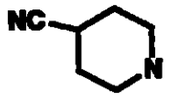
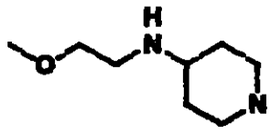
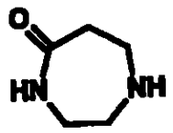
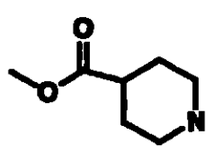
		[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	
25		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[(furan-2-ilmetil-metil-amino)-metil]-pirrolo[2,1-f][1,2,4] triazin-4-il}-amina	1.46
26		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metoxi-etil)-piperazin-1-ilmetil]-pirrolo[2,1f][1,2,4]triazin-4-il}-amina	1.23
27		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-pirrolidin-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-amina	1.31
28	 racémico	[5-(3-dimetilamino-pirrolidin-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.21
29		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-{[(2-metoxi-etil)-metil-amino]-metil} -pirrolo[2,1-f][1,2,4]triazin-4-il)-amina	0.20*
30		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1f] [1,2,4]triazin-5-ilmetil}-(3R)-pirrolidin-3-ol	1.10*
31		N-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-N,N'-dimetil-etano-1,2-diamina	0.98*

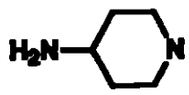
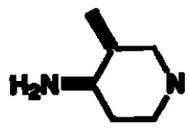
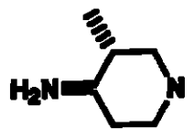
32		amina de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-(2S)-pirrolidino-2-carboxílico	1.11*
33		(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} -(2S)-pirrolidin-2-il)-metanol	1.11*
34		(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4] triazin-5-ilmetil}-piperidin-4-il)-metanol	1.26
35	 racémico	(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidin-3-il)-metanol	1.28
36		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-ol	1.10*
37		amida de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidino-4-carboxílico	1.24
38		(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-(2R)-pirrolidin-2-il)-metanol	1.11*
39		[1-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-ciclopentil]-metanol	1.43

40		(2R)-3-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo [2,1-f][1,2,4]triazin-5-ilmetil} - amino)-propano-1,2-diol	1.25
41		trans-4-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-amino)-ciclohexanol	1.30
42		(5-ciclopentilaminometil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.46
43		2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-etanol	1.24
44		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-(3S)-pirrolidin-3-ol	1.27
45		[5-(1,4-dioxa-8-aza-spiro[4.5] dec-8-ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.35
46		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-ciano-etil)-piperazin-1-ilmetil]-pirrolo [2,1-f][1,2,4]triazin-4-il}-amina	1.01*
47		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-cianometil-ciclohexilmetil)-pirrolo[2,1-f] [1,2,4] triazin-4-il]-amina	1.30

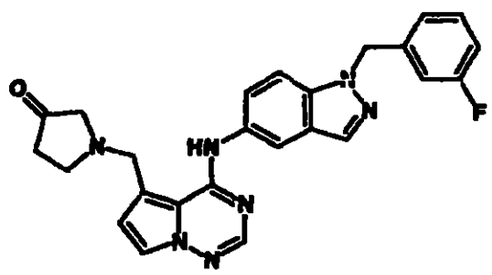
48		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metanosulfonil-etil)-piperazin-1-ilmetil]-pirrolo [2,1-f][1,2,4]triazin-4-il} -amina	1.22
49		3-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} -amino)-propionamida	1.26
50	 mezcla diastereomérica	[5-(3,5-dimetil-piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.06*
51		[5-(2,5-diaza-biciclo[2.2.1] hept-2-ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.17
52		2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil} -amino)-propan-2-ol	1.35
53		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-((3S)-3-metil-piperazin-1-ilmetil)-pirrolo [2,1-f] [1,2,4]triazin-4-il]-amina	1.02*
54		[5-(trans-2,5-dimetil-piperazin-1-ilmetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.27
55	 racémico	amida de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} -	1.07

		piperazino-2-carboxílico	
56		amida de ácido 4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} - piperazino-2-carboxílico	1.17
57		4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} - piperazin-2-ona	1.24
58		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} -(3R)-piperidin-3-ol	1.29
59		(2S)-2-({4-[1-(3-fluoro-bencil) - 1H-indazol-5-ilamino]-pirrolo [2,1-f] [1,2,4]triazin-5-ilmetil} - amino)-propan-1-ol	1.26
60		(2R)-2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo [2,1-f][1,2,4]triazin-5-ilmetil}-amino)-propan-1-ol	1.26
61		2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-2-metil-propano-1,3-diol	1.25
62		2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-2-metil-propano-1,3-diol	1.21

63		[1-(3-fluoro-bencil)-1*H*-indazol]-5-il]-(5-piperazin-1-ilmetil-pirrolo[2,1-f] [1,2,4] triazin-4-il) amina	1.02
64		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(tiomorfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-amina	1.92
65		N-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} - transciclohexano-1,4-diamina	1.09**
66		[5-(4-amino-4-metil-piperidin-1-ilmetil)-pirrolo[2,1-f] [1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	0.99*
67		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidino-4-carbonitrilo	1.28
68		[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metoxi-etilamino)-piperidin-1-ilmetil]-pirrolo[2,1-f] [1,2,4] triazin-4-il}-amina	1.30
69		1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-[1,4]diazepan-5-ona	2.05***
70		éster metílico de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil} - piperidino-4-carboxílico	1.41

71		[5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f] [1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.03*
72		(±)-[5-(*cis*-4-amino-3-metil-piperidin-1-ilmetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.08*
73		(±)-[5-(*trans*-4-amino-3-metil-piperidin-1-ilmetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.31
A menos que se indique otra cosa, los Tiempos de Retención HPLC se determinaron usando una columna YMC Xterra ODS S7 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min. Los Tiempos de Retención HPLC marcados con un "*" se determinaron usando una columna YMC S7 C18 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min; con "**" se determinaron usando una columna YMC ODS-A S7 C18 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min; y aquellos con "***" se determinaron usando una columna YMC ODS-A C18 S5 4.6 x 33 mm con un tiempo de gradiente de 4 minutos y un caudal de 4 mL/min			

Ejemplo 74

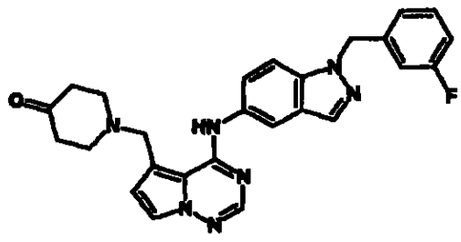


1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5- ilmetil}-pirrolidin-3-ona

Perrutenato de tetrapropilamonio (3.2 mg, 0.1 equiv) se agregó a una

suspensión agitada de 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1f][1,2,4]triazin-5-ilmetil}-(3R)-pirrolidin-3-ol (42 mg, 0.092 mmoles), N-metilmorfolina N-óxido (16 mg, 1.5 equiv), y se secó, mallas moleculares 4A pulverizadas (100 mg) en DCM seco bajo N_2. Luego de 0.75 horas, la suspensión verde oscuro se filtró a través de una almohadilla corta de gel de sílice usando acetato de etilo como eluyente. El retiro del solvente de las fracciones que contenían el producto seguido por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con mezclas de hexano que contenía 30 a 50% EtOAc) proporcionó el compuesto del título como un aceite (26 mg, 61%). MS: 456 $(M+H)^+$; tiempo de retención HPLC: 1.28 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Ejemplo 75

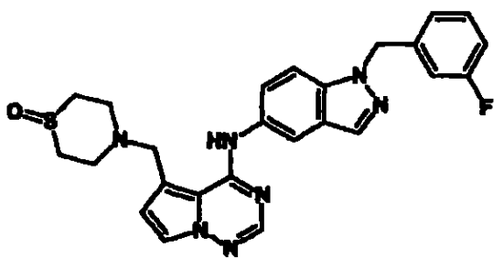


1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-ona

Una solución de [5-(1,4-dioxa-8-aza-spiro[4.5]dec-8-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (54 mg, 0.105 mmoles) en una mezcla de THF (1 mL) y 1 N HCl acuoso (1 mL) que contenía 16 gotas de HCl concentrado se dejó agitando a temperatura ambiente durante 7 días. La reacción se diluyó con DCM y se neutralizó con solución de $NaHCO_3$ acuoso saturado. Luego de secar (Na_2SO_4), el solvente se retiró para dejar el compuesto del título como un aceite (19 mg, 39 %). MS: 488 $(M+H_2O+H)^+$; tiempo de retención HPLC: 2.35 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 5 min

(componente B se varió de 20 a 60%), 5 mL/min).

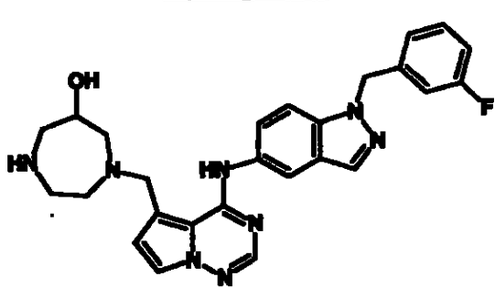
Ejemplo 76



[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(1-oxo-1λ^4-tiomorfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina

Una solución de [1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(tiomorfolin-4-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina (46 mg, 0.096 mmoles) en cloroformo (2 mL) se enfrió en un baño helado y se agregó ácido m-cloroperbenzoico (26 mg, 65 %, 1 equiv) en porciones durante 12 minutos. Luego de 1 hora, la reacción se diluyó entonces con cloroformo, se lavó con 6 % solución de $NaHSO_3$ acuoso, solución de $NaHCO_3$ acuoso saturado y se secó (Na_2SCO_4). El solvente se retiró y la purificación por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 5 % MeOH) proporcionó el compuesto del título como un aceite (13 mg, 27 %). MS: 490 $(M+H)^+$; tiempo de retención HPLC: 1.62 min (columna YMC S5 C18, 4.60 x 50 mm, gradiente 3 min, 4 mL/min).

Ejemplo 77

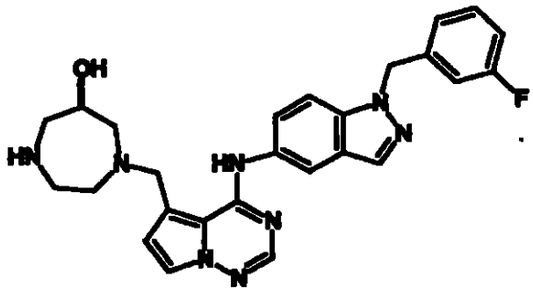


(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4] triazin-5-ilmetil}-(±)-[1,4]diazepan-6-ol

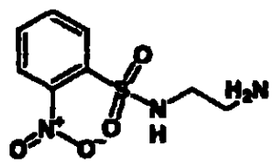
Una mezcla de (5-bencenosulfinilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (397 mg, 0.8 mmoles) y [1,4]diazepan-6-ol (417 mg, 4.5 equiv, Saari y colaboradores, J. Org. Chem., 1971, 36, 1711) en DMSO seco (1.5 mL) en un tubo sellado se calentó a 140°C durante 11 horas. Esto se diluyó con DCM (150 ml), se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice 4 mm; elución de gradiente con DCM que contenía 0 a 3 % de una solución 2N NH_3 en MeOH) produjo el compuesto del título como un sólido (242 mg, 62%), MS: 487 $(M+H)^+$; tiempo de retención HPLC: 0.96 min (columna Xterra S7 3.0 x 50 mm S7 C18, gradiente 2 min, 5 ml/min).

El material racémico pudo separarse en una columna Chiralpak AD 4.6 x 250 mm, eluyendo con 0.05% dietilamina en EtOH durante 25 minutos con un caudal de 0.7 mL/min). Los enantiómeros *S* y R tuvieron tiempos de retención de 16.20 y 18.90 minutos respectivamente. El enantiómero R se sintetizó como se describe más adelante.

Ejemplos 78

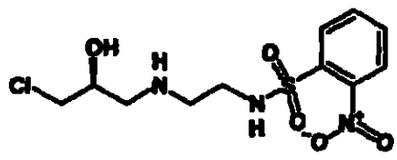


1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-(6R)-[1,4]diazepan-6-ol



A. Preparación de N-(2-amino-etil)-2-nitro-bencenosulfonamida

Una solución de etilen diamina (268 mL, 20 equiv) en DCM (400 mL) se agregó a una solución helada de sulfonil cloruro de o-nitrobenceno (44.4 gm, 0.2 mole) en DCM (200 mL) durante 1 hora. La concentración en el evaporador rotatorio dejó un aceite que se dividió en porciones entre DCM y solución de Na_2CO_3 acuoso saturado. Se re-extrajo la fase acuosa con DCM y las fases orgánicas combinadas se secaron (Na_2SO_4). El retiro de los solventes seguido por cromatografía en gel de sílice (elución de gradiente gradual con DCM que contenía 0, 5, 10, 20, 30% MeOH) proporcionó el compuesto del título como un aceite (37.2 gm, 76%). ^1H NMR ($CDCl_3$ + D_2O) δ 2.82 (t, 2H, J = 5.1 Hz), 3.10 (t, 2H, J = 5.1 Hz), 7.73 (m, 2H), 7.83 (m, 1H), 8.11 (m, 1H); MS: 246 (M+H)+; tiempo de retención HPLC: 0.39 min (columna YMC Xterra 3.0 x 50 mm S7 C18, gradiente 3 min, 4 mL/min).

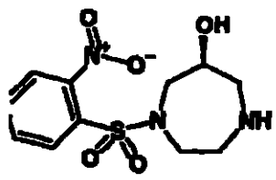


B. Preparación de N-[2-({2S}-3-cloro-2-hidroxi-propilamino)-etil]-2-nitro-bencenosulfonamida

S-(+)-epiclorohidrina (5.92 mL, 0.5 equiv) se agregó a una suspensión de N-(2-amino-etil)-2-nitro-bencenosulfonamida (37.2 gm, 0.152 mole) y $MgSO_4$ (9.1 gm, 0.5 equiv) en MeOH seco (38 mL) a temperatura ambiente. Luego de 8 horas, el sólido se retiró por filtración. El filtrado se concentró y dividió en porciones entre DCM y agua. La fase orgánica se separó, se secó (Na_2SO_4) y el solvente se retiró. La cromatografía en gel de sílice (elución de gradiente gradual con DCM que contenía 0, 1, 1.5, 2, 2.5,

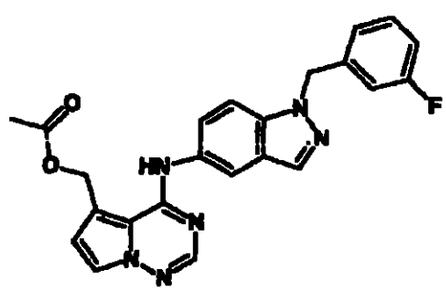
90

3% MeOH) proporcionó el compuesto del título como un aceite (20.73 gm, 81%). ^{1}H NMR ($CDCl_3$ + D_2O) δ 2.59 - 2.76 (m, 2H), 2,80 (t, 2H, J = 5.4 Hz), 3.17 (t, 2H, J = 5.4 Hz), 3.53 (d, 2H, J = 5.7 Hz), 3.79 (m, 1H), 7.74 (m, 2H), 7.85 (m, 1H), 8.13 (m, 1H); MS: 338 ($M+H^+$); tiempo de retención HPLC: 0.67 min (columna YMC Xterra 3.0 x 50 mm S7 C18, gradiente 3 min, 4 mL/min).



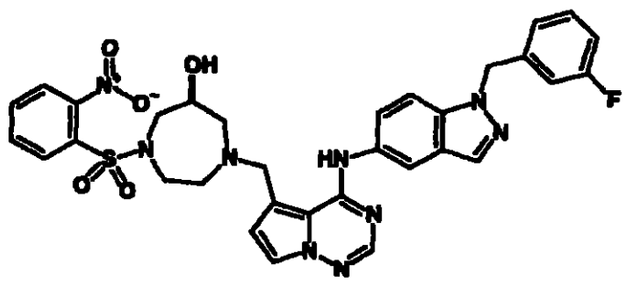
C. Preparación de 1-(2-nitro-bencenosulfonil)-(6S)-[1,4]diazepan-6-ol

Una suspensión de N-[2-({2S}-3-cloro-2-hidroxi-propilamino)-etil]-2-nitro-bencenosulfonamida (20.73 gm, 61.4 mmoles) y Cs_2CO_3 (73 gm, 3 equiv) en acetonitrilo seco (600 mL) bajo una atmósfera de N_2 se calentó a 60 °C durante 6.5 horas. El sólido se retiró por filtración y entonces el solvente se retiró del filtrado. El residuo se dividió en porciones entre DCM (400 mL) y agua (100 mL). Se secó la fase orgánica (Na_2SO_4) y el solvente se retiró. La cromatografía en gel de sílice (elución de gradiente gradual con DCM que contenía: 0, 1, 2, 3, 4% MeOH) proporcionó el compuesto del título como un aceite (5.68 gm, 31%). ^{1}H NMR ($CDCl_3$ + D_2O) δ 2.3 (br. s, 2H), 2,85 (m, 4H), 3.09 (m, 4H), 7.68 (m, 3H), 8.00 (m, 1H); MS: 302 ($M+H^+$); tiempo de retención HPLC: 0.56 min (columna YMC Xterra 3.0 x 50 mm S7 C18, gradiente 3 min, 4 mL/min).



D. Preparación de ácido acético 4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetiléster

Se agregaron una solución de 5-bromometil-cloropirrolo[2,1-f][1,2,4]triazina cruda (15.3 gm, 0.062 mole) en EtOAc (300 mL) y enfriada en un baño helado bajo una atmósfera de N_2 y ácido acético (17.8 mL, 5 equiv) seguido por diisopropiletilamina (54.3 mL, 5 equiv.). El recipiente de reacción se retiró del baño y se agitó durante 18 horas a temperatura ambiente. El precipitado se retiró por filtración y el filtrado resultante se diluyó con hexano (250 mL). Esto se lavó con agua (2 x 125 mL), solución de NaCl saturado (50 mL), se secó (Na_2SO_4) y se concentró *in vacuo* para producir un aceite marrón viscoso que solidificó al reposar. Se obtuvo una muestra de ácido acético puro 4-cloro-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil éster por cromatografía en gel de sílice (elución de gradiente con 0 a 30% EtOAc en hexano) como un sólido cristalino amarillo. ^{1}H NMR ($CDCl_3$,) δ 2.09 (s, 3H), 5.48 (s, 2H), 7.00 (d, J = 2.7 Hz, 1H), 7.80 (d, J = 2.7 Hz, 1H), 8.18 (s, 1H), 7.80 (d, J = 2.7 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 5.48 (s, 2H), 2.09 (s, 3H). El ácido acético crudo 4-cloro-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil éster se disolvió entonces en acetonitrilo (300 mL) y se trató con bicarbonato de sodio (26.2 gm, 5 equiv.) y (18.1 gm, 1.2 equiv.). Luego de agitar a temperatura ambiente durante 20 horas, la mezcla se concentró *in vacuo* y se disolvió en DCM (500 mL). Esto se lavó con 100 mL de agua, se secó sobre sulfato de sodio anhidro, se filtró y se concentró *in vacuo* para producir un sólido de color oscuro. Esto se cristalizó de acetonitrilo para producir 10 g del compuesto del título. El agua madre se cromatografió en gel de sílice eluyendo con 70% hexano/EtOAc para producir otros 8 gm de material puro (rendimiento total, 67%): ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 5.42 (s, 2H), 5.59 (s, 2H), 6.76 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.98 - 6.90 (bm, 2H), 7.35 - 7.22 (bin, 3H), 7.56 (d, J = 2.6 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 8.06 (s, 1H), 8.17 (s, 1H), 9.42 (s, 1H); MS: 431($M + H^+$); tiempo de retención HPLC = 2.59 min (columna YMC Xterra 4.5 x 50 mm S7 C18, gradiente 3 min, 4 mL/min).



E. Preparación de 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-4-(2-nitro-bencenosulfonil)-(6S)-[1,4]diazepan-6-ol

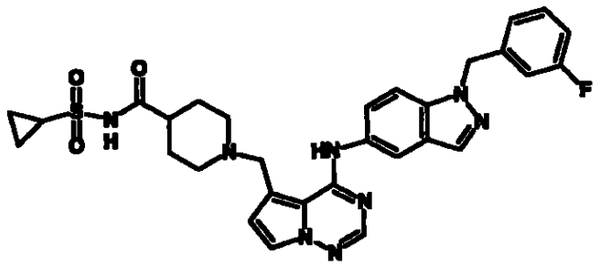
Una mezcla de ácido acético 4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil éster (860 mg, 2 mmoles), 1-(2-nitro-bencenosulfonil)-[1,4]diazepan-6R-ol (602mg, 2 mmoles) y diisopropiletilamina (0.522 mL, 3 mmol, 1.5 equiv.) en acetonitrilo seco (4 ml) en un recipiente a presión se calentó a 102 °C durante 17 horas. Tras el retiro del solvente, el residuo se tomó en DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido cromatografía en gel de sílice (elución de gradiente con DCM que contenía 0 a 2% 2M NH_3 en MeOH) proporcionó el compuesto del título como un sólido (1.14g, 85%). ^{1}H NMR ($CDCl_3$) δ 2.87 - 3.08 (m, 5H), 3.36 - 3.60 (m, 4H), 3.97 - 4.05(m, 3H), 5.52 (s, 2H), 6.51 (d, 1H, J = 2.5Hz), 6.82 (m, 1H), 6.91-6.96 (m, 2H), 7.21-7.25 (m, 1H), 7.25 - 7.31 (m, 1H), 7.44 (d, 1H, J = 3.0 Hz), 7.47-7.49 (m, 1H), 7.58 - 7.66 (m, 3H), 7.85 (s, 1H), 7.91 (d, 1H, J = 1.5 Hz), 7.98 (d, 1H, J = 1.0 Hz), 8.03 (d, 1H, J = 1.5 Hz), 11.02 (s, 1H). MS: 672 ($M+H^+$); tiempo de retención HPLC: 1.37 min (Tiempor de Gradiente = 2 min, Caudal = 5 ml/min, columna Xterra C18 S7, 3.0 x 50 mm C18 S7).

F. Preparación de 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-(6R)-[1,4]diazepan-6-ol

Bencenotiol (54 mg, 2 equiv) se agregó a una suspensión de 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1f][1,2,4]triazin-5-ilmetil}-4-(2-nitro-bencenosulfonil)-(6S)-[1,4]diazepan-6-ol (164 mg, 0.244

mmoles) y K_2CO_3 (168 mg, 1.22 mmol, 5 equiv.) en 2.5 ml de DMF anhidro bajo nitrógeno. Luego de agitar a temperatura ambiente durante 50 minutos, el sólido se retiró por filtración. El filtrado se concentró y dividió en porciones entre DCM y agua. La fase orgánica se secó (Na_2SO_4) y se retiró el solvente. Cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con 0 a 5% 2M NH_3 en MeOH) proporcionó el compuesto del título como un sólido (109 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 2.69 - 2.77 (m, 2H), 2.84 - 3.03 (m, 6H), 3.78 - 3.81 (m, 1H), 3.90 (d, 1H, J = 13.4 Hz), 3.96 (d, 1H, J = 13.4 Hz), 5.55 (s, 2H), 6.48 (d, 1H, J = 2.5 Hz), 6.86 - 6.88 (m, 1H), 6.92 - 6.98 (m, 2H), 7.23 - 7.27 (m, 1H), 7.32 - 7.33 (m, 1H), 7.44 (d, 1H, 2.5 Hz), 7.54 - 7.56 (m, 1H), 7.86 (s, 1H), 8.02 (d, 1H, J = 1.0 Hz), 8.04 (d, 1H, J = 2.0 Hz), 11.54 (s, 1H). MS: 487 $(M+H)^+$; tiempo de retención HPLC: 18.86 min (columna Chiralpak AD 4.6 x 250 mm, eluyendo con 0.05% dietilamina en EtOH durante 25 minutos con un caudal de 0.7 mL/min).

Ejemplo 79



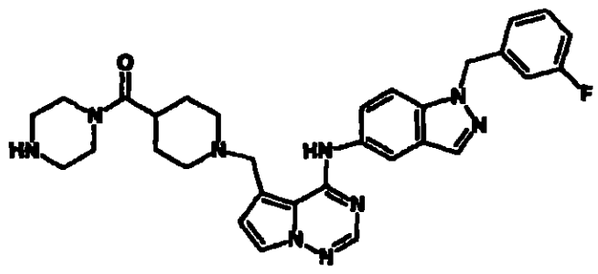
Ácido ciclopropanosulfónico (1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidino-4-carbonil)-amida

NaOH acuoso (2.1 mL, 1.0 N) se agregó a una solución de éster metílico de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidino-4-carboxílico (352 mg, 0.686 mmoles) en una mezcla de MeOH (0.2 ml) y THF (0.2 ml) a 0°C. Luego de agitar a 0 °C durante 1 hora, la mezcla de reacción se dejó calentar a temperatura

ambiente y se dejó agitar durante la noche. Se agregó gota a gota HCl acuoso (2.1 ml, 1.0 N) y se extrajo la reacción con DCM. Se secaron los extractos orgánicos (Na_2SO_4) y se retiraron los solventes para dejar ácido 1-{4-[1-(3-fluorobencil)indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidino-4-carboxílico, como un sólido (329 mg, pureza 84% por LCMS), el cual se usó en ese estado.

Una solución del ácido crudo (100 mg, 0.168 mmoles) en THF (2 ml) se agregó gota a gota a una solución de 1,1'-carbonildiimidazol (33 mg, 0.2 mmoles) en THF (0.3 ml) y esto se calentó a reflujo durante 30 minutos. Después de enfriar a temperatura ambiente, se agregó ciclopropilsulfonamida (82 mg, 0.67 mmol, 4 equiv.) seguida por una solución de DBU (50 uL, 0.336 mmol, 2 equiv.) en THF (0.2 ml). Se agitó la reacción durante 18 horas, se diluyó con EtOAc (120 ml), se lavó con tampón de pH 4.0 (9 mL), salmuera (5 mL) y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (elución de gradiente con placa de gel de sílice de 2 mm con DCM que contenía 1 a 5% MeOH) proporcionó el compuesto del título como un sólido (58 mg, 57%). ^1H NMR ($CDCl_3$) δ 0.98-1.00 (m, 2H), 1.22-1.27 (m, 2H), 1.84-1.92 (m, 4H), 2.03-2.16 (m, 2H), 2.03-2.16 (m, 2H), 2.24-2.32 (m, 1H), 2.83-2.92 (m, 1H), 3.08-3.11 (m, 2H), 3.74 (s, 2H), 5.54 (s, 2H), 6.46 (d, 1H, J = 2.5 Hz), 6.81-6.97 (m, 3H), 7.20-7.27 (m, 1H), 7.36-7.51 (m, 3H), 7.84 (s, 1H), 8.06 (s, 2H), 11.82 (bs, 1H). MS: 603.7 ($M+H^+$); tiempo de retención HPLC: 1.21 min (Tiempo de Gradiente = 2 min, Caudal = 5 ml/min, columna Xterra 3.0 x 50 mm S7 C18).

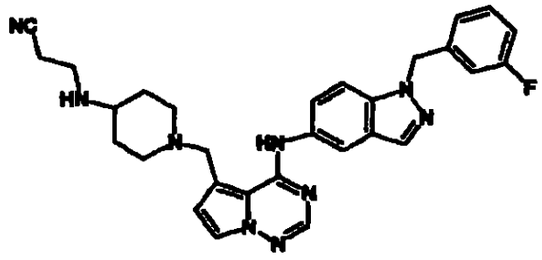
Ejemplo 80



(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-il)-piperazin-1-il-metanona

Una mezcla de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidino-4-carboxílico crudo (75 mg, 0.15 m... (72 mg, 0.376 mmoles), y DMAP (37 mg, 0.3 mmoles) en DCM seco (1 mL) se agitó a temperatura ambiente durante 0.5 horas. Se agregó piperazina (104 mg, 1.2 mmoles) y, luego de 64 horas, la reacción se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con DCM que contenía 1 a 5% MeOH) proporcionó el compuesto del título como un sólido (11mg, 13 %). ^{1}H NMR ($CDCl_3$) δ 1.67-1.80 (m, 4H), 1.96-2.09 (m, 2H), 2.15-2.18 (m, 1H), 2.58-2.65 (m, 1H), 2.82-2.86 (m, 4H), 3.17-3.20 (m, 2H), 3.43-3.48 (m, 2H), 3.57-3.62 (m, 2H), 3.77 (s, 2H), 5.57 (s, 2H), 6.48 (d, 1H, J = 2.5 Hz), 6.83-6.88 (m, 1H), 6.90-6.97 (m, 2H), 7.21-7.29 (m, 1H), 7.36-7.39 (m, 1H), 7.44 (d, 1H, J = 2.7 Hz), 7.55-7.58 (m, 1H), 7.89 (s, 1H), 8.08 (s, 1H), 8.18 (d, 1H, J = 1.5 Hz), 11.87 (br, 1H). MS: 568.67 ($M+H^+$); tiempo de retención HPLC: 1.03 min (Tiempo de Gradiente = 2 min, Caudal = 5 ml/min, columna Xterra 3.0 x 50 mm S7 C18).

Ejemplo 81

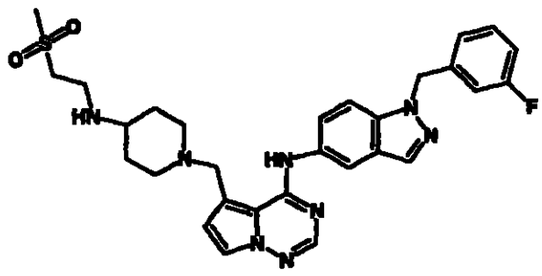


3-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-ilamino)-propionitrilo

Acrilonitrilo (0.2 mL, 30 equiv.) se agregó a una solución de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.1 mmoles) en MeOH (3 mL) a

temperatura ambiente. El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con DCM que contenía 0 a 2% MeOH) proporcionó 40 mg (76%) del compuesto del título como un sólido. MS: 524 $(M+H)^+$; tiempo de retención HPLC: 0.99 min (columna Xterra 3.0 x 50 mm S7 C18, gradiente de 2 min, 5 mL/min).

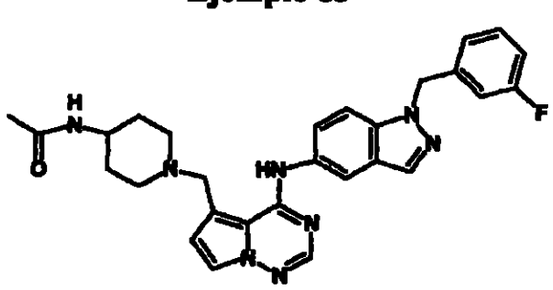
Ejemplo 82



[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metanosulfonil-etilamino)-piperidin-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina

Sulfona metilvinílica (0.011 mL, 0.1 mmoles) se agregó a una solución de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.1 mmoles) en MeOH (3 mL) a temperatura ambiente. Luego de agitar durante la noche, el compuesto del título (54 mg, 94 %) se recogió por filtración, se lavó con MeOH y se secó. MS: 577 $(M+H)^+$; tiempo de retención HPLC: 0.98 min (columna Xterra 3.0 x 50 mm S7 C18, gradiente 2 min, 5 ml/min).

Ejemplo 83

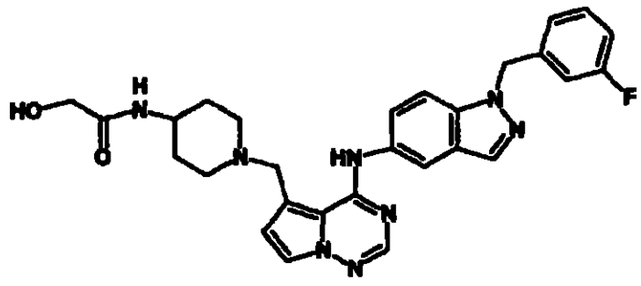


N-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f]

[1,2,4]triazin-5-ilmetil}-piperidin-4-il)-acetamida

Anhídrido acético (25 uL, 2.3 equiv.) se agregó a una mezcla de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.1 mmoles) y K_2CO_3 (21 mg 0.15 mmoles) en MeOH (3 mL) a 0° C bajo nitrógena. Después de 1 hora, la reacción se retiró del baño helado y la mezcla se dejó agitar a temperatura ambiente durante la noche. El solvente se retiró y el residuo se tomó en DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con DCM que contenía 0 a 3% MeOH) proporcionó el compuesto del título como un sólido (41 mg, 80%). MS: 513 $(M+H)^+$; tiempo de retención HPLC: 1.12 min (columna Xterra 3.0 x 50 mm S7 C18, gradiente 2 min, 5 mL/min).

Ejemplo 84

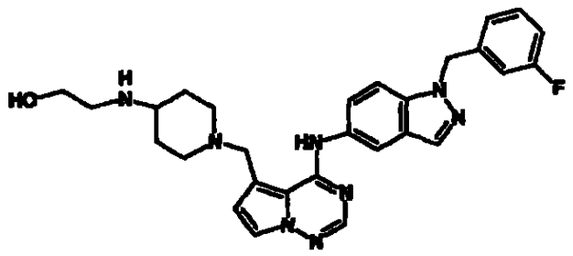


N-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidin-4-il)-2-hidroxi-acetamida

Cloruro de acetoxiacetilo (46 mg, 2 equiv) se agregó gota a gota a una solución de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.1 mmoles) (80 mg, 0.17 mmoles) y trietilamina (71 µL, 3 equiv.) en DCM seco (3 mL) a 0 °C bajo nitrógeno. Después de agitar a 0 °C durante 3 horas y a temperatura ambiente durante 1hora, se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con DCM que contenía 0 a 2% MeOH) proporcionó de ácido acético (1-{4-[1-(3-fluoro-

bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-ilcarbamoil)-metil éster como un sólido (73 mg, 75%). Una solución de este éster en THF (0.4 mL) se trató con NaOH acuoso (1N, 0.38 mL, 3 equiv.). Trascurridas 2 horas a temperatura ambiente se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 3% MeOH) proporcionó el compuesto del título como un sólido (47 mg, 70%). MS: 529 $(M+H)^+$; tiempo de retención HPLC: 1.37 min (columna YMC Xterra ODS S7 3.0 x 50 mm, gradiente 2min, 5 ml/min).

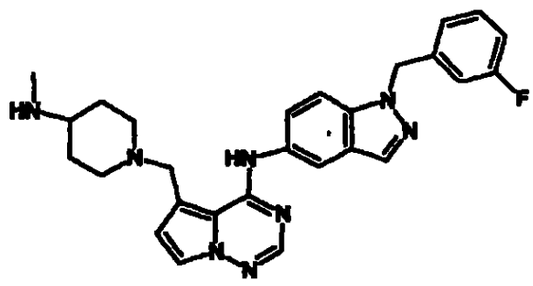
Ejemplo 85



2-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-ilamino)-etanol

Una mezcla de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (188 mg, 0.4 mmoles) y [1,3]dioxolan-2-ona (352 mg, 10 equiv) en un tubo sellado se calentó a 100 °C durante 3.5 horas. El compuesto del título se aisló por cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con DCM que contenía 0 a 3% MeOH) proporcionó el compuesto del título como un sólido (43 mg, 21%); MS: 515 $(M+H^+)$; tiempo de retención HPLC: 1.29 min (columna YMC Xterra ODS S7 3.0 x 50 mm, gradiente 2 min, 5 ml/min).

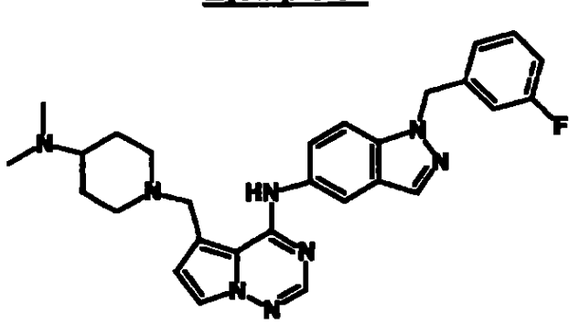
Ejemplo 86



[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-metilamino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazm-4-il]-amina

Una mezcla de (5-bencenosulfinilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (200 mg, 0.4 mmoles) y 4-amino-piperidina (1.2 g, 30 equiv.) en un frasquito se puso en un reactor de microondas (Personal Chemistry's Smith Creator) y se irradió a 150°C durante 20 minutos. Se agregó formato de etilo (3 ml) a la mezcla anterior y se continuó la irradiación a 135°C durante 30 minutos. La concentración de la mezcla de reacción seguida por purificación de HPLC preparativa proporcionó N-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidin-4-il)-formamida (71 mg, 36%). Esto se disolvió en THF seco (0.3 ml) y se agregó gota a gota a una solución agitada de $LiAlH_4$; (1M en éter, 0.57 ml, 4 equiv.). Se agregó agua (0.5 mL) lentamente después de 20 horas y el compuesto del título (16 mg, 23%) se aisló por HPLC preparativa. MS: 485 $(M+H)^+$; tiempo de retención HPLC: 1.02min (columna Xterra 3.0 x 50 mm S7 C18, gradiente 2 min, 5 ml/min).

Ejemplo 87



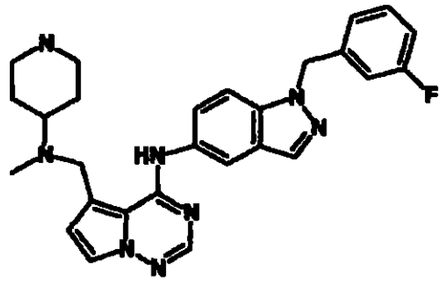
[5-(4-dimetilamino-piperidin-1-ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-

100

il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

Cianoborohidruro de sodio (5 mg, 2 equiv.) se agregó a una solución de [5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (20 mg, 0.042 mmoles), ácido acético (3 uL), y 37% formaldehído (7 uL, 2 equiv.) en DCM (0.3 ml) a 0 °C. Trascurridas 0.5 horas, la reacción se retiró del baño de aceite y, luego de 4 horas más, se diluyó con DCM y se hizo alcalina con solución de $NaCO_3$ saturado. Se secó la capa orgánica (Na_2SO_4) y el solvente se retiró. El compuesto del título (4 mg, 8%) se aisló por HPLC preparativa. MS: 499 $(M+H)^+$; tiempo de retención HPLC: 1.04 min (columna YMC ODS-A C18 S7 3.0 x 50 mm, gradiente 2 min, 5 ml/min).

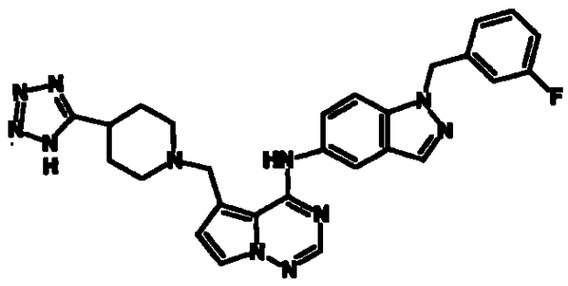
Ejemplo 88



[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[(metil-piperidin-4-il-amino)-metil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina

Similarmente, éster *tert*-butílico de ácido 4-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-piperidin-1-carboxílico se convirtió en éster *tert*-butílico de ácido 4-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-metilamino)-piperidin-1-carboxílico el cual se trató con TFA a 0°C durante 1 hora para producir el compuesto del título como un sólido (rendimiento total 37%). MS: 485 $(M+H)^+$; tiempo de retención HPLC: 0.95 min (columna YMC 3.0 x 50 mm S7 C18, gradiente 2 min, 5 ml/min).

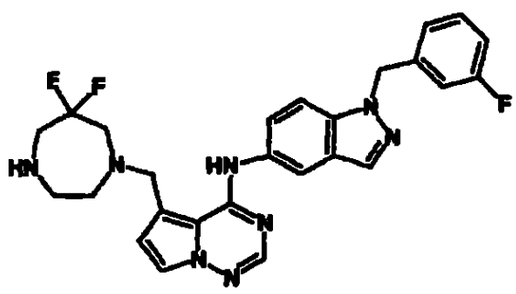
Ejemplo 89



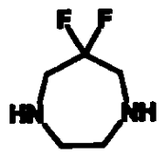
[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(1H-tetrazol-5-il)-piperidin-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina

Una mezcla de 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-piperidino-4-carbonitrilo (145 mg, 0.3 mmoles), azida de sodio (59 mg, 3 equiv.) y cloruro de amonio (48 mg, 3 equiv.) en DMF (0.6 mL) en un frasquito sellado se agitó a 100°C durante 20 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con DCM que contenía 2 a 7% 2 M NH_3 en MeOH) proporcionó el compuesto del título como un sólido (38 mg, 24%); MS: 524 ($M+H^+$); tiempo de retención HPLC: 1.13 min (columna Xterra 3.0 x 50 mm S7 C18, gradiente de 2 min, 5 ml/min).

Ejemplo 90



[5-(6,6-Difluoro-[1,4]diazepan-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina



A. Preparación de 6,6-difluoro-[1,4]diazepán

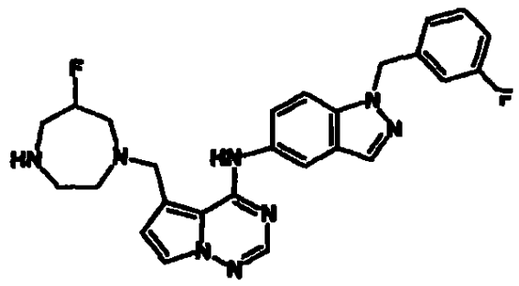
Perrutenato de tertrapropilamonio (0.75 gm, 0.05 equiv) se agregó a una suspensión agitada de 1,4-bis-(tolueno-4-sulfonil)-[1,4]diazepan-6-ol (13 gm, 30.7 mmoles, Saari y colaboradores, J. Org. Chem., 1971, 36, 1711), N-metilmorfolina N-óxido (5.38 gm, 1.5 equiv) y mallas moleculares 4A trituradas (20 gm) en DCM seco (100 mL). Trascurridas 1.5 horas, esto se vertió en una columna corta de gel de sílice y se eluyó con una mezcla de 10% EtOAc en DCM para producir 1,4-bis-(tolueno-4-sulfonil)-[1,4]diazepan-6-ona (8.9 gm, 60%) como un sólido blanco: ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 6H), 3.71 (s, 4H), 3.91 (s, 4H), 7.32 (d, 4H, J = 8.1 Hz), 7.65 (d, 4H, J = 8.1 Hz). Una solución de esta cetona (8.9 gm, 21.1 mmoles) en DCM seco se enfrió en un baño de acetona/hielo seco y se agregó DAST (8.4 mL, 3 equiv) durante 5 minutos. La reacción se dejó calentar a temperatura ambiente y, luego de 20 horas, se enfrió en un baño helado y se agregó agua gota a gota para descomponer el exceso de reactivo. Se ajustó el pH de la fase acuosa 10 con solución de NaOH acuoso y se agregó más DCM (300 mL). La fase orgánica se separó, se secó (Na_2SO_4) y se retiró el solvente. El residuo se cristalizó de acetona/aguar para producir 6,6-difluoro-1,4-bis-(tolueno-4-sulfonil)-[1,4]diazepán (6.47 gm, 69%) como cristales blancos esponjosos: ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 6H), 3.41 (s, 4H), 3.68 (t, 4H, J = 12.3 Hz), 7.33 (d, 4H, J = 8.0 Hz), 7.64 (d, 4H, J = 8.0 Hz). Una solución del difluoruro (3.41 gm, 7.75 mmoles) y fenol (2.9 gm, 4 equiv) en una solución de HBr en HOAc (50 mL) se calentó a 60 oC durante 6 horas. La reacción se concentró y el residuo se suspendió en etanol para depositar la sal bis-HBr de 6,6-difluoro-[1,4]diazepán como un sólido color bronce (1.82 gm, 79%). Esta sal (600 mg, 2.04 mmoles) se suspendió en MeOH (10 mL) y se agregó NaOH acuoso (0.41 mL, 10 N, 2 equiv) agitando simultáneamente. La solución resultante se eluyó a través de un cartucho Varian Mega Bond

Elut SCX seguido por 10 mL de MeOH. Se extrajo por elución 6,6-difluoro-[1,4]diazepán del cartucho SCX con 50 mL de solución 2 N de NH_3 en MeOH. El retiro de los solventes lo dejó como un aceite (211 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 4H), 3.21 (t, 4H, J = 13.9 Hz).

B. Preparación de [5-(6,6-difluoro-[1,4]diazepan-1-ilmetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

Una solución de anhídrido metanosulfónico (114 mg, 3.2 equiv.) en DCM (0.6 mL) se agregó a una solución de {4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-il}-metanol (78 mg, 2 mmoles) en DCM seco (1.4 mL) a 0°C bajo nitrógeno seguido por trietilamina (0.140 mL, 5 equiv.). Luego de agitar a 0 °C durante 1hora, se agregaron 6,6-difluoro-[1,4]diazepán (82 mg, 3 equiv.) y 1,2 dicloroetano (2 mL). La mezcla de reacción se pasó a un reactor de microondas (Personal Chemistry's Smith Creator) y se irradió a 65 °C durante 50 minutos. El retiro del solvente seguido por HPLC preparativa proporcionó el compuesto del título como un sólido (29 mg, 29 %). MS: 507 ($M+H^+$); tiempo de retención HPLC: 1.47 min (columna YMC Xterra ODS S7 3.0 x 50 mm, gradiente de 2 min, 5 ml/min).

Ejemplo 91

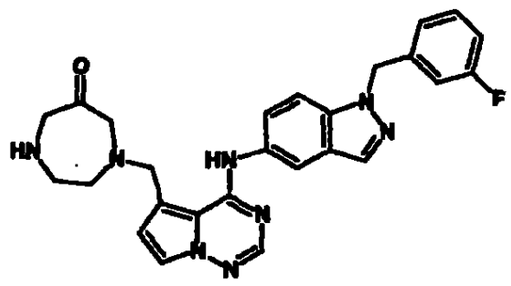


(+)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(6-fluoro-[1,4]diazepan-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina

Siguiendo el procedimiento de acoplamiento anterior con 6-fluoro-[1,4]diazepán (Ziegler y colaboradores, J. Med. Chem., 1990, 33, 142)

produjo el compuesto del título como un sólido (rendimiento 26%). MS: 489 $(M+H)^+$; tiempo de retención HPLC: 1.33 min (columna YMC Xterra ODS S7 3.0 x 50 mm, gradiente de 2 min, 5 ml/min).

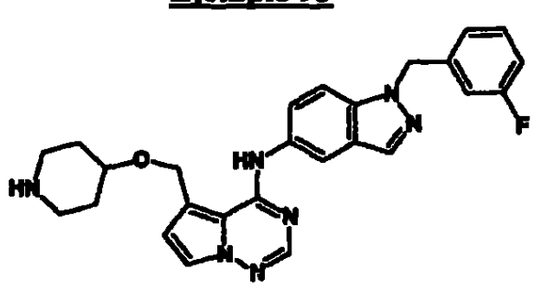
Ejemplo 92



1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-[1,4]diazepan-6-ona

La oxidación de éster *tert*-butílico de ácido 4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-6-hidroxi-[1,4]diazepan-1-carboxílico como se describe para ejemplo 74 produjo éster *tert*-butílico de ácido 4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-6-oxo-[1,4]diazepan-1-carboxílico el cual se desprotegió con TFA para producir el compuesto del título como un sólido (rendimiento total 61%). MS: 485 $(M+H)^+$; tiempo de retención HPLC: 1.01 min (columna Xterra S7 3.0 x 50 mm S7 C18, gradiente de 2 min, 5 ml/min).

Ejemplo 93



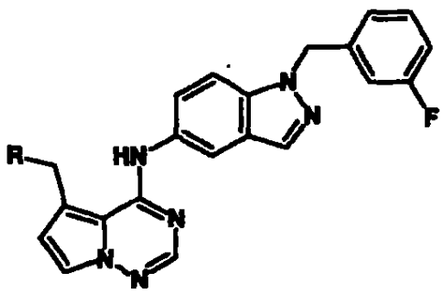
[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-4-iloximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina

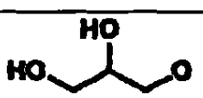
Una suspensión de 5-bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina (61 mg, 0.25 mmoles), éster *tert*-butílico de ácido 4-hidroxi-piperidino-1-carboxílico (500 mg, 10 equiv) y $NaHCO_3$ (42 mg, 2 equiv) en CH_3CN seco (0.5 mL) bajo N_2 se dejó agitando a temperatura ambiente durante 3 días. Se agregaron 1-(3-fluoro-bencil)-1H-indazol-5-ilamina (54 mg, 0.9 equiv) y más $NaHCO_3$ (42 mg, 2 equiv) y la reacción se dejó agitando durante la noche. La reacción se diluyó con DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2mm, elución de gradiente con DCM que contenía 0 a 3% MeOH) proporcionó éster butílico de ácido 4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetoxi}-piperidino-1-carboxílico como una espuma (47 mg, 33%). Esto se trató con una mezcla de DCM (1.5 mL) y TFA (1 mL) durante 40 minutos y, seguidamente, se retiraron los solventes. El residuo se tomó en DCM, se lavó con solución de $NaHCO_3$ acuoso saturado, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm, elución de gradiente con DCM que contenía 0 a 5 % MeOH) proporcionó la amina pura (11 mg, 29%) como un aceite. ^1H NMR ($CDCl_3$) 61.1-1.3 (m, 2H), 1.7-1.9 (m, 4H), 2.5 -2.6 (m, 2H), 3.0 - 3.1 (m, 2H), 3.44 (d, 2H, J = 7 Hz), 4.85 (s, 2H), 5.59 (s, 2H), 6.55 (d, 1H, J = 2 Hz), 6.8 - 7.0 (m, 3H), 7.2 - 7.5 (m, 4H), 7.97 (s, 1H), 8.05 (s, 1H), 8.20 (d, 1H, J = 2 Hz), 9.70 (s, 1H); MS: 486 $(M+H)^+$; tiempo de retención HPLC: 1.35 min (YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min.

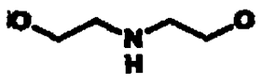
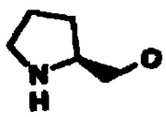
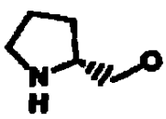
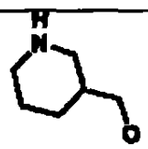
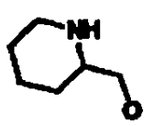
Ejemplos 94 a 116

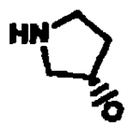
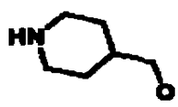
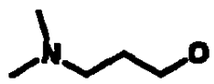
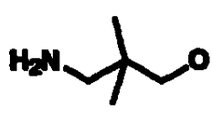
Los siguientes análogos de éter se prepararon usando el procedimiento descrito para ejemplo **93**. Cuando el alcohol inicial no llevaba un grupo protector Boc, se omitió el paso de desprotección. Alcoholes que llevaban un grupo amino primario o secundario se convirtieron primero en su derivado N-Boc usando dicarbonato di-*tert*-butílico de acuerdo con

procedimientos generales de literatura (T. Greene y P. Wuts, Protective Groups in Organic Synthesis, 3rd edition).



Ej.	R	Nombre del Compuesto	Tiempo de Retención HPLC (min)
94		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(2-metoxi-etoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina	1.33*
95		[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-metoximetil-pirrolo [2,1-f][1,2,4]triazin-4-il)-amina	2.18*
96		[5-(2-dimetilamino-etoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.24
97		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(3-imidazol- 1-il-propoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina	1.33
98		2-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetoxi}-etanol	1.4
99		3- {4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f]	1.33

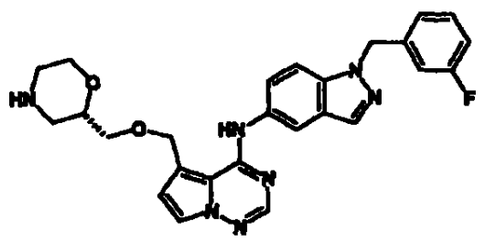
	racémico	[1,2,4]triazin-5-ilmetoxi}-propano-1,2-diol	
100		2-(2-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetoxi}-etilamino)-etanol	1.25
101		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(2S)-pirrolidin-2-ilmetoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina	1.27
102		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(2R)-pirrolidin-2-ilmetoximetil)-pirrolo [2,1-f][1,2,4]triazin-4-il]-amina	1.27
103		[5- {(2R)2-amino-propoximetil}-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.33
104		[5- {(2S)-2-amino-propoximetil}-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.33
105		[5-(2-amino-etoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.29
106	 **racémico**	[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-3-ilmetoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina	1.34
107		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-2-ilmetoximetil)-pirrolo[2,1-f]	1.38

	racémico	[1,2,4]triazin-4-il]-amina	
108		3-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4] triazin-5-ilmetoxi}-propan-1-ol	2.15**
109		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-{(3S)-pirrolidin-3-iloximetil} -pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina	1.24*
110		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-{(3R)-pirrolidin-3-iloximetil}-pirrolo[2,1-f] [1,2,4] triazin-4-il]-amina	1.24*
111		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-4-ilmetoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina	1.35*
112		2-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetoxi}-propano-1,3-diol	1.41
113		[5-(3-dimetilamino-propoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.95***
114		[5-(4-amino-butoximetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-[1 -(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.84****
115		[5-(3-amino-2,2-dimetil-propoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	2.12***

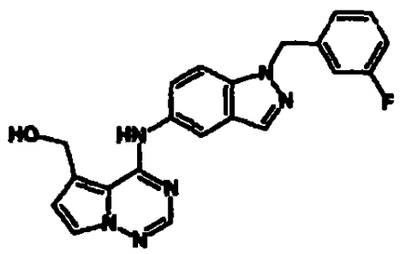
116		[5-(4-amino-propoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.98***

A menos que se indique lo contrario, los tiempos de retención HPLC se determinaron usando una columna YMC Xterra ODS S7 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min. Los tiempos de retención HPLC marcados con un "*" se determinaron usando una columna YMC C18 SF 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min; con un "**" se determinaron usando una columna YMC C18 SF 4.6 x 50 mm con un tiempo de gradiente de 3 minutos y un caudal de 4 mL/min; con un "***" en una columna YMC Xterra C18 S5 4.6 x 50 mm con un tiempo de gradiente de 3 minutos y un caudal de 4 mL/ min; con un "****" en una columna YMC Xterra C18 S5 3.0 x 50 mm con una gradiente de 3 minutos y un caudal de 4 mL/min.

Ejemplo 117



([1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-({2S}-morfolin-2-ilmetoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina



A. Preparación de {4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-il}-metanol

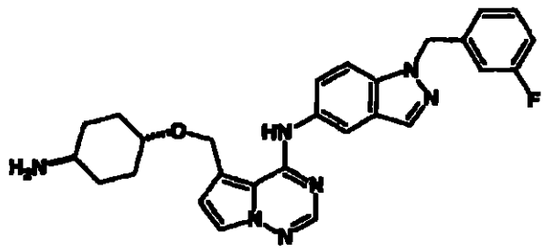
Una mezcla de 5-bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina cruda (3.69 gm, 0.015 moles) y $NaHCO_3$ (2.51 gm, 2 equiv) en una mezcla de acetonitrilo (50 mL) y agua (5 mL) se agitó bajo una atmósfera de N_2 durante 3 días. Esto se trató con Na_2SO_4 y, a continuación, con 1-(3-flurobencil)-1H-indazol-5-ilamina (3.24 gm, 0.90 equiv) y $NaHCO_3$ (1 gm) y se dejó agitando durante 18 horas a temperatura ambiente. La reacción se filtró y la torta filtrante se lavó con DCM (100 mL). El filtrado se concentró y la cromatografía en gel de sílice (elusión con 30% EtOAc en hexano) del residuo produjo el compuesto del título como un sólido color bronce (3.78 gm, rendimiento 65%): ^{1}H NMR ($CDCl_3$) δ 3.03 (t, J = 5.9 Hz, 1H), 4.98 (d, J = 5.7 Hz, 2H), 5.55 (s, 2H), 6.76 (d, J = 2.7 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.98 - 6.90 (m, 3H), 7.43 (d, J = 2.5 Hz, 1H), 7.51 (dd, J = 2.1, 8.8 Hz, 1H), 7.96 (s, 1H), 8.03 (s, 1H), 8.22 (s, 1H), 9.91 (s, 1H); MS: (M+H+); tiempo de retención HPLC: 2.38 min (YMC C18 S5, 3.0 x 50 mm, gradiente de 4 min, 4 mL/min.

B. Preparación de ([1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-({2S}-morfolin-2-ilmetoximetil)-pirrolo[2,1 -f][1,2,4]triazin-4-il]-amina

Cloruro de tionilo (18 µL, 1.1 equiv) se agregó a una solución de {4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-il}-metanol (80 mg, 0.205 mmoles) en DCM seco (4 mL) a temperatura ambiente. Luego de 12 minutos, se agregó éster *tert*-butílico de ácido (2S)-2-hidroximetil-morfolino-4-carboxílico (65.3 mg, 1.5 equiv, H. Yanagisawa y colaboradores, Heterocycles, 1993, 35, 105.) seguido por DEPEA (39.5 µL, 1.1 equiv). Trascurridas 72 horas a temperatura ambiente, el solvente se retiró y la cromatografía en gel de sílice del residuo (elución de gradiente con 0 a 50% EtOAc en hexano) proporcionó éster *tert*-butílico de ácido 2-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetoximetil} -morfolino-4-carboxílico (60 mg, rendimiento 50%); MS: 588 $(M+H)^+$; tiempo de retención HPLC: 2.69 min (Xterra C18 S5, 3.0 x 50

mm, gradiente 3 min, 4 mL/min. Una solución de este material en DCM (2 mL) se enfrió a 0°C y se trató con TFA (1 mL). Trascurridos 90 minutos, los solventes se retiraron y el residuo se disolvió en DCM. Esto se lavó con solución de $NaHCO_3$ saturado y se secó la fase orgánica (Na_2SO_4) y los solventes se retiraron. La purificación por HPLC preparativa y, seguidamente, cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con 0 a 3% NH_3 (2N en MeOH) en DCM produjo el compuesto del título (30 mg, rendimiento 60%): ^1H NMR ($CDCl_3$) δ 2.84 - 2.58 (m, 4H), 3.65 - 3.35 (m, 4H) 3.65 - 3.35 (m, 4H), 4.87 (s, 2H), 5.58 (s, 2H), 6.54 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 9.5 Hz, 1H), 6.98 - 6.90 (m, 2H), 7.32 -7.20 (m, 3H), 7.48 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 1.8, 8.8 Hz, 1H), 7.94 (s, 1H), 8.19 (s, 1H), 9.58 (s, 1H); MS: 488 $(M+H)^+$; tiempo de retención HPLC: 1.65 min (Xterra C18 S5, 3.0 x 50 mm, gradiente 3 min, 4 mL/min).

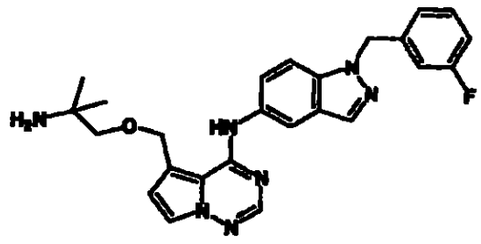
Ejemplo 118



[trans-5-(4-amino-ciclohexiloximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

El compuesto del título se preparó de éster *tert*-butílico de ácido (trans-4-hidroxi-ciclohexil)-carbámico en una manera similar: MS: 486 $(M+H)^+$; tiempo de retención HPLC: 2.13 min (Xterra C18 S5,4.6 x 50 mm, gradiente 3 min, 4 mL/min).

Ejemplo 119

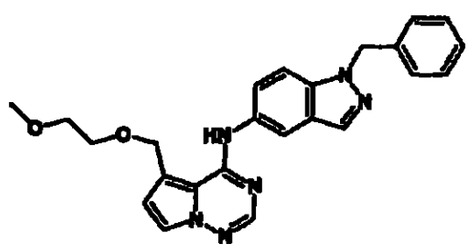


[5-(2-amino-2-metil-propoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

Una mezcla de ácido acético 4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil éster (100 mg, 0.24 mmol), éster *tert*-butílico de ácido (2-hidroxi-1,1-dimetil-etil)-carbámico 156 mg, 3 equiv) y DIPEA (62 µL, 1.5 equiv) en acetonitrilo seco (0.2 mL) en un frasquito se puso en un reactor de microondas (Personal Chemistry's Smith Creator) y se irradió durante 10 minutos a 109°C. El solvente se retiró y el residuo se tomó en DCM seco (3mL) y se enfrió a 0°C. Se agregó TFA (3 mL) y trascurridas 1.5 horas, los solventes se retiraron. El residuo se dividió en porciones entre DCM y solución de $NaHCO_3$ saturado. Se secó la fase orgánica (Na_2SO_4) y el solvente se retiró. La purificación por cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con 0 a 5 % MeOH en DCM) produjo el compuesto del título (13 mg, rendimiento 12%): MS: 460 $(M+H)^+$; tiempo de retención HPLC: 1.34 min, YMC Xterra ODS S7 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

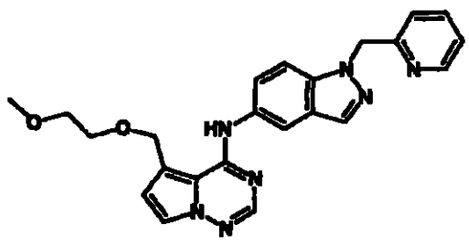
Ejemplo 120

(1-bencil-1H-indazol-5-il)-[5-(2-metoxi-etoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina



Una suspensión de 5-bromometil-4-cloro-pirrolo[2,1-f][1,2,4]triazina (50 mg, 0.202 mmoles y $NaHCO_3$ (75 mg, 4.4 equiv) en 2-metoxietanol (1.0 mL) bajo N_2 se dejó agitando a temperatura ambiente durante 6 horas. La reacción se diluyó con DCM, se extrajo con agua y se secó (Na_2SO_4). El retiro del solvente dejó 4-cloro-5-(2-metoxi-etoximetil)-pirrolo[2,1-f][1,2,4] triazina (41 mg, 84%) como un aceite. ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H), 3.67 (m, 4H), 4.96 (s, 2H), 7.05 (d, 1H, J = 3 Hz), 7.82 (d, 1H, J = 3 Hz), 8.16 (s, 1H). Una suspensión de 4-cloro-5-(2-metoxi-etoximetil)-pirrolo[2,1-f][1,2,4]triazina (5 mg, 0.020 mmoles), $NaHCO_3$ (3 mg, 2 equiv) y 1-bencil-1H-indazol-5-ilamina (4.5 mg, 1 equiv, preparada en la misma manera que 1-(3-fluoro-bencil)-1H-indazol-5-ilamina pero usando cloruro de bencilo) en CH_3CN seco (0.5 mL) se dejó agitando a temperatura ambiente durante 2 horas. La reacción se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con DCM que contenía 0 a 1% MeOH) proporcionó el producto como un aceite (1.8 mg, 21%). ^1H NMR ($CDCl_3$) δ 3.16 (s, 3H), 3.63 (m, 4H), 4.83 (s, 2H), 5.53 (s, 2H), 6.48 (d, 1H, J = 3 Hz), 7.1 - 7.5 (m, 8H), 7.88 (s, 1H), 7.96 (s, 1H), 8.11 (s, 1H), 9.56 (s, 1H); MS: 429 $(M+H)^+$; tiempo de retención HPLC: 2.58 min (YMC C18 S5, 4.6 x 50 mm, gradiente 3 min (comenzando con 0% solvente B y terminando con 70% solvente B), 4 mL/min.

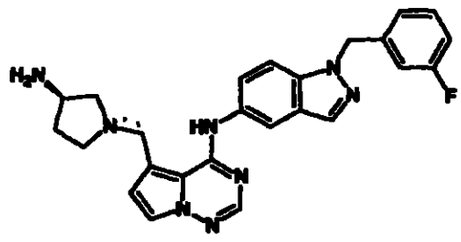
Ejemplo 121



[5-(2-metoxi-etoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-(1-piridin-2-ilmetil-1H-indazol-5-il)-amina

Una suspensión de 4-cloro-5-(2-metoxi-etoximetil)-pirrolo[2,1-f] [1,2,4]triazina (24 mg, 0.099 mmoles), $NaHCO_3$ (42 mg, 5 equiv) y 1-piridin-2-ilmetil-1H-indazol-5-ilamina (22 mg, 1 equiv, preparada en la misma manera que 1-(3-fluoro-bencil)-1H-indazol-5-ilamina pero usando 2-cloruro de picolilo) en CH_3CN seco (1 mL) se dejó agitando a temperatura ambiente durante 1 hora. La reacción se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 1 mm, elución de gradiente con DCM que contenía 0 a 1 % MeOH) proporcionó el producto como un aceite (4.8 mg, 11%). ^1H NMR ($CDCl_3$) δ 3.26 (s, 3H), 3.76 (m, 4H), 4.90 (s, 2H), 5.75 (s, 2H), 6.56 (d, 1H, J = 3 Hz), 6.83 (d, 1H, J = 5 Hz), 7.18 (m, 1H), 7.40 (d, 1H, J = 5 Hz), 7.49 (d, 1H, J = 2 Hz), 7.56 (m, 2H), 7.96 (s, 1H), 8.07 (s, 1H), 8.22 (d, 1H, J = 1 Hz), 8.59 (m, 1H), 9.65 (s, 1H); MS: 429 $(M+H)^+$; tiempo de retención HPLC: 1.30 min (YMC ODS-A C18 S7, 3.0 x 50 mm, gradiente 2 min (comenzando con 0% solvente B y terminando con 70% solvente B), 5 mL/min.

Ejemplo 122



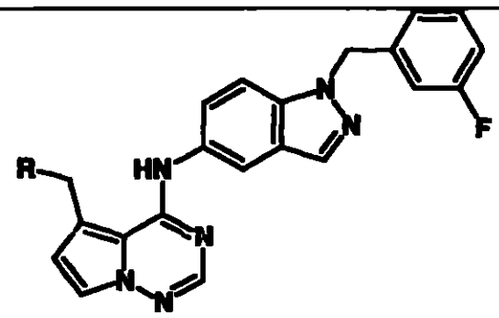
{5-[(3R)-3-amino-pirrolidin-1-ilmeti]-pirrolo[2,1-f][1,2,4]triazin-4-il}-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina

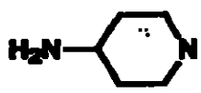
Una mezcla de (5-bencenosulfinilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (100 mg, 0.20 mmoles) y (3R)-3-(N-tert-butoxicarbonilamino)pirrolidina; (380 mg, 10 equiv) en un tubo sellado se calentó a 130 °C durante 35 horas. La mezcla de reacción se tomó en DCM, se lavó con agua y se secó (Na_2SO_4). Luego del retiro del solvente el residuo se tomó en DCM (1.5 mL) y se agregó TFA (1 mL).

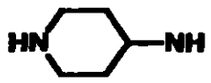
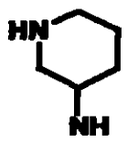
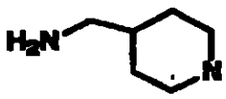
Los solventes se retiraron y el residuo se disolvió en DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 1 a 5% MeOH) proporcionó el compuesto del título como un aceite (13 mg, 14%). ^{1}H NMR ($CDCl_3$) δ 1.49 (br s, 2H), 1.66 (m, 1H), 2.29 (m, 1H), 2.43 (m, 1H), 3.69 (m, 1H), 3.87 (d, 1H, J = 13.5 Hz), 3.96 (d, 1H, J = 13.5 Hz), 5.58 (s, 2H), 6.49 (d, 1H, J = 3 Hz), 6.8 - 7.6 (m, 7H), 7.92 (s, 1H), 8.04 (s, 1H), 8.26 (d, 1H, J = 2 Hz); MS: 457 $(M+H)^+$; tiempo de retención HPLC: 1.15 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Ejemplos 123 a 127

Los siguientes ejemplos se prepararon en la misma manera que **Ejemplo 122.**

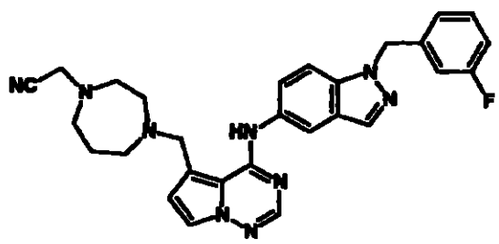


Ej.	R	Nombre del Compuesto	Tiempo de Ret. HPLC (min)
123		[5-(4-amino-piperidin-1 -ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.03

124		[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-4-ilaminometil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina	0.98
125		[5-((3R)-3-amino-pirrolidin-1 -ilmetil)-pirrolo[2,1-f] [1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.15*
126		(+)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-3-ilaminometil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina	0.97*
127		[5-(4-aminometil-piperidin-1 ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina	1.53**

A menos que se indique otra cosa, los tiempos de retención HPLC se determinaron usando una columna YMC S7 C18 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min. Los tiempos de retención HPLC marcados con un "*" se determinaron usando una columna YMC S7 C18 3.0 x 50 mm con un tiempo de gradiente de 2 minutos y un caudal de 5 mL/min; con un "**" se determinaron usando una columna YMC ODS-A C18 S7 3.0 x 50 mm con un tiempo de gradiente de 3 minutos y un caudal de 4 mL/min.

Ejemplo 128

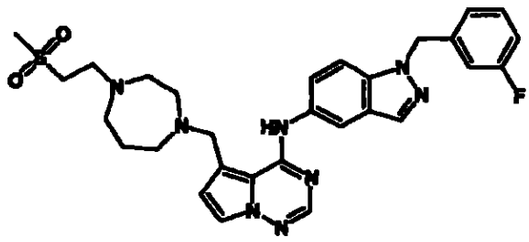


[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-cianometil-[1,4]diazepan-1-

ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina

Bromoacetonitrilo (0.028 mL, 4 equiv) se agregó a una solución helada de 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.10 mmoles) y TEA (0.055 mL, 4 equiv) en DCM (3 mL). Esto se dejó agitando durante 1 hora y, a continuación, de retiró del baño helado. Luego de reposar durante la noche, la reacción se diluyó con DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 1 % MeOH) proporcionó el compuesto del título como un aceite (49 mg, 95%). MS: 510 $(M+H)^+$; tiempo de retención HPLC: 1.17 min (columna YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

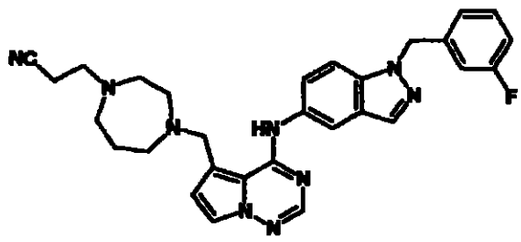
Ejemplo 129



[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metanesulfonil-etil)-[1,4]diazepan-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina

Sulfona metilvinílica (0.042 mL, 4 equiv) se agregó a una solución de 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.10 mmoles) en DCM (3 mL). Luego de agitar durante la noche, el solvente se retiró y la purificación por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 1% MeOH) proporcionó el compuesto del título como un aceite (54 mg, 93%).); MS: 577 $(M+H)^+$; tiempo de retención HPLC: 1.08 min (columna YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

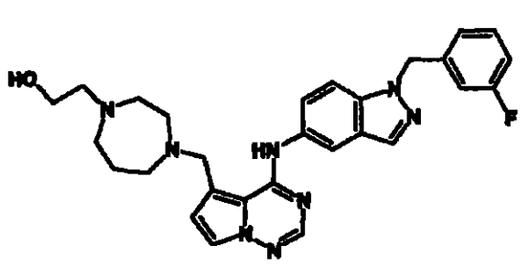
Ejemplo 130



[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-ciano-etil)-[1,4]diazepan-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina

Acrilonitrilo (0.302 mL, 45 equiv) se agregó en 3 porciones durante 2 días a una solución de 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.10 mmoles) en DCM (3 mL) a temperatura ambiente. El solvente se retiró y la purificación por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 1% MeOH) proporcionó el compuesto del título como un aceite (34 mg, 64%).); MS: 524 $(M+H)^+$; tiempo de retención HPLC: 1.08 min (columna YMC S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Ejemplo 131

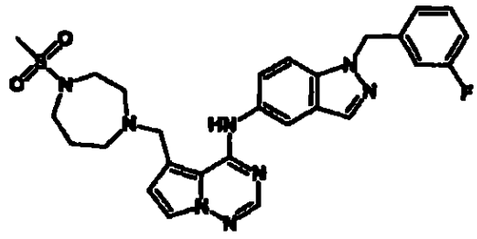


2-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-[1,4]diazepan-1-il)-etanol

Una mezcla de 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47 mg, 0.10 mmoles), 2-bromoetanol (0.019 mL, 1.5 equiv) y K_2CO_3 (35 mg, 2.5 equiv) en CH_3CN

(2.5 mL) se calentó a reflujo durante la noche. A renglón seguido la reacción se diluyó con DCM, se lavó con agua y se secó (Na_2SO_4). El solvente se retiró y la purificación por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 5 % MeOH) proporcionó el compuesto del título como un aceite (21 mg, 41%). MS: 515 $(M+H)^+$; tiempo de retención HPLC: 1.15 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Ejemplo 132

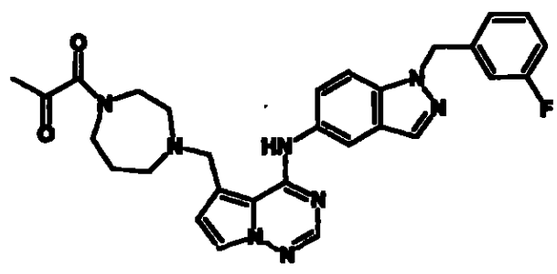


[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-metanesulfonil-[1,4]diazepan-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina

Cloruro de metanosulfonilo (0.034 mL, 4 equiv) se agregó a una solución congelada de 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (35 mg, 0.074 mmoles) y TEA (0.041 mL, 4 equiv) en DCM (2.5 mL). Esto se dejó agitando durante 1 hora y, a continuación, se retiró del baño de hielo. Luego de reposar durante la noche, la reacción se diluyó con DCM, se lavó con agua, y se secó (Na_2SO_4). El retiro del solvente seguido por cromatografía radial (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 2% MeOH) proporcionó el compuesto del título como un aceite (22 mg, 54%).); MS: 549 $(M+H)^+$; tiempo de retención HPLC: 1.26 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

120

Ejemplo 133



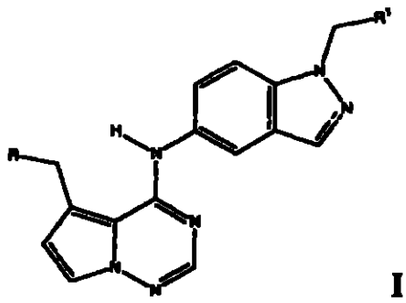
1-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4]triazin-5-ilmetil}-[1,4]diazepan-1-il)-propano-1,2-diona

Una solución de ácido pirúvico (0.008 mL, 1 equiv) y 5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina (47mg, 0.10 mmoles) en EtOAc (3 mL) se enfrió a -16 °C y se agregó una solución de diciclohexilcarbodiimida (22 mg, 1.1 equiv) en EtOAc (0.5 mL). Esto se dejó calentar lentamente a temperatura ambiente y se dejó agitando durante la noche. La reacción se filtró y el solvente se retiró del filtrado. Cromatografía radial del residuo (placa de gel de sílice de 2 mm empleando una elución de gradiente con DCM que contenía 0 a 2% MeOH) proporcionó el compuesto del título como un aceite (8 mg, 14%). MS: 541 $(M+H)^+$; tiempo de retención HPLC: 1.27 min (columna YMC Xterra ODS S7 C18, 3.0 x 50 mm, gradiente 2 min, 5 mL/min).

Reivindicaciones

Lo que se reivindica es:

1. Un compuesto de fórmula I



I

sus enantiómeros, diastereómeros, y sales farmacéuticamente aceptables, profármacos y solvatos del mismo, en donde

R se selecciona del grupo conformado por SR^2, SOR^2, SO_2R^2, OR^2, y NR^3R^4;

R^1 se selecciona del grupo conformado por arilo, arilo sustituido, heterociclo, y heterociclo sustituido;

R^2 se selecciona del grupo conformado por hidrógeno, alquilo, alquilo sustituido arilo, arilo sustituido, aralalquilo, heterociclo, y heterociclo sustituido;

R^3 y R^4 se seleccionan independientemente del grupo conformado por hidrógeno, alquilo, alquilo sustituido, arilo, arilo sustituido, heterociclo, y heterociclo sustituido; o R^2 y R^3 pueden formar conjuntamente un anillo carbocíclico o heterocíclico, saturado o insaturado, de 4-8 miembros, monocíclico opcionalmente sustituido, o un anillo carbocíclico o heterocíclico, saturado o insaturado, bicíclico de 7 a 12 miembros, opcionalmente sustituido.

2. El compuesto de acuerdo con la reivindicación 1 en donde R^1 se selecciona del grupo conformado por benceno, fluoro sustituido benceno y piridina.

3. El compuesto de acuerdo con la reivindicación 2 en donde R^1

es un benceno fluoro sustituido.

4. El compuesto de acuerdo con la reivindicación 3 en donde R es un éter.

5. El compuesto de acuerdo con la reivindicación 1 seleccionado del grupo conformado por: (5-[1,4]diazepan-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;
[1-(3-fluoro-bencil)-1H-indazol-5-il]-(5-imidazol-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)-amina;
amida de ácido 1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperidino-3-carboxílico;
[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-metil-piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;
2-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperazin-1-il)-etanol;
1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1f][1,2,4] triazin-5-ilmetil} -(3R)-pirrolidin-3-ol;
(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperidin-4-il)-metanol;
1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperidin-4-ol;
(2R)-3-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-amino)-propano-1,2-diol;
2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-amino)-etanol;
1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil} -(3S)-pirrolidin-3-ol;
[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-cianometil-ciclohexilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina;
[5-(3,5-Dimetil-piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-((3S)-3-metil-piperazin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;

amida de ácido 4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperazino-2-carboxílico;

4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperazin-2-ona;

2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-amino)-2-metil-propano-1,3-diol;

2-({4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-amino)-propano-1,3-diol;

[1-(3-fluoro-bencil)-1H-indazol]-5-il]-(5-piperazin-1-ilmetil-pirrolo[2,1-f][1,2,4]triazin-4-il)amina;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-{5-[4-(2-metoxi-etilamino)-piperidin-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-amina;

1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-[1,4]diazepan-5-ona;

[5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

(+)-[5-(cis-4-amino-3-metil-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

(+)-[5-(trans-4-amino-3-metil-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4] triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-piperidin-4-ona;

(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-(+)-[1,4]diazepan-6-ol;

1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-(6R)-[1,4]diazepan-6-ol;

2-(1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f] [1,2,4]triazin-5-ilmetil}-piperidin-4-ilamino)-etanol;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(4-metilamino-piperidin-1-ilmetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina;

[5-(6,6-difluoro-[1,4]diazepan-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

(+)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(6-fluoro-[1,4]diazepan-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;

1-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-[1,4]diazepan-6-ona;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-4-iloximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;

2-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetoxi}-etanol;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-3-ilmetoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;

3-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetoxi}-propano-1,2-diol;

[5-(4-amino-butoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

[5-(4-amino-propoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

([1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-({2S}-morfolin-2-ilmetoximetil)-pirrolo[2,1-f] [1,2,4]triazin-4-il]-amina;

[trans-5-(4-amino-ciclohexiloximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

[5-(2-amino-etoximetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

3-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetoxi}-propan-1-ol;

{5-[(3R)-3-amino-pirrolidin-1-ilmetil]-pirrolo[2,1-f][1,2,4]triazin-4-il}-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

[5-(4-amino-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;

[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-4-ilaminometil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;

(+)-[1-(3-fluoro-bencil)-1H-indazol-5-il]-[5-(piperidin-3-ilaminometil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-amina;
[5-(4-aminometil-piperidin-1-ilmetil)-pirrolo[2,1-f][1,2,4]triazin-4-il]-[1-(3-fluoro-bencil)-1H-indazol-5-il]-amina;
2-(4-{4-[1-(3-fluoro-bencil)-1H-indazol-5-ilamino]-pirrolo[2,1-f][1,2,4] triazin-5-ilmetil}-[1,4]diazepan-1-il)-etanol.

6. Una composición farmacéutica que comprende un compuesto de la reivindicación 1 y un trasportador farmacéuticamente aceptable.

7. Una composición farmacéutica que comprende un compuesto de la reivindicación 1 en combinación con un trasportador farmacéuticamente aceptable y por lo menos otro agente anti-cáncer o citotóxico formulado como una dosis fija.

8. La composición farmacéutica de la reivindicación 7 en donde dicho agente anti-cáncer o citotóxico se selecciona del grupo conformado por: tamoxifeno, toremifeno, raloxifeno, droloxifeno, iodoxifeno, acetato de megestrol, anastrozol, letrazol, borazol, exemestane, flutamida, nilutamida, bicalutamida, acetato de ciproterona, acetato de goserelina, luprolide, finasteride, herceptina, metotrexato, 5-fluorouracil, citarabina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicin-C, dactinomicina, mitramicina, cisplatino, carboplatino, melfalan, clorambucil, busulfan, ciclofosfamida, ifosfamida, nitrosoureas, tiotefan, vincristina, taxol, taxotere, etopósido, tenipósido, amsacrina, irinotecan, topotecan y una epotilona.

9. Un método para tratar una enfermedad proliferante, que comprende administrar a una especie de sangre caliente necesitada de él, una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

10. El método de la reivindicación 9 en donde la enfermedad proliferante se selecciona del grupo conformado por cáncer, psoriasis y artritis reumatoide.

11. El método de la reivindicación 10 en donde la enfermedad proliferante es cáncer.

12. El método de la reivindicación 11 que comprende además administrar a una especie de sangre caliente necesitada de él, una cantidad terapéuticamente efectiva de por lo menos un otro agente anti-cáncer o citotóxico en combinación con un compuesto de la reivindicación 1.

13. El método de la reivindicación 12 en donde dicho agente anti-cáncer o citotóxico se selecciona del grupo conformado por: tamoxifeno, toremifeno, raloxifeno, droloxifeno, iodoxifeno, acetato de megestrol, anastrozol, letrazol, borazol, exemestane, flutamida, nilutamida, bicalutamida, acetato de ciproterona, acetato de goserelina, luprolide, finasteride, herceptin, metotrexato, 5-fluorouracil, citarabina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicin-C, dactinomicina, mitramicina, cisplatino, carboplatino, melfalan, clorambucil, busulfan, ciclofosfamida, ifosfamida, nitrosoureas, tiotefan, vincristina, taxol, taxotere, etopósido, tenipósido, amsacrina, irinotecan, topotecan y una epotilona.

14. Un método de modular actividad tirosina cinasa de receptor que comprende administrar a una especie de sangre caliente necesitada de él una cantidad efectiva de un compuesto de la reivindicación 1.

15. El método de la reivindicación 14 en donde dicha tirosina quinasa de receptor se selecciona del grupo conformado por HER1, HER2 y HER4.

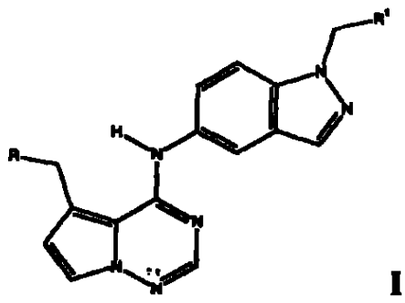
16. Un método para tratar enfermedades asociadas con vías de transducción de señales que operan a través de receptores de factor de crecimiento, que comprende administrar a una especie de sangre caliente necesitada de él una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

Folio 128 extracto publicacion
Mayo 27 2004

Indazolilpirrolotriazinas Modificadas C-5

Extracto

La presente invención proporciona compuestos de fórmula I



I

Los compuestos de fórmula I inhiben actividad tirosina cinasa de receptores de factor de crecimiento tales como HER1, HER2 y HER4 haciéndolos así útiles como agentes antiproliferantes. Los compuestos de fórmula I son igualmente útiles para el tratamiento de otras enfermedades asociadas con vías de transducción de señales que operan a través de receptores de factor de crecimiento.

LD0280-WO-PCT

AS:93882

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	04 DEC 2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
LD0280	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/36528	12 November 2002 (12.11.2002)	14 November 2001 (14.11.2001)

Applicant

BRISTOL-MEYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

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

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

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

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Nirmal Shah Telephone No. (703) 308-1235
Facsimile No. (703) 305-3230	

Form PCT/IPEA/416 (July 1992)

Docketed Item NO SIPE
Due Date _____
Attorney EK

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LD0280	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/36528	International filing date *(day/month/year)* 12 November 2002 (12.11.2002)	Priority date *(day/month/year)* 14 November 2001 (14.11.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 403/12,401/14; A61K 31/53; A61P 35/00 and US Cl.: 514/183; 544/243		
Applicant BRISTOL-MEYERS SQUIBB COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05 June 2003 (05.06.2003)	10 November 2003 (10.11.2003)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Mukund Shah Telephone No. (703) 308-1235

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/36528

I. Basis of the report

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

☒ the international application as originally filed.

☒ the description:
pages 1-67 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 68-73, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

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

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

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

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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

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

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

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/fig NONE

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

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/36528

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	1-16	YES
	Claims	NONE	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 or fairly suggest the compounds, compositions, and uses of the present invention.

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.

TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

Remitente:
OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

KENNETH PEIST
BRISTOL-MYERS SQUIBB COMPANY
P.O BOX 4000
PRINCETON. NJ 08543-4000

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Regla 71.1 PCT)

	Fecha de envío *(Día/Mes/Año)* **04 DE DICIEMBRE DE 2003**
No. de Expediente del Solicitante o Apoderado LD0280	**COMUNICACIÓN IMPORTANTE**

No. de Solicitud Internacional	Fecha Internacional de Presentación *(día/mes/año)*	Fecha de Prioridad *(día/mes/año)*
PCT/US02/36528	12 de noviembre 2002 (12.11.2002)	14 de noviembre 2001 (14.11.2001)

Solicitante
BRISTOL-MEYERS SQUIBB COMPANY

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.

2. Una copia del informe, en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.

3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4. **RECORDATORIO**

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

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

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

Nombre y dirección postal de la oficina encargada del examen internacional (IPEA/US)	Empleado Autorizado
Mail Stop PCT, Attn: IPEA/US Comisionado de Patentes P.O Box 1450 Alexandria, Virginia 22313-1450	**Mukund Shah**
Fax No. (703) 305 – 3230	Teléfono No. (703)-308-1235

Formulario PCT/IPEA/416 (Julio 1992)

TRATADO SOBRE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado LD0280	**PROCEDIMIENTO POSTERIOR**	Véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/416)
No. Solicitud Internacional PCT/US02/36528	Fecha Internacional de Presentación *(día/mes/año)* 12 de noviembre 2002 (12.11.2002)	Fecha de Prioridad *(día/mes/año)* 14 de noviembre 2001 (14.11.2001)
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC IPC(7): C07D 403/12, 401/14; A61K 31/53; A61P 35/00 y US Cl.: 514/183; 544/243		
Solicitante BRISTOL-MEYERS SQUIBB COMPANY		

1. Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.

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

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

   Estos anexos comprenden en total de - hojas.

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

   I ☒ Base del informe

   II ☐ Prioridad

   III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial

   IV ☐ Falta de unidad de la invención

   V ☒ Comprobación justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones sustentando esta comprobación

   VI ☐ Ciertos documentos enumerados

   VII ☐ Ciertas deficiencias del registro internacional

   VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición	Fecha de la conclusión de este informe
05 de junio de 2003 (05.06.2003)	10 de noviembre de 2003 (10.11.2003)
Nombre y dirección postal de la oficina encargada del examen internacional (IPEA/US) Mail Stop PCT, Attn: IPEA/US Comisionado de Patentes P.O Box 1450 Alexandria, Virginia 22313-1450 Fax No. (703) 305 – 3230	Empleado Autorizado **Mukund Shah** Teléfono No. (703)-308-1235

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

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL	Solicitud Internacional No. PCT/US02/36528

I. Base del Informe

1. Con respecto a los **elementos** de la solicitud internacional:*
   - ☒ la solicitud internacional tal como se radicó originalmente
   - ☒ la descripción:
     - páginas 1-67 como se radicaron originalmente
     - páginas NINGUNA, radicadas con la petición
     - páginas NINGUNA, radicadas con la carta de _____
   - ☒ las reivindicaciones:
     - Páginas 68-73, como se radicaron originalmente
     - páginas NINGUNA, como se modificaron (junto con cualquier declaración) bajo artículo 19
     - páginas NINGUNA, radicadas con la petición
     - páginas NINGUNA, radicadas con la carta de _____
   - ☐ los dibujos:
     - páginas NINGUNA, como se radicaron originalmente
     - páginas NINGUNA, radicadas con la petición
     - páginas NINGUNA, radicadas con la carta de _____
   - ☐ la parte del listado de secuencias de la descripción:
     - páginas NINGUNA, como se radicaron originalmente
     - páginas NINGUNA, radicadas con la petición
     - páginas NINGUNA, radicadas con la carta de _____

2. En lo concerniente al **idioma**, todos los elementos indicados más arriba estuvieron a disposición de la administración o le fueron enviados en el idioma en el cual se radicó la solicitud internacional, salvo indicación en contrario consignada bajo este punto.
   Estos elementos estuvieron a disposición de la administración o le fueron enviados en el idioma siguiente _____ que es:
   - ☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23.1 (b)).
   - ☐ el idioma de publicación de la solicitud internacional (según la regla 48.3 (b)).
   - ☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55.2 y/o 55.3).

3. En lo que concierne a cualquier **secuencia de nucleótidos y/o aminoácidos** divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:
   - ☐ contenido en la solicitud internacional, por escrito.
   - ☐ Presentado con la solicitud internacional, en formato de lectura por computador.
   - ☐ remitido posteriormente a la administración, por escrito.
   - ☐ remitido posteriormente a la administración, en formato de lectura por computador.
   - ☐ se ha rendido la declaración, según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó.
   - ☐ se ha rendido la declaración, según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias, presentados por escrito.

4. ☐ Las modificaciones han acarreado la anulación:
   - ☐ de la descripción, páginas NINGUNA.
   - ☐ de las reivindicaciones, Nos. NINGUNA.
   - ☐ de los dibujos, hojas/fig NINGUNA.

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

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

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

INF RME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/US02/36528

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

1. DECLARACIÓN

Novedad (N)	Reivindicaciones 1-16	SÍ
	Reivindicaciones NINGUNA	NO
Actividad Inventiva (IS)	Reivindicaciones 1-16	SÍ
	Reivindicaciones NINGUNA	NO
Posibilidad de Aplicación Industrial (IA)	Reivindicaciones 1-16	SÍ
	Reivindicaciones NINGUNA	NO

2. CITAS Y EXPLICACIONES

Las reivindicaciones 1-16 satisfacen los criterios expuestos en el Artículo 33(2)-(3) PCT, porque el arte previo no enseña o medianamente sugiere los compuestos, composición y usos de la presente invención.

Las reivindicaciones 1-16 satisfacen los criterios expuestos en el Artículo 33(4) PCT y, en consecuencia, tienen posibilidad de aplicación industrial porque el tema revindicado puede estar o usarse en la industria.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

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

Date of mailing (day/month/year) 13 March 2003 (13.03.03)	
Applicant's or agent's file reference LD0280	**IMPORTANT NOTIFICATION**
International application No. PCT/US02/36528	International filing date (day/month/year) 12 November 2002 (12.11.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 14 November 2001 (14.11.01)
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
14 Nove 2001 (14.11.01)	60/333,014	US	31 Janu 2003 (31.01.03)

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

Facsimile No. (41-22) 740-1435

Authorized officer
Brigitte WYSS

Telephone No. (41-22) 338 8388

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (day/month/year) 29 JUL 2003
Applicant's or agent's file reference LD0280	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/36528	International filing date (day/month/year) 12 November 2002 (12.11.2002)
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 Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Melissa D. Roberts for Kathleen McKenzie Telephone No. (703) 308-1235

RECEIVED BMS PATENT LAW

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

8/4 JUL 31 2003

Docketed Item US-IDS
Due Date 10/29/03
Attorney EK

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

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

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of Mailing (*day/month/year*) 29 JUL 2003
Applicant's or agent's file reference LD0280	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/36528	International filing date (*day/month/year*) 12 November 2002 (12.11.2002)
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 Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Thelma McKenzie Telephone No. (703) 308-1235

Form PCT/ISA/220 (April 2002) (*See notes on accompanying sheet*)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LD0280	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/36528	International filing date (*day/month/year*) 12 November 2002 (12.11.2002)	(Earliest) Priority Date (*day/month/year*) 14 November 2001 (14.11.2001)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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

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

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

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

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

6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/36528

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 403/12,401/14; A61K 31/53; A61P 35/00
US CL : 514/183; 544/243
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. : 514/243; 544/183

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/071129 A1 (BRISTOL-MYERS SQUIBB COMPANY), 30 November 2000 (30.11.00), Examples 71, 138, and 140-143.	1-13
A	FRY, D.W. Chapter 16. Recent Advances in Tyrosine Kinase Inhibitors. Ann. Rep. Med. Chem., 1996, Vol. 31, pages 151-160.	1-13

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 February 2003 (09.02.2003)	29 JUL 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Thomas McKenzie Telephone No. (703) 308-1235

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

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.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded 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 should 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.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

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

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

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, where 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 Volume II of the PCT Applicant's Guide.

The demand must be filed directly with the competent International Preliminary Examining Authority ..., if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: LD0280 PCT
International application No.: PCT/US02/36528	International filing date *(day/month/year)*: 12 November 2002	(Earliest) Priority date *(day/month/year)*: 14 November 2001
Title of invention: C-D MODIFIED INDAZOLYLPYRROLOTRIAZINES		

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.)*	Telephone No. / Facsimile No. / Teleprinter No. / Applicant's registration No. with the Office
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:	State *(that is, country)* of residence:
United States of America	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.)*
MASTALERZ, Harold
70 Robin Lane
Guilford, CT 06437
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	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.)*
ZHANG, Guifen
883 Durham Road
Wallingford, CT 06492
United States of America

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

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US02/36528

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.)*

TARRANT, James G.
156 Handy Road
Hamden, CT 06518
United States of America

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VITE, Gregory
28 Continental Lane
Titusville, NJ 08560
United States of America

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/US02/36528

145

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

The following person is [X] agent [ ] common representative

and [X] 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:

   [X] the international application as originally filed

   the description [X] as originally filed
   [ ] as amended under Article 34

   the claims [X] as originally filed
   [ ] as amended under Article 19 (together with any accompanying statement)
   [ ] as amended under Article 34

   the drawings [X] 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

[X] 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:

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Sheet No. .4.

International application No.
PCT/US02/36528

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:				For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	0	sheets	☐	☐
2. amendments under Article 34	:	0	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	0	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	0	sheets	☐	☐
5. letter	:	0	sheets	☐	☐
6. other *(specify)*	:	0	sheets	☐	☐

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

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

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

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

Elliott K , Agent Date: June 5, 2003
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:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/36528	For International Preliminary Examining Authority use only
Applicant's or agent's file reference LD0280.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 *(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.)*	146.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	896.00 TOTAL	

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify):*

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ US

- [X] Authorization to charge the total fees indicated above.
- [X] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 19-3880

Date: June 5, 2003

Name: Elliott Korsen

Signature: Elliott K

PCT REQUEST LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:08:57 PM

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 01.10.2002)
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	LD0280
I	Title of invention	C-5 MODIFIED INDAZOLYLPYRROLOTRIAZINES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	MASTALERZ, Harold
III-1-5	Address:	70 Robin Lane Guliford, CT 06437 United States of America
III-1-6	State of nationality	CA
III-1-7	State of residence	US

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PCT REQUEST LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:08:57 PM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ZHANG, Guifen
III-2-5	Address:	883 Durham Rd Wallingford, CT 06492 United States of America
III-2-6	State of nationality	CN
III-2-7	State of residence	US
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	TARRANT, James, G
III-3-5	Address:	156 Handy Rd Hamden, CT 06518 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	VITE, Gregory, D.
III-4-5	Address:	28 Continental Lane Titusville, NJ 08560 United States of America
III-4-6	State of nationality	US
III-4-7	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)	PEIST, Kenneth
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.	609-252-3342
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	45,006

PCT REQUEST

LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:06:57 PM

IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	WINSLOW, Anastasia(40875); ALGIERI, Aldo(31,697); BABAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); DUBOFF, Samuel(25,969); GIBBONS, Maureen(44,121); HERMENAU, Ronald(34,620); KILCOYNE, John(33,100); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); MORSE, David(25,742); PATEL, Rena(41,412); PROVOOST, Jonathan(44,292); DAVIS, Stephen(26,693); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); FERGUSON, Blair(34,329); LARSEN, Scott(38,532); VANATTEN, Mary(39,408); GODDARD, Catherine, A.(46,731)
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 f the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE 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

PCT REQUEST LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:08:57 PM

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 NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under Item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	14 November 2001 (14.11.2001)
VI-1-2	Number	60/333,014
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)

VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
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

LB0280

Original (for SUBMISSION) - printed on 30.10.2002 12:06:57 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	67	-
IX-3	Claims	6	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	79	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	PEIST, Kenneth	

FOR RECEIVING OFFICE USE ONLY

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

FOR INTERNATIONAL BUREAU USE ONLY

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

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PCT (ANNEX - FEE CALCULATION SHEET)

LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:08:57 PM

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

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using		PCT-EASY Version 2.92 (updated 01.10.2002)		
0-9	Applicant's or agent's file reference		LD0280		
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	407		
12-4	Remaining sheets		49		
12-5	Additional amount	(X)	9		
12-6	Total additional amount	b2	441		
12-7	b1 + b2 =	B	848		
12-8	Designation fees				
	Number of designations contained in international application		94		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	88		
12-11	Total designation fees	D	440		
12-12	PCT-EASY fee reduction	R	-125		
12-13	Total international fee (B+D-R)	I	⇨	1,163	
12-14	Fee for priority document				
	Number of priority documents requested		1		
12-15	Fee per document	(X)	15		
12-16	Total priority document fee	P	⇨	15	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	2,118	
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 30.10.2002 12:08:57 PM

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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	30 October 2002 (30.10.2002)
12-23	Name and signature	PEIST, Kenneth

VALIDATION LOG AND REMARKS

13-1-1	Applicant remarks	Abstract contains a chemical drawing should be inserted as indicated in brackets with the fokllowing text, "INSERT CHEMICAL DRAWING HERE"

13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
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.

The present invention provides compounds of formula I [INSERT CHEMICAL DRAWING HERE]

and pharmaceutically acceptable salts thereof.

The formula I compounds inhibit tyrosine kinase activity of growth factor receptors such as HER1, HER2 and HER4 thereby making them useful as antiproliferative agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

PCT

LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:06:57 PM

PCT-EASY INFORMATION SHEET

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

VALIDATION LOG

Green?	Contents The international application contains no drawings. Please verify.
Green?	Payment Please ensure that you have a valid deposit account with the receiving Office selected.
Green?	Annotate All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

Before submitting the International Application, please carefully verify that:

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

ATTENTION

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

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LD0280

PCT POWER OF ATTORNEY

Printed on 19.09.2002 07:31:18 AM

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)

1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	PEIST, Kenneth; ALGIERI, Aldo; BABAJKO, Suzanne; BUCHHOLZ, Briana; D'AMICO, Stephen; DUBOFF, Samuel; GIBBONS, Maureen; HERMENAU, Ronald; KILCOYNE, John; KLEIN, Christopher; LANGE, Keith; MAKUJINA, Shah; MORSE, David; PATEL, Rena; DAVIS, Stephen; PROVOOST, Jonathan; RODNEY, Burton; RYAN, Richard; SHER, Audrey; SWITZER, Joan; O'BRIEN, Maureen; BELFIELD, Jing; FERGUSON, Blair; LARSEN, Scott; VANATTEN, Mary; GODDARD, Catherine, A. 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	C-MODIFIED INDAZOLYLPYRROLOTRIAZINES
1-4-2	Applicant's or agent's file reference	LD0280
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-1	Signature of applicant	Stephen B Davis
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Stephen B. Davis
2-1-3	Capacity	Patent Counsel
3	Date	19 September 2002 (19.09.2002)

CERTIFICATION

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

Suzanne Babajko
Stephen B. Davis
Blair Q. Ferguson
John M. Kilcoyne
Christopher Klein
David Morse
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 22nd day of May 2002.

John L. McGoldrick
Executive Vice President
and General Counsel

Secretary

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

MASTALERZ, Harold
70 Robin Lane
Guilford, CT 06437
UNITED STATES OF AMERICA

hereby appoint(s) the following person as: [X] agent [ ] common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ALGIERI, Aldo; BABAJKO, Suzanne, BUCHHOLZ, Briana, DAVIS, Stephen B.; D'AMICO, Stephen; DUNCAN, Laurelee, GIBBINS, Maureen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Johathan; RODNEY, Burt n; SHER, Audrey; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; DUBOFF, Samuel; MAKUJINA, Shah; MORSE, David; RYAN, Richard; BELFIELD, Jing FERGUSON, Blair; GODDARD, Christine; GOLIAN, Paul; LARSEN, Scott; VANATTEN, Mary; BAXAM, Deanna

to represent the undersigned before

[X] all the competent International Authorities
[ ] the International Searching Authority only
[ ] the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

United States Patent & Trademark Office as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; 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 this power):*

Harold Mastalerz

Harold Mastalerz

Date: Sept 26 2002

PCT

GENERAL POWER F ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

160

The undersigned person(s):
(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

ZHANG, Guifen
883 Durham Rd.
Wallingford, CT 06492
UNITED STATES OF AMERICA

hereby appoint(s) the following person as: [X] agent [ ] common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ALGIERI, Aldo; BABAJKO, Suzanne, BUCHHOLZ, Briana, DAVIS, Stephen B.; D'AMICO, Stephen; DUNCAN, Laurelee, GIBBINS, Maureen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Johathan; RODNEY, Burton; SHER, Audrey; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; DUBOFF, Samuel; MAKUJINA, Shah; MORSE, David; RYAN, Richard; BELFIELD, Jing FERGUSON, Blair; GODDARD, Christine; GOLIAN, Paul; LARSEN, Scott; VANATTEN, Mary; BAXAM, Deanna

to represent the undersigned before

[X] all the competent International Authorities

[ ] the International Searching Authority only

[ ] the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

United States Patent & Trademark Office as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; 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 this power):*

Guifen Zhang

Date: 9-26-2002

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

TARRANT, James G.
156 Handy Rd.
Hamden, CT 06518
UNITED STATES OF AMERICA

hereby appoint(s) the following person as: [X] agent [ ] common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ALGIERI, Aldo; BABAJKO, Suzanne, BUCHHOLZ, Briana, DAVIS, Stephen B.; D'AMICO, Stephen; DUNCAN, Laurelee, GIBBINS, Maureen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maure n; PATEL, Rena; PEIST, Kenneth; PROVOOST, Johathan; RODNEY, Burton; SHER, Audrey; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; DUBOFF, Samuel; MAKUJINA, Shah; MORSE, David; RYAN, Richard; BELFIELD, Jing FERGUSON, Blair; GODDARD, Christine; GOLIAN, Paul; LARSEN, Scott; VANATTEN, Mary; BAXAM, Deanna

to represent the undersigned before

[X] all the competent International Authorities

[ ] the International Searching Authority only

[ ] the International Preliminary Examining Authority only

in connection with my and all international applications filed by the undersigned with the following Office

United States Patent & Trademark Office as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; 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 this power):*

James G. Tarrant

Date: 26 Sept 2002

PCT

GENERAL POWER OF ATTORNEY

(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

16 2

The undersigned person(s):
(Family name followed by given name; for a full legal entity, full official designation. The address must include postal code and name of country.)

VITE, Gregory D.
28 Continental Lane
Titusville, NJ 08560
UNITED STATES OF AMERICA

hereby appoint(s) the following person as: [X] agent [ ] common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ALGIERI, Aldo; BABAJKO, Suzanne, BUCHHOLZ, Briana, DAVIS, Stephen B.; D'AMICO, Stephen; DUNCAN, Laurelee, GIBBINS, Maureen; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Johathan; RODNEY, Burton; SHER, Audrey; WILK-ORESCAN, Rosemarie; WINSLOW, Anastasia; DUBOFF, Samuel; MAKUJINA, Shah; MORSE, David; RYAN, Richard; BELFIELD, Jing; FERGUSON, Blair; GODDARD, Christine; GOLIAN, Paul; LARSEN, Scott; VANATTEN, Mary; BAXAM, Deanna

to represent the undersigned before

[X] all the competent International Authorities

[ ] the International Searching Authority only

[ ] the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

United States Patent & Trademark Office as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; 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 this power):*

Gregory D Vite

Date: October 1, 2002

The present invention pro\ s compounds of formula I [INSERT C. MICAL DRAWING HERE] 163

and pharmaceutically acceptable salts thereof.

The formula I compounds inhibit tyrosine kinase activity of growth factor receptors such as HER1, HER2 and HER4 thereby making them useful as antiproliferative agents. The formula I compounds are also useful for the treatment of other diseases associated with signal transduction pathways operating through growth factor receptors.

PCT

LD0280

Original (for SUBMISSION) - printed on 30.10.2002 12:06:57 PM

PCT-EASY INFORMATION SHEET

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

VALIDATION LOG

Green?	**Contents** The international application contains no drawings. Please verify.
Green?	**Payment** Please ensure that you have a valid deposit account with the receiving Office selected.
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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.

Docket No. LD0280 PCT

New Int'l. Application No. based on USSN 60/333,014 Filed: November 14, 2001.

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

Express mail mailing label number ET979324606US

Date of Deposit Nov. 11, 2002

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.

Diane C. Bartram
(Typed or printed name of person mailing paper or fee)

Diane C. Bartram
(Signature of person mailing paper or fee)

15:93.882

Col

160

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
EVELYN VAZQUEZ

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
EVELYN VAZQUEZ, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

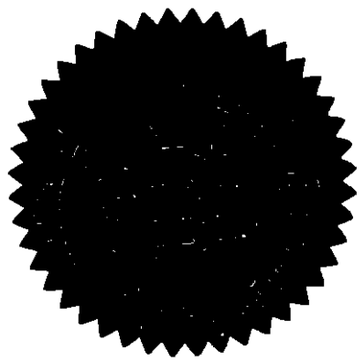
6. THE 19TH DAY OF MARCH 2004

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A193253

9. SEAL/STAMP:

10. SIGNATURE



Cd

60/333,014-LD0280

167

I, Stephen B. Davis, Patent Counsel, Patent Department, Bristol-Myers Squibb Company

do hereby certify that this document is a notarized true and accurate copy of the original assignment signed by the inventors.

Stephen B. Davis

STATE OF New Jersey :
: ss.
COUNTY OF Mercer :

Subscribed before me on this 16th day of March, 2004

Notary Public

(SEAL)

EVELYN VAZQUEZ
Notary Public of New Jersey
No. 2106606
My Commission Expires Dec. 8, 2007
Registered in Middlesex County

168

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE RECD	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/333,014	11/14/2001		160	LD0280 (PSP)			

CONFIRMATION NO. 5183

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

FILING RECEIPT

OC000000007153481

Date Mailed: 12/04/2001

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Harold Mastalerz, Guilford, CT;
Gulfen Zhang, Wallingford, CT;
James G. Tarrant, Hamden, CT;
Gregory D. Vite, Titusville, NJ;

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

C-5 modified indazolylpyrrolotriazines

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

169

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

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Commissioner for Patents
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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/294,281	11/14/2002	1614	740	LD0280 (NP)		16	1

CONFIRMATION NO. 9343

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

FILING RECEIPT

OC000000009280222

Date Mailed: 12/18/2002

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)

Harold Mastalerz, Guilford, CT;
Gulfen Zhang, Wallingford, CT;
James G. Tarrant, Hamden, CT;
Gregory D. Vite, Titusville, NJ;

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/333,014 11/14/2001

Foreign Applications

If Required, Foreign Filing License Granted: 12/18/2002

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

C-5 Modified indazolylpyrrolotriazines

Preliminary Class
514

LICENSE FOR FOREIGN FILING UNDER
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Title 37, Code of Federal Regulations, 5.11 & 5.15

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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.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/294,281	11/14/2002	1614	870	LD0280 (NP)		16	1

CONFIRMATION NO. 9343

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

UPDATED FILING RECEIPT

OC000000009498384

Date Mailed: 02/10/2003

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Applicant(s)

Harold Mastalerz, Guilford, CT;
Guifen Zhang, Wallingford, CT;
James G. Tarrant, Hamden, CT;
Gregory D. Vite, Titusville, NJ;

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/333,014 11/14/2001

Foreign Applications

If Required, Foreign Filing License Granted: 12/18/2002

Projected Publication Date: 05/22/2003

Non-Publication Request: No

Early Publication Request: No

Title

C-5 Modified Indazolylpyrrolotriazines

123

Preliminary Class
514

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

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UNITED STATES DEPARTMENT OF COMMERCE
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JANUARY 27, 2003

PTAS

700023053A

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

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RECORDATION DATE: 01/24/2003 REEL/FRAME: 013382/0282
NUMBER OF PAGES: 5

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

ASSIGNOR:
MASTALERZ, HAROLD DOC DATE: 01/13/2003

ASSIGNOR:
ZHANG, GUIFEN DOC DATE: 01/14/2003

ASSIGNOR:
TARRANT, JAMES G. DOC DATE: 01/09/2003

ASSIGNOR:
VITE, GREGORY D. DOC DATE: 01/08/2003

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

SERIAL NUMBER: 10294281 FILING DATE: 11/14/2002
PATENT NUMBER: ISSUE DATE:

175

013382/0282 PAGE 2

STEVEN POST, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

126

FORM PTO-1595 (Rev. 9-98)
OMB No. 0651-0011 (exp. 4/94)
LD0280 (NP)

RECORDATION FORM COVER SHEET
700023053
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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

1. Name of conveying party(ies):

Harold Mastalerz, Guifen Zhang, James G. Tarrant, Gregory D. Vite

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

3. Nature of conveyance:

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

Execution Date: 1/13/03, 1/14/03, 1/9/03, 1/8/03.

2. Name and address of receiving party(ies)
Name: Bristol-Myers Squibb Company
Internal Address: _____

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

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

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)
10/294,281

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

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

Name: Stephen B. Davis
Internal Address: Bristol-Myers Squibb Company
Patent Department
Street Address: P.O. Box 4000
City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40

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

8. Deposit account number:
19-3880 (in the name of Bristol-Myers Squibb Company)
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

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

Kenneth W. Peist — Signature — January 24, 2003
Name of Person Signing
Reg. No. 45,008
Date

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FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)
LD0280 (NP)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

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

1. Name of conveying party(ies):

Harold Mastalerz, Gulfen Zhang, James G. Tarrant, Gregory D. Vite

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

2. Name and address of receiving party(ies)
Name: Bristol-Myers Squibb Company
Internal Address:

Street Address: Lawrenceville-Princeton Road

City: Princeton State: NJ ZIP: 08543-4000

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

3. Nature of conveyance:

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

Execution Date: 1/13/03, 1/14/03, 1/9/03, 1/8/03.

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

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

A. Patent Application No.(s)
10/294,281

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

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

Name: Stephen B. Davis
Internal Address: Bristol-Myers Squibb Company
Patent Department
Street Address: P.O. Box 4000
City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40

☐ Enclosed

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

8. Deposit account number:
19-3880 (In the name of Bristol-Myers Squibb Company)
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Kenneth W. Peist — Name of Person Signing
Reg. No. 45,006

Signature

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Worldwide
Case LD0280 (NP)

ASSIGNMENT

We,

Harold Mastalerz	residing at	70 Robin Lane Guilford, Connecticut 06437 United States of America
Guifen Zhang	residing at	883 Durham Road Wallingford, Connecticut 06492 United States of America
James G. Tarrant	residing at	156 Handy Road Hamden, Connecticut 06518 United States of America
Gregory D. Vite	residing at	28 Continental Lane Titusville, New Jersey 08560 United States of America,

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

C-5 Modified Indazolylpyrrolotriazines

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

Application No. 10/294,281, filed November 14, 2002,

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors

and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

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

Signed this 13 day of January, 2003 by Harold Mastalerz
Harold Mastalerz

Signed this 14 day of January, 2003 by
Gulfen Zhang

Signed this 9 day of January, 2003 by
James G. Tarrant

Signed this 8 day of January, 2003 by
Gregory D. Vite

STATE OF CONNECTICUT)
) ss. Wallingford
COUNTY OF New Haven)

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

Janet C Sudol
Notary Public

[SEAL]

JANET C. SUDOL
Notary Public, State Of Connecticut
My Commission Expires August 31, 2007

STATE OF CONNECTICUT)
) ss. Wallingford
COUNTY OF New Haven)

On this day 14 of January, 2003, before me came Guifen Zhang, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Janet C Sudol
Notary Public

[SEAL]

JANET C. SUDOL
Notary Public, State Of Connecticut
My Commission Expires August 31, 2007

STATE OF CONNECTICUT)
) ss. Wallingford
COUNTY OF New Haven)

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

Janet C Sudol
Notary Public

[SEAL]

JANET C. SUDOL
Notary Public, State Of Connecticut
My Commission Expires August 31, 2007

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

On this day 8th of January, 2003, before me came Gregory D. Vite, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Lisa Swidra
Notary Public

[SEAL]

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

182 182

SUPERINDUSTRIA Y COMERCIO
Radicación 04043611 00000000 Folios 181
Fecha (AMD) 2004-05-12 10 55 12
Trámite 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
Indicación de que se solicita la concesión de una patente	( )	(✓)
Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	(✓)
Descripción de la invención.	( )	(✓)
Dibujo de esto pertinente	( )	(✓)
Comprobante del Pago de la tasa 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 fotográfica del Diseño industrial 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	( )	( )
CÓMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable Claudia M Nieva

Fecha

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Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Fecha 27/05/2004

MANTENIMIENTO DE PROTOCOLOS

Numero : 19358
Fecha : 07/05/1999
Conferido: BRISTOL-MYERS SQUIBB COMPANY

Pais : US ESTADOS UNIDOS DE AMERICA
Ciudad : 82 PRINCETON, NEW JERSEY
Represent: S Sustituir : S Desistir : S
No. Radicacion : 99 28346 Clase: 0 Seev: 0 Seac: 0

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scncia	Codigo	Ctr	Nombre
1	340	A	CASTRO DUQUE RAMIRO
2	3002		GOMEZ MEJIA HECTOR

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Industria y Comercio
SUPERINTENDENCIA

Folio 184

2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)

REFERENCIA:	Radicación N°	04-043611
	Solicitud internacional	PCT/US2002/36528
	Fecha inicio fase nacional	14/06/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	748
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C, 31 MAYO 2004

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044

Industria y Comercio
SUPERINTENDENCIA

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04-043611

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **542**

DE FECHA **30** DE **JULIO DEL 2004** EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **26** DE **OCTUBRE** DEL **2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI __ __ _____ NO__ _X _ _ _ _____

Bogotá D.C, AGOSTO DE 2006

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 4-43611 EDICTO No. 13739

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 23295 de 31-AGO-2006. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT), de acuerdo con las razones expuestas en la parte considerativa de la presente resolución.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Ramiro Castro Duque, o a quien haga sus veces, en su calidad de apoderado de Bristol – Myers Squibb Company., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 31 AGO. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME BURGOS ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaria General Ad-Hoc 15-SEP-2006 _____ Este edicto se desfija hoy 28-SEP-2006 a las cinco (5:00 p.m.) _____
Secretaria General Ad-Hoc
EDICTO No. 13739