PCT

QF

Industria y Comercio

SUPERINTENDENCIA

11-9242

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-009242- -00000-0000
Fecha: 2011-01-27 16:39:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 158

SOLICITUD DE P
INVENCI

TITULO: 5-ALQUINIL-PIRIMIDINAS

SOLICITANTE: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DIRECCIÓN: Binger Strasse 173, 55216 Ingelheim Am Rhein, Alemania

APODERADO: CARLOS R. OLARTE

BOGOTÁ 27 de Enero 2011

P2011/000015

29-02-2011

OLARTEM

OLARTE MOURE & ASOCI

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-009242- -00000-0000
Fecha: 2011-01-27 16:39:36 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 158

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000015**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMH** GMBH
Dirección: Binger Strasse 173, 55216 Ingelheim Am Rhein
Nacionalidad o Domicilio: Alemania
Lugar de Constitución: Alemania
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Diagonal 34 No. 5-28 Bogotá, Colombia
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2009/059763 Fecha Julio 28, 2009

Publicación Internacional No. WO 2010/012740 Fecha Febrero 4, 2010

(6) **Título (54)** **5-ALQUINIL-PIRIMIDINAS**

Clasificación Internacional (51) C07D 239/48, C07D 401/04, C07D 401/06, C07D 403/06, C07D 403/14, C07D 409/06, C07D 413/14 A61K 31/495

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Julio 29, 2008	08161369.7

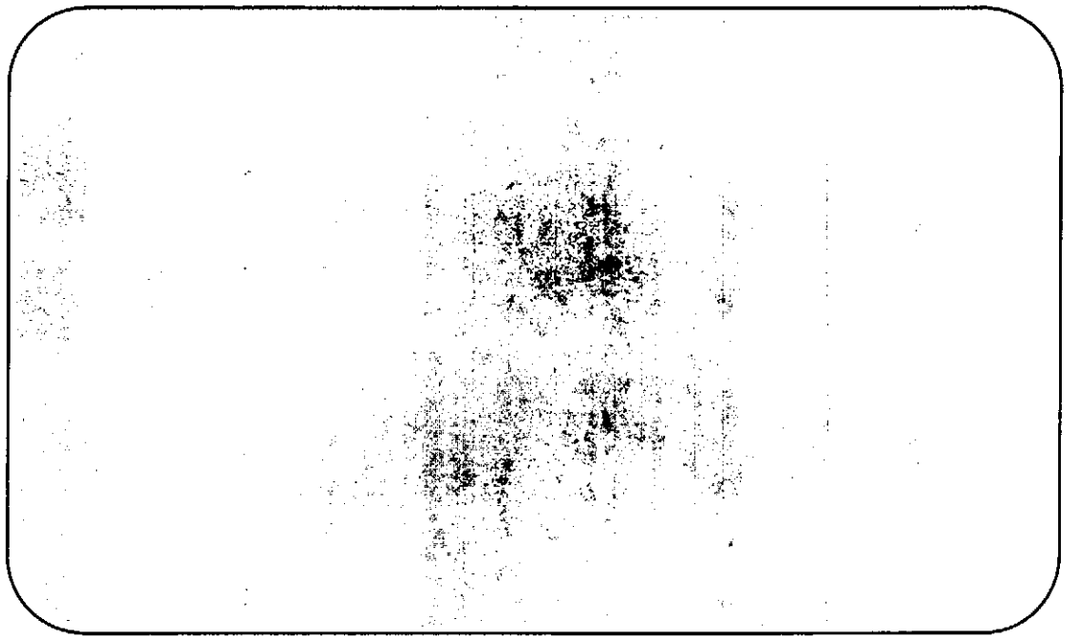
(9) **Comprobante de pago No.** 11- **Fecha** Enero 27 de 2011

ANEXOS

9

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. Copia Autentica.
- [ ] 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).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional 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 12 x 12.
- [ ] 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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES

PCT/EP2009/059763

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Nacionalidad: Alemana

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van der VEEN Lars,
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Nacionalidad: Alemana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 007878

Bogotá D.C., Enero 27 de 2011 - 16:16:22

RECIBIDO DE : OLARTERAISBECK NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	353914455	27/01/2011	2.855.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-009242- -00000-0000
Fecha: 2011-01-27 16:39:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 158

5

TESTIMONIO

ESCRITURA: 001416
MINUTA: 000657

K: 007735

DELEGACION DE PODER
QUE OTORGA
BOEHRINGER INGELHEIM INTERNATIONAL GMBH
REPRESENTADO POR
JANNE IVETTE LUQUE CARDENAS
A FAVOR DE
CARLOS REINALDO OLARTE

&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&&

INTRODUCCION ==========

EN LA CIUDAD DE LIMA AL VEINTISEIS DE JULIO DEL DOS MIL DIEZ, ANTE MI; MARIO GINO BENVENUTO MURGUIA, NOTARIO DE ESTA CAPITAL. ==========

COMPARECEN: ==========

JANNE IVETTE LUQUE CARDENAS, QUIEN MANIFIESTA SER DE NACIONALIDAD: PERUANA, DE ESTADO CIVIL CASADA, DE PROFESION U OCUPACIÓN: ABOGADA Y DOMICILIAR EN AVENIDA REPUBLICA DE PANAMA 3531, OFICINA 1203, DISTRITO DE SAN ISIDRO PROVINCIA Y DEPARTAMENTO DE LIMA, DEBIDAMENTE IDENTIFICADA CON DOCUMENTO NACIONAL DE IDENTIDAD NUMERO 29562321, QUIEN PROCEDE EN REPRESENTACION DE **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, CUYAS FACULTADES CONSTAN EN EL PODER OTORGADO CON FECHA QUINCE DE JULIO DEL DOS MIL DIEZ, DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES ESTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, QUE SE INSERTA. ====
LA COMPARECIENTE ES INTELIGENTE EN EL IDIOMA CASTELLANO, QUIEN SE OBLIGA CON CAPACIDAD, LIBERTAD Y CONOCIMIENTO SUFICIENTE DE CONFORMIDAD CON EL EXAMEN QUE LE HE EFECTUADO DE LO QUE DOY FE; Y ME ENTREGO UNA MINUTA QUE ARCHIVO EN SU LEGAJO RESPECTIVO BAJO EL NUMERO DE ORDEN CORRESPONDIENTE Y CUYO TENOR LITERAL ES COMO SIGUE: ==========

MINUTA: ==========

SEÑOR NOTARIO: ==========

SÍRVASE EXTENDER EN SU REGISTRO DE ESCRITURAS PÚBLICAS UNA DE **DELEGACION DE PODER** QUE OTORGA LA SEÑORA **IVETTE LUQUE CARDENAS**, IDENTIFICADA CON DNI N° 29562321, DE NACIONALIDAD PERUANA, ESTADO CIVIL CASADA, OCUPACIÓN ABOGADO Y CON DOMICILIO EN AV. REPÚBLICA DE PANAMÁ N° 3531, OFICINA 1203, SAN ISIDRO, QUIEN ACTÚA EN REPRESENTACIÓN DE **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, SEGÚN PODER OTORGADO CON FECHA 13 DE OCTUBRE DE 2009, Y A QUIEN EN ADELANTE SE LE DENOMINARÁ **EL PODERDANTE**; A FAVOR DEL SEÑOR **CARLOS REINALDO OLARTE**, IDENTIFICADO CON CÉDULA N° 79.782.747, A QUIEN EN ADELANTE SE LE DENOMINARÁ **EL APODERADO**; EN LOS SIGUIENTES TÉRMINOS Y CONDICIONES: ==========

PRIMERO: CON FECHA 15 DE JULIO DE 2010, LA EMPRESA **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, OTORGÓ PODER A FAVOR DE **EL PODERDANTE**, EL CUAL USTED SEÑOR NOTARIO SE SERVIRÁ INSERTAR. ==

SEGUNDO: POR EL PRESENTE DOCUMENTO, **EL PODERDANTE** DELEGA PODER A FAVOR DE **EL APODERADO** PARA QUE REPRESENTE EN LA REPÚBLICA DE COLOMBIA A LA SOCIEDAD **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, TAL COMO CONSTA EN EL PODER ADJUNTO, ANTE CUALQUIER AUTORIDAD ADMINISTRATIVA O JUDICIAL, INCLUYENDO LA SECRETARÍA Y TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA, PARA EL INICIO, TRAMITACIÓN, OBTENCIÓN, DEFENSA Y HACER RESPETAR TODAS Y CUALQUIERA DE LAS PATENTES DE INVENCIÓN, MODELOS DE UTILIDAD, DISEÑOS INDUSTRIALES, MARCAS, LEMAS COMERCIALES, NOMBRES COMERCIALES, PROTECCIÓN DE DATOS DE PRUEBA, PROTECCIÓN DE SECRETOS EMPRESARIALES, DERECHOS DE AUTOR, REGISTRO DE NOMBRES DE DOMINIO, O SEGUIMIENTO DE PROCEDIMIENTOS EN MATERIAS TALES COMO PROPIEDAD INTELECTUAL. ==========

AUTENTICACION DE COPIA DE ORIGINAL
LA SUSCRITA NOTARIA TREINTA Y OCHO (38)(E) CERTIFICA QUE LA PRESENTE COPIA COINCIDE EXACTAMENTE CON EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA.
27 ENE 2011
MONICA ZU... BAUTISTA ...
Notaria 38(E) DEL CIRCULO DE BOGOTÁ

10

TESTIMONIO

EL APODERADO ACTUANDO EN FORMA INDIVIDUAL PODRÁ DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENCIONES, PRESENTAR TODO TIPO DE SOLICITUDES, RECURSOS, RESPUESTAS U OPOSICIONES, PRESENTAR TODO TIPO DE RECURSOS DE IMPUGNACIÓN, PRESENTAR DECLARACIONES, JURADAS O NO, PRESENTAR CUALQUIER OTRO RECURSO O REMEDIO PROCESAL PERMITIDO POR LEY, PAGAR IMPUESTOS Y ANUALIDADES, SOLICITAR TESTIMONIOS; RENUNCIAR A LOS DERECHOS DE REGISTRO SOBRE UN ELEMENTO DE LA PROPIEDAD INDUSTRIAL, DESISTIRSE DEL PROCESO Y DE LA PRETENSIÓN, ALLANARSE A LA PRETENSIÓN, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SOLICITAR Y EJECUTAR MEDIDAS CAUTELARES ASÍ COMO VISITAS INSPECTIVAS, RATIFICAR LOS ACTOS JURÍDICOS PROCESALES SUSCRITOS CON ANTERIORIDAD AL OTORGAMIENTO Y/O PRESENTACIÓN DEL PRESENTE PODER, SUSTITUIR O DELEGAR LA REPRESENTACIÓN, REVOCAR LOS PODERES OTORGADOS, RECIBIR NOTIFICACIONES EN NOMBRE DE LA COMPAÑÍA Y LOS DEMÁS ACTOS QUE EXPRESE LA LEY. ==========
AGREGUE USTED SEÑOR NOTARIO, LAS CLÁUSULAS DE LEY, E INSERTE EL PODER AL QUE SE HA HECHO REFERENCIA. =======
LIMA, 21 DE JULIO DE 2010. ==========
FIRMADO.- UNA FIRMA ILEGIBLE.- ==========
ABOGADO QUE AUTORIZA, UN SELLO QUE DICE.- JURGEN STROBACH FLORIAN.- ABOGADO.- C.A.L. 30548.- UNA FIRMA ILEGIBLE.-
INSERTO UNO: TRADUCCION OFICIAL ==========
MARIO GINO BENVENUTO MURGUIA, ABOGADO NOTARIO DE LIMA, CERTIFICO QUE HE TENIDO A LA VISTA **LA TRADUCCION OFICIAL DEL PODER ESPECIAL,** DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES EXTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, CUYO TENOR LITERAL ES COMO SIGUE: ==========

TRADUCCIÓN OFICIAL

TRA. N° TOI.0077.10

Primera página del documento original:

PODER ESPECIAL de fecha 15 de julio de 2010 redactado en idioma castellano e inglés

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Segunda página del documento original:

UR. Nr. 1446/2010

Por la presente se certifica que las firmas que anteceden de:

- Dr. Michael Kompter, nacido el 11 de mayo de 1955, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.
- Dr. Christian Hauke, nacido el 31 de agosto de 1947, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.

a quienes he conocido en persona,
han sido estampadas en mi presencia

Asimismo, certifico que Boehringer Ingelheim International GmbH. es una sociedad debidamente constituida bajo las leyes de la República Federal de

Mary Ann Montaguth Medina
Traductora Pública Juramentada
Registro Art. N° 105

Estados Unidos 688 - Lima 11 - Perú - Telfs. (511) 460-1659 • (511) 463-1167 • Fax: (511) 463-4548
maenim@terra.com.pe

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27 ENE 2011
(38)
MONICA ZULIMA BAUTISTA NAVARRO
Notaria 38(E) DEL CIRCULO DE BOGOTÁ D.C.

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
Central: 719 – 1667 / 719 – 1668 / 719 – 1669 / Telefax.: 717 – 1031
www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com

Mario Gino Benvenuto Morosi

ABOGADO NOTARIO DE LIMA

TESTIMONIO

TRA. N° TOI.0077.10

Alemania, con domicilio en Binger Strasse 173, 55216 Ingelheim am Rhein, Alemania.

Dicha sociedad se encuentra inscrita en el Registro Mercantil del Juzgado de Distrito de Bingen, bajo el número HR B 1063 desde el 14 de mayo de 1968. Dicha inscripción ha sido transferida por ley al Registro Mercantil del Juzgado de Distrito de Mainz, donde se encuentra inscrita bajo el número HR B 21063 desde el 28 de diciembre de 2005.

Asimismo, certifico que los doctores Michael Kompter y Christian Hauke, han sido autorizados para firmar el documento que antecede y actualmente se encuentran debidamente autorizados para firmar a nombre de Boehringer Ingelheim International GmbH en calidad de apoderados.

Ingelheim am Rhein, 15 de julio de 2010

(firmado ilegible)

Notario Público

Mary Ann Montealegre Medina
Traductora Pública Juramentada
Registro JVT N° 105

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maelrm@terra.com.pe

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
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27 ENE 2011
MONICA ZULMA BAUTISTA NAVARRO
Notaria (38) DEL CIRCULO DE BOGOTA D.C.

8

TESTIMONIO

TRA. N° TOI.0077.10

Reverso de la segunda página del documento original:

(sello en idioma extranjero distinto al inglés, de fecha 16 de julio de 2010)

(sello en idioma castellano del Consulado del Perú, de fecha 20 de julio de 2010)

(sello) **MINISTERIO DE RELACIONES EXTERICORES**

DIRECCIÓN GENERAL DE POLÍTICA CONSULAR

Legalización N° 092720

Se legaliza la firma que antecede del Sr.(a) Alfredo Arecco-Sablich sin juzgar el contenido del documento

Lima, 23 de julio de 2010

(fdo.) Maribel del Rosario LUYO JAVIER

Departamento de Legalizaciones

Dirección de Trámites Consulares/sello

La infrascrita, Traductora Pública Juramentada, certifica que la presente traducción es fiel y correcta del texto original en idioma Castellano..... adjunto. Esta traducción no debe interpretarse como reconocimiento de la autenticidad del documento traducido.
En fe de lo cual, firmo y sello en.....Lima..... a los...26.....días del mes de...julio.....de.2010..

MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR
Legalización Nº
Se legaliza la firma que antecede del Sr.(a)
SIN JUZGAR EL CONTENIDO DEL DOCUMENTO
Julia Adela Moreno de Dueñas
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA 27 JUL. 2010

Mary Ann Montesjudo Medina
Traductora Pública Juramentada
Registro JVT 3 Nº 105

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27 ENE 2011
NOTARIA 32
MONICA ZUTA ESPINOZA
NOTARIA DEL CIRCULO DE BOGOTA D.C.

TESTIMONIO

FERNÁNDEZ - DÁVILA & BUENO
ABOGADOS

PODER ESPECIAL

Consta por el presente documento el Poder Especial que otorga *[insertar nombre de poderdante]*, domiciliada en *[insertar domicilio]* constituida de acuerdo a las leyes de *[insertar país de constitución]*, representada por su *[insertar cargo en la cía.]* Sr.(a) *[insertar nombre del representante de la cía.]*, a favor de FERNÁNDEZ-DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DAVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS y/o CLARISA SILES VASCONES, domiciliados en Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, para que la representen en la República de Perú, República de Bolivia, República de Chile, República de Colombia, República de Ecuador y República Bolivariana de Venezuela, ante cualquier autoridad administrativa o judicial, incluyendo la Secretaría y Tribunal de Justicia de la Comunidad Andina, para el inicio, tramitación, obtención, defensa y hacer respetar todas y cualquiera de las patentes de invención, modelos de utilidad, diseños industriales, marcas, lemas comerciales, nombres comerciales, protección de datos de prueba, protección de secretos empresariales, derechos de autor, registro de nombres de dominio, o seguimiento de procedimientos en materias tales como Propiedad Intelectual.

Los apoderados podrán ejercer el presente poder actuando en forma individual e indistinta, y gozarán de las siguientes facultades, tales como demandar, reconvenir, contestar demandas y reconvenciones, presentar todo tipo de solicitudes, recursos, respuestas u oposiciones, presentar todo tipo de recursos de impugnación, presentar declaraciones, juradas o no, presentar cualquier otro recurso o remedio procesal permitido por ley, pagar impuestos y anualidades, solicitar testimonios, renunciar a los derechos de registro sobre un elemento de la propiedad industrial, desistirse del proceso y de la pretensión, allanarse a la pretensión, conciliar, transigir, someter a arbitraje las pretensiones controvertidas en el proceso, solicitar y ejecutar medidas cautelares así como visitas inspectivas, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal, revocar los poderes otorgados, recibir notificaciones en nombre de la compañía y los demás actos que exprese la ley.

Suscrito en..... el ..... de ..... de 2010

ESTE PODER REQUIERE DE LEGALIZACIÓN NOTARIAL (PRECISANDO QUE EL REPRESENTANTE TIENE LAS FACULTADES PARA OTROGARLO Y QUE ESTUVO PRESENTE AL MOMENTO DE HACERLO) Y DE CONSUL PERUANO (CUANDO ES OTORGADO EN EL EXTRANJERO)

SPECIAL POWER OF ATTORNEY

By means of this Special Power of Attorney *Boehringer Ingelheim International GmbH* with address in *Binger Strasse 173, 55216 Ingelheim am Rhein, Germany* and incorporated under the laws of *Germany* duly represented by its *Authorized Signatories* Dr. Michael KOMPTER and Dr. Christian HAUKE, grants to FERNÁNDEZ-DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DAVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS and/or CLARISA SILES VASCONES, with address at Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, the powers to represent in the Republic of Perú, the Republic of Bolivia, Republic of Chile, Republic of Colombia, Republic of Ecuador and the Bolivarian Republic of Venezuela before any administrative or judicial authority of any class, including the Andean Secretariat and the Andean Court of Justice to initiate, prosecution, obtain, defend and enforce any and all of the company's Patents for Invention, Utility Models, Industrial Designs, Trademarks, Trade Names, Commercial Emblems, Test Data Protection, Protection of Trade Secrets, Copyrights, Registration of Domain names and handle proceedings related to Intellectual Property.

The empowered representatives will exert this power of attorney acting individually and indistinctively with the following powers, having authority to claim, to counter-claim, to answer complaints and counter-claims, to file petitions, recourses, replies and oppositions, to withdraw the registration of an industrial property element, to abandon the action and the requested relief, to defend a suit, to file standard or sworn declarations, to file all sort of petitions, appeal and motions permitted by law, pay taxes and annuities, request testimonies, to accept in total or part the demanded pretensions, conciliate, settle, submit to arbitration the contradicted pretensions in the process, to require and execute precautionary measures and inspections among others, to ratify all the acts in regular procedures and proceedings entered into before the granting and/or presentation of this document, substitute or delegate the representation, revoke such substitutions, receive notifications on behalf of the Company and for the rest of the acts which the law provides.

Executed in Ingelheim, on 15th July of 2010

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

ppa.

Dr. Michael KOMPTER
Authorized Signatory

ppa.

Dr. Christian HAUKE
Authorized Signatory

THIS POWER OF ATTORNEY REQUIRES LEGALIZATION OF A NOTARY (STATING THAT THE REPRESENTATIVE HAS ENOUGH POWERS TO GRANT IT AND APPEARED AND EXECUTED IT PERSONALLY) AND OF A PERUVIAN CONSUL (WHEN GRANTED ABROAD)

AUTENTICACION DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIA TREINTA Y OCHO(38) CERTIFICA QUE LA PRESENTE COPIA COINCIDE EXACTAMENTE CON EL DOCUMENTO ORIGINAL QUE HA TENIDO A LA VISTA.
27 ENE 2011
NOTARIA

TESTIMONIO

UR.Nr. 1446/2010

It is herewith certified that above signatures of:

- Dr. Michael **K o m p t e r**, born 11th day of May 1955, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,
- Dr. Christian **H a u k e**, born 31st day of August 1947, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,

personally known,
were duly given in my presence.

It is herewith certified that **Boehringer Ingelheim International GmbH** is a corporation duly organized and existing under the laws of the Federal Republic of Germany having its principal place of business at Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

It had been entered into the Commercial Register of the District Court of Bingen under HR B 1063 as of 14th day of May 1968. This registration was transferred by law to the Commercial Register of the District Court of Mainz, where it has been registered under HR B 21063 since 28th day of December 2005.

Furthermore, I certify that Dr. Michael Kompter and Dr. Christian Hauke were authorized to sign the foregoing document and still are duly authorized to sign on behalf as procurists of **Boehringer Ingelheim International GmbH.**

Ingelheim am Rhein, the 15th day of July 2010/Ge

Notary public

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NOTARÍA TRENTA Y OCHO CAPITAL
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27 ENE 2011
MÓNICA ZULMA BAUTISTA ALVARO
NOTARIA 38 DEL CIRCULO DE BOGOTA D.C.

Mario Cino Benvenuto Morgan
ABOGADO NOTARIO DE LIMA

TESTIMONIO

AL DORSO: ==========

910 E 1

Die Echtheit vorstehender Unterschrift des

Notars Horst Heintskill in Ingelheim am Rhein

und die Echtheit des beigedrückten Dienstsiegels

werden hierdurch bestätigt. Zugleich wird bescheinigt, dass der

Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Präsidentin des Landgerichts 2 Mainz

Kostenrechnung:
Gebühr für die Erteilung
der Legalisation
Wert: 50.000,00 €
JVKostO v. 26.7.1957
i.V.m. § 45 KostO
Gebühr: 33,00 €
Mainz, 16.07.10
Heppes-Schwarz
Amtsinspektorin

Präsidentin des Landgerichts 2 Mainz

Mainz, den 16. Juli 2010
Die Präsidentin des Landgerichts
In Vertretung
Dr. Matthias Friedrich
Vorsitzender Richter am Landgericht

CONSULADO GENERAL DEL PERU
FRANCFORT DEL MENO

Se legaliza la firma de:
DR. MATTHIAS FRIEDRICH

Quien desempeña el cargo de:
REPRESENTANTE DEL PRESIDENTE
DEL JUZGADO REGIONAL
EN MAINZ

N° de Orden: 0363
N° de Actuación: 4474
N° de Tarifa: 22 a
Derechos percibidos: S/. 80.-
€ 22.-

Francfort del Meno, 20 DE JULIO DE 2010

ALFREDO ARECCO-SABLICH
Cónsul General del Perú

CONSULADO GENERAL DEL PERU FRANCFORT DEL MENO

MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLITICA CONSULAR
Legalización Nº 092720
Se legaliza la firma que antecede del Sr(a)
Alfredo Arecco - Sablich
SIN JUZGAR EL CONTENIDO DEL DOCUMENTO

Meribel del Rosario Luyo Jayler
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA, 23 JUL. 2010

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
Central: 719 – 1667 / 719 – 1668 / 719 – 1669 / Telefax.: 717 – 1031
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NOTARIA 38 DEL CIRCULO DE BOGOTA D.C.

Mario Gino Benvenuto Murguía
ABOGADO NOTARIO DE LIMA

TESTIMONIO

INSERTO. ==========

DE CONFORMIDAD CON LA LEY DEL NOTARIADO, ARTICULO 59, INCISO D), TRANSCRIBO: ==========

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 74º.- FACULTADES GENERALES.- LA REPRESENTACIÓN JUDICIAL CONFIERE AL REPRESENTANTE LAS ATRIBUCIONES Y POTESTADES GENERALES QUE CORRESPONDEN AL REPRESENTADO, SALVO AQUELLAS PARA LAS QUE LA LEY EXIGE FACULTADES EXPRESAS. LA REPRESENTACIÓN SE ENTIENDE OTORGADA PARA TODO EL PROCESO, INCLUSO PARA LA EJECUCIÓN DE LA SENTENCIA Y EL COBRO DE COSTAS Y COSTOS, LEGITIMANDO AL REPRESENTANTE PARA SU INTERVENCIÓN EN EL PROCESO Y REALIZACIÓN DE TODOS LOS ACTOS DEL MISMO, SALVO AQUELLOS QUE REQUIERAN LA INTERVENCIÓN PERSONAL Y DIRECTA DEL REPRESENTADO." ==========

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 75º.- FACULTADES ESPECIALES.- SE REQUIERE EL OTORGAMIENTO DE FACULTADES ESPECIALES PARA REALIZAR TODOS LOS ACTOS DE DISPOSICIÓN DE DERECHOS SUSTANTIVOS Y PARA DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENCIONES, DESISTIRSE DEL PROCESO Y DE LA PRETENSIÓN, ALLANARSE A LA PRETENSIÓN, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SUSTITUIR O DELEGAR LA REPRESENTACIÓN PROCESAL Y PARA LOS DEMÁS ACTOS QUE EXPRESE LA LEY. EL OTORGAMIENTO DE FACULTADES ESPECIALES SE RIGE POR EL PRINCIPIO DE LITERALIDAD. NO SE PRESUME LA EXISTENCIA DE FACULTADES ESPECIALES NO CONFERIDAS EXPLÍCITAMENTE." ==========

CONCLUSION: ==========

FORMALIZADO EL INSTRUMENTO LA COMPARECIENTE LE DIO LECTURA, DESPUES DE LO CUAL SE AFIRMA Y RATIFICA EN SU CONTENIDO, DECLARANDO QUE SE TRATA DE UN ACTO VALIDO Y NO SIMULADO, MANIFESTANDO IGUALMENTE CONOCER LOS ANTECEDENTES Y/O TITULOS QUE SE ORIGINAN POR EL PRESENTE INSTRUMENTO Y DECLARANDO RECONOCER COMO SUYA LA FIRMA DE LA MINUTA QUE LA ORIGINA. ==========

DEJO CONSTANCIA DE HABER ADVERTIDO A LA INTERESADA DE LOS EFECTOS LEGALES DEL PRESENTE INSTRUMENTO NOTARIAL. ==========

LA PRESENTE ESCRITURA PUBLICA SE INICIA EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706090 Y CONCLUYE EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706093(VUELTA), DE LO QUE DOY FE. ==========

FIRMADO: JANNE IVETTE LUQUE CARDENAS.- UNA HUELLA DIGITAL.- UNA FIRMA ILEGIBLE.- FIRMÓ EL VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ.- ==========

EL PROCESO DE FIRMAS CONCLUYO EL: VEINTISEIS DE JULIO DEL DOS MIL DIEZ.- ==========

FIRMADO: DR. MARIO GINO BENVENUTO MURGUIA. ABOGADO - NOTARIO DE LIMA. ==========

ES TRANSCRIPCION DE LA ESCRITURA PUBLICA QUE OBRE EN EL REGISTRO CON FECHA VEINTISEIS DIAS DEL MES DE JULIO DEL AÑO DOS MIL DIEZ DE FOJAS 004590 A FOJAS 004593(VUELTA), Y A SOLICITUD DE PARTE INTERESADA EXPIDO EL PRESENTE, DE ACUERDO A LEY EL QUE RUBRICO EN CADA UNA DE SUS HOJAS, SELLO, SIGNO Y FIRMO EN LIMA, VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ. ==========

MARIO GINO BENVENUTO MURGUIA
ABOGADO
NOTARIO DE LIMA

COLEGIO DE NOTARIOS DE LIMA

O DE NOTARIOS DE LIMA CERTIFICA:
ıı y sellos que anteceden en esta foja
en al (la) Notario(a) de Lima,
Benvenuto Murguía
e Nº 116766 Fecha: 26 JUL 2010
ıma del Notario(a) más no el contenido

COLEGIO DE NOTARIOS DE LIMA

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27 ENE 2011
MONICA ZULMA BAQUISTA NAVARRO
Notaria Treinta y Ocho del Circulo de Bogotá D.C.
Jerman Gutiérrez Aparicio
FISCAL

B

CONSULADO GENERAL DE COLOMBIA
Lima – Perú

No. 1793

Lima, 02 Agosto 2010

El suscrito Cónsul General Consulares hace constar que el(a) señor (a) JULIA ADELA MOREANO DE DUEÑAS - DIRECION DE TRAMITES CONSULARES. Cuya firma aparece al pie del presente documento desempeñaba las funciones allí indicadas.
El suscrito Cónsul General no asume responsabilidad alguna por el contenido de este documento.

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JAIRO MONTES MORENO
Cónsul General

Dirección: Jorge Basadre 1580 TEL. (511) 4410530- 4410954 Fax: 2213661-4416922-4218029
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27 ENE 2011
MONICA LUCIA BAUTISTA NAVARRO
Notaria 38 del Circulo de Bogota D.C.

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(72) Inventors; and

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(74) Agents: **HAMMANN, Heinz**, et al.; Boehringer Ingelheim Gmbh, CD Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

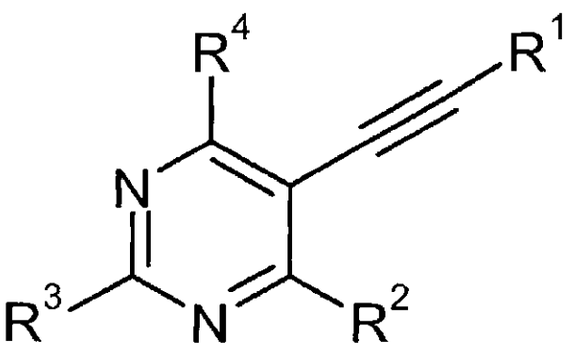
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Declarations under Rule 4.17:

[Continued on next page]

(54) Title: 5-ALKYNYL-PYRIMIDINES



(1)

(57) Abstract: The present invention encompasses compounds of general Formula (1) wherein R^1 to R^4 are defined as in claim 1, which are suitable for the treatment of diseases characterised by excessive or abnormal cell proliferation, and the use thereof for preparing a medicament having the above-mentioned properties.

WO 2010/012740 A1

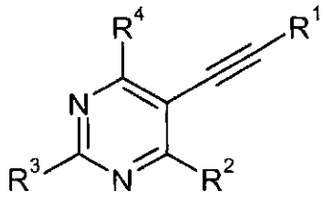
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

5-ALKYNYL-PYRIMIDINES

The present invention relates to new 5-alkynyl-pyrimidines of general formula (1)



(1),

wherein the groups R^1 to R^4 have the meanings given in the claims and specification, the isomers thereof, processes for preparing these alkynyl-pyrimidines and their use as medicaments.

Background to the invention

A number of protein kinases have already proved to be suitable target molecules for therapeutic intervention in a variety of indications, e.g. cancer and inflammatory and autoimmune diseases. Since a high percentage of the genes involved in the development of cancer which have been identified thus far encode kinases, these enzymes are attractive target molecules for the therapy of cancer in particular.

Phosphatidylinositol-3-kinases (PI3-kinases) are a subfamily of the lipid kinases which catalyse the transfer of a phosphate group to the 3'-position of the inositol ring of phosphoinositides.

They play an important role in numerous cell processes such as e.g. cell growth and differentiation processes, the control of cytoskeletal changes and the regulation of intracellular transport processes. On the basis of their *in vitro* specificity for certain phosphoinositide substrates the PI3-kinases can be divided into different categories.

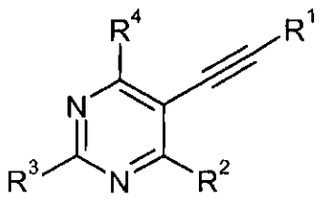
5-Alkynyl-pyrimidines are described for example as protein kinases inhibiting compounds in WO2006044823.

Detailed description of the invention

It has now surprisingly been found that compounds of general formula (1), wherein the groups R^1 to R^4 have the meanings given below, act as inhibitors of kinases. Thus, the

compounds according to the invention may be used for example for the treatment of diseases connected with the activity of kinases and characterised by excessive or abnormal cell proliferation.

The present invention relates to compounds of general formula (1)



(1),

wherein

R^1 denotes a group selected from among C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-10}aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R^5; and

R^2 denotes a group selected from among C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-10}aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R^5 and

R^3 denotes hydrogen or a group selected from among halogen, $-OR^e$, $-NR^eR^e$, $-CF_3$, -CN, -NC, $-NO_2$ and C_{1-6}alkyl; and

R^4 denotes a group selected from among C_{1-3}alkyl, C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, halogen, $-OR^e$, $-NR^eR^e$, $-CF_3$, $-CN$, -NC and $-NO_2$, and

each **R**^{5} denotes a group selected from among R^a, R^b and R^a substituted by one or more identical or different R^b and/or R^c; and

each **R**^{a} independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different **R**^{b} and/or **R**^{c}, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl,

each **R**^{b} denotes a suitable group and is selected independently of one another from among =O, $-OR^c$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^c$, $=NR^c$, $=NOR^c$, $=NNR^cR^c$, $=NN(R^g)C(O)NR^cR^c$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halogen, $-CF_3$, -CN,

–NC, –OCN, –SCN, –NO, $–NO_2$, $=N_2$, $–N_3$, $–S(O)R^c$, $–S(O)OR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$, $-S(O)NR^cR^c$, $–S(O)_2NR^cR^c$, $–OS(O)R^c$, $–OS(O)_2R^c$, $-OS(O)_2OR^c$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $–C(O)R^c$, $–C(O)OR^c$, $–C(O)SR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, -$-C(O)N(R^g)OR^c$, $–C(NR^g)NR^cR^c$, $–C(NOH)R^c$, $-C(NOH)NR^cR^c$, $-OC(O)R^c$, $–OC(O)OR^c$, $–OC(O)SR^c$, $–OC(O)NR^cR^c$, $-OC(NR^g)NR^cR^c$, $–SC(O)R^c$, $-SC(O)OR^c$, $–SC(O)NR^cR^c$, $-SC(NR^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $–N[C(O)R^c]_2$, $-N(OR^g)C(O)R^c$, $–N(R^g)C(NR^g)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $–N[C(O)R^c]NR^cR^c$, $-N(R^g)C(S)R^c$, $–N(R^g)S(O)R^c$, $-N(R^g)S(O)OR^c$, $-N(R^g)S(O)_2R^c$, $–N[S(O)_2R^c]_2$, $-N(R^g)S(O)_2OR^c$, $-N(R^g)S(O)_2NR^cR^c$, $–N(R^g)[S(O)_2]_2R^c$, $-N(R^g)C(O)OR^c$, $-N(R^g)C(O)SR^c$, $-N(R^g)C(O)NR^cR^c$, $–N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^cR^c$, $–[N(R^g)C(O)]_2R^c$, $–N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$, $-N(R^g)[C(O)]_2OR^c$, $–N(R^g)[C(O)]_2NR^cR^c$, $–N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$, $-[N(R^g)C(O)]_2OR^c$, $–N(R^g)C(NR^g)OR^c$, $–N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$, $-N(R^g)C(NR^g)NR^cR^c$ and $-N=C(R^g)NR^cR^c$ and

each $\mathbf{R^c}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^d}$ and/or $\mathbf{R^e}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, and

each $\mathbf{R^d}$ denotes a suitable group and is selected independently of one another from among =O, $–OR^e$, C_{1-3}haloalkyloxy, $–OCF_3$, =S, $–SR^e$, $=NR^e$, $=NOR^e$, $=NNR^eR^e$, $=NN(R^g)C(O)NR^eR^e$, $–NR^eR^e$, $–ONR^eR^e$, $–N(R^g)NR^eR^e$, halogen, $–CF_3$, –CN, -NC, -OCN, –SCN, –NO, $–NO_2$, $=N_2$, $–N_3$, $–S(O)R^e$, $–S(O)OR^e$, $–S(O)_2R^e$, $–S(O)_2OR^e$, $-S(O)NR^eR^e$, $-S(O)_2NR^eR^e$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)_2OR^e$, $–OS(O)NR^eR^e$, $-OS(O)_2NR^eR^e$, $-C(O)R^e$, $–C(O)OR^e$, $–C(O)SR^e$, $–C(O)NR^eR^e$, $–C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-C(NR^g)NR^eR^e$, $–C(NOH)R^e$, $–C(NOH)NR^eR^e$, $–OC(O)R^e$, $-OC(O)OR^e$, $–OC(O)SR^e$, $-OC(O)NR^eR^e$, $–OC(NR^g)NR^eR^e$, $–SC(O)R^e$, $-SC(O)OR^e$, $-SC(O)NR^eR^e$, $–SC(NR^g)NR^eR^e$, $–N(R^g)C(O)R^e$, $–N[C(O)R^e]_2$, $-N(OR^g)C(O)R^e$, $-N(R^g)C(NR^g)R^e$, $–N(R^g)N(R^g)C(O)R^e$, $-N[C(O)R^e]NR^eR^e$, $-N(R^g)C(S)R^e$, $-N(R^g)S(O)R^e$, $–N(R^g)S(O)OR^e$ $–N(R^g)S(O)_2R^e$, $-N[S(O)_2R^e]_2$, $-N(R^g)S(O)_2OR^e$, $-N(R^g)S(O)_2NR^eR^e$, $–N(R^g)[S(O)_2]_2R^e$, $–N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$, $-N(R^g)C(O)NR^eR^e$, $–N(R^g)C(O)NR^gNR^eR^e$, $-N(R^g)N(R^g)C(O)NR^eR^e$, $-N(R^g)C(S)NR^eR^e$, $–[N(R^g)C(O)]_2R^e$, $–N(R^g)[C(O)]_2R^e$, $-N\{[C(O)]_2R^e\}_2$,

$-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$, $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$, $-N(R^g)C(NR^g)NR^eR^e$ and $-N=C(R^g)NR^eR^e$

each $\mathbf{R^e}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^f}$ and/or $\mathbf{R^g}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, and

each $\mathbf{R^f}$ denotes a suitable group and in each case is selected independently of one another from among =O, $-OR^g$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^g$, $=NR^g$, $=NOR^g$, $=NNR^gR^g$, $=NN(R^h)C(O)NR^gR^g$, $-NR^gR^g$, $-ONR^gR^g$, $-N(R^h)NR^gR^g$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^g$, $-S(O)OR^g$, $-S(O)_2R^g$, $-S(O)_2OR^g$, $-S(O)NR^gR^g$, $-S(O)_2NR^gR^g$, $-OS(O)R^g$, $-OS(O)_2R^g$, $-OS(O)_2OR^g$, $-OS(O)NR^gR^g$, $-OS(O)_2NR^gR^g$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)SR^g$, $-C(O)NR^gR^g$, $-C(O)N(R^h)NR^gR^g$, $-C(O)N(R^h)OR^g$, $-C(NR^h)NR^gR^g$, $-C(NOH)R^g$, $-C(NOH)NR^gR^g$, $-OC(O)R^g$, $-OC(O)OR^g$, $-OC(O)SR^g$, $-OC(O)NR^gR^g$, $-OC(NR^h)NR^gR^g$, $-SC(O)R^g$, $-SC(O)OR^g$, $-SC(O)NR^gR^g$, $-SC(NR^h)NR^gR^g$, $-N(R^h)C(O)R^g$, $-N[C(O)R^g]_2$, $-N(OR^h)C(O)R^g$, $-N(R^h)C(NR^h)R^g$, $-N(R^h)N(R^h)C(O)R^g$, $-N[C(O)R^g]NR^gR^g$, $-N(R^h)C(S)R^g$, $-N(R^h)S(O)R^g$, $-N(R^h)S(O)OR^g$, $-N(R^h)S(O)_2R^g$, $-N[S(O)_2R^g]_2$, $-N(R^h)S(O)_2OR^g$, $-N(R^h)S(O)_2NR^gR^g$, $-N(R^h)[S(O)_2]_2R^g$, $-N(R^h)C(O)OR^g$, $-N(R^h)C(O)SR^g$, $-N(R^h)C(O)NR^gR^g$, $-N(R^h)C(O)NR^hNR^gR^g$, $-N(R^h)N(R^h)C(O)NR^gR^g$, $-N(R^h)C(S)NR^gR^g$, $-[N(R^h)C(O)]_2R^g$, $-N(R^h)[C(O)]_2R^g$, $-N\{[C(O)]_2R^g\}_2$, $-N(R^h)[C(O)]_2OR^g$, $-N(R^h)[C(O)]_2NR^gR^g$, $-N\{[C(O)]_2OR^g\}_2$, $-N\{[C(O)]_2NR^gR^g\}_2$, $-[N(R^h)C(O)]_2OR^g$, $-N(R^h)C(NR^h)OR^g$, $-N(R^h)C(NOH)R^g$, $-N(R^h)C(NR^h)SR^g$, $-N(R^h)C(NR^h)NR^gR^g$; and $-N=C(R^h)NR^hR^h$; and

each $\mathbf{R^g}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^h}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl; and

each $\mathbf{R^h}$ is selected independently of one another from among hydrogen, C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl,

C_{7-16}arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl,
optionally in the form of the prodrugs, the tautomers, the racemates, the enantiomers, the diastereomers, the prodrugs and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

One aspect of the invention relates to compounds of general formulae (1), wherein $\mathbf{R^4}$ denotes $-CH_3$ or $-CH_2CH_3$.

Another aspect of the invention relates to compounds of general formula (1), wherein $\mathbf{R^3}$ denotes hydrogen or $-NR^cR^c$.

Another aspect of the invention relates to compounds of general formula (1), wherein $\mathbf{R^3}$ denotes $-NH_2$.

Another aspect of the invention relates to compounds of general formula (1), wherein $\mathbf{R^2}$ denotes phenyl or pyridyl, optionally substituted by one or more identical or different R^5.

Another aspect of the invention relates to compounds of general formula (1), wherein $\mathbf{R^2}$ denotes heterocycloalkyl, optionally substituted by one or more identical or different R^5.

Another aspect of the invention relates to compounds of general formula (1), wherein $\mathbf{R^1}$ denotes phenyl, pyridyl or pyrimidinyl, optionally substituted by one or more identical or different R^5.

One aspect of the invention relates to compounds of general formula (1), or the pharmacologically effective salts thereof, as medicaments.

One aspect of the invention relates to compounds of general formula (1), or the pharmacologically effective salts thereof, for preparing a medicament with an antiproliferative activity.

One aspect of the invention is a pharmaceutical preparations, containing as active substance one or more compounds of general formula (1), or the pharmacologically

effective salts thereof, optionally in combination with conventional excipients and/or carriers.

One aspect of the invention is the use of compounds of general formula (1) for preparing a medicament for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

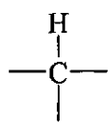
One aspect of the invention is a pharmaceutical preparation comprising a compound of general formula (1) and at least one other cytostatic or cytotoxic active substance, different from formula (1), optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, as well as optionally the pharmacologically acceptable salts thereof.

Definitions

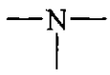
As used herein the following definitions apply, unless stated otherwise.

By alkyl substituents are meant in each case saturated, unsaturated, straight-chain or branched aliphatic hydrocarbon groups (alkyl group) and this includes both saturated alkyl groups and unsaturated alkenyl and alkynyl groups. Alkenyl substituents are in each case straight-chain or branched, unsaturated alkyl groups, which have at least one double bond. By alkynyl substituents are meant in each case straight-chain or branched, unsaturated alkyl groups, which have at least one triple bond.

The term **heteroalkyl** refers to groups which can be derived from alkyl as defined above in its broadest sense by replacing one or more of the groups $-CH_3$ in the hydrocarbon chains independently of one another by the groups –OH, –SH or $-NH_2$, one or more of the groups $-CH_2-$ independently of one another by the groups –O–, –S– or –NH– , one or more of the groups



by the group



one or more of the groups =CH– by the group =N–, one or more of the groups $=CH_2$ by the group =NH or one or more of the groups ≡CH by the group ≡N, while in all only a maximum of three heteroatoms may be present in a heteroalkyl, there must be at least one carbon atom between two oxygen and between two sulphur atoms or between one oxygen and one sulphur atom and the group as a whole must have chemical stability.

It flows from the indirect definition/derivation from alkyl that heteroalkyl is made up of the sub-groups of saturated hydrocarbon chains with hetero-atom(s), heteroalkenyl and heteroalkynyl, while further subdivision into straight-chain (unbranched) and branched may be carried out. If a heteroalkyl is supposed to be substituted, the substitution may take place independently of one another, in each case mono- or polysubstituted, at all the hydrogen-carrying oxygen, sulphur, nitrogen and/or carbon atoms. Heteroalkyl itself may be linked to the molecule as substituent both through a carbon atom and through a heteroatom.

By way of example, the following representative compounds are listed: dimethylaminomethyl; dimethylaminoethyl (1-dimethylaminoethyl; 2-dimethyl-aminoethyl); dimethylaminopropyl (1-dimethylaminopropyl, 2-dimethylaminopropyl, 3-dimethylaminopropyl); diethylaminomethyl; diethylaminoethyl (1-diethylaminoethyl, 2-diethylaminoethyl); diethylaminopropyl (1-diethylaminopropyl, 2- diethylamino-propyl, 3-diethylaminopropyl); diisopropylaminoethyl (1-diisopropylaminoethyl, 2-di-isopropylaminoethyl); bis-2-methoxyethylamino; [2-(dimethylamino-ethyl)-ethyl-amino]-methyl; 3-[2-(dimethylamino-ethyl)-ethyl-amino]-propyl; hydroxymethyl; 2-hydroxy-ethyl; 3-hydroxypropyl; methoxy; ethoxy; propoxy; methoxymethyl; 2-methoxyethyl etc.

Haloalkyl relates to alkyl groups, wherein one or more hydrogen atoms are replaced by halogen atoms. Haloalkyl includes both saturated alkyl groups and unsaturated alkenyl and alkynyl groups, such as for example $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$,$-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$, $-CCl=CH_2$, $-CBr=CH_2$, $-Cl=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$ and $-CHFCH_2CF_3$.

Halogen refers to fluorine, chlorine, bromine and/or iodine atoms.

By cycloalkyl is meant a mono or bicyclic ring, while the ring system may be a saturated ring or, however, an unsaturated, non-aromatic ring, which may optionally also contain double bonds, such as for example cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, norbornyl and norbornenyl.

Cycloalkylalkyl includes a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by a cycloalkyl group.

Aryl relates to monocyclic or bicyclic aromatic rings with 6 – 10 carbon atoms such as phenyl and naphthyl, for example.

Arylalkyl includes a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by an aryl group.

By heteroaryl are meant mono- or bicyclic aromatic rings, which instead of one or more carbon atoms contain one or more, identical or different hetero atoms, such as e.g. nitrogen, sulphur or oxygen atoms. Examples include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and triazinyl. Examples of bicyclic heteroaryl groups are indolyl, isoindolyl, benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzopyrazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl and benzotriazinyl, indolizinyl, oxazolopyridyl, imidazopyridyl, naphthyridinyl, indolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuryl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridyl, benzotetrahydrofuryl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridyl-*N*-oxide tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl,

isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, quinolinyl-*N*-oxide, indolyl-*N*-oxide, indolinyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalinyl-*N*-oxide, phthalazinyl-*N*-oxide, imidazolyl-*N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, indolizinyl-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide, pyrrolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, benzothiopyranyl-*S*-oxide and benzothiopyranyl-*S,S*-dioxide.

Heteroarylalkyl encompasses a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by a heteroaryl group.

Heterocycloalkyl relates to saturated or unsaturated, non-aromatic mono-, bicyclic or bridged bicyclic rings comprising 3 – 12 carbon atoms, which instead of one or more carbon atoms carry heteroatoms, such as nitrogen, oxygen or sulphur. Examples of such heterocyloalkyl groups are tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidinyl, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-*S*-oxide, thiomorpholinyl-*S,S*-dioxide, tetrahydropyranyl, tetrahydrothienyl, homothiomorpholinyl-*S,S*-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-oxide, 2-oxa-5-azabicyclo[2,2,1]heptane, 8-oxa-3-aza-bicyclo[3.2.1]octane, 3.8-diaza-bicyclo[3.2.1]octane, 2,5-diaza-bicyclo[2.2.1]heptane, 3.8-diaza-bicyclo[3.2.1]octane, 3.9-diaza-bicyclo[4.2.1]nonane and 2.6-diaza-bicyclo[3.2.2]nonane.

Heterocycloalkylalkyl relates to a non-cyclic alkyl group wherein a hydrogen atom bound to a carbon atom, usually to a terminal C atom, is replaced by a heterocycloalkyl group.

The following Examples illustrate the present invention without restricting its scope.

General Procedure 1 (GP1): Iodination of Pyrimidines or Pyridines

A solution of the pyrimidine or pyridine (1.0 eq.) in acetic acid is cooled to 0 °C and *N*-

iodosuccinimide (1.0 eq.) is added in one portion. The reaction mixture is stirred at RT until conversion of the starting material is completed (2 - 6 h). The mixture is poured on ice-cooled water and treated with a mixture of 5 % $Na_2S_2O_3$ and 10 % $NaHCO_3$. The precipitate is filtered off, intensely washed with water and dried under vacuum at 40°C. The crude product can be used without further purification or is further purified by chromatography on silica gel using a CH_2Cl_2/MeOH gradient.

General Procedure 2 (GP2): Sonogashira Reaction

The halide (1.0 eq.) is dissolved in DMF or THF and $PdCl_2(PPh_3)_2$ (0.1 eq.) and CuI (0.1 eq.) are added. Subsequently, triethylamine (10.0 eq.) and finally the alkyne (1.5 eq.) are added and the reaction mixture is stirred at 65 °C. The reaction is monitored by LC-MS. If the iodide is not completed converted after 4 h, additional amounts of alkyne are added in small portions. The product either precipitates from the reaction mixture (and is filtered off and if necessary re-crystallized) and/or, after removal of the solvent, is purified by preparative RP-HPLC.

General Procedure 3 (GP3): Desilylation of Alkynes

The TMS-alkyne (1.0 eq.) is dissolved in MeOH, K_2CO_3 (0.5 eq.) is added in one portion and the reaction mixture is stirred at RT until conversion is complete (3 – 16 h). The solvent is removed *in vacuo*, the crude product is dissolved in ethyl acetate and the organic phase is extracted with water. The organic phase is dried, filtered off and the solvent removed *in vacuo*. The product is either used without further purification or purified by chromatography on silica gel using a DCM/MeOH or (cyclo-)hexane/ethyl acetate.

General Procedure 4 (GP4): Suzuki Coupling

The 4-chloropyrimidine (1.0 eq.) is dissolved in DME/water (20:1 v/v), boronic acid (1.3 eq.), K_2CO_3 (2.0 eq.) and $Pd(PPh_3)_4$ (0.2 eq.) are added and the reaction mixture is stirred for 4 h under reflux. In case the conversion of the starting material is not complete, additional amounts of boronic acid and Pd-catalyst are added and the reaction is run over night under reflux. After cooling to RT water is added. The precipitate is filtered off. In cases where the product is not precipitated it is extracted with diethylether, the organic phase is dried, filtered off, and the solvent removed under reduced pressure. The obtained product can either be used without further purification or is purified by chromatography.

General Procedure 5 (GP5): Oxidation of a Thioalkyl Group

The 2-methylsulfanyl-pyrimidine (1.0 eq.) is taken up in DCM, *meta*-chloroperbenzoic acid (2.5 eq.) is added and the reaction mixture is stirred for one day. The reaction mixture is filtered, washed with water and concentrated *in vacuo*. The crude product can be used without further purification.

General Procedure 6 (GP6): Nucleophilic Substitution of 2-Sulfonylpyrimidines with Amines

The starting material is dissolved in NMP, an excess of amine is added and the reaction mixture is heated in the microwave at 120-150 °C. After cooling to RT the product is purified by NP-HPLC.

General Procedure 7 (GP7): Nucleophilic Substitution of 4-Chloropyrimidines with Amines

The starting material is dissolved in NMP, an excess of amine is added and the reaction mixture is heated in the microwave at 120-150°C. After cooling to RT the product is purified by NP-HPLC.

General Procedure 8 (GP8): Saponification of Esters

The ester is taken up in either THF or dioxane, 1.1-1.5 eq. of 1N NaOH are added and the mixture is heated under reflux until reaction control shows complete conversion of the starting material. The product either precipitates from the reaction mixture and is used without additional purification steps or can further be purified by chromatography.

General Procedure 9 (GP9): Amide Formation with Amines

To a mixture of 0.21 mmol starting material, 0.31 mmol TBTU or HATU and 0.42 mmol Huenig's base in 2 mL DMSO is stirred for 5 min. 0.31 mmol of amine is added and the resultant mixture is stirred at room temp. over night. Purification is performed via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 10 (GP10) Amide Formation with Acid Chlorides

To a mixture of 0.13 mmol of starting material and 67 µL Huenig's base in 2 mL THF is added 0.26 mmol acid chloride. The reaction mixture is stirred over night at RT. The

solvent is evaporated and the residue is taken up in 1mL DMSO insoluble material is filtered off and the resulting solution is purified via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 11 (GP11): Urea Formation with Isocyanates

To a mixture of 0.16 mmol of starting material and 64.4 µL Huenig's base in 2 mL THF is added 0.49 mmol isocyanate. The reaction mixture is stirred over night at RT. The solvent is evaporated and the residue is taken up in 1mL DMSO insoluble material is filtered off and the resulting solution is purified via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

General Procedure 12 (GP12): Urea Formation via Pre-activation of the Amine.

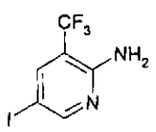
To a mixture of 0.34 mmol amine and 0.34 mmol *N,N'*-carbonyldiimidazole and 0.34 mmol 1,8-diazabicyclo[5.4.0]undec-7-ene is stirred for 10 min at RT. 0.32 mmol of starting material are added in one portion. The reaction mixture is heated at 100 °C for 1 h in the microwave. The solvent is evaporated and the residue is taken up in 1mL DMSO insoluble material is filtered off and the resulting solution is purified via preparative RP-HPLC yielding the desired product.

General Procedure 13 (GP13): Amide formation with carbonic acids

To a mixture of 0.62 mmol carbonic acid, 0.93 mmol TBTU and 1.2 mmol Huenig's base in 2 mL DMSO is stirred for 5 min. 0.31 mmol of starting material is added and the resultant mixture is stirred at RT over night. Purification is performed via preparative RP-HPLC yielding after evaporation of the solvent the desired product.

Intermediates A

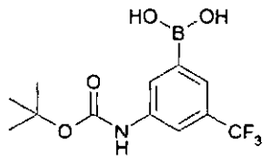
A-1) 5-Iodo-3-trifluoromethyl-pyridin-2-ylamine



The title compound is synthesized according to general procedure GP1 starting from 5.0 g

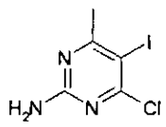
(31 mmol) 3-trifluoro-2-amino pyridine and 6.9 g (31 mmol) NIS. Yield after precipitation from the reaction mixture: 6.78 g (76%).

A-2) 5-Trifluoromethyl-3-(*tert*-butyl-oxyxcarbonyl)amino-phenylboronic acid



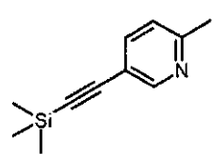
A solution of 1.5 g (4.4 mmol) 3-bromo-5-trifluoromethyl-tert.-butyl-oxyxcarbonyl-aniline and 1.2 mL (5.3 mmol) triisopropylborate in a mixture of 4.5 mL dry THF / 10.5 mL dry toluene is cooled to -70 °C under an inert atmosphere before 6.9 mL of a 1.6 M solution of n-BuLi in hexane are added dropwise (syringe pump) over 30 min. The reaction mixture is stirred for additional 50 min at –70 °C before the reaction temperature is allowed to rise to -20 °C. After addition of 4.4 mL of 2.2 M HCl the reaction mixture warmed to RT and the layers are separated. The organic phase is diluted with ethyl acetate, washed with brine (pH of the aqueous phase < 3), dried over Na_2SO_4, filtered off and the solvent is removed under reduced pressure. The product is purified by PR-HPLC using an ACN/water gradient. Yield: 635 mg (47 %).

A-3) 4-Chloro-5-iodo-6-methyl-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP1 starting from 10 g (70 mmol) 2-amino-4-chloro-6-methylpyrimidine and 16 g NIS (70 mmol). Yield: 18 g (95 %). The crude product is used in next steps without further purification.

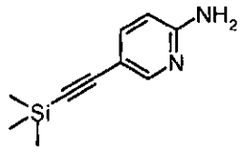
A-4) 2-Methyl-5-trimethylsilanylethynyl-pyridine



The title compound is synthesized according to general procedure GP2 starting from 2.0 g

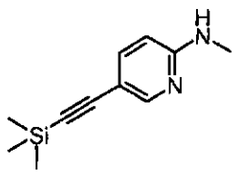
(11.6 mmol) 5-bromo-2-methy-pyridine and 2.3 mL (16.3 mmol) 1-trimethylsilyl-ethyne using 68 mg (0.36 mmol) CuI, 305 mg (1.2 mmol) triphenylphosphine, 213 mg (0.30 mmol) $PdCl_2(PPh_3)_2$ and 18 mL (127 mmol) triethylamine in 18 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 1.5 g (68 %).

A-5) 5-Trimethylsilanylethynyl-pyridin-2-ylamine



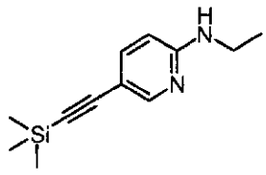
The title compound is synthesized according to general procedure GP2 starting from 5.0 g (28.9 mmol) 5-bromo-2-amino-pyridine and 5.7 mL (40.5 mmol) 1-trimethylsilyl-ethyne using 168 mg (0.88 mmol) CuI, 758 mg (2.9 mmol) triphenylphosphine, 533 mg (0.76 mmol) $PdCl_2(PPh_3)_2$ and 40 mL (288 mmol) triethylamine in 40 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using hexane/ethyl acetate (10/1 v/v). Yield: 5.0 g (91 %).

A-6) Methyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine



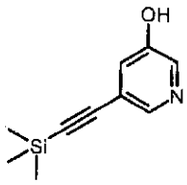
The title compound is synthesized according to general procedure GP2 starting from 4.3 g (23.0 mmol) 5-bromo-2-methylamino-pyridine and 4.5 mL (32.2 mmol) 1-trimethylsilyl-ethyne using 134 mg (0.71 mmol) CuI, 601 mg (2.3 mmol) triphenylphosphine, 420 mg (0.60 mmol) $PdCl_2(PPh_3)_2$ and 32 mL (101 mmol) triethylamine in 40 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 4.0 g (85 %).

A-7) Ethyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine



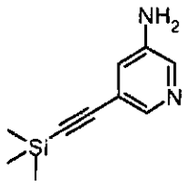
The title compound is synthesized according to general procedure GP2 starting from 909 mg (4.5 mmol) 5-bromo-2-ethylamino-pyridine and 0.89 mL (6.3 mmol) 1-trimethylsilyl-ethyne using 26 mg (0.13 mmol) CuI, 118 mg (0.45 mmol) triphenylphosphine, 82 mg (0.12 mmol) $PdCl_2(PPh_3)_2$ and 6.3 mL (45.0 mmol) triethylamine in 7 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 980 mg (99 %).

A-8) 5-Trimethylsilanylethynyl-pyridin-3-ol



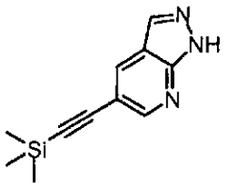
The title compound is synthesized according to general procedure GP2 starting from 2.0 g (11.6 mmol) 5-bromo-3-hydroxy-pyridine and 2.3 mL (16.2 mmol) 1-trimethylsilyl-ethyne using 66 mg (0.3 mmol) CuI, 303 mg (1.2 mmol) triphenylphosphine, 243 mg (0.3 mmol) $PdCl_2(PPh_3)_2$ and 19 mL (139 mmol) triethylamine in 20 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.0 g (91 %).

A-9) 5-Trimethylsilanylethynyl-pyridin-3-ylamine



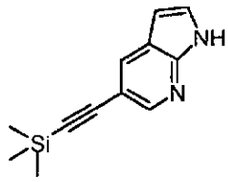
The title compound is synthesized according to general procedure GP2 starting from 2.0 g (11.6 mmol) 5-bromo-3-amino-pyridine and 2.3 mL (16.2 mmol) 1-trimethylsilyl-ethyne using 66 mg (0.3 mmol) CuI, 303 mg (1.2 mmol) triphenylphosphine, 243 mg (0.3 mmol) $PdCl_2(PPh_3)_2$ and 19 mL (139 mmol) triethylamine in 20 mL dry THF. For the work-up the reaction mixture is diluted with ethyl acetate and small amounts of cyclohexane, the organic phase is extracted with water and brine. The product is purified by chromatography on silica gel using a DCM/MeOH gradient. The product precipitated on the column and was subsequently extracted from the silica gel with pure MeOH. Yield: 2.0 g (91 %).

A-10) 5-Trimethylsilanylethynyl-1*H*-pyrazolo[3,4-*b*]pyridine



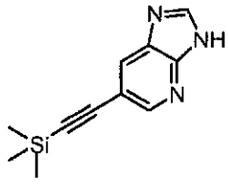
The title compound is synthesized according to general procedure GP2 starting from 1.0 g (5.1 mmol) 5-bromo-1H-pyrazolo[4,5-b]pyridine and 1.0 mL (7.1 mmol) 1-trimethylsilyl-ethyne using 29 mg (0.15 mmol) CuI, 133 mg (0.51 mmol) triphenylphosphine, 106 mg (0.15 mmol) $PdCl_2(PPh_3)_2$ and 8.4 mL (60.6 mmol) triethylamine in 8 mL dry THF. The formed precipitate is filtered off and the product is purified by RP-HPLC using an ACN/H_2O gradient. Yield: 542 mg (50 %).

A-11) 5-Trimethylsilanylethynyl-1*H*-pyrrolo[2,3-*b*]pyridine



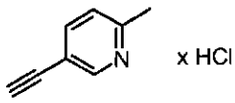
The title compound is synthesized according to general procedure GP2 starting from 3.0 g (15.2 mmol) 5-bromo-1H-pyrrolo[2,3-B]pyridine and 3.0 mL (21.3 mmol) 1-trimethylsilyl-ethyne using 87 mg (0.46 mmol) CuI, 400 mg (1.5 mmol) triphenylphosphine, 312 mg (0.46 mmol) $PdCl_2(PPh_3)_2$ and 25.4 mL (182 mmol) triethylamine in 25 mL dry THF. The formed precipitate is filtered off and the product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 3.05 g (94 %).

A-12) 6-Trimethylsilanylethynyl-3*H*-imidazo[4,5-*b*]pyridine



The title compound is synthesized according to general procedure GP2 starting from 1.2 g (6.1 mmol) 5-bromo-3H-imidazo[4,5-b]pyridine and 1.2 mL (8.4 mmol) 1-trimethylsilyl-ethyne using 34 mg (0.18 mmol) CuI, 159 mg (0.61 mmol) triphenylphosphine, 128 mg (0.18 mmol) $PdCl_2(PPh_3)_2$ and 10.1 mL (72.7 mmol) triethylamine in 10 mL dry THF. The formed precipitate is filtered off and the product is purified by RP-HPLC using an ACN/H_2O gradient. Yield: 606 mg (46 %).

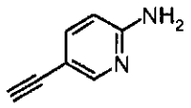
A-13) 5-Ethynyl-2-methyl-pyridine



The title compound is synthesized according to general procedure GP3 starting from 2.2 g (12 mmol) 2-methyl-5-trimethylsilanylethynyl-pyridine (A4) and 0.80 g (5.8 mmol) K_2CO_3 in 13 mL MeOH. The crude product is purified by chromatography on silica gel

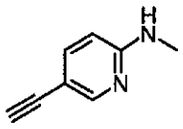
using a cyclohexane/ethyl acetate gradient. The product is extracted from the organic phase with 1 N HCl and isolated as the hydrochloride after lyophilization. Yield: 1.3 g (73 %).

A-14) 5-Ethynyl-2-amino-pyridine



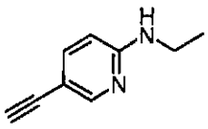
The title compound is synthesized according to general procedure GP3 starting from 5.5 g (29 mmol) 5-trimethylsilanylethynyl-pyridin-2-ylamine (A5) and 2.0 g (14 mmol) K_2CO_3 in 30 mL MeOH. The product is purified by chromatography on silica gel using a hexane/ethyl acetate gradient. Yield: 2.9 g (85 %).

A-15) (5-Ethynyl-pyridin-2-yl)-methyl-amine



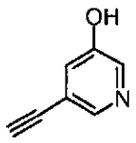
The title compound is synthesized according to general procedure GP3 starting from 1.5 g (7.3 mmol) methyl-(5-trimethylsilanylethynyl-pyridin-2-yl)-amine (A6) and 507 mg (3.7 mmol) K_2CO_3 in 10 mL MeOH. Yield: 698 mg (56 %) after chromatography on silica gel.

A-16) (5-Ethynyl-pyridin-2-yl)-ethyl-amine



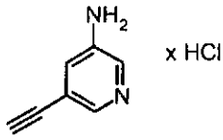
The title compound is synthesized according to general procedure GP3 starting from 980 mg (4.5 mmol) TMS-alkyne and 310 mg (2.3 mmol) K_2CO_3 in 6 mL MeOH. Yield: 388 mg (59 %) after chromatography on silica gel.

A-17) 5-Ethynyl-pyridin-3-ol



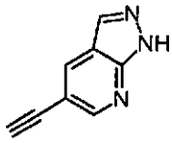
The title compound is synthesized according to general procedure GP3 starting from 2.0 g (10.5 mmol) TMS-alkyne and 722 mg (5.2 mmol) K_2CO_3 in 10 mL MeOH. Yield: 804 mg (49 %) after chromatography on silica gel.

A-18) 5-Ethynyl-pyridin-3-ylamine



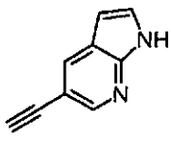
The title compound is synthesized according to general procedure GP3 starting from 2.0 g (11 mmol) TMS-alkyne and 722 mg (5.2 mmol) K_2CO_3 in 10 mL MeOH. Yield: 1.2 g (74 %) after chromatography on silica gel and precipitation from dioxane/HCl.

A-19) 5-Ethynyl-1*H*-pyrazolo[3,4-*b*]pyridine



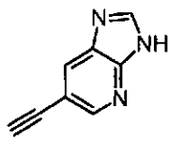
The title compound is synthesized according to general procedure GP3 starting from 542 mg (2.5 mmol) TMS-alkyne and 174 mg (1.3 mmol) K_2CO_3 in 6 mL MeOH. Yield: 330 mg (92 %) after extraction.

A-20) 5-Ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine



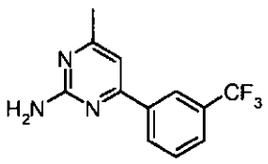
The title compound is synthesized according to general procedure GP3 starting from 3.1 g (14 mmol) TMS-alkyne and 983 mg (7.1 mmol) K_2CO_3 in 15 mL MeOH. Yield: 1.2 g (61 %) after chromatography on silica gel.

A-21) 6-Ethynyl-3*H*-imidazo[4,5-*b*]pyridine



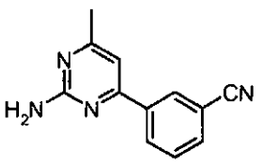
The title compound is synthesized according to general procedure GP3 starting from 706 mg (3.3 mmol) TMS-alkyne and 227 mg (1.6 mmol) K_2CO_3 in 6 mL MeOH. Yield: 491 mg (94 %) after extraction.

A-22) 4-Methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-2-ylamine



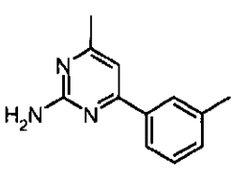
The title compound is synthesized according to general procedure GP4 starting from 2.0 g (14 mmol) 2-amino-4-chloro-6-methyl pyrimidine and 3.4 g (18 mmol) 3-trifluoromethyl-phenyl boronic acid. Yield after extraction: 5.0 g (99 %).

A-23) 4-Methyl-6-(3-cyano-phenyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP4 starting from 2.0 g (14 mmol) 2-amino-4-chloro-6-methyl pyrimidine and 2.7 g (18 mmol) 3-cyano-phenyl boronic acid. Yield after extraction and crystallization from diethylether: 3.2 g (100 %).

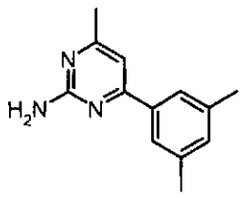
A-24) 4-Methyl-6-(3-methyl-phenyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP4 starting from 2.0 g

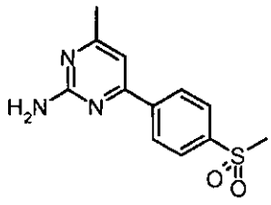
(14 mmol) 2-amino-4-chloro-6-methylpyrimidine and 2.5 g (18 mmol) 3-methyl-phenyl boronic acid. Yield after extraction and re-crystallization from diethylether: 4.1 g (>100 %, approximately 70 % pure).

A-25) 4-Methyl-6-(3,5-dimethyl-phenyl)-pyrimidin-2-ylamine



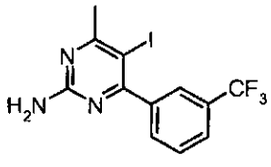
The title compound is synthesized according to general procedure GP4 starting from 2.0 g (14 mmol) 2-amino-4-chloro-6-methyl pyrimidine and 2.7 g (18 mmol) 3,5-dimethyl-phenyl boronic acid. Yield after extraction and crystallization from diethylether: 3.2 g (75 %, approximately 70 % pure).

A-26) 4-Methyl-6-(4-methanesulfonyl-phenyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP4 (A) starting from 1.5 g (10 mmol) 2-amino-4-chloro-6-methyl pyrimidine and 2.7 g (14 mmol) 4-sulfonyl-phenyl boronic acid. After treatment of the precipitated product with diethyl ether 2.3 g (75 %) of the desired product are obtained.

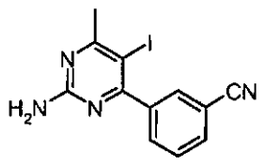
A-27) 5-Iodo-4-methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP1 starting from 5.0 g

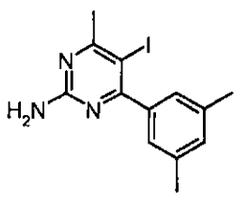
(14 mmol) 4-methyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-2-ylamine and 3.3 g (15 mmol) NIS. Yield after chromatography on silica gel with DCM/MeOH: 3.8 g (73 %).

A-28) 5-Iodo-4-methyl-6-(3-cyano-phenyl)-pyrimidin-2-ylamine



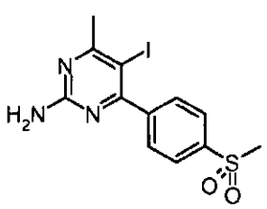
The title compound is synthesized according to general procedure GP1 starting from 3.2 g (12 mmol) 4-methyl-6-(3-cyano-phenyl)-pyrimidin-2-ylamine and 2.8 g (13 mmol) NIS. Yield after chromatography on silica gel with DCM/MeOH: 3.5 g (78 %).

A-29) 5-Iodo-4-methyl-6-(3,5-dimethyl-phenyl)-pyrimidin-2-ylamine



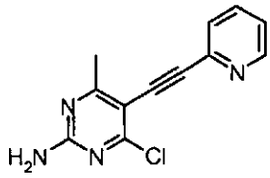
The title compound is synthesized according to general procedure GP1 starting from 3.2 g (11 mmol) 4-methyl-6-(3,5-dimethyl-phenyl)-pyrimidin-2-ylamine and 2.5 g (11 mmol) NIS. Yield after chromatography on silica gel with DCM/MeOH: 1.1 g (31 %).

A-30) 5-Iodo-4-methyl-6-(4-methanesulfonyl-phenyl)-pyrimidin-2-ylamine



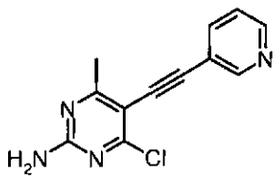
The title compound is synthesized according to general procedure GP1 starting from 2.3 g (7.9 mmol) 4-methyl-6-(4-sulfonyl-phenyl)-pyrimidin-2-ylamine and 1.8 g (7.9 mmol) NIS. Yield after precipitation from the reaction mixture with water: 3.1 g (91 %).

A-31) 4-Chloro-6-methyl-5-pyridin-2-ylethynyl-pyrimidin-2-ylamine



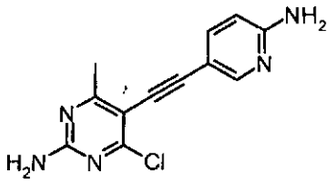
The title compound is synthesized according to general procedure GP2 starting from 1.5 g (5.6 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 0.84 mL (8.4 mmol) 2-ethynyl-pyridine using 106 mg (0.57 mmol) CuI, 390 mg (0.56 mmol) $PdCl_2(PPh_3)_2$ and 7.8 mL (56 mmol) triethylamine in 10 mL dry DMF. Additional amounts are added after 24 h and 48 h reaction time, respectively. For the work-up the solvent is removed *in vacuo* and the product is purified by chromatography on silica gel using a DCM/MeOH gradient. Yield: 2.0 g (>100 %, approximately 70 % pure).

A-32) 4-Chloro-6-methyl-5-pyridin-3-ylethynyl-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 4.0 g (15 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 2.0 g (19 mmol) 3-ethynyl-pyridine using 282 mg (1.5 mmol) CuI, 1.0 g (1.5 mmol) $PdCl_2(PPh_3)_2$ and 21 mL (148 mmol) triethylamine in 200 mL dry DMF. For the work-up the reaction mixture is concentrated *in vacuo* before water is added. The precipitate is collected, dried at 40 °C and crystallized from MeOH/H_2O. Yield: 3.0 g (83 %).

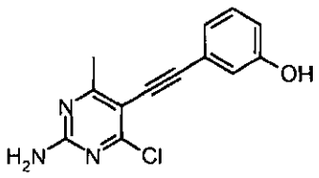
A-33) 5-(6-Amino-pyridin-3-ylethynyl)-4-chloro-6-methyl-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 1.5 g (5.7 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 1.7 g (15 mmol)

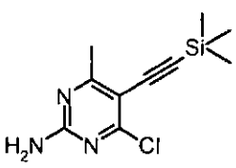
2-amino-5-ethynyl-pyridine (GP15) using 106 mg (0.56 mmol) CuI, 390 mg (0.56 mmol) $PdCl_2(PPh_3)_2$ and 8 mL (55 mmol) triethylamine in 12 mL dry DMF. For the work-up water is added to the reaction mixture. The precipitate is collected, dried at 40 °C and re-crystallized from MeOH. Yield: 1.5 g (83 %, approximately 80 % pure).

A-34) 3-(2-Amino-4-chloro-6-methyl-pyrimidin-5-ylethynyl)-phenol



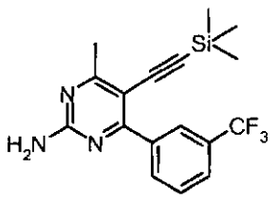
The title compound is synthesized according to general procedure GP2 starting from 1.5 g (5.7 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 986 mg (8.4 mmol) 3-ethynyl-phenol using 106 mg (0.56 mmol) CuI, 390 mg (0.56 mmol) $PdCl_2(PPh_3)_2$ and 8 mL (55 mmol) triethylamine in 12 mL dry DMF. For the work-up the solvent is removed *in vacuo* and the product is purified by chromatography on silica gel (DCM/MeOH gradient) and subsequently RP-HPLC (ACN/H_2O gradient). Yield: 419 mg (29 %).

A-35) 4-Chloro-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine



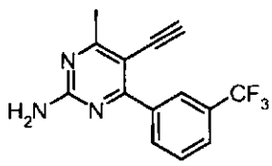
The title compound is synthesized according to general procedure GP2 starting from 5.0 g (19 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 3.6 mL (26 mmol) trimethylsilylethyne using 352 mg (1.9 mmol) CuI, 485 mg triphenylphosphine (1.9 mmol), 1.3 g (1.9 mmol) $PdCl_2(PPh_3)_2$ and 26 mL (185 mmol) triethylamine in 100 mL dry DMF. For the work-up the solvent is removed *in vacuo* and the product is purified by RP-MPLC (ACN/H_2O gradient). Yield: 1.6 g (38 %).

A-36) 4-(3-Trifluoromethyl-phenyl)-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine



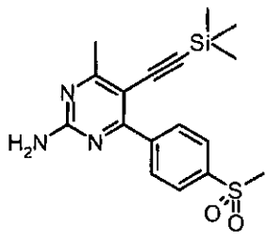
The title compound is synthesized according to general procedure GP2 starting from 1.7 g (7.0 mmol) 4-chloro-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine (A-35) and 2.7 g (14 mmol) 3-trifluorophenylboronic acid using 571 mg (0.70 mmol) $PdCl_2(dppf)_2$ and 3.4 g (11 mmol) Cs_2CO_3 in a mixture of 36 mL THF/3.3 mL water. For the work-up the solvent is removed *in vacuo* and the product is purified by chromatography on silica (DCM/MeOH gradient). Yield: 1.23 g (50 %).

A-37) 5-Ethynyl-4-(3-trifluoromethyl-phenyl)-6-methyl-pyrimidin-2-ylamine



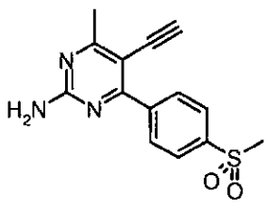
The title compound is synthesized according to general procedure GP3 starting from 1.2 g (3.5 mmol) 4-(3-trifluoromethyl-phenyl)-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine (A-36) and 120 mg (0.87 mmol) potassium carbonate in 5 mL MeOH. After stirring for 2 h at RT, the reaction mixture is diluted with DCM and the organic phase is extracted with water. The organic phase is dried over NGP_2SO_4 and the solvent is removed *in vacuo*. Yield: 523 mg (54 %).

A-38) 4-(4-Methanesulfonyl-phenyl)-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine



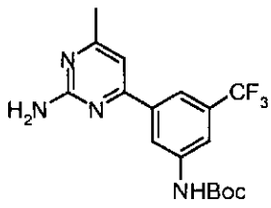
The title compound is synthesized according to general procedure GP2 starting from 3.0 g (7.7 mmol) 5-iodo-4-methyl-6-(4-methanesulfonyl-phenyl)-pyrimidin-2-ylamine (A-33) and 1.6 mL (12 mmol) trimethylsilylethyne using 147 mg (0.77 mmol) CuI, 541 mg (0.77 mmol) $PdCl_2(PPh_3)_2$ and 11 mL (7.7 mmol) triethylamine in 18 mL dry DMF. For the work-up the solvent is removed *in vacuo* and the product is purified by chromatography on silica (DCM/MeOH gradient). Yield: 2.45 g (71 %, approximately 80 % pure).

A-39) 5-Ethynyl-4-(4-methanesulfonyl-phenyl)-6-methyl-pyrimidin-2-ylamine



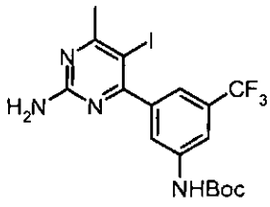
The title compound is synthesized according to general procedure GP3 starting from 2.7 g (6.0 mmol) 4-(4-methanesulfonyl-phenyl)-6-methyl-5-trimethylsilanylethynyl-pyrimidin-2-ylamine (A-36) and 415 mg (3.0 mmol) potassium carbonate in 40 mL MeOH. After stirring for 2 h at 0 °C the precipitated product is filtered off and dried over night at 40 °C. The product is treated with water, filtered off and dried again. Yield: 1.8 g (83 %).

A-40) [3-(2-Amino-6-methyl-pyrimidin-4-yl)-5-trifluoromethyl-phenyl]-carbamic acid *tert*-butyl ester



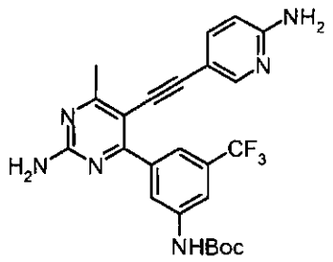
The title compound is synthesized according to general procedure GP4 (A) starting from 215 mg (1.5 mmol) 2-amiono-4-chloro-6-methyl pyrimidine and 2.7 g (14 mmol) 5-trifluoromethyl-3-(*tert*-butyl-oxyxcarbonyl)aminophenyl boronic acid (GP2). The product is precipitated from the reaction mixture by addition of water. Yield after drying at 40 °C: 550 mg (100 %).

A-41) [3-(2-Amino-5-iodo-6-methyl-pyrimidin-4-yl)-5-trifluoromethyl-phenyl]-carbamic acid *tert*-butyl ester



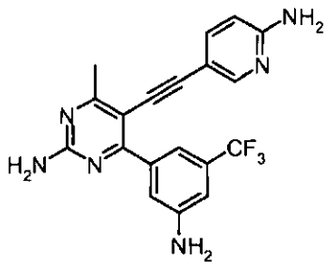
The title compound is synthesized according to general procedure GP1 starting from 550 mg (1.5 mmol) [3-(2-amino-6-methyl-pyrimidin-4-yl)-5-trifluoromethyl-phenyl]-carbamic acid *tert*-butyl ester (GP40) and 336 mg (1.5 mmol) NIS. Yield: 733 mg (99 %).

A-42) {3-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-5-trifluoromethyl-phenyl}-carbamic acid *tert*-butyl ester



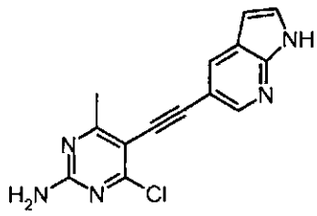
The title compound is synthesized according to general procedure GP2 starting from 733 mg (1.5 mmol) [3-(2-amino-5-iodo-6-methyl-pyrimidin-4-yl)-5-trifluoromethyl-phenyl]-carbamic acid *tert*-butyl ester (A-41) and 262 mg (2.2 mmol) 2-amino-5-ethynyl-pyridine (A-15) using 28 mg (0.15 mmol) CuI, 104 mg (0.15 mmol) $PdCl_2(PPh_3)_2$ and 2 mL (15 mmol) triethylamine in 14 mL dry DMF. For the work-up the solvent is removed *in vacuo* and the product is purified by chromatography on silica gel (DCM/MeOH gradient). Yield: 632 mg (88 %).

A-43) 5-(6-Amino-pyridin-3-ylethynyl)-4-(3-amino-5-trifluoromethyl-phenyl)-6-methyl-pyrimidin-2-ylamine



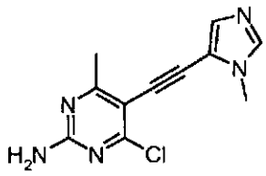
The title compound is synthesized starting from 632 mg (1.3 mmol) {3-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-5-trifluoromethyl-phenyl}-carbamic acid *tert*-butyl ester (A-42) by treatment with a 4 M solution of HCl in dioxane. After completion of the reaction the solvent is removed *in vacuo* followed by extraction with DCM and a saturated aqueous solution of $NaHCO_3$. Yield: 310 mg (62 %).

A-44) 3-(2-Amino-4-chloro-6-methyl-pyrimidin-5-ylethynyl)-phenol



The title compound is synthesized according to general procedure GP2 starting from 500 mg (1.9 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (GP3) and 396 mg (2.8 mmol) 5-ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine (A-20) using 35 mg (0.19 mmol) CuI, 130 mg (0.19 mmol) $PdCl_2(PPh_3)_2$ and 2.6 mL (19 mmol) triethylamine in 6 mL dry DMF. The product precipitates from the reaction mixture, is filtered off and washed with DMF. Yield: 436 mg (75 %).

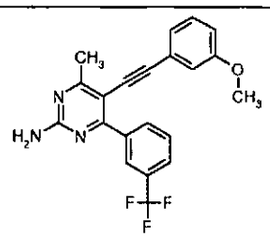
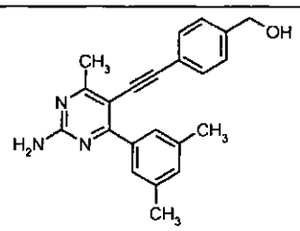
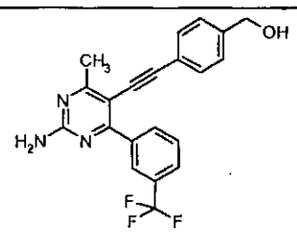
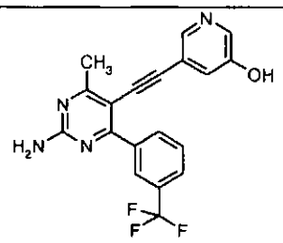
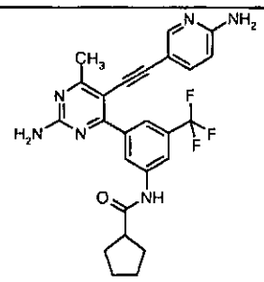
A-45) 4-Chloro-6-methyl-5-(3-methyl-3*H*-imidazol-4-ylethynyl)-pyrimidin-2-ylamine

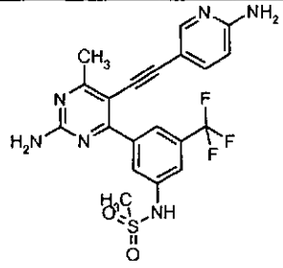
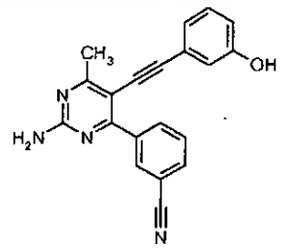
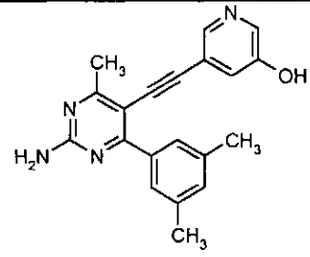
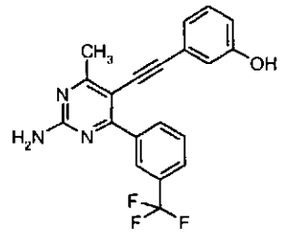
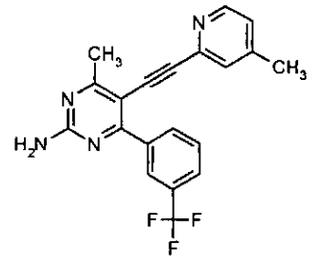


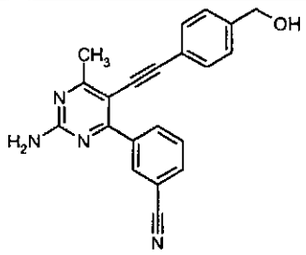
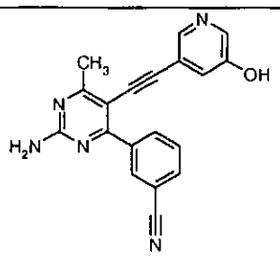
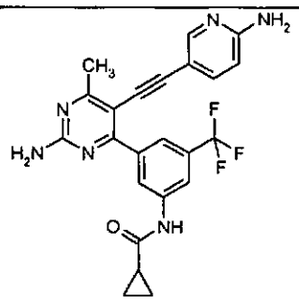
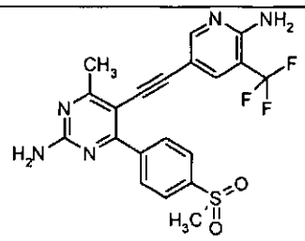
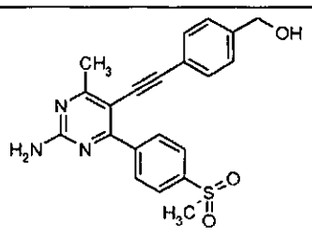
The title compound is synthesized according to general procedure GP2 starting from 1.4 g (5.3 mmol) 4-chloro-5-iodo-6-methyl-pyrimidin-2-ylamine (A-3) and 900 mg (8.5 mmol) 5-ethynyl-1-methyl-1H-imidazole using 10 mg (0.05 mmol) CuI, 112 mg (0.03 mmol) $PdCl_2(PPh_3)_2$, 5.3 mL (5.3 mmol) of 9-methoxy-9-BBN and 1.3 mL (9.5 mmol) triethylamine in 125 mL degassed and dry acetonitril. The product precipitates from the reaction mixture and is filtered off. Yield: 780 mg (54 %).

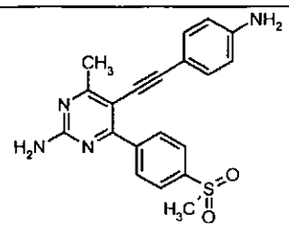
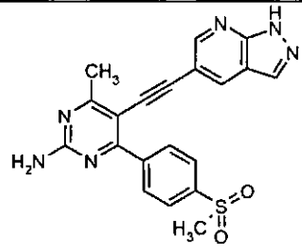
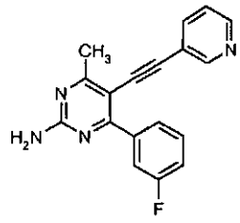
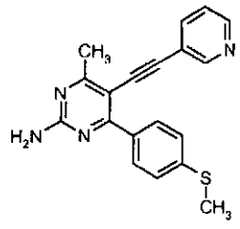
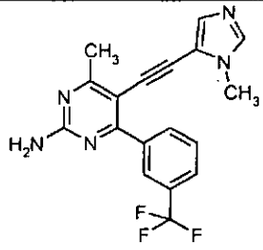
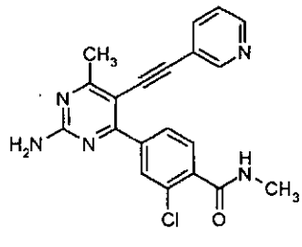
Examples 1 - 86

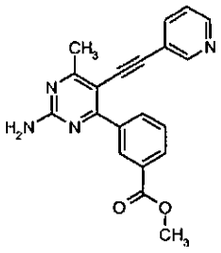
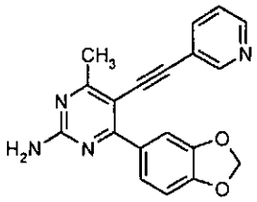
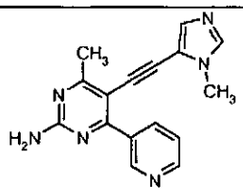
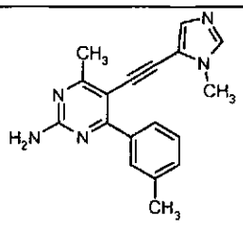
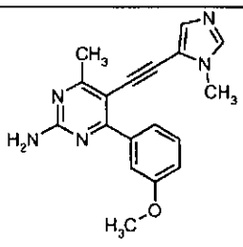
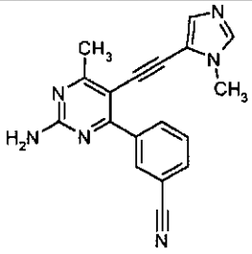
Examples 1 to 86 are synthesized according to the general procedures GP2 (Sonogashira reaction), GP4 (Suzuki coupling) or GP6 (nucleophilic displacement) as outlined above. The appropriate halides required for synthesis can be deduced from the table of the examples.

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
1	A-37		384	2.40
2	A-29		344	1.98
3	A-27		384	2.06
4	A-27		371	1.32
5	A-43		481	1.04

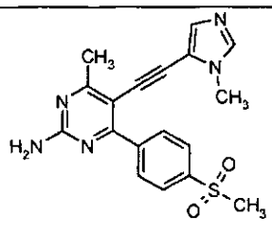
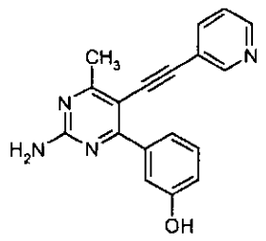
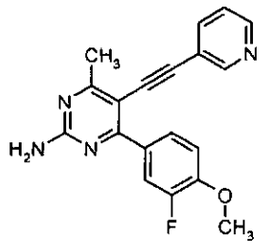
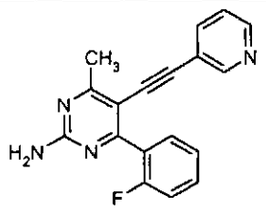
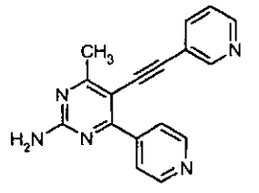
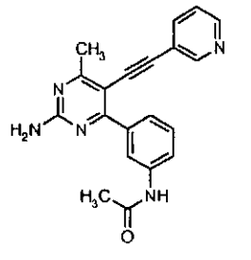
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
6	A-43		463	1.36
7	A-28		327	1.67
8	A-29		331	1.22
9	A-27		370	1.90
10	A-37		369	2.14

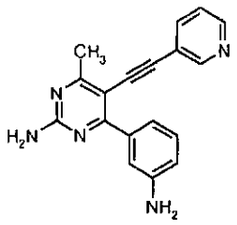
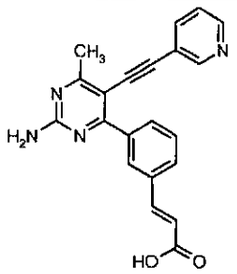
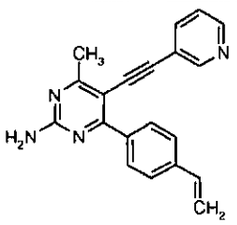
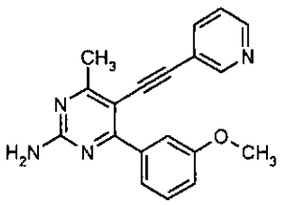
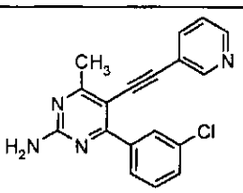
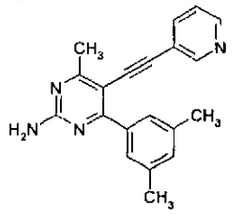
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
11	A-28		341	1.79
12	A-28		328	1.11
13	A-43		453	1.87
14	A-39		448	1.84
15	A-30		394	1.66

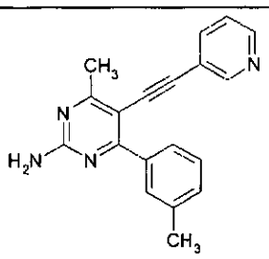
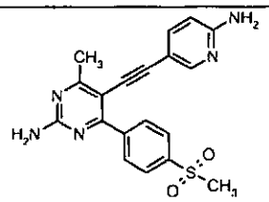
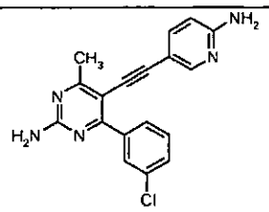
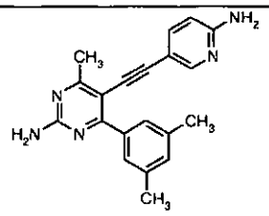
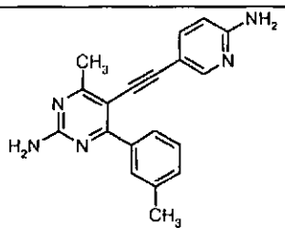
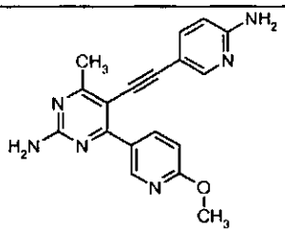
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
16	A-39		379	1.69
17	A-30		405	1.59
18	A-32		305	1.06
19	A-32		333	1.10
20	A-45		358	1.04
21	A-32		378/379	0.94

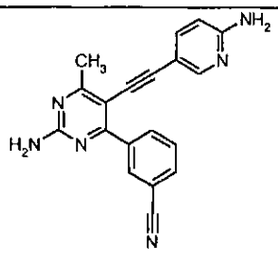
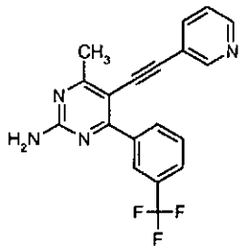
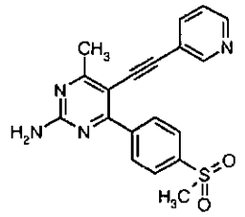
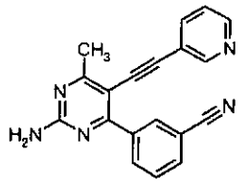
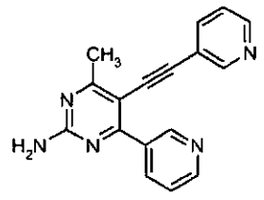
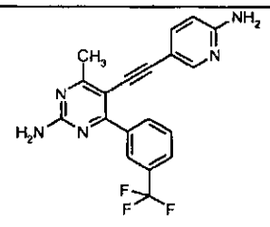
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
22	A-32		345	1.05
23	A-32		331	1.03
24	A-45		291	0.80
25	A-45		304	0.98
26	A-45		320	0.94
27	A-45		315	0.92

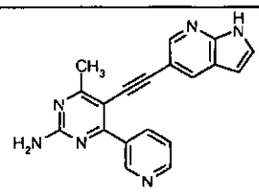
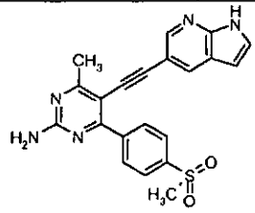
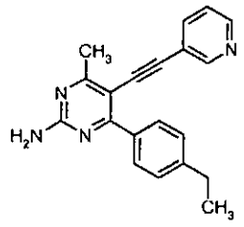
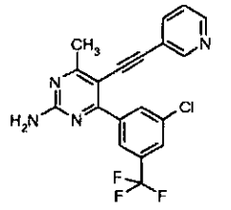
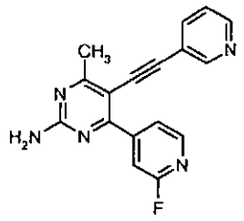
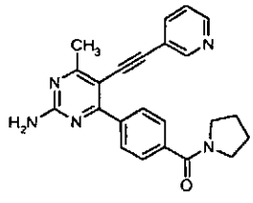
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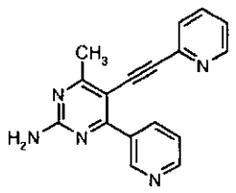
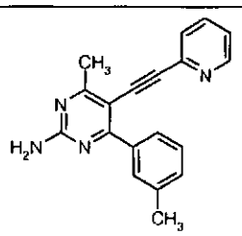
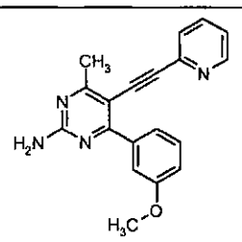
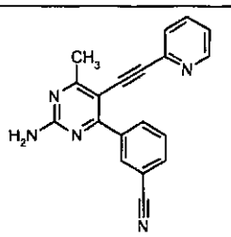
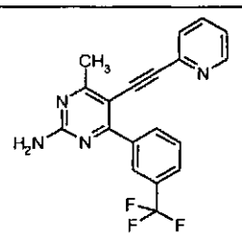
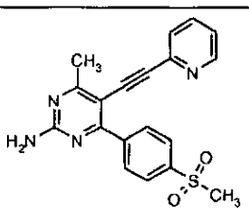
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
28	A-45		368	0.86
29	A-32		303	0.81
30	A-32		335	1.06
31	A-32		305	1.01
32	A-32		288	0.89
33	A-32		344	0.92

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
34	A-32		302	0.92
35	A-32		357	0.73
36	A-32		313	1.11
37	A-32		317	1.80
38	A-32		321	1.96
39	A-32		315	1.99

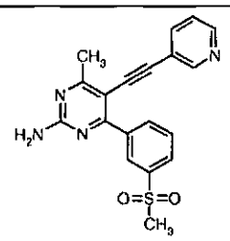
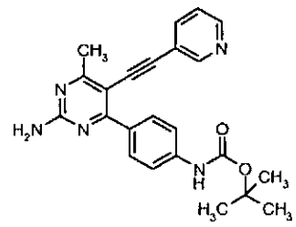
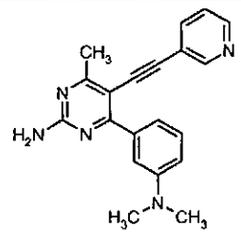
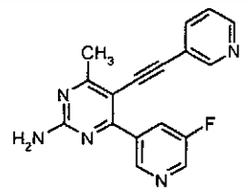
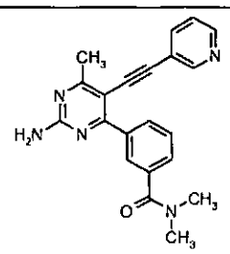
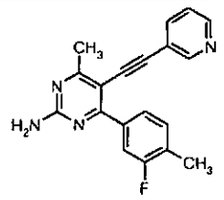
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
40	A-32		301	1.89
41	A-30		380	1.52
42	A-33		336/338	1.83
43	A-33		330	1.85
44	A-33		316	1.74
45	A-33		333	1.59

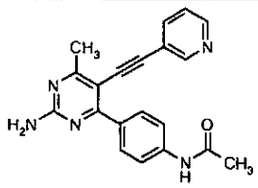
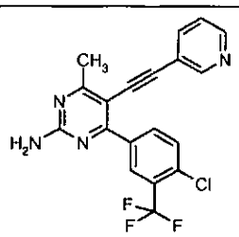
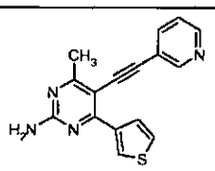
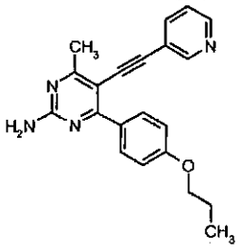
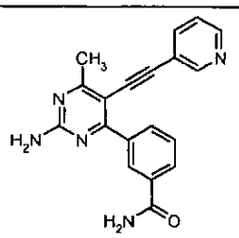
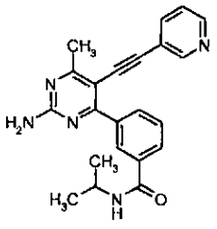
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
46	A-28		327	1.65
47	A-27		355	2.04
48	A-30		365	1.60
49	A-32		312	1.77
50	A-32		288	1.50
51	A-33		370	1.90

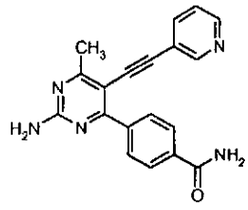
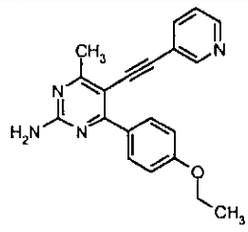
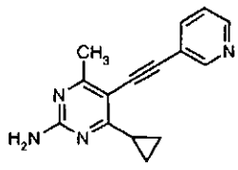
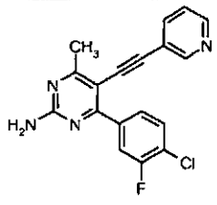
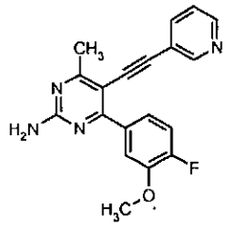
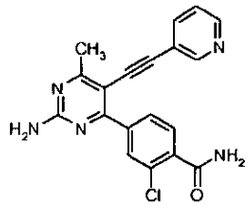
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
52	A-44		327	1.63
53	A-44		404	1.72
54	A-32		315	1.15
55	A-32		389/391	1.23
56	A-32		306	0.96
57	A-32		384	0.97

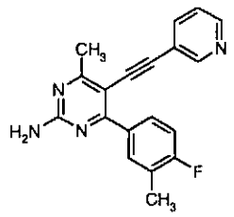
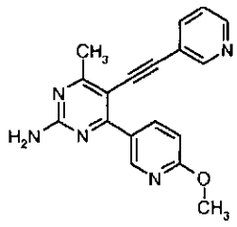
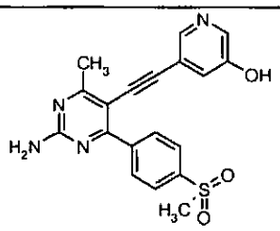
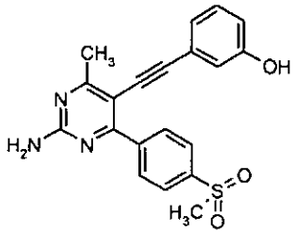
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
58	A-31		288	0.89
59	A-31		301	1.09
60	A-31		317	1.04
61	A-31		312	1.02
62	A-31		355	1.14
63	A-31		365	2.92

35

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
64	A-32		365	0.95
65	A-32		402	1.12
66	A-32		330	1.06
67	A-32		306	0.95
68	A-32		358	0.93
69	A-32		319	1.11

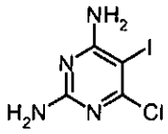
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
70	A-32		344	0.91
71	A-32		389/391	1.20
72	A-32		293	1.03
73	A-32		345	1.15
74	A-32		330	0.88
75	A-32		372	0.98

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
76	A-32		330	0.87
77	A-32		331	1.09
78	A-32		251	1.00
79	A-32		339/341	1.14
80	A-32		335	1.06
81	A-32		364/366	0.90

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
82	A-32		319	1.10
83	A-32		318	0.99
84	A-30		381	0
85	A-30		380	1.50

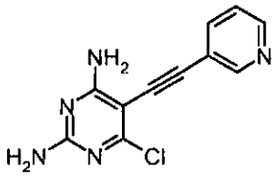
Intermediates B

B-1) 6-Chloro-5-iodo-pyrimidine-2,4-diamine



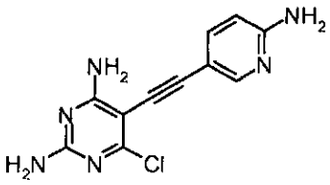
The title compound is synthesized according to general procedure GP1 starting from 25 g (173 mmol) 6-chloro-pyrimidine-2,4-diamine and 39 g (173 mmol) NIS. Yield after precipitation of the product from water: 38.8 g (83 %).

B-2) 6-Chloro-5-pyridin-3-ylethynyl-pyrimidine-2,4-diamine



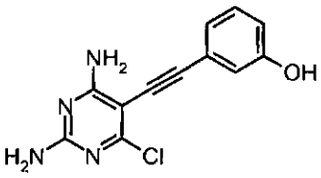
The title compound is synthesized according to general procedure GP2 starting from 1.0 g (3.7 mmol) 6-chloro-5-iodo-pyrimidine-2,4-diamine, 494 g (4.79 mmol) 3-ethynylpyridine, 70 mg (0.37 mmol) CuI, 259 mg (0.37 mmol) $PdCl_2(PPh_3)_2$ and 85 mL triethylamine in 60 mL dry DMF. Yield after purification by chromatography on silica gel: 800 mg (88 %).

B-3) 5-(6-Amino-pyridin-3-ylethynyl)-6-chloro-pyrimidine-2,4-diamine



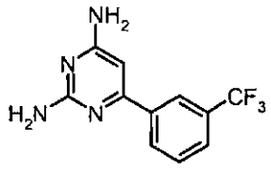
The title compound is synthesized according to general procedure GP2 starting from 850 mg (3.1 mmol) 6-chloro-5-iodo-pyrimidine-2,4-diamine, 2.2 g (19 mmol) 5-ethynyl-2-amino-pyridine, 59 mg (0.31 mmol) CuI, 218 mg (0.31 mmol) $PdCl_2(PPh_3)_2$ and 21 mL triethylamine in 25 mL dry DMF. Yield after purification by RP-HPLC: 720 mg (88 %).

B-4) 3-(2,4-Diamino-6-chloro-pyrimidin-5-ylethynyl)-phenol



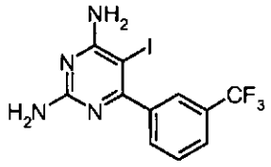
The title compound is synthesized according to general procedure GP2 starting from 500 mg (1.8 mmol) 6-chloro-5-iodo-pyrimidine-2,4-diamine, 827 mg (7.0 mmol) 3-ethynyl-phenol, 35 mg (0.19 mmol) CuI, 129 mg (0.19 mmol) $PdCl_2(PPh_3)_2$ and 4.1 mL triethylamine in 4 mL dry DMF. Yield after purification by RP-HPLC: 511 mg (100 %).

B-5) 6-(3-Trifluoromethyl-phenyl)-pyrimidine-2,4-diamine



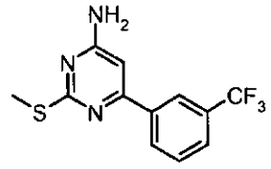
The title compound is synthesized according to general procedure GP4 (A) starting from 1.3 g (9.0 mmol) 6-chloro-pyrimidine-2,4-diamine, 2.2 g (12 mmol) 3-trifluorophenyl boronic acid, 260 mg Pd(PPh3)4 and 7.7 mL 2 M aqueous solution of K_2CO_3 and 26 mL dimethoxyethane. Yield after chromatography by RP-HPLC: 1.25 g (55 %).

B-6) 5-Iodo-6-(3-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine



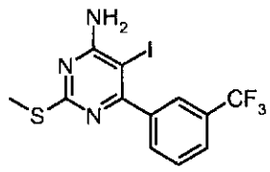
The title compound is synthesized according to general procedure GP1 starting from 1.8 g (7.1 mmol) 6-(3-trifluoromethyl-phenyl)-pyrimidine-2,4-diamine and 1.8 g (7.8 mmol) NIS. Yield: 2.0 g (74 %).

B-7) 2-Methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine



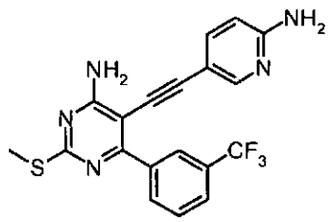
The title compound is synthesized according to general procedure GP4 (C) starting from 1.0 g (5.7 mmol) 6-chloro-2-methylsulfanyl-pyrimidin-4-ylamine, 1.4 g (7.4 mmol) 3-trifluorophenylboronic acid, 164 mg $Pd(PPh_3)_4$ and 1.6 g (11 mmol) K_2CO_3 in a DME/water mixture 16/5 v/v). The solvent is removed under reduced pressure, the crude product separated between water and ethyl acetate. The organic layer is separated, dried over NGP_2SO_4 and filtered off. The solvent is removed under reduced pressure. The crude product is used without further purification. Yield: 2.14 g (100 %).

B-8) 5-Iodo-2-methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine



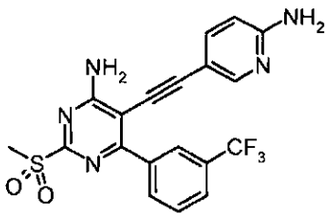
The title compound is synthesized according to general procedure GP2 starting from 2.0 g (7.0 mmol) 2-methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine and 1.6 g (7.0 mmol) NIS. Yield after precipitation: 1.9 g (66 %).

B-9) 5-(6-Amino-pyridin-3-ylethynyl)-2-methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine



The title compound is synthesized according to general procedure GP2 starting from 850 mg (2.1 mmol) 5-iodo-2-methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine, 1.5 g (12.4 mmol) 5-ethynyl-2-amino-pyridine, 39 mg (0.21 mmol) CuI, 145 mg (0.21 mmol) $PdCl_2(PPh_3)_2$ and 2.9 mL triethylamine in 15 mL dry DMF. Yield after purification by RP-HPLC: 427 mg (52 %).

B-10) 5-(6-Amino-pyridin-3-ylethynyl)-2-methanesulfonyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine

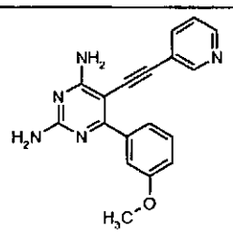
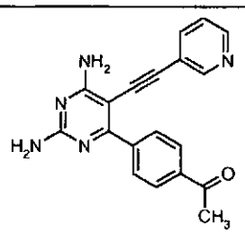
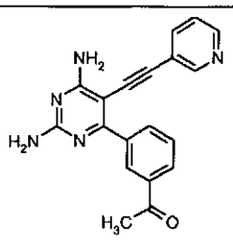
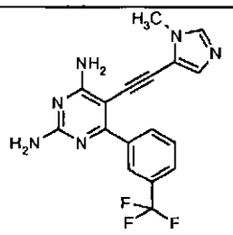


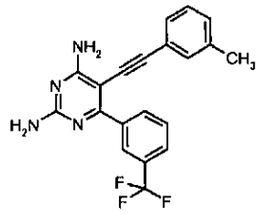
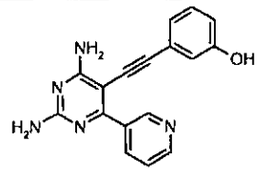
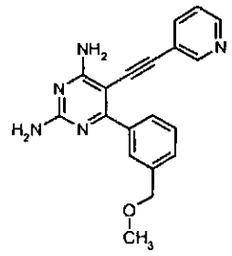
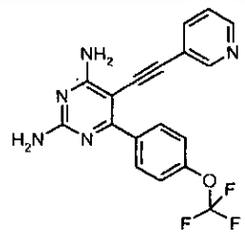
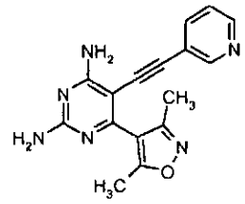
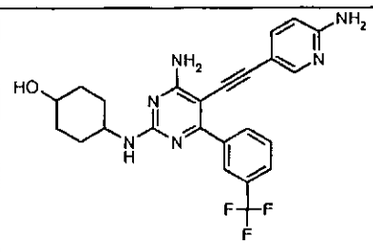
m-CPBA (859 mg, 5.0 mmol) is added to a solution of 1.0g (2.5 mmol) 5-(6-amino-pyridin-3-ylethynyl)-2-methylsulfanyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine in 100 mL DCM. After stirring for 48 h at RT additional 215 mg m-CPBA are added and

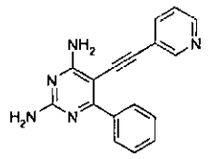
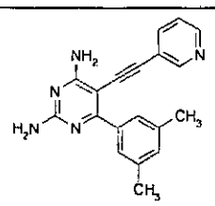
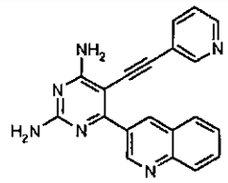
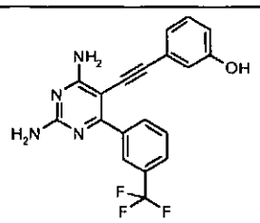
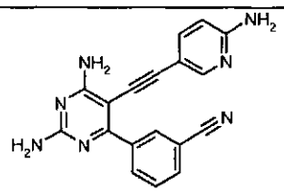
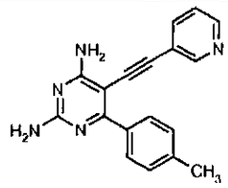
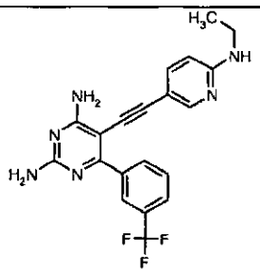
the mixture is stirred for additional 24 h. A mixture of sulfone and sulfoxide is formed. The precipitate is filtered off and washed with DCM (510 mg). Additional product is isolated from the liquid phase after extraction with water and removal of the solvent from the organic phase. Yield: 1.1 g (100 %).

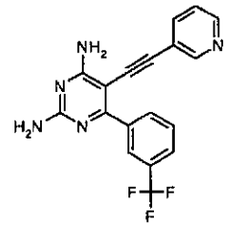
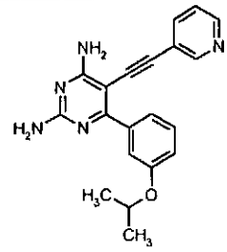
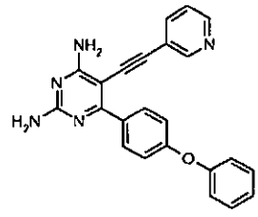
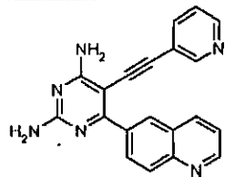
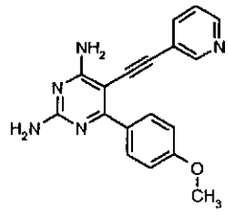
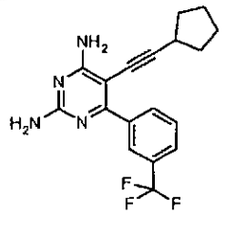
Examples 86 - 139

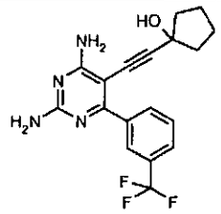
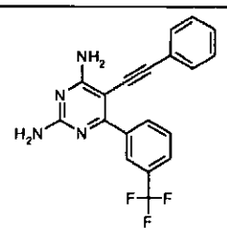
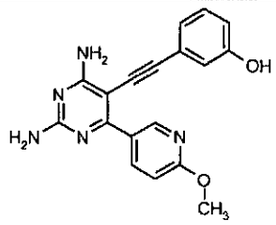
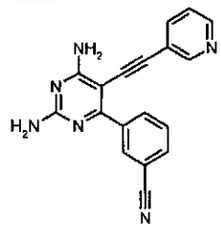
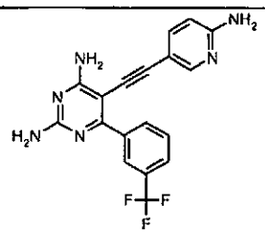
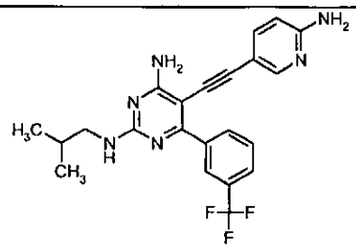
Examples 86 - 139 are synthesized according to the general procedures GP2 (Sonogashira reaction), GP4 (Suzuki coupling) or GP6 (nucleophilic displacement) outlined above. The appropriate halides required for synthesis can be deduced from the table of examples.

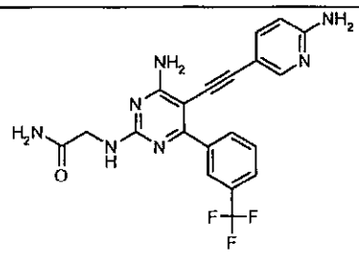
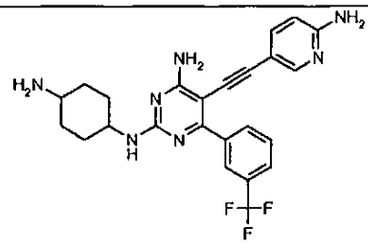
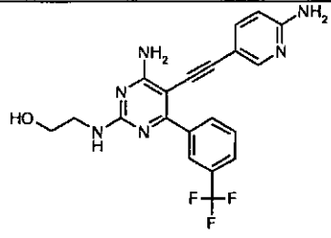
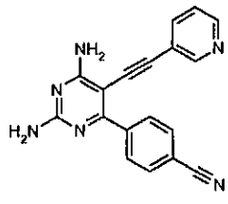
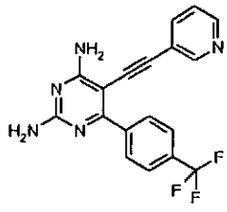
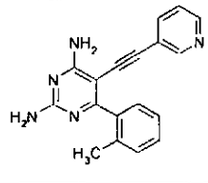
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
86	B-2		318	0.96
87	B-2		330	0.91
88	B-2		330	0.91
89	B-6		359	0.97

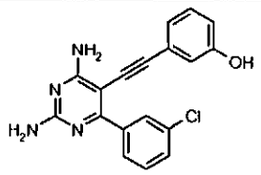
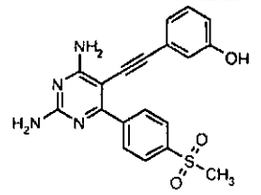
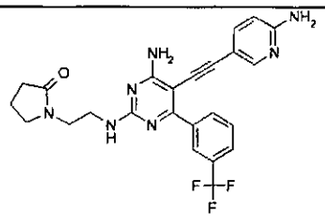
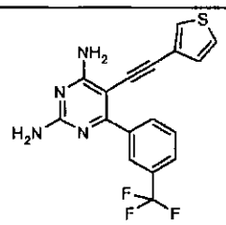
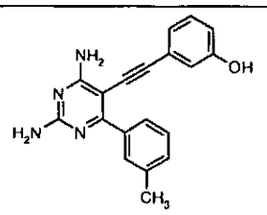
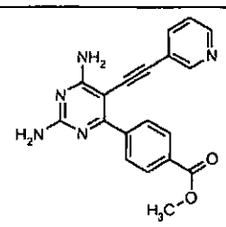
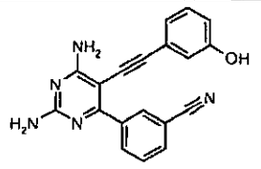
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
90	B-6		369	1.25
91	B-4		304	1.41
92	B-2		332	0.92
93	B-2		372	1.09
94	B-2		307	0.85
95	B-10		469	1.89

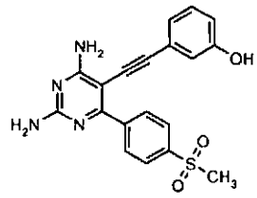
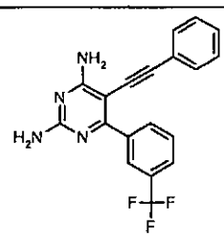
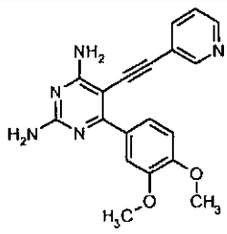
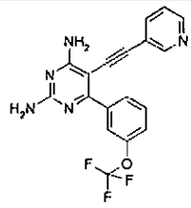
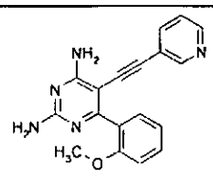
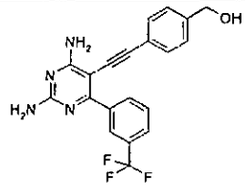
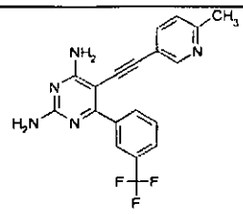
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
96	B-2		288	1.55
97	B-2		316	1.04
98	B-2		339	0.94
99	B-4		371	1.93
100	B-3		328	1.49
101	B-2		302	1.00
102	B-6		399	2.00

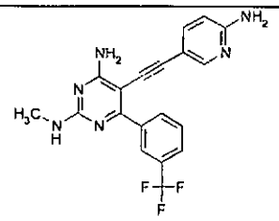
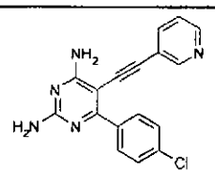
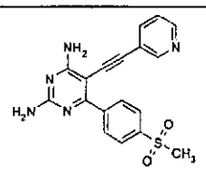
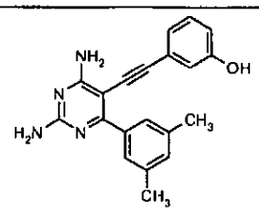
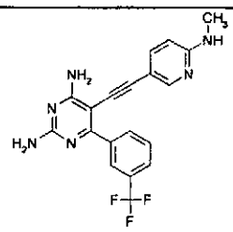
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
103	B-6		356	1.86
104	B-2		346	1.05
105	B-2		380	1.12
106	B-2		339	0.88
107	B-2		318	0.96
108	B-6		347	1.24

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
109	B-6		363	1.11
110	B-6		355	2.50
111	B-4		334	1.62
112	B-2		313	1.60
113	B-6		371	1.76
114	B-10		427	2.28

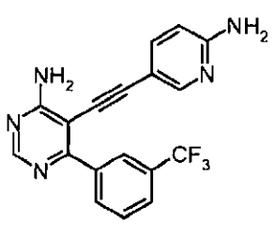
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
115	B-10		428	1.68
116	B-10		468	1.91
117	B-10		415	1.76
118	B-2		313	0.94
129	B-2		356	1.08
120	B-2		302	0.95

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
121	B-4		337	1.85
122	B-4		381	1.52
123	B-10		482	1.85
124	B-6		361	1.19
125	B-4		317	1.79
126	B-2		346	0.96
127	B-4		328	1.68

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
128	B-4		381	1.31
129	B-6		355	2.10
130	B-2		348	0.91
131	B-2		372	1.08
132	B-2		318	0.91
133	B-6		385	1.06
134	B-6		370	1.94

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
135	B-10		385	1.94
136	B-2		322/324	1.03
137	B-2		366	0.86
138	B-4		331	1.88
139	B-6		385	1.88

140) 5-(6-Amino-pyridin-3-ylethynyl)-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine

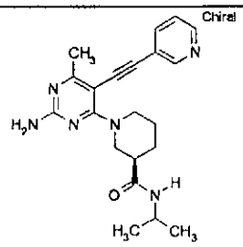
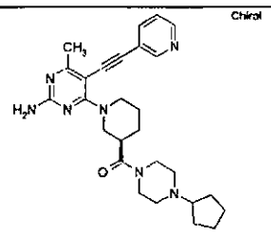
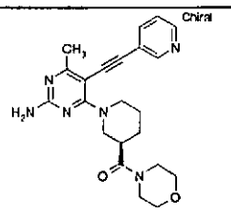
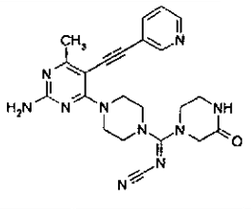


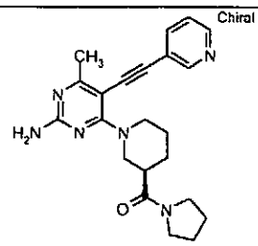
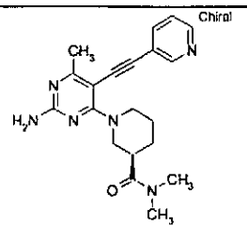
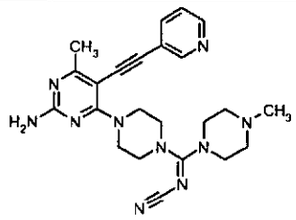
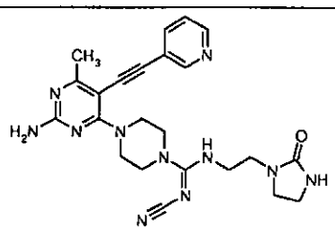
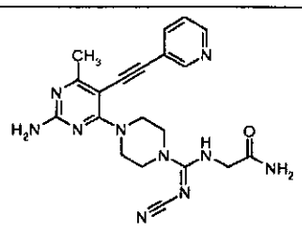
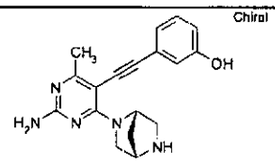
To a solution of 60 mg (0.080 mmol) 5-(6-amino-pyridin-3-ylethynyl)-2-methanesulfonyl-6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamine (B-10) and 15.7 mg (0.42 mmol)

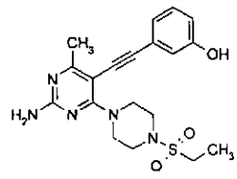
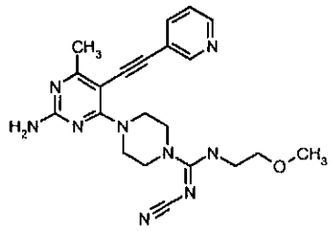
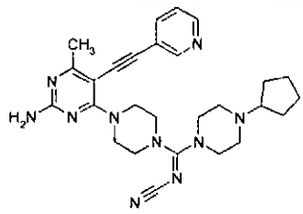
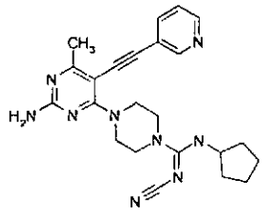
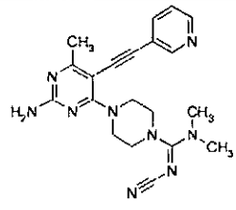
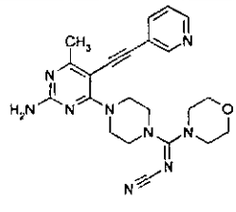
sodiumborohydride in 1 mL EtOH is stirred at 80 °C for 60 minutes. The title compound is purified from the crude reaction mixture by RP-HPLC (ACN/H_2O gradient). Yield: 1.4 mg (5 %).

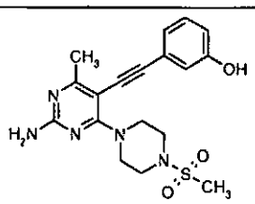
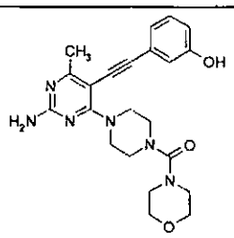
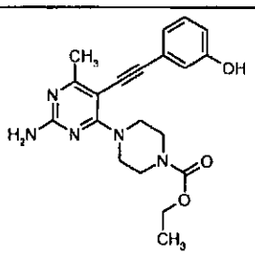
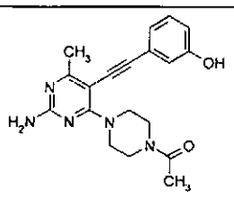
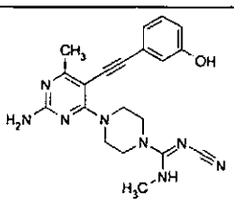
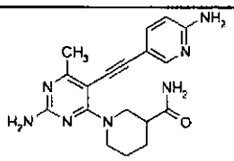
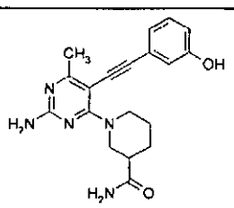
Examples 141 – 212

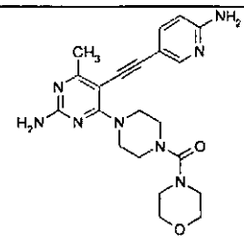
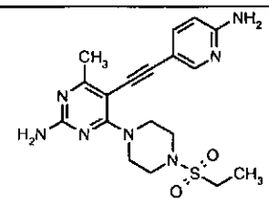
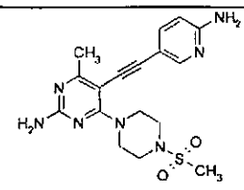
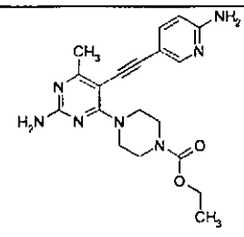
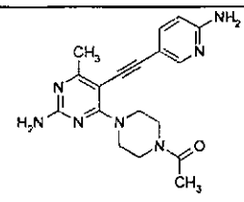
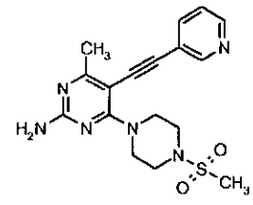
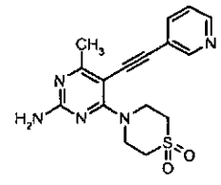
Examples 141 to 212 are synthesized according to the general procedures GP2 (Sonogashira reaction) and GP6 (nucleophilic displacement) outlined above. The appropriate halides required for synthesis can be deduced from the table of examples.

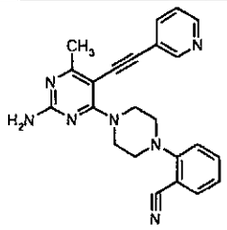
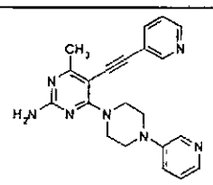
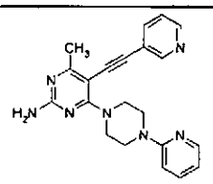
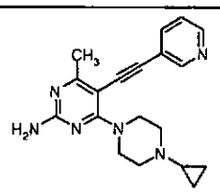
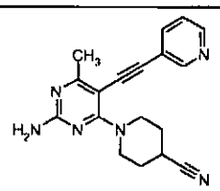
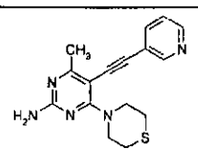
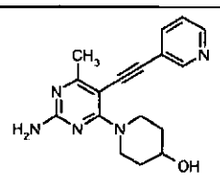
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
141	A-32		379	1.63
142	A-32		474	1.84
143	A-32		407	1.56
144	A-32		445	1.42

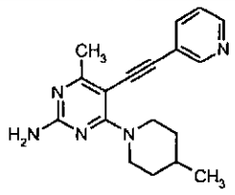
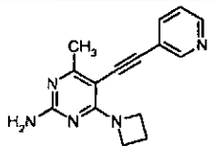
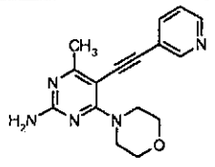
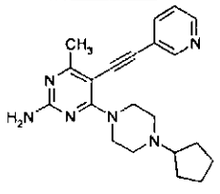
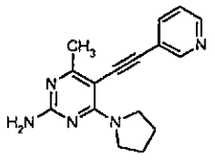
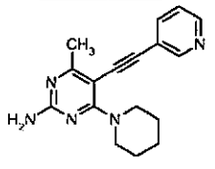
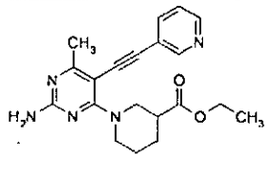
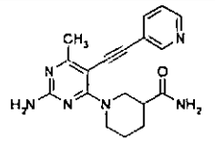
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
145	A-32		391	1.67
146	A-32		365	1.57
147	A-32		445	1.53
148	A-32		474	1.44
149	A-32		419	1.37
150	A-34		322	1.2-1.4

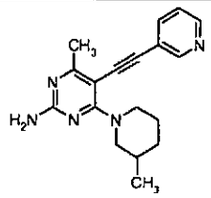
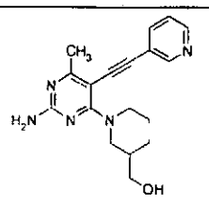
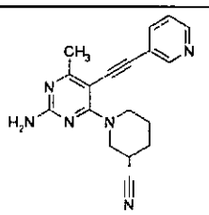
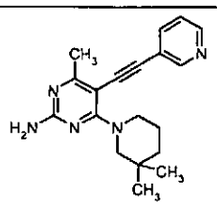
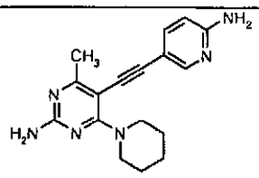
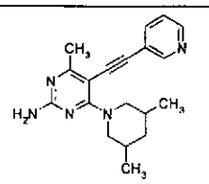
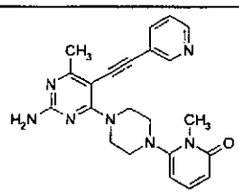
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
151	A-34		402	1.63
152	A-32		420	1.54
153	A-32		499	1.80
154	A-32		402	1.57
155	A-32		390	1.54
156	A-32		432	1.53

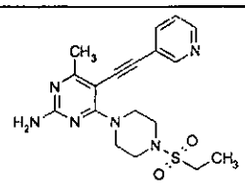
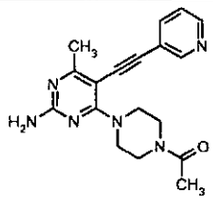
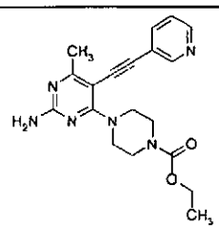
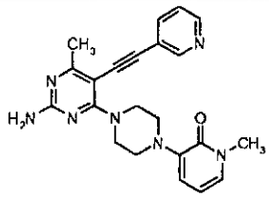
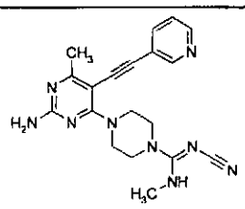
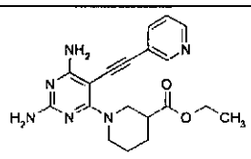
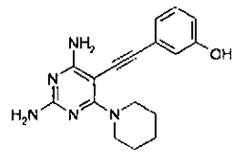
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
157	A-34		388	1.53
158	A-34		423	
159	A-34		382	1.74
160	A-34		352	1.42
161	A-34		391	1.45
162	A-33		352	1.33
163	A-34		352	1.38

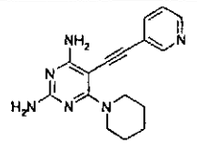
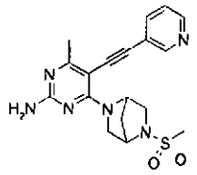
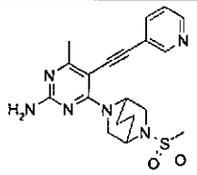
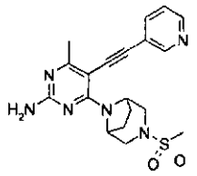
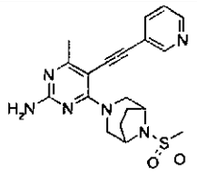
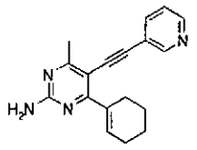
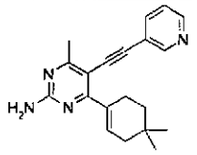
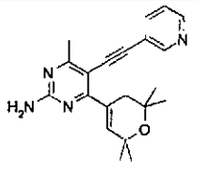
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
164	A-33		423	1.47
165	A-33		402	1.54
166	A-33		388	1.49
167	A-33		382	1.65
168	A-33		352	1.41
169	A-32		373	1.56
170	A-32		344	1.69

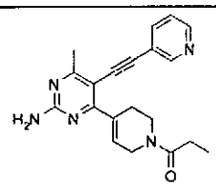
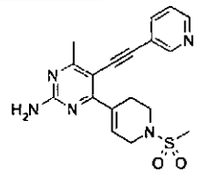
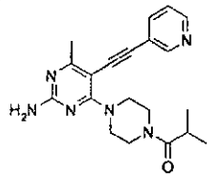
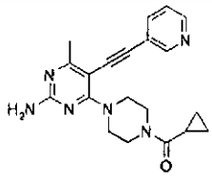
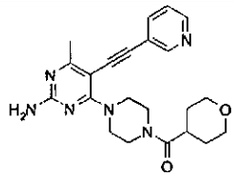
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
171	A-32		396	2.24
172	A-32		372	1.61
173	A-32		372	1.63
174	A-32		335	1.42
175	A-32		319	2.34
176	A-32		312	2.45
177	A-32		310	2.13

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
178	A-32		308	2.69
179	A-32		266	2.25
180	A-32		296	2.21
181	A-32		363	2.02
182	A-32		280	1.91
183	A-32		294	1.86
184	A-32		366	1.88
185	A-32		337	1.39

No.	Educt	Structure	$[M+H]^+$	t_{Rot} [min]
186	A-32		308	1.98
187	A-32		324	1.57
188	A-32		319	1.64
189	A-32		322	2.04
190	A-33		309	1.72
191	A-32		322	2,06/2,09
192	A-32		402	1,63

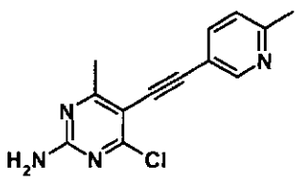
No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
193	A-32		387	1.66
194	A-32		337	1.47
195	A-32		367	1.76
196	A-32		402	1.64
197	A-32		376	1.49
198	B-2		367	1.74
199	B-4		310	1.81

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
200	B-2		295	1.71
201	A-32		385	
202	A-32		399	
203	A-32		399	
204	A-32		399	
205	A-32		291	
206	A-32		319	
207	A-32		349	

No.	Educt	Structure	$[M+H]^+$	t_{Ret} [min]
208	A-32		348	
209	A-32		370	
210	A-32		365	
211	A-32		363	
212	A-32		407	

Intermediates C

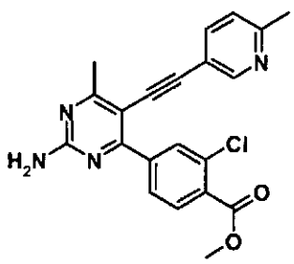
C-46) 4-Chloro-6-methyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 1.0 g (3.7 mmol) 4-chloro-6-methyl-5iodo-pyrimidin-2-ylamine using 570 mg (3.7 mmol) 5-ethynyl-2-methyl-pyridine, 71 mg (0.37 mmol) CuI, 260 mg (0.37 mmol) bis-(triphenylphoshine)palladium(II) chloride, 5.1 mL (27 mmol) triethylamine in 40 mL

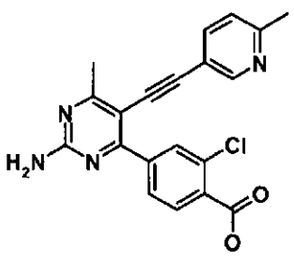
DMF. The reaction mixture is stirred over night at 55 °C. After removal of the solvent under reduced pressure, the product is purified by chromatography on silica gel using a DCM/MeOH gradient (100:0 -> 85:15, 30 min). Yield: 270 mg (28 %).

C-47) 4-[2-Amino-6-methyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester



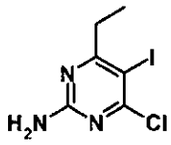
The title compound is synthesized according to general procedure GP4 starting from 200 mg (0.77 mmol) 4-chloro-6-methyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 249 mg (1.16 mmol) 3-chloro-4-methoxycarbonylphenyl boronic acid, 24 mg (0.16 mmol) $Pd(PPh_3)_4$, 205 mg (1.47 mmol) K_2CO_3 in 3 mL dioxane/H_2O (3:1 v/v). The product precipitates from the reaction mixture, is filtered off and can be used without further purification. Yield: 235 mg (77 %).

C-48) 4-[2-Amino-6-methyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid



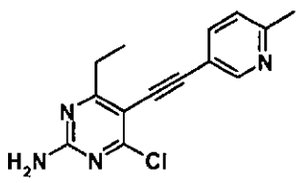
The title compound is synthesized according to general procedure GP8 starting from 235 mg (0.6 mmol) 4-[2-amino-6-methyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid using 0.9 mL (0.9 mmol) 1 N NaOH in THF.
Yield: 130 mg (57 %).

C-49) 4-Chloro-6-ethyl-5-iodo-pyrimidin-2-ylamine



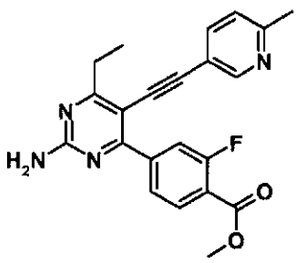
The title compound is synthesized according to general procedure GP1 starting from 2.5 g (16 mmol) 4-chloro-6-ethyl-pyrimidin-2ylamine and 3.7 g (16 mmol) NIS. Yield after precipitation from the reaction mixture: 3.83 g (85 %).

C-50) 4-Chloro-6-Eethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 300 mg (1.1 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidin-2-ylamine using 160 mg (1.1 mmol) 5-ethynyl-2-methyl-pyridine hydrochloride, 20 mg (0.11 mmol) CuI, 74 mg (0.11 mmol) bis-(triphenylphoshine)palladium(II) chloride, 1.5 mL (10.6 mmol) triethylamine in 11 mL DMF. The reaction mixture is stirred over night at 60 °C. After removal of the solvent under reduced pressure, the product is purified by PR-HPLC. Yield: 130 mg (45 %).

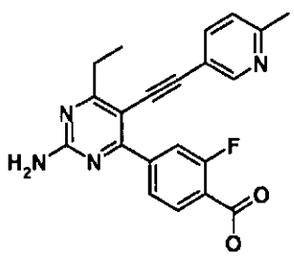
C-51) 4-[2-Amino-6-ethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester



The title compound is synthesized according to general procedure GP4 starting from 130 mg (0.48 mmol) 4-chloro-6-ethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-2-

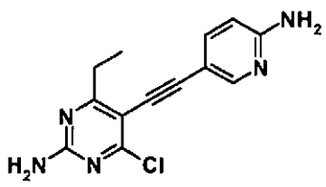
ylamine using 142 mg (0.7 mmol) 3-fluoro-4-methoxycarbonylphenyl boronic acid, 14 mg (0.01 mmol) $Pd(PPh_3)_4$, 133 mg (1.0 mmol) K_2CO_3 in 2.25 mL DME/H_2O (10:1 v/v). The product precipitates from the reaction mixture, is filtered off and can be used without further purification. Yield: 125 mg (67 %).

C-52) 4-[2-Amino-6-ethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 130 mg (0.47 mmol) 4-[2-amino-6-ethyl-5-(6-methyl-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester using 470 µL (0.47 mmol) 1 N NaOH in 3 mL THF. The product precipitates from the reaction mixture and is isolated by filtration. Yield: 77 mg (62%).

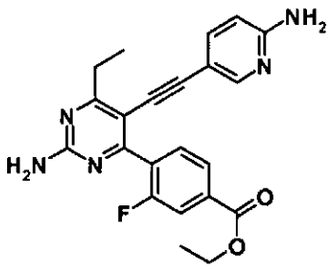
C-53) 5-(6-Amino-pyridin-3-ylethynyl)-4-chloro-6-ethyl-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 3.0 g (10.6 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidin-2-ylamine using 1.37 mg (12 mmol) 5-ethynyl-2-amino-pyridine, 200 mg (1.1 mmol) CuI, 740 mg (1.1 mmol) bis-(triphenylphoshine)palladium(II) chloride, 15 mL (106 mmol) triethylamine in 60 mL DMF. The reaction mixture is stirred over night at 65 °C. Small amounts of water are added to the reaction mixture, the precipitated product is filtered off and washed subsequently with DMF, H_2O and diethylether. The crude product is re-crystallized from

DMF (Yield: 1.65 g). Additional product is isolated from the mother liquid by RP-HPLC. (Yield: 325 mg). Overall yield: 1.97 g (68 %).

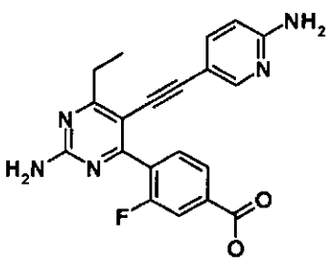
C-54) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-3-fluoro-benzoic acid ethyl ester



The title compound is synthesized according to general procedure GP4 starting from 300 mg (1.1 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 349 mg (1.6 mmol) 2-fluoro-4-ethoxycarbonylphenyl boronic acid, 34 mg (0.22 mmol) $Pd(PPh_3)_4$, 291 mg (2.1 mmol) K_2CO_3 in 5 mL DME/H_2O (5:2 v/v). After stirring twice for 60 min at 130°C under microwave irradiation, conversion of the starting material is about 75 %, an about 1:1 mixture of the desired product and the saponified ester is formed. The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether. Yield: 155 mg (35 %).

The mother liquid contains the corresponding carboxylic acid which can be isolated together with acid obtained from the saponification of the ester.

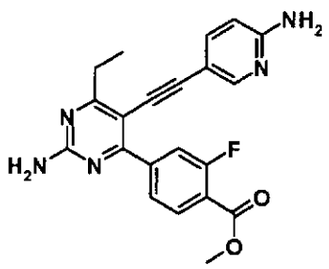
C-55) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-3-fluoro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 200 mg (0.54 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-

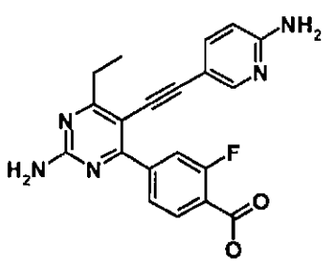
3-fluoro-benzoic acid methyl ester using 0.81 mL (0.81 mmol) 1 N NaOH in 4 mL THF. After completion of the reaction, the reaction mixture is combined with the mother liquid from the proceeding Suzuki coupling. The pH is adjusted to 4-5 (using 1 N HCl) upon which the product precipitates from the reaction mixture and is isolated by filtration. Yield: 240 mg (58 % over two steps).

C-56) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester



The title compound is synthesized according to general procedure GP4 starting from 500 mg (1.8 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 542 mg (2.7 mmol) 3-Fluoro-4-methoxycarbonylphenyl boronic acid, 56 mg (0.37 mmol) $Pd(PPh_3)_4$, 611 mg (4.4 mmol) K_2CO_3 in 10 mL DME/H_2O (9:1 v/v). After stirring twice for 60 min at 130°C under microwave irradiation, conversion of the starting material is about 75 %, an about 1:4 mixture of the desired product and the saponified ester is formed. The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether. Yield: 537 mg (75 %).

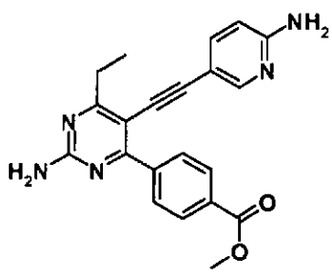
C-57) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-fluoro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from

630 mg (1.6 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester using 1.6 mL (1.6 mmol) 1 N NaOH in 10 mL THF. The precipitate is collected by filtration and washed with THF. Yield: 580 mg (96 %).

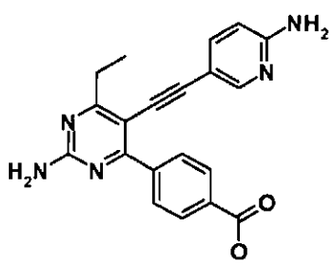
C-58) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-benzoic acid methyl ester (



The title compound is synthesized according to general procedure GP4 starting from 300 mg (1.1 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 296 mg (1.6 mmol) 4-methoxycarbonylphenyl boronic acid, 34 mg (0.22 mmol) $Pd(PPh_3)_4$, 290 mg (2.1 mmol) K_2CO_3 in 5 mL DME/H_2O (5:2 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether. Yield: 120 mg (29 %).

The mother liquid contains the corresponding carboxylic acid which can be isolated together with acid obtained from the saponification of the ester.

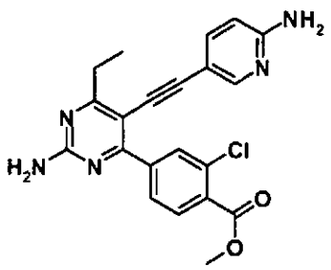
C-59) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 120 mg (0.32 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-benzoic acid methyl ester using 0.48 mL (0.48 mmol) 1 N NaOH in 3 mL THF.

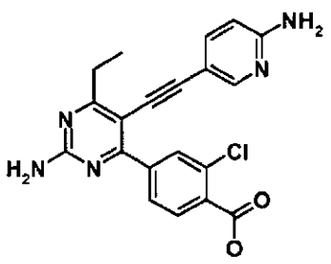
For the work-up the reaction mixture is combined with the mother liquid from the proceeding Suzuki coupling (contains additional amounts of the product), the pH is adjusted to pH 4-5 (using 1 N HCl) upon which the product precipitates and is isolated by filtration. The product is washed with water and diethylether. Yield: 400 mg (>100 % over 2 steps).

C-60) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester



The title compound is synthesized according to general procedure GP4 starting from 700 mg (2.6 mmol) 4-chloro-6-ethyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 822 mg (3.8 mmol) 3-Chloro-4-methoxycarbonylphenyl boronic acid, 80 mg (0.37 mmol) $Pd(PPh_3)_4$, 678 mg (4.8 mmol) K_2CO_3 in 9 mL DME/H_2O (7:2 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water, diethylether, isopropanol and again diethylether. Yield: 951 mg (91 %).

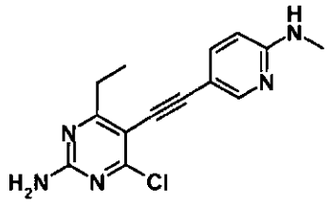
C-61) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-chloro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 951 mg (2.3 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-ethyl-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester using 3.5 mL (3.5 mmol) 1 N NaOH in 16 mL THF.

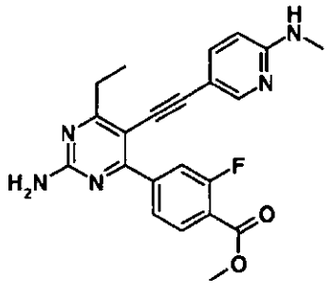
The product precipitates from the reaction mixture and is isolated by filtration. The product is washed with THF and diethylether. Yield: 345 mg (38 %).

C-62) 4-Chloro-6-ethyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 3.0 g (10.6 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidin-2-ylamine using 1.5 g (11.6 mmol) 5-ethynyl-2-aminomethyl-pyridine, 201 mg (1.1 mmol) CuI, 743 mg (1.1 mmol) bis-(triphenylphoshine)palladium(II) chloride, 15 mL (106 mmol) triethylamine in 25 mL DMF. The reaction mixture is stirred for 3 days at 55 °C. The reaction mixture is concentrated under reduced pressure and the product is isolated by chromatography on silica gel. Yield: 1.54 g (51 %).

C-63) 4-[2-Amino-6-ethyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester

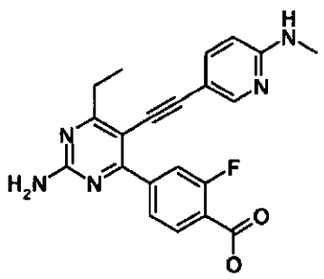


The title compound is synthesized according to general procedure GP4 starting from 330 mg (1.2 mmol) 4-chloro-6-ethyl-5-(6-aminomethyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 344 mg (1.7 mmol) 3-fluoro-4-methoxycarbonylphenyl boronic acid, 36 mg (0.23 mmol) $Pd(PPh_3)_4$, 307 mg (2.2 mmol) K_2CO_3 in 7 mL DME/H_2O (5:2 v/v). After stirring for 60 min at 130°C under microwave irradiation, an about 1:1 mixture of the desired product and the saponified ester is formed. The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether.

Yield: 238 mg (51 %).

The mother liquid contains the corresponding carboxylic acid which can be isolated together with acid obtained from the saponification of the ester.

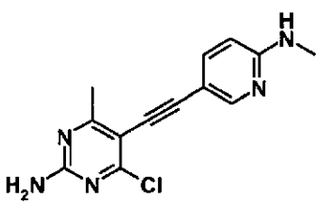
C-64) 4-[2-Amino-6-ethyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid (



The title compound is synthesized according to general procedure GP8 starting from 238 mg (0.59 mmol) 4-[2-amino-6-ethyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester using 0.88 mL (0.88 mmol) 1 N NaOH in 3 mL THF.

For the work-up the reaction mixture is combined with the mother liquid from the proceeding Suzuki coupling (contains additional amounts of the product), the pH is adjusted to pH 4-5 (using 1 N HCl) upon which the product precipitates and is isolated by filtration. The product is washed with water and diethylether. Yield: 517 mg (114 % over 2 steps).

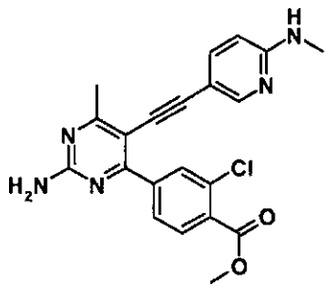
C-65) 4-Chloro-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine



The title compound is synthesized according to general procedure GP2 starting from 3.0 g (10.6 mmol) 4-chloro-6-ethyl-5-iodo-pyrimidin-2-ylamine using 1.5 g (11.6 mmol) 5-ethynyl-2-aminomethyl-pyridine, 201 mg (1.1 mmol) CuI, 743 mg (1.1 mmol)

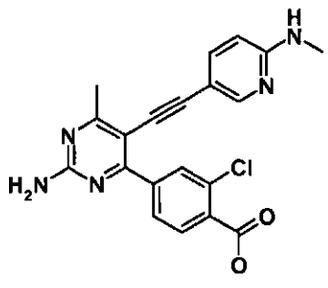
bis-(triphenylphoshine)palladium(II) chloride, 15 mL (106 mmol) triethylamine in 25 mL DMF. The reaction mixture is stirred for 3 days at 55°C. The reaction mixture is concentrated under reduced pressure and the product is isolated by chromatography on silica gel. Yield: 1.54 g (51 %).

C-66) 4-[2-Amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester



The title compound is synthesized according to general procedure GP4 starting from 500 mg (1.8 mmol) 4-chloro-6-methyl-5-(6-aminomethyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 587 mg (2.7 mmol) 3-chloro-4-methoxycarbonylphenyl boronic acid, 56 mg (0.23 mmol) $Pd(PPh_3)_4$, 5100 mg (3.7 mmol) K_2CO_3 in 6 mL DME/H_2O (5:1 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water. Yield: 740 mg (99 %).

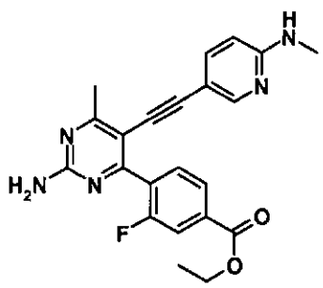
C-67) 4-[2-Amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 700 mg (1.7 mmol) 4-[2-amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester using 2.6 mL (2.6 mmol) 1 N NaOH in

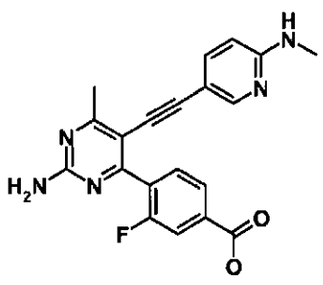
10 mL THF. The product precipitates and is isolated by filtration. The product is washed with water and used without further purification. Yield: 370 mg (55 %).

C-68) 4-[2-Amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-3-fluoro-benzoic acid ethyl ester (



The title compound is synthesized according to general procedure GP4 starting from 500 mg (1.8 mmol) 4-chloro-6-methyl-5-(6-aminomethyl-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 581 mg (2.7 mmol) 2-fluoro-4-ethoxycarbonylphenyl boronic acid, 56 mg (0.37mol) $Pd(PPh_3)_4$, 510 (3.7 mmol) K_2CO_3 in 6 mL DME/H_2O (5:1 v/v). After stirring for 2 x 30 min at 120 °C under microwave irradiation, the product precipitates from the reaction mixture, is filtered off and is washed with DMF, MeOH, water and diethylether. Yield: 637 mg (86 %).

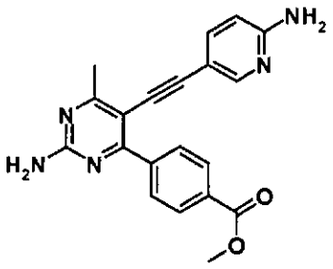
C-69) 4-[2-Amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-3-fluoro-benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 640 mg (1.6 mmol) 4-[2-amino-6-methyl-5-(6-methylamino-pyridin-3-ylethynyl)-pyrimidin-4-yl]-2-chloro-benzoic acid ethyl ester using 2.4 mL (2.4 mmol) 1 N NaOH in 10 mL THF. The product precipitates and is isolated by filtration. The product is washed

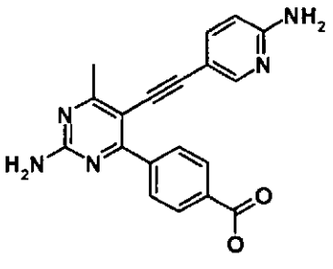
with water. Yield: 620 mg (104 %, contains some starting material from the preceding Suzuki coupling).

C-70) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-benzoic acid methyl ester



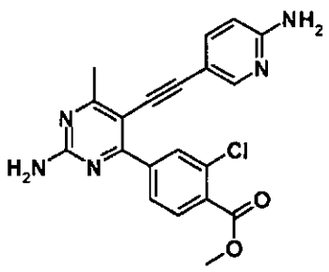
The title compound is synthesized according to general procedure GP4 starting from 2.0 g (7.7 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 2.1 g (11.6 mmol) 4-methoxycarbonylphenyl boronic acid, 240 mg (1.5 mmol) $Pd(PPh_3)_4$, 2.2 g (15.4 mmol) K_2CO_3 in 20 mL DME/H_2O (4:1 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether.
Yield: 2.3 g (98 %).

C-71) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-benzoic acid (



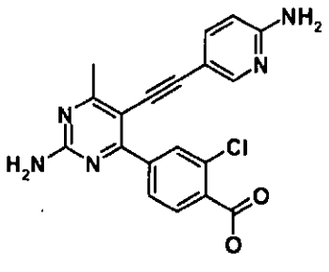
The title compound is synthesized according to general procedure GP8 starting from 2.3 g (6.4 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-benzoic acid methyl ester using 9.6 mL (9.6 mmol) 1 N NaOH in 20 mL THF. The product precipitates and is isolated by filtration and is washed with water. Yield: 2.2 g (99 %).

C-72) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro benzoic acid methyl ester



The title compound is synthesized according to general procedure GP4 starting from 1.0 mg (3.9 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 1.2 g (5.8 mmol) 2-chloro-4-methoxycarbonylphenyl boronic acid, 120 mg (0.77 mmol) $Pd(PPh_3)_4$, 1.0 g (7.3 mmol) K_2CO_3 in 12 mL DME/H_2O (5:1 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether. Yield: 1.24 g (82 %).

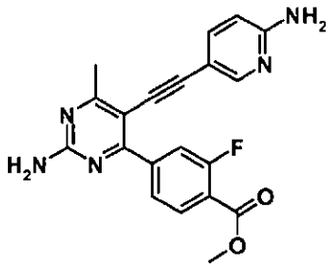
C-73) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro benzoic acid



The title compound is synthesized according to general procedure GP8 starting from 1.24 g (3.1 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester using 4.7 mL (4.7 mmol) 1 N NaOH in 22 mL THF. The product precipitates and is isolated by filtration. The product is washed with THF and diethylether. Yield: 1.13 g (95 %).

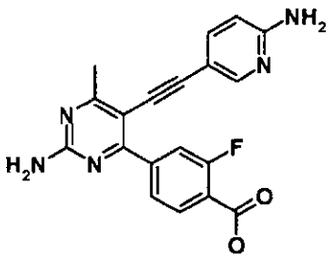
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C-74) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluoro benzoic acid methyl ester



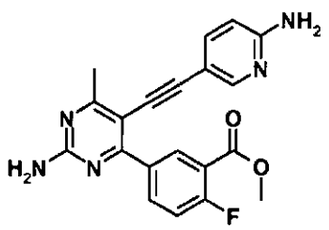
The title compound is synthesized according to general procedure GP4 starting from 2.0 g (7.7 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 2.3 g (11.6 mmol) 2-fluoro-4-methoxycarbonylphenyl boronic acid, 240 mg (1.5 mmol) $Pd(PPh_3)_4$, 2.6 g (18.5 mmol) K_2CO_3 in 24 mL DME/H_2O (5:1 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether. Yield: 2.9 g (100 %).

C-75) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluoro benzoic acid



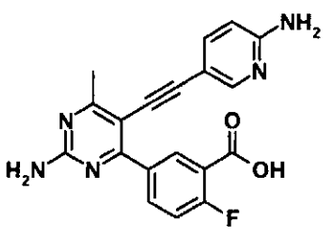
The title compound is synthesized according to general procedure GP8 starting from 3.0 g (8.0 mmol) 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluorobenzoic acid methyl ester using 12 mL (12 mmol) 1 N NaOH in 30 mL THF. The product precipitates and is isolated by filtration. The product is washed with water. Yield: 2.2 g (76 %).

C-76) 5-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester



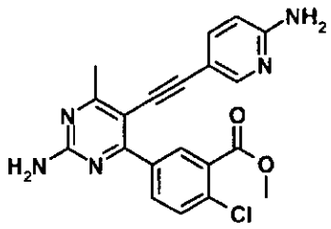
The title compound is synthesized according to general procedure GP4 starting from 1.5 g (5.8 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 1.7 g (8.7 mmol) (4-fluoro-3-methoxycarbonyl)phenyl boronic acid, 67 mg (0.58 mmol) $Pd(PPh_3)_4$, 2.6 g (18.5 mmol) K_2CO_3 in 18 mL DME/H_2O/ethanol (10:5:1 v/v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether yielding 1.95 g (5.2 mmol) of the desired product, which is used without further purification.

C-77) 5-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluoro-benzoic acid



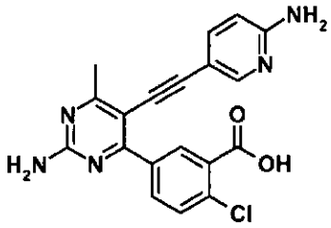
The title compound is synthesized according to general procedure GP8 starting from 1.95 g (5.1 mmol) 5-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-fluoro-benzoic acid methyl ester using 500 mg (11.9 mmol) LiOH in 40 mL THF and 10 mL water. The product precipitates and is isolated by filtration. The product is washed with MeOH yielding 1.76 g (4.48 mmol) of the desired product.

C-78) 5-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester (



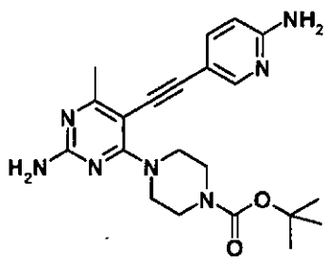
The title compound is synthesized according to general procedure GP4 starting from 1.5 g (5.8 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine using 1.36 g (6.35 mmol) (4-chloro-3-methoxycarbonyl)phenyl boronic acid, 202 mg (0.29 mmol) $Pd(PPh_3)_4$, 2.6 g (18.5 mmol) K_2CO_3 in 16 mL DME/H_2O (5:1 v/v). The product precipitates from the reaction mixture, is filtered off and is washed with water and diethylether yielding 1.76 g (4.4 mmol) desired product, which is used without further purification.

C-79) 5-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro-benzoic acid



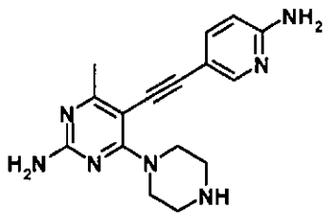
The title compound is synthesized according to general procedure GP8 starting from 2.28 g (5.78 mmol) 5-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-2-chloro-benzoic acid methyl ester using 347 mg (14.4 mmoL) LiOH in 20 mL THF and 1 mL water. The product precipitates and is isolated by filtration. The product is washed with water/acetonitrile (1:1 v/v) yielding 1.30 g (3.44 mmol) desired product, which is used without further purification.

C-84) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester



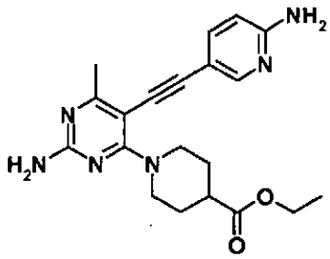
The title compound is synthesized according to general procedure GP7 starting from 5.0 g (19.3 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine and 3.94 g (21.2 mmol) *N*-Boc-piperazine using 2.94 mL (21.2 mmol) triethylamine in 30 mL NMP. Work up is performed by addition of 500 mL water to the reaction mixture and stirring for 30 min. The solid material is filtered off, washed with water (50 mL three times) yielding 7.25 g (17.7 mmol) of the desired product with sufficient purity.

C-85) 5-(6-Amino-pyridin-3-ylethynyl)-4-methyl-6-piperazin-1-yl-pyrimidin-2-ylamine



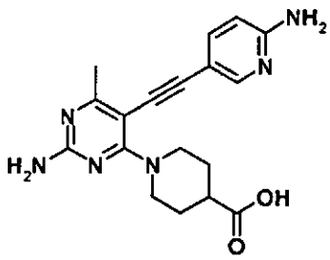
7.1 g (17.3 mmol) of 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester are dissolved in DCM (400 mL) and 40 mL TFA are added. The reaction mixture is stirred over night at RT. The reaction mixture is adjusted to neutral pH using concentrated aqueous Na_2CO_3 solution and the DCM is evaporated at reduced pressure. The residue is washed with water, taken up in acetonitrile and freeze dried yielding 4.0 g (13.0 mmol) of the desired product which is used for the next step without further purification.

C-86) 1-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester



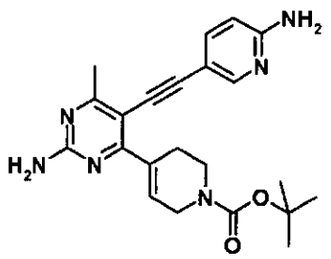
The title compound is synthesized according to general procedure GP7 starting from 2.0 g (7.7 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine and 1.33 g (8.47 mmol) piperidine-4-carboxylic acid ethyl ester using 1.18 mL (8.5 mmol) triethylamine in 12 mL NMP. Work up is performed by addition of 50 mL water to the reaction mixture and stirring for 30 min. The solid material is filtered off, washed with water (50 mL three times) yielding 1.58 g (4.15 mmol) of the desired product with sufficient purity.

C-87) 1-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidine-4-carboxylic acid



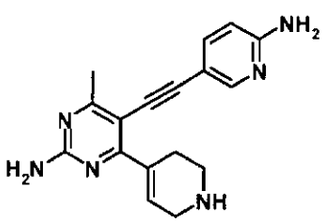
The title compound is synthesized according to general procedure GP8 starting from 1.0 g (2.63 mmol) 1-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidine-4-carboxylic acid ethyl ester and 126 mg (5.26 mmol) LiOH in 80 mL THF and 20 ml water. Yielding 772 mg (2.19 mmol) of the desired product.

C-88) 4-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester



A mixture of 500 mg (1.9 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine, 1.2 g (3.9 mmol) 4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester, 135 mg (1.9 mmol) $Pd(PPh_3)_2Cl_2$, 40 mL 1 M aqueous Na_2CO_3 solution and 244 mg LiCl (5.78 mmol) in 100 mL toluene/ethanol (4:1 v/v) is kept over 2 days at reflux. After cooling the solvent is evaporated, water is added and the aqueous suspension is extracted 4 times with ethyl acetate (200 mL each). The organic layer is dried over MgSO4 and the solvent is removed under reduced pressure. The residue is purified using flash column chromatography yielding 635 mg (1.56 mmol) of the desired product which is used without further purification in the next step.

C-89) 5-(6-Amino-pyridin-3-ylethynyl)-4-methyl-6-(1,2,3,6-tetrahydro-pyridin-4-yl)-pyrimidin-2-ylamine

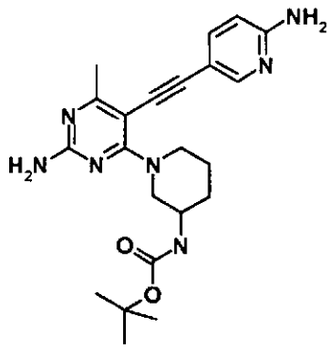


630 mg (1.5 mmol) of 4-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester are dissolved in DCM (40 mL) and 2 mL TFA are added. The reaction mixture is stirred for 3 h, concentrated aqueous Na_2CO_3 solution is added until pH 7 is reached and DCM is evaporated at reduced pressure. The residue is washed with water, taken up in acetonitrile and freeze dried

58

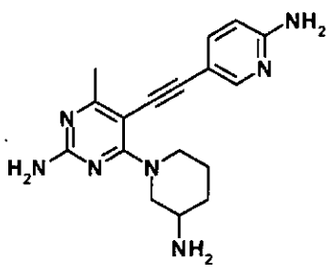
yielding 253 mg (0.83 mmol) of the desired product which is used for the next step without further purification.

C-90) {1-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-3-yl}-carbamic acid *tert*-butyl ester



The title compound is synthesized according to general procedure GP7 starting from 2.0 g (7.7 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine and 2.0 g (10.0 mmol) piperidin-3-yl-carbamic acid *tert*-butyl ester using 1.29 mL (9.2 mmol) triethylamine in 5 mL NMP and 5 mL DMSO. 200 mL ethyl acetate and 100 mL half concentrated aqueous Na_2CO_3 solution are added and the phases are separated. The aqueous phase is extracted 2 times with ethyl acetate (100 mL each). The combined organic layers are dried over sodium sulfate and the solvent is removed under reduced pressure. The crude product is used without further purification in the next step.

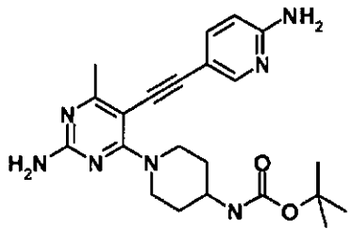
C-91) 4-(3-Amino-piperidin-1-yl)-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-2-ylamine



3.3 g (7.8 mmol) of {1-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-3-yl}-carbamic acid *tert*-butyl ester are dissolved in DCM (50 mL) and

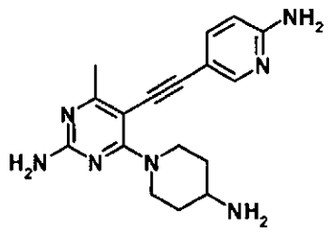
26 mL TFA are added. The reaction mixture is stirred over night at RT. The reaction mixture is adjusted to neutral pH using concentrated aqueous Na_2CO_3 solution and the DCM is evaporated at reduced pressure. The residue is washed with water, taken up in acetonitrile and freeze dried. The crude product is used without further purification in the next step.

C-92) {1-[2-Amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester



The title compound is synthesized according to general procedure GP7 starting from 2.0 g (7.7 mmol) 4-chloro-6-methyl-5-(6-amino-pyridin-3-ylethynyl)-pyrimidin-2-ylamine and 1.7 g (8.47 mmol) piperidin-4-yl-carbamic acid *tert*-butyl ester using 1.07 ml (7.7 mmol) triethylamine in 3 mL NMP and 12 mL DMSO. 200 mL ethyl acetate and 100 mL half concentrated aqueous Na_2CO_3 solution are added and the phases are separated. The aqueous phase is extracted 2 times with ethyl acetate (100 mL each). The combined organic layers are dried over sodium sulfate and the solvent is removed under reduced pressure. The crude product is used without further purification in the next step.

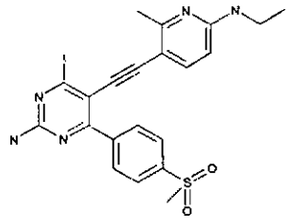
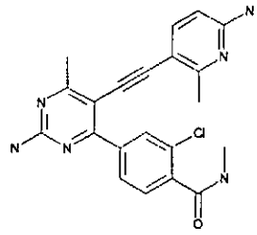
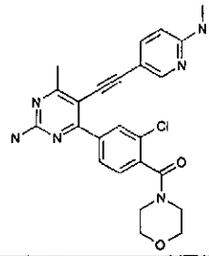
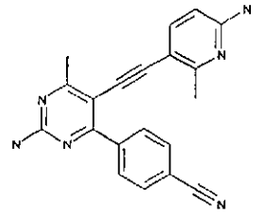
C-93) 4-(4-Amino-piperidin-1-yl)-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-2-ylamine

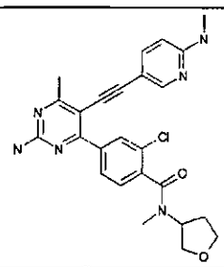
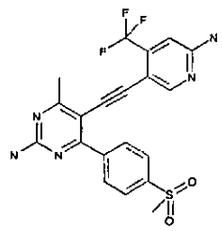
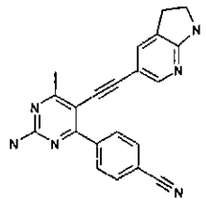
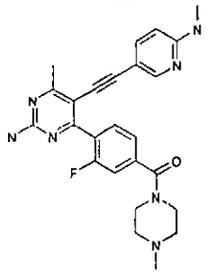
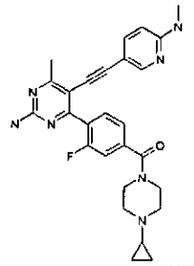
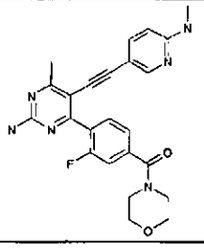


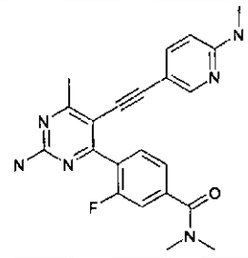
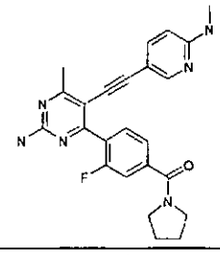
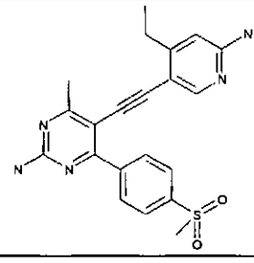
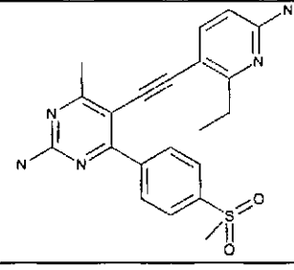
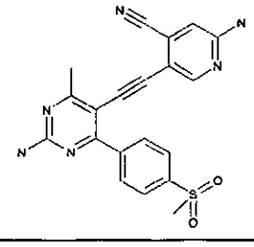
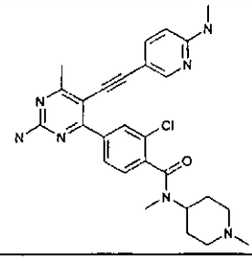
3.2 g (7.6 mmol) of {1-[2-amino-5-(6-amino-pyridin-3-ylethynyl)-6-methyl-pyrimidin-4-yl]-piperidin-4-yl}-carbamic acid *tert*-butyl ester are dissolved in DCM (50 mL) and

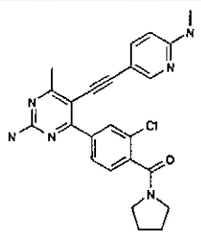
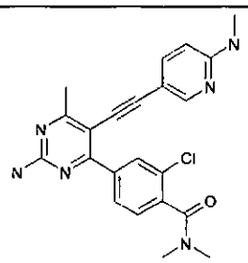
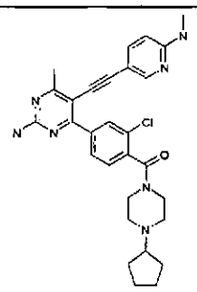
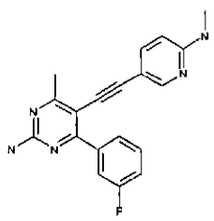
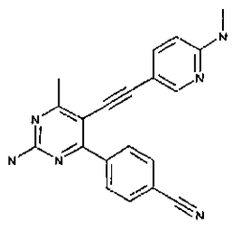
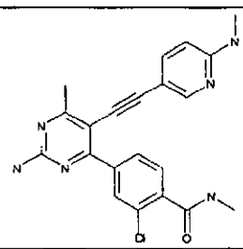
26 mL TFA are added. The reaction mixture is stirred over night at RT. The reaction mixture is adjusted to neutral pH using concentrated aqueous Na_2CO_3 solution and the DCM is evaporated at reduced pressure. The residue is washed with water, taken up in acetonitrile and freeze dried. The crude product is used without further purification in the next step.

Examples 213 - 418

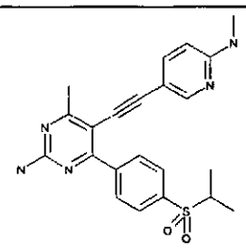
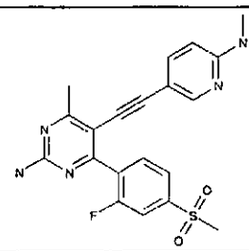
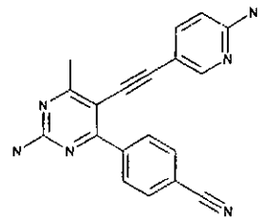
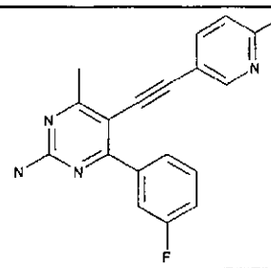
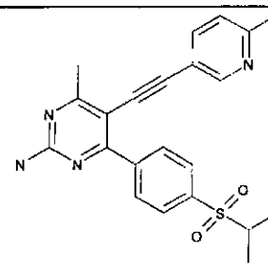
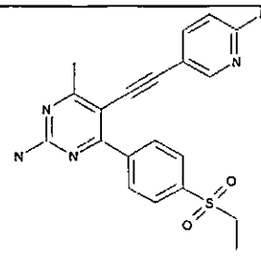
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
213		A-39	421.5	422	1.58
214			406.9	407	1.19
215			462.9	463	1.45
216			340.4	341	1.39

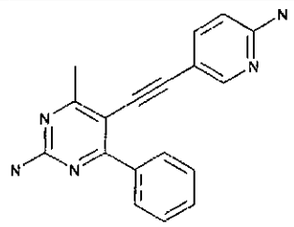
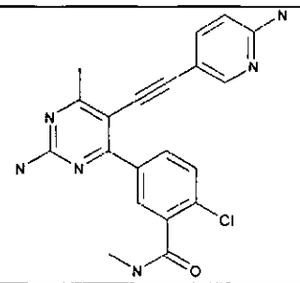
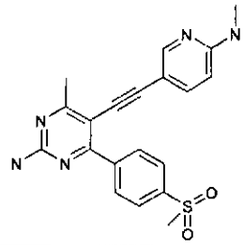
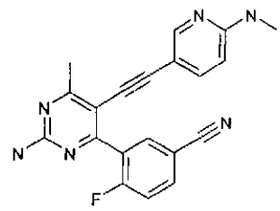
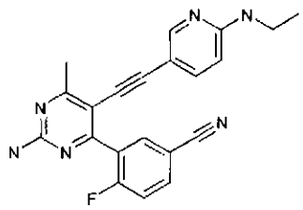
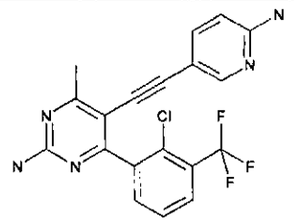
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
217		C-67	477	477/479	1.50
218		A-39	447.4	448	1.47
219			352.4	353	1.49
220		C-69	459.5	460	1.33
221		C-69	485.6	486	1.67
222		C-69	446.5	447	1.37

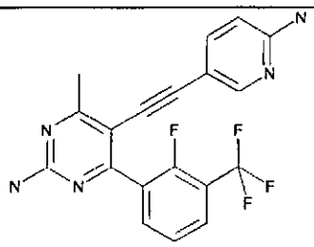
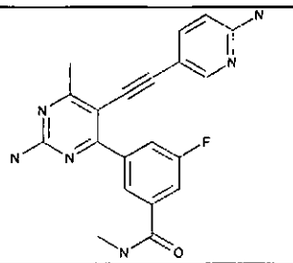
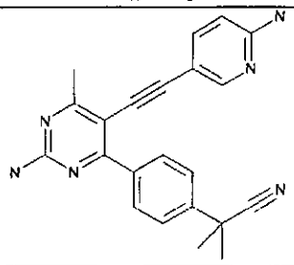
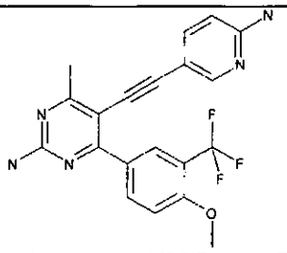
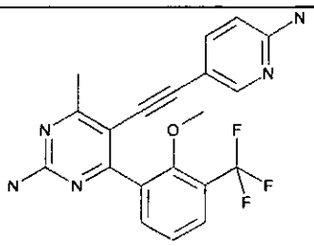
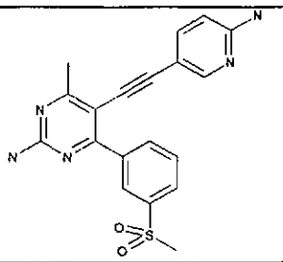
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
223		C-69	404.4	405	1.34
224		C-69	430.5	431	1.60
225		A-39	407.5	408	1.43
226		A-39	407.5	408	1.47
227		A-39	404.5	M-H=403	
228		C-67	504	504/506	1.48

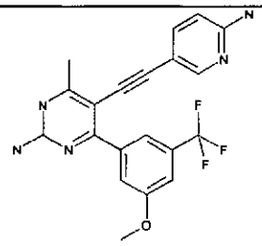
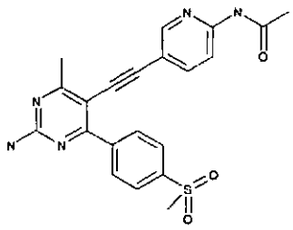
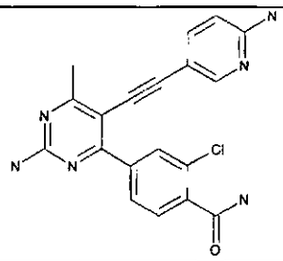
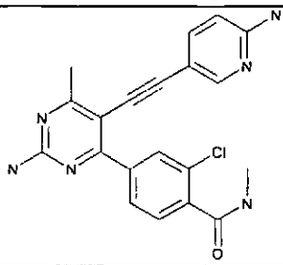
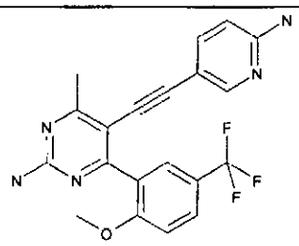
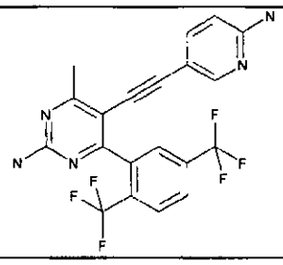
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
229		C-67	446.9	447/449	1.56
230		C-67	420.9	421	1.49
231		C-67	530.1	530/532	1.75
232		C-65	333.4	334	1.61
233		C-65	340.4	341	1.55
234		C-65	406.9	407	1.40

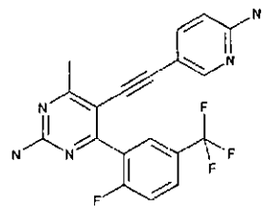
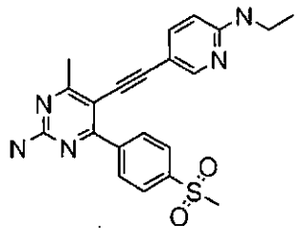
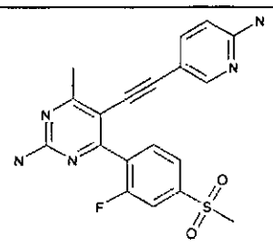
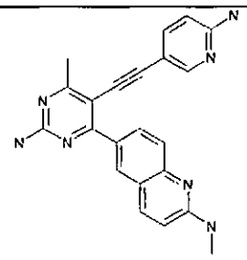
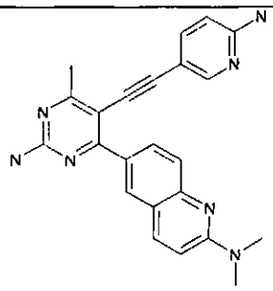
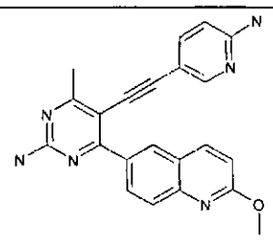
61

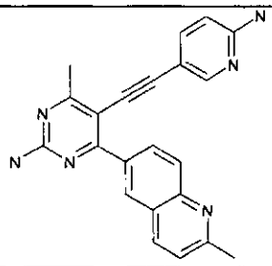
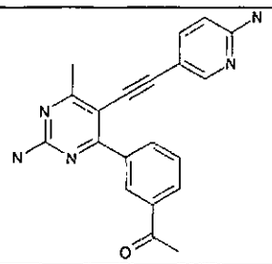
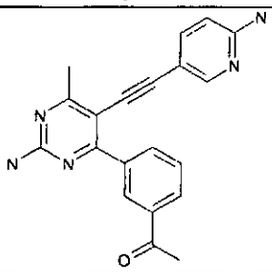
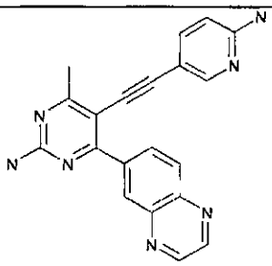
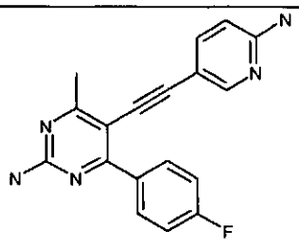
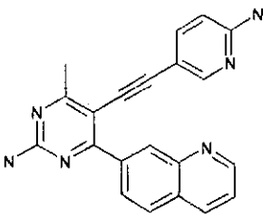
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
235		C-65	421.5	422	1.55
236		C-65	411.5	412	
237		A-33	326.4	327	1.40
238		A-33	319.3	320	1.26
239		A-33	407.5	408	1.42
240		A-33	393.5	394	1.34

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
241		A-33	301.4	302	1.39
242		A-33	392.8	393	1.27
243		A-30	393.5	394	1.50
244		A-30	358.4	359	1.52
245			372.4	373	1.64
246		A-33	403.8	404	1.59

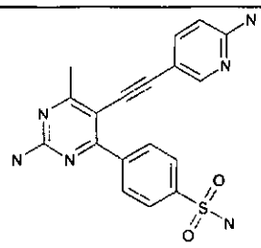
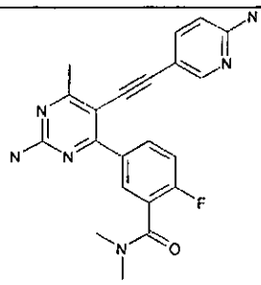
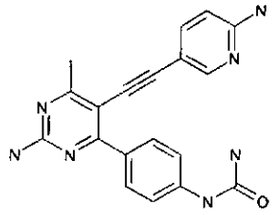
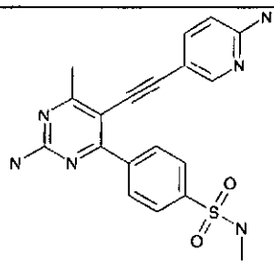
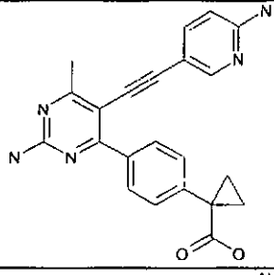
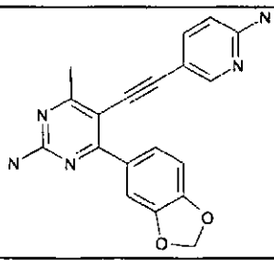
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
247		A-33	387.3	388	1.56
248		A-33	376.4	377	1.28
249		A-33	368.4	369	1.51
250		A-33	399.4	400	1.64
251		A-33	399.4	400	1.63
252		A-33	379.4	380	1.26

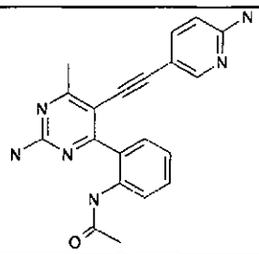
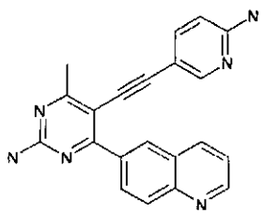
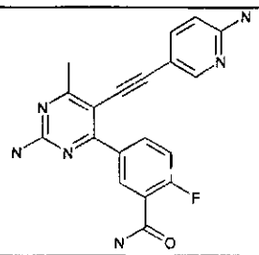
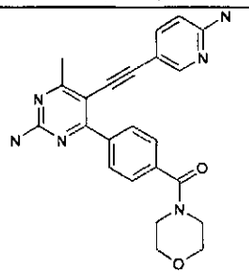
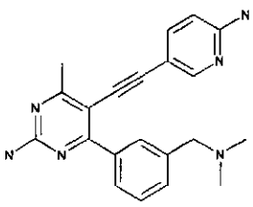
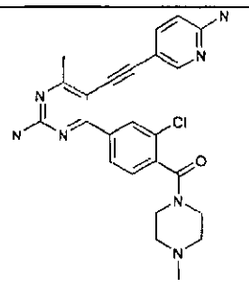
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
253		A-33	399.4	400	1.68
254		A-39	421.5	422	
255		A-33	378.8	379	
256		A-33	392.8	393	
257		A-33	399.4	400	1.54
258		A-33	437.3	438	1.65

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
259		A-33	387.3	388	1.60
260		A-39	407.5	408	1.53
261		A-33	397.4	398	1.29
262		A-33	381.4	382	1.42
263		A-33	395.5	396	1.62
264		A-33	382.4	383	1.65

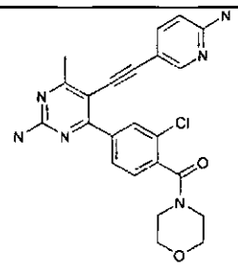
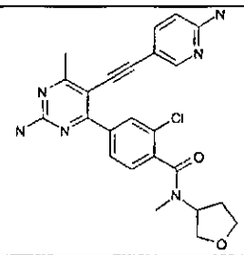
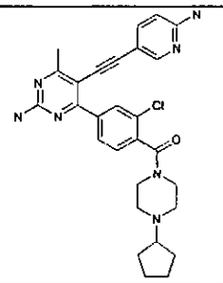
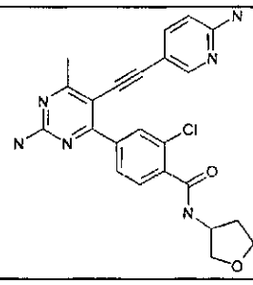
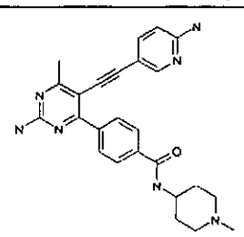
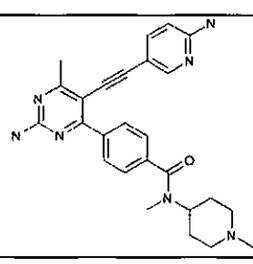
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
265		A-33	366.4	367	1.48
266		A-33	343.4	344	1.29
267		A-33	343.4	344	
268		A-33	353.4	354	1.21
269		A-33	319.3	320	
270		A-33	352.4	353	1.28

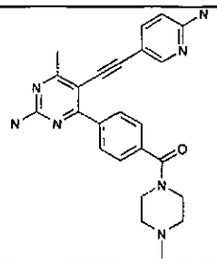
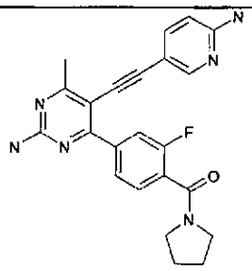
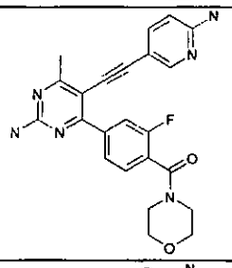
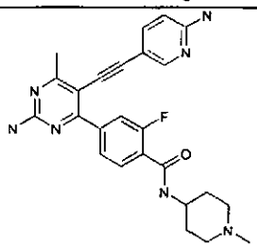
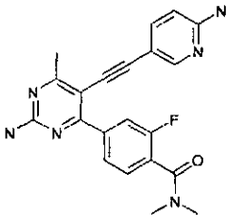
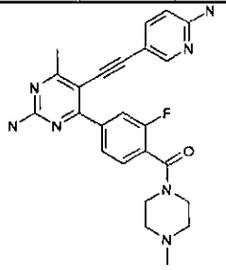
64

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
271		A-33	380.4		
272		A-33	390.4	391	1.23
273		A-33	359.4	360	1.01
274		A-33	394.5	395	
275		A-33	385.4	386	
276		A-33	345.4	346	

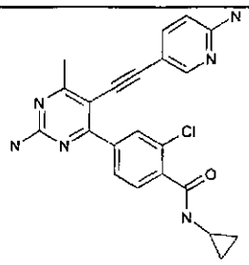
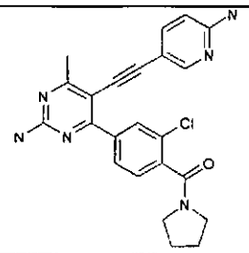
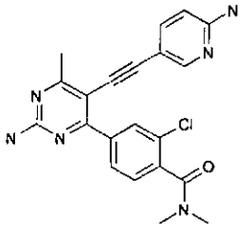
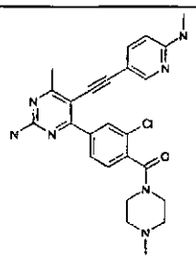
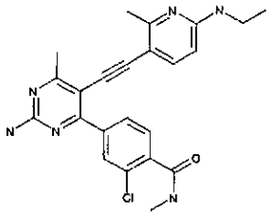
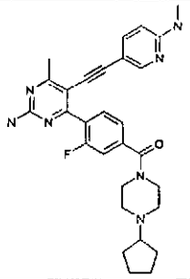
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
278		A-33	358.4	359	
279		A-33	352.4	353	1.25
280		A-33	362.4	363	1.08
281		C-71	414.5	415	1.39
282		A-33	358.4	359	
283		C-73	462	462/464	1.44

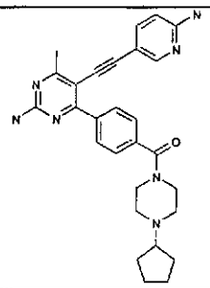
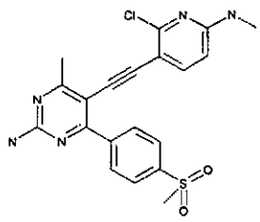
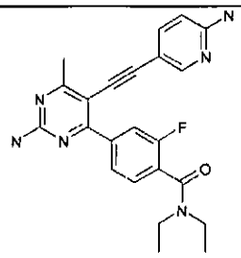
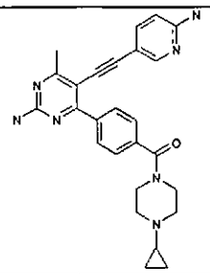
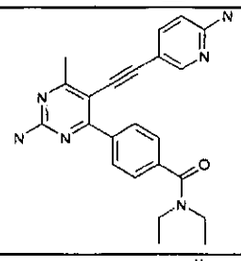
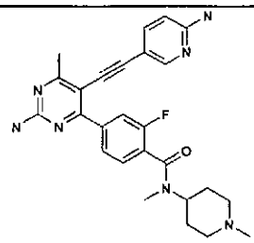
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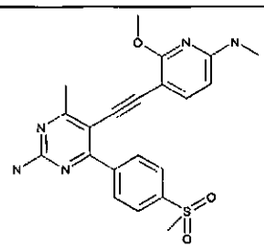
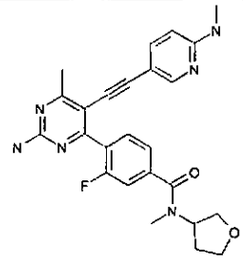
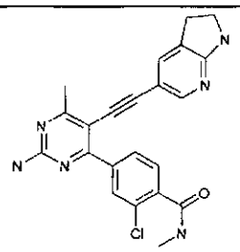
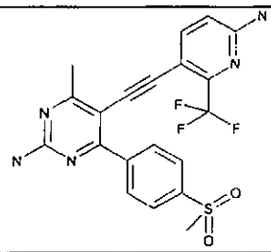
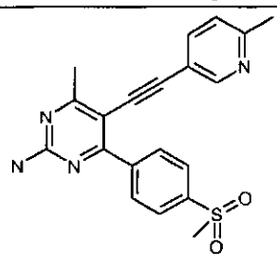
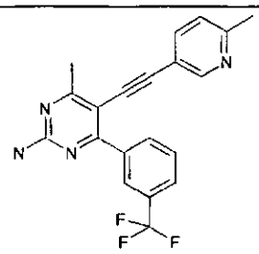
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
284		C-73	448.9	449	1.42
285		C-73	462.9	463/465	1.47
286		C-73	516	516/518	1.76
287		C-73	448.9	449	1.40
288		C-71	441.5	442	1.36
289		C-71	455.6	456	1.40

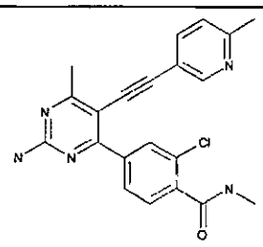
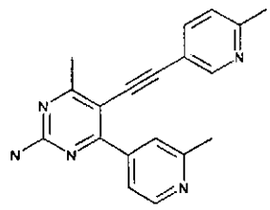
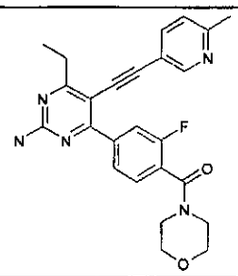
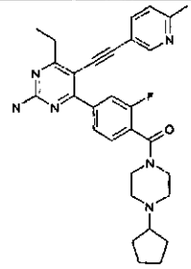
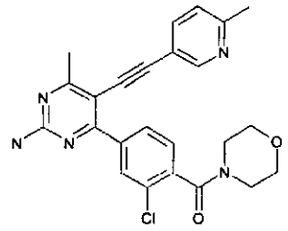
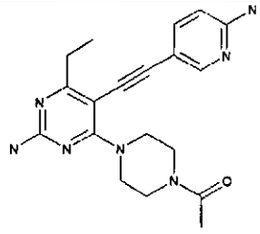
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Rot}
290		C-71	427.5	428	1.35
291		C-75	416.5	417	1.49
292		C-75	432.5	433	1.38
293		C-75	459.5	460	1.45
294		C-75	390.4	391	1.40
295		C-75	445.5	446	1.40

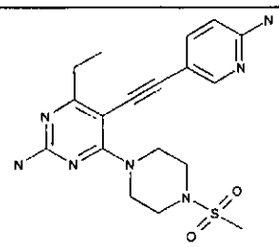
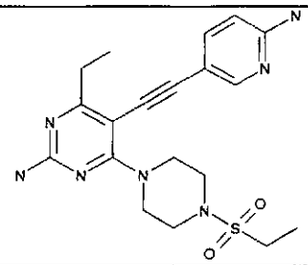
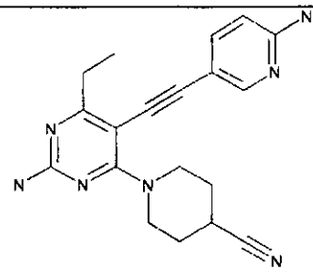
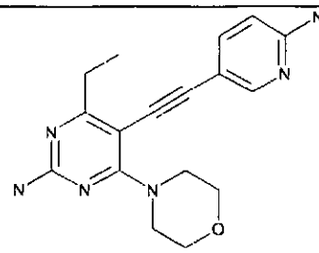
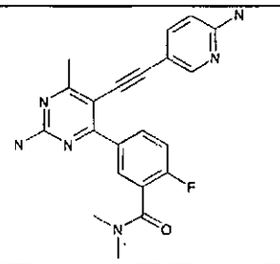
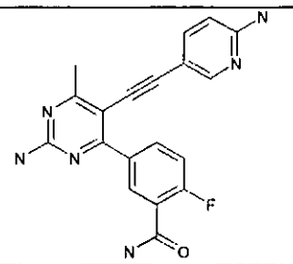
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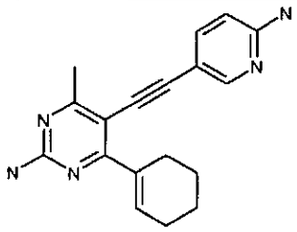
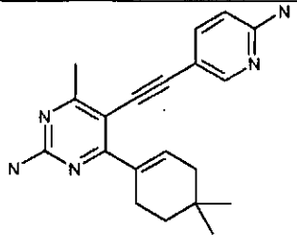
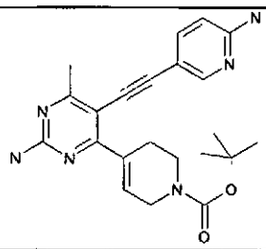
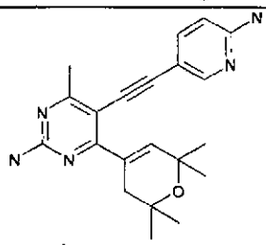
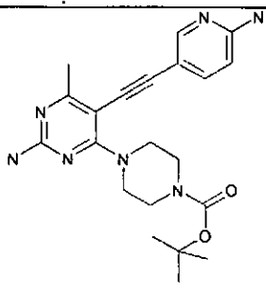
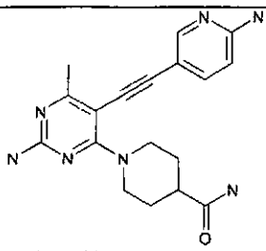
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
296		C-73	418.9	419	
297		C-73	432.9	433/435	1.55
298		C-73	406.9	407/409	1.45
299		C-67	476	476	1.58
300			434.9	435/437	1.71
301		C-69	513.6	514	1.79

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
302		C-71	481.6	482	1.65
303		A-39	427.9	428/430	1.86
304		C-75	418.5	419	1.58
305		C-71	453.5	454	1.54
306		C-71	400.5	401l	1.52
307		C-75	473.6	474	1.46

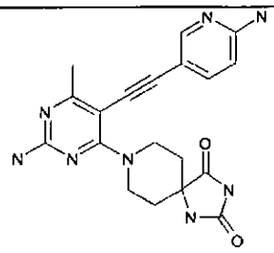
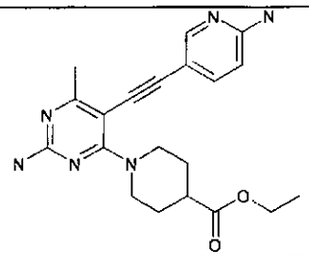
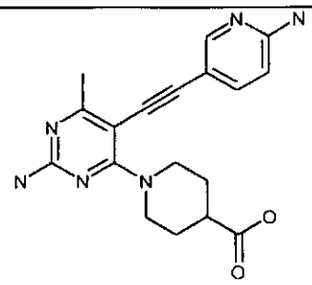
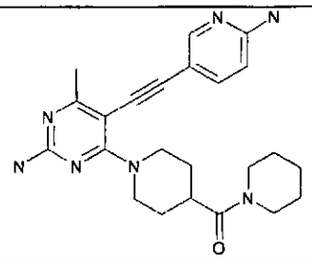
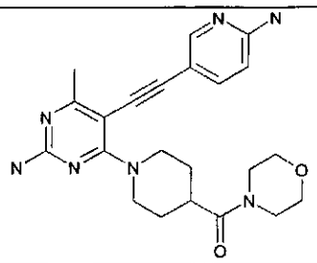
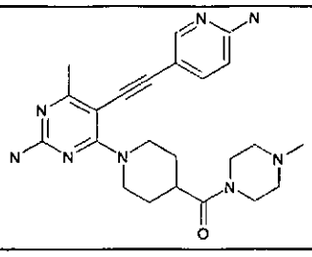
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
308		A-39	423.5	424	1.92
309		C-69	460.1	461	
310			418.9	419	1.53
311		A-39	447.4	M-H=446 (571)	1.61
312		A-30	378.5	379	1.72
313		A-27	368.4	369	2.13

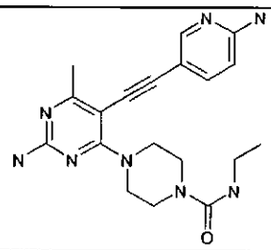
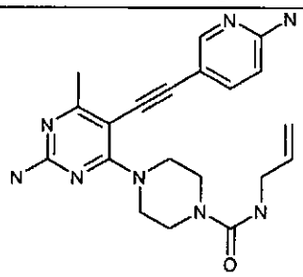
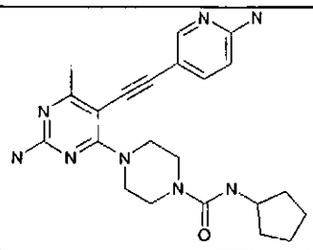
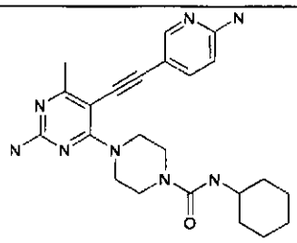
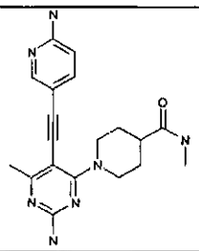
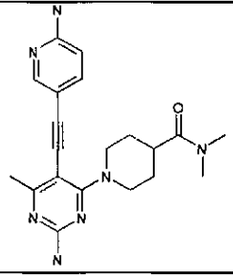
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
314		C-46	391.9	392/394	1.51
315		C-46	315.4	316	1.46
316		C-52	445.5	446	1.65
317		C-52	512.6	513	1.95
318		C-48	447.9	448/450	1.57
319		C-53	365.4	366	

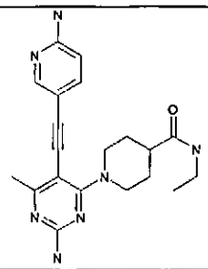
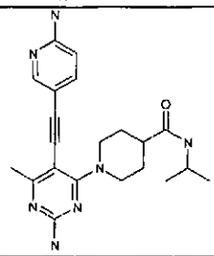
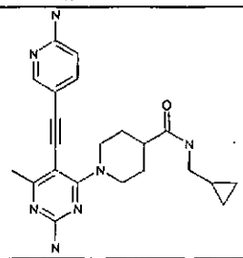
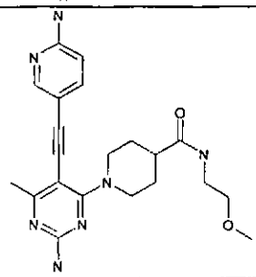
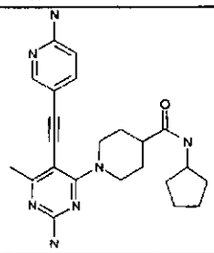
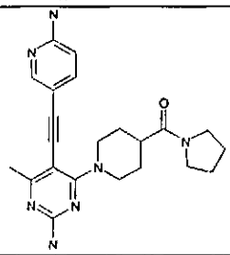
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
320		C-53	401.5	402	1.33
321		C-53	415.5	416	
322		C-53	347.4	348	1.39
323		C-53	324.4	325	1.32
324		A-33	390.4	391	1.23
325		A-33	362.4	363	1.08

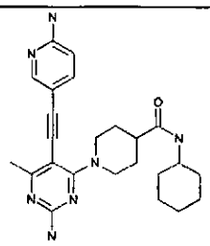
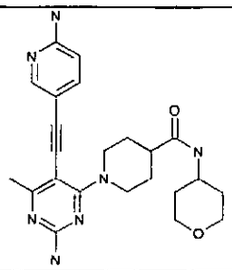
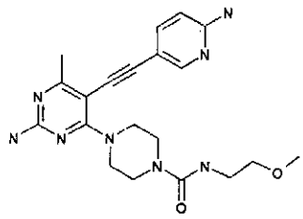
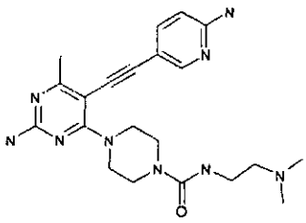
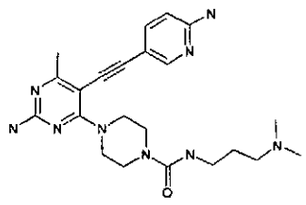
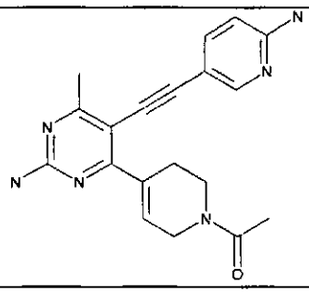
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
326		A-33	305.4	306	1.58
327		A-33	333.4	334	1.78
328			406.5	407	1.69
329		A-33	363.5	364	1.61
330			409.5	410	1.70
331		A-33	351.4	352	

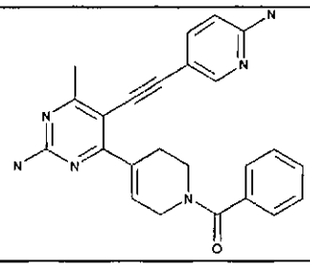
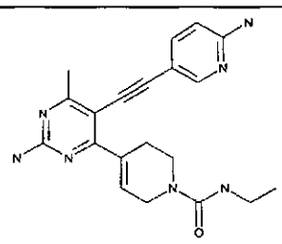
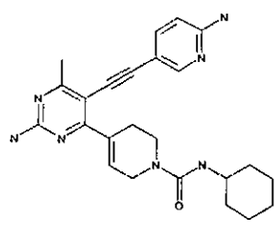
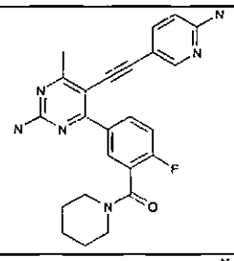
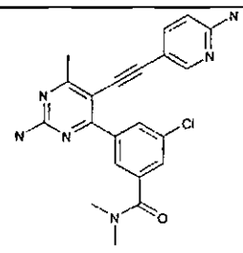
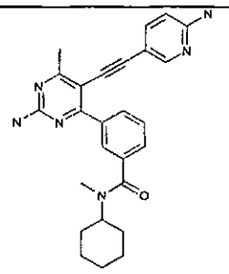
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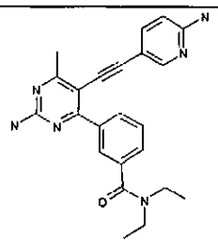
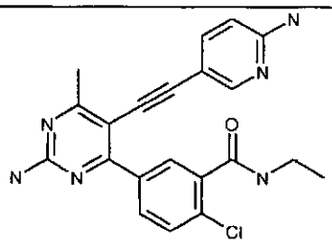
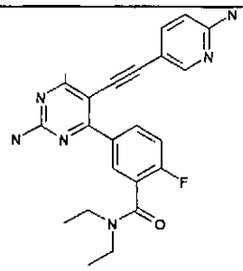
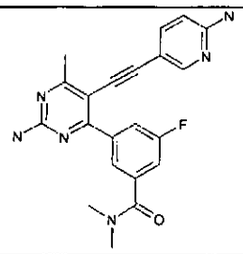
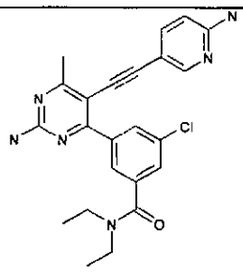
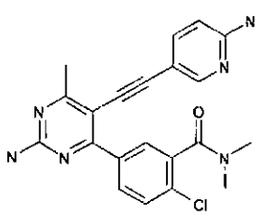
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
332		A-33	392.4	393	
333		A-33	380.4	381	
334			352.4	353	0.62
335		C-87	419.5	420	
336		C-87	421.5	422	
337		C-87	434.6	435	

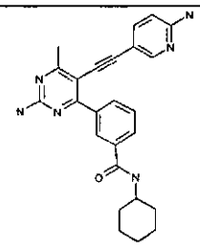
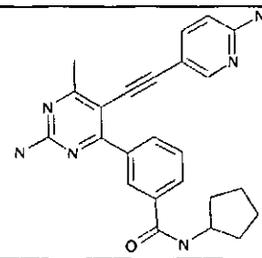
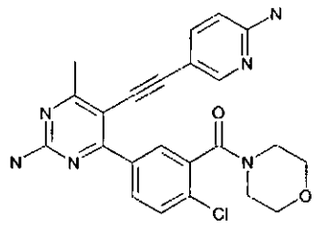
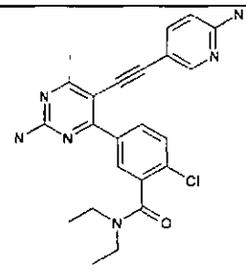
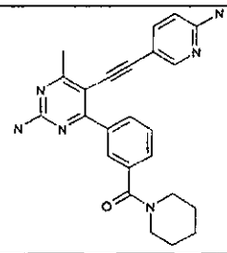
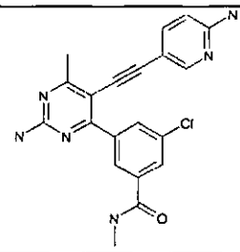
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Rel}
338		C-85	380.5	381	
339		C-85	392.5	393	0.15
340		C-85	420.5	421	1.28
341		C-85	434.6	435	1.43
342		C-87	365.4	366	1.18
343		C-87	379.5	380	

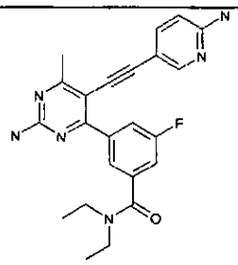
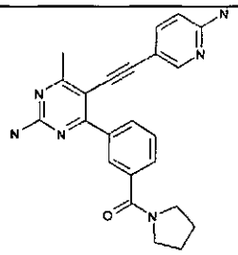
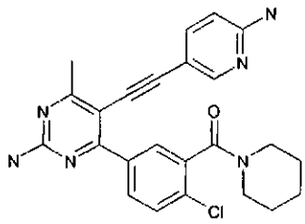
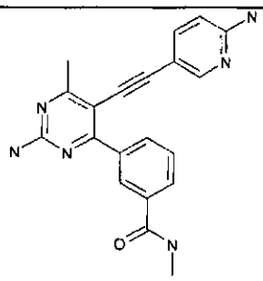
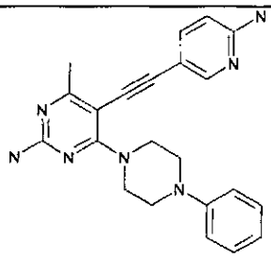
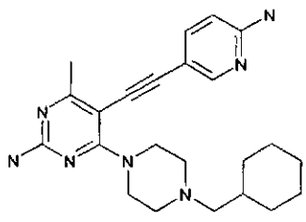
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
344		C-87	379.5	380	1.26
345		C-87	393.5	394	1.35
346		C-87	405.5	406	
347		C-87	409.5	410	
348		C-87	419.5	420	
349		C-87	405.5	406	1.41

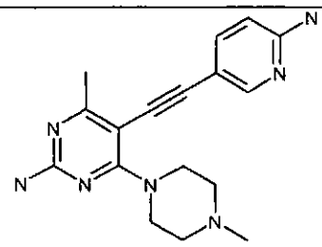
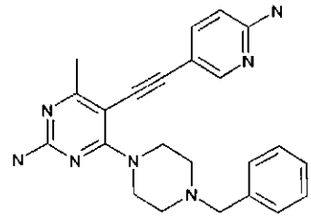
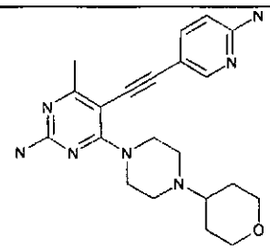
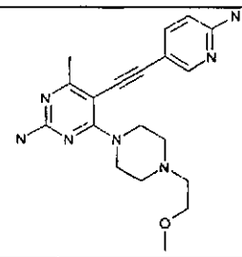
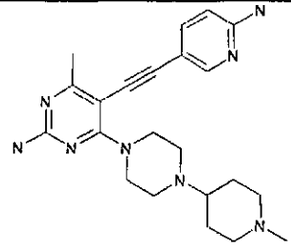
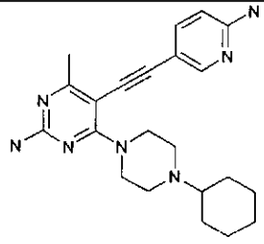
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
350		C-87	433.6	434	1.58
351		C-87	435.5	436	1.26
352		C-85	410.5	411	1.23
353		C-85	423.5	424	1.28
354		C-85	437.5	438	1.35
355		C-89	348.4	349	

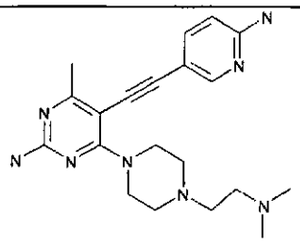
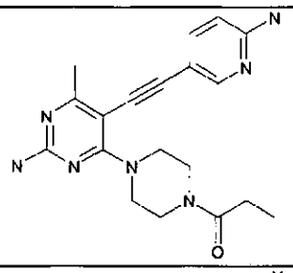
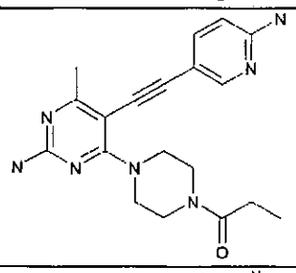
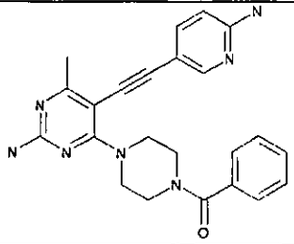
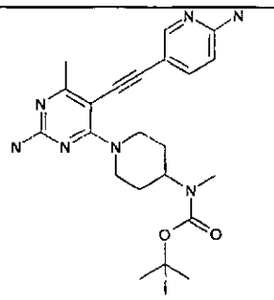
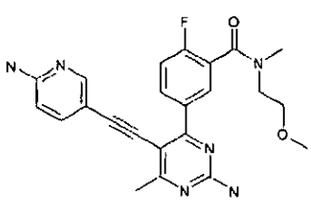
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
356		C-89	410.5	411	1.44
357		C-89	377.4	378	
358		C-89	431.5	432	
359		A-33	430.5	431	
360		A-33	406.9	407	
361		A-33	440.5	441	

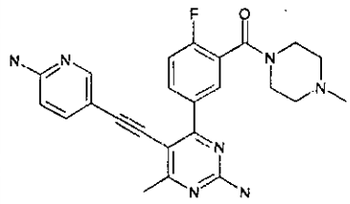
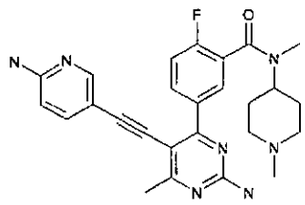
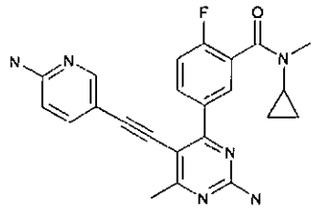
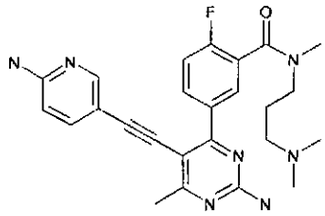
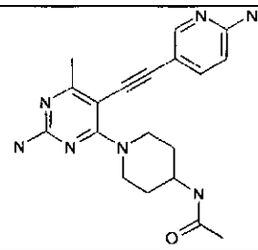
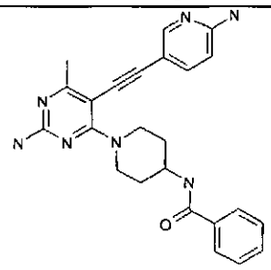
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
362		A-33	400.5	401	
363		A-33	406.9	407	
364		A-33	418.5	419	
365		A-33	390.4	391	
366		A-33	434.9	435	
367		A-33	406.9	407	

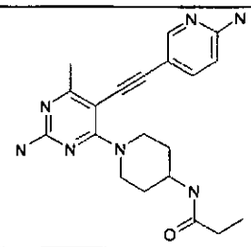
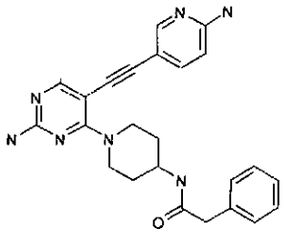
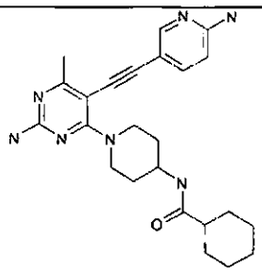
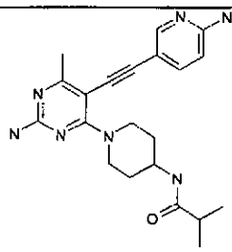
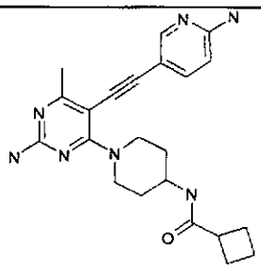
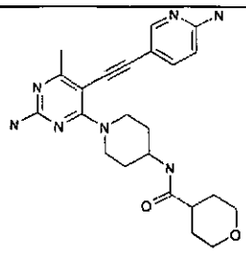
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
368		A-33	426.5	427	
369		A-33	412.5	414	
370		A-33	448.9	449	
371		A-33	434.9	435	
372		A-33	412.5	413	1.48
373		A-33	392.8	393	

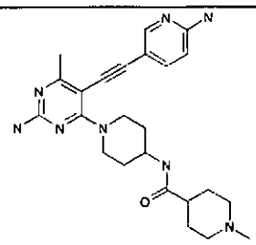
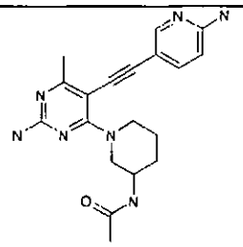
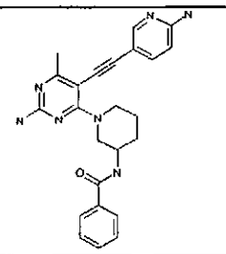
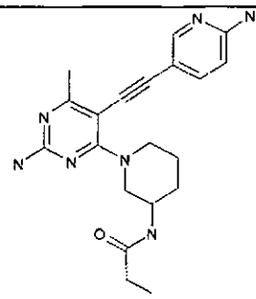
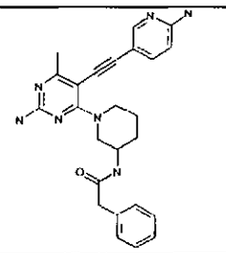
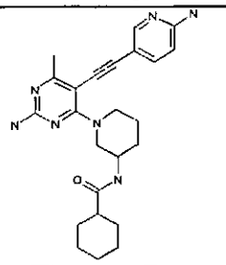
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
374		A-33	418.5	419	1.53
375		A-33	398.5	399	1.37
376		A-33	446.9	447	
377		A-33	358.4	359	
378		A-33	385.5	386	1.66
379		A-33	405.5	406	1.91

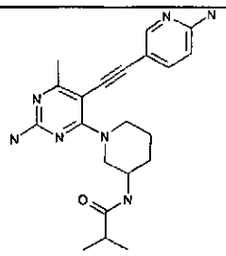
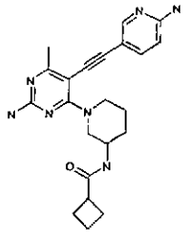
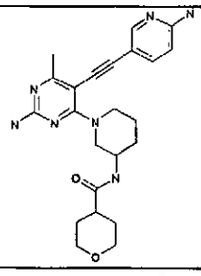
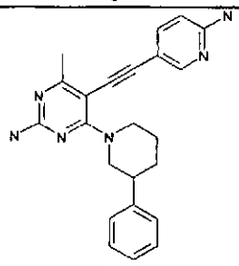
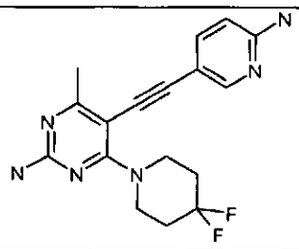
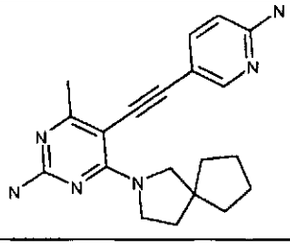
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
380		A-33	323.4	324	1.22
381		A-33	399.5	400	1.64
382		A-33	393.5	394	1.28
383		A-33	367.5	368	1.27
384		A-33	406.5	407	1.36
385		A-33	391.5	392	1.68

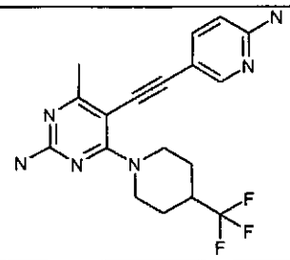
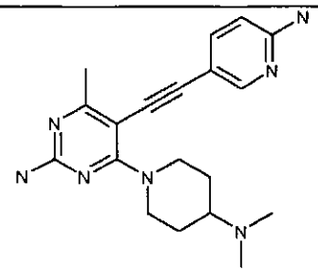
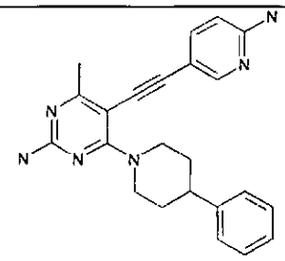
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
386		A-33	380.5	381	1.30
387		A-33	365.4	366	1.25
388		A-33	419.5	420	1.57
389		A-33	413.5	414	1.42
390			437.5	438	1.71
391		C-77	434.5	435	1.38

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
392		C-77	445.5	446	1.33
393		C-77	473.6	474	1.40
394		C-77	416.5	417	1.46
395		C-77	461.5	462	1.43
396		C-93	365.4	366	1.14
397		C-93	427.5	428	1.45

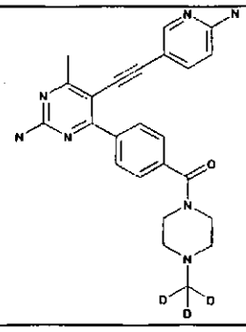
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
398		C-93	379.5	380	1.22
399		C-93	441.5	442	1.45
400		C-93	433.6	434	1.54
401		C-93	393.5	394	1.31
402		C-93	405.5	406	1.36
403		C-93	435.5	436	1.23

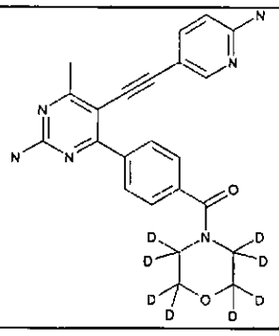
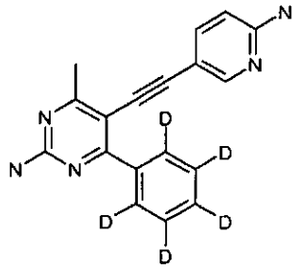
No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
404		C-93	448.6	449	1.29
405		C-91	365.4	366	1.17
406		C-91	427.5	428	1.44
407		C-91	379.5	380	1.24
408		C-91	441.5	442	1.44
409		C-91	433.6	434	1.54

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
410		C-91	393.5	394	1.33
411		C-91	405.5	406	1.37
412		C-91	435.5	436	1.25
413		A-33	384.5	385	1.78
414		A-33	344.4	345	1.49
415		A-33	348.5	349	1.72

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{Ret}
416		A-33	376.4	377	1.60
417		A-33	351.5	352	1.35
418		A-33	384.5	385	

In order to prepare compounds bearing one or more deuterium instead of hydrogen may prepared as outlined above. The following examples have been prepared using building blocks from commercial vendors (identified via e.g. ACD-Finder or SciFinder) using GP4 (Suzuki coupling) or GP9 (Formation of amides) :

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{ret}
419		C-71	430.5	431	1.24

No.	Structure	Starting Material	MW	MS $[M+H]^+$	HPLC t_{ret}
420		C-71	422.5	423	1.22
421		A-33	306.4	307	

Analytical method 1

HPLC: Agilent 1100 Series

MS: Agilent LC/MSD SL

column: Phenomenex, Mercury Gemini C18, 3 µm, 2.0x20 mm, Part.No. 00M-4439-B0-CE

solvent A: 5 mM NH_4HCO_3/ 20mM NH_3

B: acetonitrile HPLC grade

detection: MS: Positive and negative

mass range: 120 - 700 m/z

fragmentor: 70

gain EMV: 1

threshold: 150

stepsize: 0.25

UV: 315 nm

bandwidth: 170 nm

reference: off

range: 210 - 400 nm

range step: 2.00 nm
peakwidth: < 0.01 min
slit: 2 nm
injection: 5 µL
flow: 1.00 mL/min
column temperature: 40 °C

gradient:		
	0.00 min	5 % B
	0.00 – 2.50 min	5 % -> 95 % B
	2.50 – 2.80 min	95 % B
	2.81 – 3.10 min	95 % -> 5 % B

Analytical method 2

Instrument: Agilent 1100-SL: incl. ELSD / DAD / MSD
Chromatography:
Column: Phenomenex Gemini® C18, 50×2.0mm, 3µ
Method "Acid"
Eluent A: 0.1 % formic acid in acetonitrile
Eluent B: 0.1 % formic acid in Water
Linear Gradient program: t_0 = 2 % A, $t_{3.5min}$ = 98 % A, t_{6min} = 98 % A
Flow: 1 mL/min
Column oven temperature: 35 °C
Method "Base"
Eluent A: 10 mM ammonia in acetonitrile
Eluent B: 10 mM ammonia in water
Linear Gradient program: t_0 = 2 % A, $t_{3.5min}$ = 98 % A, t_{6min} = 98 % A
Flow: 1 mL/min
Column oven temperature: 35 °C
Evaporative Light Scattering Detector (ELSD):
Instrument: Polymer Laboratories PL-ELS 2100
Nebuliser gas flow: 1.1 L/min N_2
Nebuliser temp: 50°C
Evaporation temp: 80°C

Lamp: Blue LED 480 nm

Diode Array Detector (DAD):

Instrument: Agilent G1316A

Sample wavelength: 220-320 nm

Reference wavelength: Off

Mass Spectroscopy (MSD):

Instrument: Agilent LC/MSD-SL

Ionisation: ESI (Positive & Negative)

Mass range: 100-800

Abbreviations used

ACN	acetonitrile	mL	millilitre
bu	butyl	MS	mass spectrometry
CDI	carbonyl diimidazole	N	normal
d	day(s)	NIS	*N*-iodosuccinimide
DC	thin layer chromatography	NMP	N-methylpyrrolindinone
DCM	dichloromethane	NMR	nuclear resonance spectroscopy
DIPEA	diisopropylethyl amine	NP	normal phase
DMF	*N,N*-dimethylformamide	ppm	part per million
DMSO	dimethylsulphoxide	Rf	retention factor
et	ethyl	RP	reversed phase
h	hour(s)	prep	preparative
HPLC	high performance liquid chromatography	RT	room temperature
iPr	isopropyl	*tert*	tertiary
LC	liquid chromatography	t_{Ret}	retention time
M	molar	THF	tetrahydrofuran
me	methyl	TMS	tetramethylsilanyl
min	minute(s)		

The Examples that follow describe the biological activity of the compounds according to the invention without restricting the invention to these Examples.

PC3 proliferation test

The test is based on measurement of cellular DNA content via fluorescent dye binding. Because cellular DNA content is highly regulated, it is closely proportional to cell number. The extent of proliferation is determined by comparing cell counts for samples treated with drugs with untreated controls.

PC3 (human prostate carcinoma cell line) cells are sown in microtitre plates and incubated overnight in culture medium at 37 °C and 5 % CO_2. The test substances are diluted stepwise and added to the cells such that the total volume is 200 µL/well. Cells to which diluent, but not substance, is added serve as controls. After an incubation time of 3 days, the medium is replaced by 100 µL/well dye-binding solution and the cells are incubated at 37 °C in the dark for a further 60 min. For measuring the fluorescence, excitation takes place at a wavelength of 485 nm and the emission is measured at 530 nm.

EC_{50} values are calculated using the GraphPad Prism program.

Most compounds of the Examples cited have an EC_{50} (Proliferation PC3) of less than 1 µM.

P-AKT measurement in PC3 cells

P-AKT levels in PC3 cells are detected by cell-based ELISA. Cells are cultured in 96-well plates and treated with serial dilutions of test substances for 2 h. Cells to which diluent, but not substance, is added serve as controls. Subsequently, the cells are fixed rapidly to preserve protein modifications. Each well is then incubated with a primary antibody specific for Ser473-phosphorylated AKT. Subsequent incubation with secondary HRP-conjugated antibody and developing solution provides a colorimetric readout at 450 nm. EC_{50} values are calculated using the GraphPad Prism program.

Most compounds of the Examples cited have an EC_{50} (P-AKT PC3) of less than 1 µM.

The substances of the present invention are PI3 kinase inhibitors. On account of their biological properties, the novel compounds of the general formula (1) and their isomers and their physiologically tolerated salts are suitable for treating diseases which are characterized by excessive or anomalous cell proliferation.

These diseases include, for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammation and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphomas and solid tumours; skin diseases (e.g. psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophy). In addition, the compounds are useful for protecting proliferating cells (e.g. hair cells, intestinal cells, blood cells and progenitor cells) from DNA damage due to irradiation, UV treatment and/or cytostatic treatment (Davis et al., 2001).

For example, the following cancer diseases can be treated with compounds according to the invention, without, however, being restricted thereto: brain tumours, such as acoustic neurinoma, astrocytomas such as piloid astrocytomas, fibrillary astrocytoma, protoplasmic astrocytoma, gemistocytic astrocytoma, anaplastic astrocytoma and glioblastomas, brain lymphomas, brain metastases, hypophyseal tumour such as prolactinoma, HGH (human growth hormone) producing tumour and ACTH-producing tumour (adrenocorticotrophic hormone), craniopharyngiomas, medulloblastomas, meningiomas and oligodendrogliomas; nerve tumours (neoplasms) such as tumours of the vegetative nervous system such as neuroblastoma sympathicum, ganglioneuroma, paraganglioma (phaeochromocytoma and chromaffinoma) and glomus caroticum tumour, tumours in the peripheral nervous system such as amputation neuroma, neurofibroma, neurinoma (neurilemoma, schwannoma) and malignant schwannoma, as well as tumours in the central nervous system such as brain and spinal cord tumours; intestinal cancer such as rectal carcinoma, colon carcinoma, anal carcinoma, small intestine tumours and duodenal tumours; eyelid tumours such as basalioma or basal cell carcinoma; pancreatic gland cancer or pancreatic carcinoma; bladder cancer or bladder carcinoma; lung cancer (bronchial carcinoma) such as small-cell bronchial carcinomas (oat cell carcinomas) and non-small-cell bronchial carcinomas such as squamous epithelium carcinomas, adenocarcinomas and large-cell bronchial

carcinomas; breast cancer such as mammary carcinoma, such as infiltrating ductal carcinoma, colloid carcinoma, lobular invasive carcinoma, tubular carcinoma, adenoid cystic carcinoma, and papillary carcinoma; non-Hodgkin's lymphomas (NHL) such as Burkitt's lymphoma, low-malignancy non-Hodkgin's lymphomas (NHL) and mucosis fungoides; uterine cancer or endometrial carcinoma or corpus carcinoma; CUP syndrome (cancer of unknown primary); ovarian cancer or ovarian carcinoma such as mucinous, endometrial or serous cancer; gall bladder cancer; bile duct cancer such as Klatskin's tumour; testicular cancer such as seminomas and non-seminomas; lymphoma (lymphosarcoma) such as malignant lymphoma, Hodgkin's disease, non-Hodgkin's lymphomas (NHL) such as chronic lymphatic leukaemia, hair cell leukaemia, immunocytoma, plasmocytoma (multiple myeloma), immunoblastoma, Burkitt's lymphoma, T-zone mycosis fungoides, large-cell anaplastic lymphoblastoma and lymphoblastoma; laryngeal cancer such as vocal cord tumours, supraglottal, glottal and subglottal laryngeal tumours; bone cancer such as osteochondroma, chondroma, chrondoblastoma, chondromyxoidfibroma, osteoma, osteoid-osteoma, osteoblastoma, eosinophilic granuloma, giant cell tumour, chondrosarcoma, osteosarcoma, Ewing's sarcoma, reticulosarcoma, plasmocytoma, fibrous dysplasia, juvenile bone cyst and aneurysmatic bone cyst; head/neck tumours such as tumours of the lips, tongue, floor of the mouth, oral cavity, gingiva, pallet, salivary glands, pharynx, nasal cavities, paranasal sinuses, larynx and middle ear; liver cancer such as liver cell carcinoma or hepatocellular carcinoma (HCC); leukaemias, such as acute leukaemias, such as acute lymphatic/lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML); chronic leukaemias such as chronic lymphatic leukaemia (CLL), chronic myeloid leukaemia (CML); stomach cancer or stomach carcinoma such as papillary, tubular and mucinous adenocarcinoma, signet ring cell carcinoma, adenoid squamous cell carcinoma, small-cell carcinoma and undifferentiated carcinoma; melanomas such as superficially spreading, nodular malignant lentigo and acral lentiginous melanoma; renal cancer, such as kidney cell carcinoma or hypernephroma or Grawitz's tumour; oesophageal cancer or oesophageal carcinoma; cancer of the penis; prostate cancer; pharyngeal cancer or pharyngeal carcinomas such as nasopharyngeal carcinomas, oropharyngeal carcinomas and hypopharyngeal carcinomas; retinoblastoma; vaginal cancer or vaginal carcinoma;

squamous epithelium carcinomas, adeno carcinomas, in situ carcinomas, malignant melanomas and sarcomas; thyroid gland carcinomas such as papillary, follicular and medullary thyroid gland carcinoma, and also anaplastic carcinomas; spinalioma, prickle cell carcinoma and squamous epithelium carcinoma of the skin; thymomas, urethral cancer and vulvar cancer.

The novel compounds can be used for the prevention or short-term or long-term treatment of the abovementioned diseases including, where appropriate, in combination with other state-of-the-art compounds such as other anti-tumour substances, cytotoxic substances, cell proliferation inhibitors, antiangiogenic substances, steroids or antibodies.

The compounds of the general formula (1) can be used on their own or in combination with other active compounds according to the invention and, where appropriate, in combination with other pharmacologically active compounds as well. Chemotherapeutic agents which can be administered in combination with the compounds according to the invention include, without being restricted thereto, hormones, hormone analogs and antihormones (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol acetate, flutamide, nilutamide, bicalutamide, aminoglutethimide, cyproterone acetate, finasteride, buserelin acetate, fludrocortisone, fluoxymesterone, medroxyprogesterone and octreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, vorozole, exemestane and atamestane), LHRH agonists and antagonists (e.g. goserelin acetate and luprolide), inhibitors of growth factors (growth factors such as platelet-derived growth factor and hepatocyte growth factor, examples of inhibitors are growth factor antibodies, growth factor receptor antibodies and tyrosine kinase inhibitors, such as gefitinib, imatinib, lapatinib, Erbitux® and trastuzumab); antimetabolites (e.g. antifolates such as methotrexate and raltitrexed, pyrimidine analogs such as 5-fluorouracil, capecitabine and gemcitabine, purine and adenosine analogs such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine and fludarabine); antitumour antibiotics (e.g. anthracyclines, such as doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin C, bleomycin, dactinomycin, plicamycin and streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin and carboplatin); alkylating agents (e.g. estramustine, meclorethamine, melphalan, chlorambucil, busulphan, dacarbazine, cyclophosphamide, ifosfamide and

temozolomide, nitrosoureas such as carmustine and lomustine and thiotepa); antimitotic agents (e.g. vinca alkaloids such as vinblastine, vindesine, vinorelbine and vincristine; and taxans such as paclitaxel and docetaxel); topoisomerase inhibitors (e.g. epipodophyllotoxins such as etoposide and etopophos, teniposide, amsacrine, topotecan, irinotecan and mitoxantrone) and various chemotherapeutic agents such as amifostin, anagrelide, clodronate, filgrastin, interferon alpha, leucovorin, rituximab, procarbazine, levamisole, mesna, mitotan, pamidronate and porfimer.

Examples of suitable forms for use are tablets, capsules, suppositories, solutions, in particular solutions for injection (s.c., i.v., i.m.) and infusion, syrups, emulsions or dispersible powders. In this connection, the proportion of the pharmaceutically active compound(s) should in each case be in the range of 0.1-90% by weight, preferably 0.5 - 50 % by weight, of the total composition, that is in quantities which are sufficient to achieve the dosage range which is specified below. If necessary, the doses mentioned can be given several times a day.

Appropriate tablets can be obtained, for example, by mixing the active compound(s) with known auxiliary substances, for example inert diluents, such as calcium carbonate, calcium phosphate or lactose, disintegrants, such as maize starch or alginic acid, binders, such as starch or gelatine, lubricants, such as magnesium stearate or talc, and/or agents for achieving a depot effect, such as carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can also comprise several layers.

Correspondingly, sugar-coated tablets can be produced by coating cores, which have been prepared in analogy with tablets, with agents which are customarily used in sugar coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. The core can also comprise several layers in order to achieve a depot effect or to avoid incompatibilities. In the same way, the sugar coating can also comprise several layers in order to achieve a depot effect, with it being possible to use the auxiliary substances which are mentioned above in the case of the tablets.

Syrups of the active compounds or active compound combinations according to the invention can additionally comprise a sweetening agent, such as saccharine, cyclamate,

glycerol or sugar as well as a taste-improving agent, e.g. flavouring agents such as vanillin or orange extract. They can also comprise suspension aids or thickeners, such as sodium carboxymethyl cellulose, wetting agents, for example condensation products of fatty alcohols and ethylene oxide, or protectants such as p-hydroxybenzoates.

Injection and infusion solutions are produced in a customary manner, e.g. while adding isotonizing agents, preservatives, such as p-hydroxybenzoates, or stabilizers, such as alkali metal salts of ethylenediaminetetraacetic acid, where appropriate using emulsifiers and/or dispersants, with it being possible, for example, to employ, where appropriate, organic solvents as solubilizing agents or auxiliary solvents when using water as diluent, and aliquoted into injection bottles or ampoules or infusion bottles.

The capsules, which comprise one or more active compounds or active compound combinations, can, for example, be produced by mixing the active compounds with inert carriers, such as lactose or sorbitol, and encapsulating the mixture in gelatine capsules. Suitable suppositories can be produced, for example, by mixing with excipients which are envisaged for this purpose, such as neutral fats or polyethylene glycol, or their derivatives.

Auxiliary substances which may be mentioned by way of example are water, pharmaceutically unobjectionable organic solvents, such as paraffins (e.g. petroleum fractions), oils of vegetable origin (e.g. groundnut oil or sesame oil), monofunctional or polyfunctional alcohols (e.g. EtOH or glycerol), carrier substances such as natural mineral powders (e.g. kaolins, argillaceous earths, talc and chalk), synthetic mineral powders (e.g. highly disperse silicic acid and silicates), sugars (e.g. cane sugar, lactose and grape sugar), emulsifiers (e.g. lignin, sulphite waste liquors, methyl cellulose, starch and polyvinylpyrrolidone) and glidants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

Administration is effected in a customary manner, preferably orally or transdermally, in particular and preferably orally. In the case of oral use, the tablets can naturally also comprise, in addition to the abovementioned carrier substances, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with a variety of further substances such as starch, preferably potato starch, gelatine and the like. It is furthermore

also possible to use glidants, such as magnesium stearate, sodium lauryl sulphate and talc, for the tableting. In the case of aqueous suspensions, a variety of taste improvers or dyes can also be added to the active compounds in addition to the abovementioned auxiliary substances.

For parenteral administration, it is possible to employ solutions of the active compounds while using suitable liquid carrier materials. The dosage for intravenous administration is 1-1000 mg per hour, preferably between 5 and 500 mg per hour.

Despite this, it may be necessary, where appropriate, to diverge from the abovementioned quantities, depending on the body weight or the nature of the route of administration, on the individual response to the medicament, on the nature of its formulation and on the time or interval at which the administration is effected. Thus, it may, in some cases, be sufficient to make do with less than the previously mentioned lowest quantity whereas, in other cases, the abovementioned upper limit has to be exceeded. When relatively large quantities are being administered, it may be advisable to divide these into several single doses which are given over the course of the day.

The following formulation examples illustrate the present invention without, however, restricting its scope:

Pharmaceutical formulation examples

A) Tablets	per tablet
Active compound in accordance with formula (1)	100 mg
Lactose	140 mg
Maize starch	240 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	5 mg
	500 mg

The finely ground active compound, lactose and a part of the maize starch are mixed with each other. The mixture is sieved, after which it is moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granular material, the remainder of the maize starch and the magnesium stearate are sieved and mixed with

each other. The mixture is pressed into tablets of suitable shape and size.

B) Tablets	per tablet
Active compound in accordance with formula (1)	80 mg
Lactose	55 mg
Maize starch	190 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	15 mg
Sodium carboxymethyl starch	23 mg
Magnesium stearate	2 mg
	400 mg

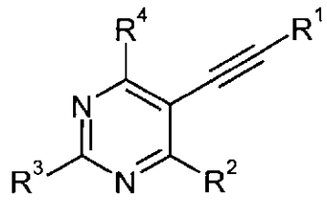
The finely ground active compound, a part of the maize starch, the lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed with each other, after which the mixture is sieved and worked, together with the remainder of the maize starch and water, into a granular material, which is dried and sieved. The sodium carboxymethyl starch and the magnesium stearate are then added to the granular material and mixed with it, and the mixture is pressed into tablets of suitable size.

C) Ampoule solution	
Active compound in accordance with formula (1)	50 mg
Sodium chloride	50 mg
Water for injection	5 mL

The active compound is dissolved, either at its intrinsic pH or, where appropriate, at pH 5.5-6.5, in water after which sodium chloride is added as isotonizing agent. The resulting solution is rendered pyrogen-free by filtration and the filtrate is aliquoted, under aseptic conditions, into ampoules, which are then sterilized and sealed by melting. The ampoules contain 5 mg, 25 mg and 50 mg of active compound.

Claims

1. Compounds of general formula (1),



(1),

wherein

R^1 denotes a group selected from among C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-10}aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R^5; and

R^2 denotes a group selected from among C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, C_{6-10}aryl and 5-12 membered heteroaryl, optionally substituted by one or more identical or different R^5 and

R^3 denotes hydrogen or a group selected from among halogen, $-OR^e$, $-NR^eR^e$, $-CF_3$, -CN, -NC, $-NO_2$ and C_{1-6}alkyl; and

R^4 denotes a group selected from among C_{1-3}alkyl, C_{3-8}cycloalkyl, 3-8 membered heterocycloalkyl, $-OR^e$, $-NR^eR^e$, $-CF_3$, -CN, -NC and $-NO_2$, and

each **R^5** denotes a group selected from among R^a, R^b and R^a substituted by one or more identical or different R^b and/or R^c; and

each **R^a** independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different **R^b** and/or **R^c**, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl,

each **R^b** denotes a suitable group and is selected independently of one another from among =O, $-OR^c$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^c$, $=NR^c$, $=NOR^c$, $=NNR^cR^c$, $=NN(R^g)C(O)NR^cR^c$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^c$, $-S(O)OR^c$, $-S(O)_2R^c$,

$-S(O)_2OR^c$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)_2OR^c$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)SR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, $-C(O)N(R^g)OR^c$, $-C(NR^g)NR^cR^c$, $-C(NOH)R^c$, $-C(NOH)NR^cR^c$, $-OC(O)R^c$, $-OC(O)OR^c$, $-OC(O)SR^c$, $-OC(O)NR^cR^c$, $-OC(NR^g)NR^cR^c$, $-SC(O)R^c$, $-SC(O)OR^c$, $-SC(O)NR^cR^c$, $-SC(NR^g)NR^cR^c$, $-N(R^g)C(O)R^c$, $-N[C(O)R^c]_2$, $-N(OR^g)C(O)R^c$, $-N(R^g)C(NR^g)R^c$, $-N(R^g)N(R^g)C(O)R^c$, $-N[C(O)R^c]NR^cR^c$, $-N(R^g)C(S)R^c$, $-N(R^g)S(O)R^c$, $-N(R^g)S(O)OR^c$, $-N(R^g)S(O)_2R^c$, $-N[S(O)_2R^c]_2$, $-N(R^g)S(O)_2OR^c$, $-N(R^g)S(O)_2NR^cR^c$, $-N(R^g)[S(O)_2]_2R^c$, $-N(R^g)C(O)OR^c$, $-N(R^g)C(O)SR^c$, $-N(R^g)C(O)NR^cR^c$, $-N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^cR^c$, $-[N(R^g)C(O)]_2R^c$, $-N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$, $-N(R^g)[C(O)]_2OR^c$, $-N(R^g)[C(O)]_2NR^cR^c$, $-N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$, $-[N(R^g)C(O)]_2OR^c$, $-N(R^g)C(NR^g)OR^c$, $-N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$, $-N(R^g)C(NR^g)NR^cR^c$ and $-N=C(R^g)NR^cR^c$ and

each $\mathbf{R^c}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^d}$ and/or $\mathbf{R^e}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, and

each $\mathbf{R^d}$ denotes a suitable group and is selected independently of one another from among =O, $-OR^e$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^e$, $=NR^e$, $=NOR^e$, $=NNR^eR^e$, $=NN(R^g)C(O)NR^eR^e$, $-NR^eR^e$, $-ONR^eR^e$, $-N(R^g)NR^eR^e$, halogen, $-CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^e$, $-S(O)OR^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^eR^e$, $-S(O)_2NR^eR^e$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)_2OR^e$, $-OS(O)NR^eR^e$, $-OS(O)_2NR^eR^e$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)SR^e$, $-C(O)NR^eR^e$, $-C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-C(NR^g)NR^eR^e$, $-C(NOH)R^e$, $-C(NOH)NR^eR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)SR^e$, $-OC(O)NR^eR^e$, $-OC(NR^g)NR^eR^e$, $-SC(O)R^e$, $-SC(O)OR^e$, $-SC(O)NR^eR^e$, $-SC(NR^g)NR^eR^e$, $-N(R^g)C(O)R^e$, $-N[C(O)R^e]_2$, $-N(OR^g)C(O)R^e$, $-N(R^g)C(NR^g)R^e$, $-N(R^g)N(R^g)C(O)R^e$, $-N[C(O)R^e]NR^eR^e$, $-N(R^g)C(S)R^e$, $-N(R^g)S(O)R^e$, $-N(R^g)S(O)OR^e$ $-N(R^g)S(O)_2R^e$, $-N[S(O)_2R^e]_2$, $-N(R^g)S(O)_2OR^e$, $-N(R^g)S(O)_2NR^eR^e$, $-N(R^g)[S(O)_2]_2R^e$, $-N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$,

$-N(R^g)C(O)NR^cR^c$, $-N(R^g)C(O)NR^gNR^cR^c$, $-N(R^g)N(R^g)C(O)NR^cR^c$, $-N(R^g)C(S)NR^eR^e$, $-[N(R^g)C(O)]_2R^e$, $-N(R^g)[C(O)]_2R^e$, $-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$, $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$, $-N(R^g)C(NR^g)NR^eR^e$ and $-N=C(R^g)NR^eR^e$

each $\mathbf{R^e}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^f}$ and/or $\mathbf{R^g}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, and

each $\mathbf{R^f}$ denotes a suitable group and in each case is selected independently of one another from among =O, $-OR^g$, C_{1-3}haloalkyloxy, $-OCF_3$, =S, $-SR^g$, $=NR^g$, $=NOR^g$, $=NNR^gR^g$, $=NN(R^h)C(O)NR^gR^g$, $-NR^gR^g$, $-ONR^gR^g$, $-N(R^h)NR^gR^g$, halogen, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^g$, $-S(O)OR^g$, $-S(O)_2R^g$, $-S(O)_2OR^g$, $-S(O)NR^gR^g$, $-S(O)_2NR^gR^g$, $-OS(O)R^g$, $-OS(O)_2R^g$, $-OS(O)_2OR^g$, $-OS(O)NR^gR^g$, $-OS(O)_2NR^gR^g$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)SR^g$, $-C(O)NR^gR^g$, $-C(O)N(R^h)NR^gR^g$, $-C(O)N(R^h)OR^g$, $-C(NR^h)NR^gR^g$, $-C(NOH)R^g$, $-C(NOH)NR^gR^g$, $-OC(O)R^g$, $-OC(O)OR^g$, $-OC(O)SR^g$, $-OC(O)NR^gR^g$, $-OC(NR^h)NR^gR^g$, $-SC(O)R^g$, $-SC(O)OR^g$, $-SC(O)NR^gR^g$, $-SC(NR^h)NR^gR^g$, $-N(R^h)C(O)R^g$, $-N[C(O)R^g]_2$, $-N(OR^h)C(O)R^g$, $-N(R^h)C(NR^h)R^g$, $-N(R^h)N(R^h)C(O)R^g$, $-N[C(O)R^g]NR^gR^g$, $-N(R^h)C(S)R^g$, $-N(R^h)S(O)R^g$, $-N(R^h)S(O)OR^g$, $-N(R^h)S(O)_2R^g$, $-N[S(O)_2R^g]_2$, $-N(R^h)S(O)_2OR^g$, $-N(R^h)S(O)_2NR^gR^g$, $-N(R^h)[S(O)_2]_2R^g$, $-N(R^h)C(O)OR^g$, $-N(R^h)C(O)SR^g$, $-N(R^h)C(O)NR^gR^g$, $-N(R^h)C(O)NR^hNR^gR^g$, $-N(R^h)N(R^h)C(O)NR^gR^g$, $-N(R^h)C(S)NR^gR^g$, $-[N(R^h)C(O)]_2R^g$, $-N(R^h)[C(O)]_2R^g$, $-N\{[C(O)]_2R^g\}_2$, $-N(R^h)[C(O)]_2OR^g$, $-N(R^h)[C(O)]_2NR^gR^g$, $-N\{[C(O)]_2OR^g\}_2$, $-N\{[C(O)]_2NR^gR^g\}_2$, $-[N(R^h)C(O)]_2OR^g$, $-N(R^h)C(NR^h)OR^g$, $-N(R^h)C(NOH)R^g$, $-N(R^h)C(NR^h)SR^g$, $-N(R^h)C(NR^h)NR^gR^g$; and $-N=C(R^h)NR^hR^h$; and

each $\mathbf{R^g}$ independently of one another denotes hydrogen or a group optionally substituted by one or more identical or different $\mathbf{R^h}$, selected from among C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl,

C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered hetero-aryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl; and each $\mathbf{R^h}$ is selected independently of one another from among hydrogen, C_{1-6}alkyl, 2-6 membered heteroalkyl, C_{1-6}haloalkyl, C_{3-10}cycloalkyl, C_{4-16}cycloalkylalkyl, C_{6-10}aryl, C_{7-16}arylalkyl, 5-12 membered heteroaryl, 6-18 membered heteroarylalkyl, 3-14 membered heterocycloalkyl and 4-14 membered heterocycloalkylalkyl, optionally in the form of the prodrugs, the tautomers, the racemates, the enantiomers, the diastereomers, the prodrugs and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

2. Compounds according to claim 1, wherein $\mathbf{R^4}$ denotes $-CH_3$ or $-C_2H_5$.

3. Compounds according to claims 1 to 2, wherein $\mathbf{R^3}$ denotes hydrogen or $-NR^cR^c$.

4. Compounds according to claims 3, wherein $\mathbf{R^3}$ denotes $-NH_2$.

5. Compounds according to claims 1 to 4, wherein $\mathbf{R^2}$ denotes phenyl or pyridyl, optionally substituted by one or more identical or different R^5.

6. Compounds according to claims 1 to 4, wherein $\mathbf{R^2}$ denotes heterocycloalkyl, optionally substituted by one or more identical or different R^5.

7. Compounds according to claim 1 to 6, wherein $\mathbf{R^1}$ denotes phenyl, pyridyl or pyrimidinyl, optionally substituted by one or more identical or different R^5.

8. Compounds, or the pharmacologically effective salts thereof, according to one of claims 1 to 7, as medicaments.

9. Compounds, or the pharmacologically effective salts thereof, according to one of claims 1 to 7, for preparing a medicament with an antiproliferative activity.

10. Pharmaceutical preparations, containing as active substance one or more compounds of general formula (1) according to one of claims 1 to 7 or the pharmacologically effective salts thereof, optionally in combination with conventional excipients and/or carriers.

11. Use of compounds of general formula (1) according to one of claims 1 to 7 for preparing a medicament for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

12. Pharmaceutical preparation comprising a compound of general formula (1) according to one of claims 1 to 7 and at least one other cytostatic or cytotoxic active substance, different from formula (1), optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, as well as optionally the pharmacologically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/059763

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/48 C07D401/04 C07D401/06 C07D403/06 C07D403/14
C07D409/06 C07D413/14 A61K31/495

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)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/044823 A (AMGEN INC [US]; CHAFFEE STUART C [US]; ALBRECHT BRIAN K [US]; HODOUS B) 27 April 2006 (2006-04-27) cited in the application claims, compounds I and II; description p. 1ff	1-12

☐ 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 document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2009	02/10/2009

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

INTERNATIONAL SEARCH REPORT

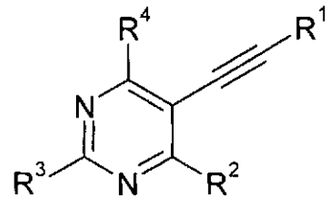
Information on patent family members

International application No
PCT/EP2009/059763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006044823 A	27-04-2006	AU 2005295414 A1	27-04-2006
		CA 2583907 A1	27-04-2006
		EP 1802586 A2	04-07-2007
		US 2006217380 A1	28-09-2006

5-ALQUINIL-PIRIMIDINAS

La presente invención se refiere a nuevas 5-alquinil-pirimidinas de fórmula general (1)



(1),

en la que los grupos R^1 a R^4 tienen los significados que se indican en las reivindicaciones y en la memoria descriptiva, a los isómeros de los mismos, a procesos para preparar estas alquinil-pirimidinas y a su uso como medicamentos.

Antecedentes de la invención

Varias proteína quinasas han demostrado ya ser moléculas diana adecuadas para la intervención terapéutica en una diversidad de indicaciones, por ejemplo cáncer y enfermedades inflamatorias y autoinmunes. Puesto que un alto porcentaje de los genes implicados en el desarrollo del cáncer que se han identificado hasta la fecha codifican quinasas, estas enzimas son moléculas diana atractivas, en particular, para la terapia del cáncer.

Las fosfatidilinositol-3-quinasas (PI3-quinasas) son una subfamilia de las quinasas lipídicas que catalizan la transferencia de un grupo fosfato a la posición 3' del anillo de inositol de fosfoinosítidos.

Desempeñan un papel importante en numerosos procesos celulares tales como, por ejemplo, procesos de crecimiento y diferenciación celular, el control de cambios citoesqueléticos y la regulación de procesos de transporte intracelular. En base a su especificidad *in vitro* para algunos sustratos de fosfoinosítidos, las PI3-quinasas pueden dividirse en diferentes categorías.

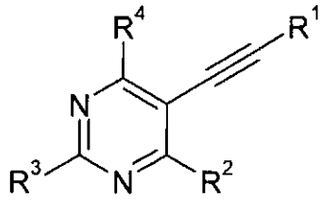
En el documento WO2006044823 se describen 5-alquinil-pirimidinas por ejemplo, como proteína quinasas que inhiben compuestos.

Descripción detallada de la invención

Se ha descubierto ahora, sorprendentemente, que compuestos de fórmula general (1), en la que los grupos R^1 a R^4 tienen los significados que se indican a continuación, actúan como inhibidores de quinasas. Por lo tanto, los compuestos de acuerdo con la invención pueden usarse, por ejemplo, para el tratamiento de

enfermedades asociadas a la actividad de quinasas y caracterizadas por una proliferación celular excesiva o anormal.

La presente invención se refiere a compuestos de fórmula general (1)



(1),

en la que

R^1 representa un grupo seleccionado entre cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, arilo C_{6-10} y heteroarilo de 5-12 miembros, opcionalmente sustituido con uno o más R^5 iguales o diferentes; y

R^2 representa un grupo seleccionado entre cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, arilo C_{6-10} y heteroarilo de 5-12 miembros, opcionalmente sustituido con uno o más R^5 iguales o diferentes y

R^3 representa hidrógeno o un grupo seleccionado entre halógeno, $-OR^e$, $-NR^eR^e$, $-CF_3$, -CN, -NC, $-NO_2$ y alquilo C_{1-6}; y

R^4 representa un grupo seleccionado entre alquilo C_{1-3}, cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, halógeno, $-OR^e$, $-NR^eR^e$, $-CF_3$, $-CN$, -NC y $-NO_2$, y

cada **R^5** representa un grupo seleccionado entre R^a, R^b y R^a sustituido con uno o más R^b iguales o diferentes y/o R^c; y

cada **R^a** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R^b** y/o **R^c** iguales o diferentes, seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arialquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros;

cada **R^b** representa un grupo adecuado y se selecciona independientemente entre sí entre =O, $-OR^c$, haloalquiloxi C_{1-3}, $-OCF_3$, =S, $-SR^c$, $=NR^c$, $=NOR^c$, $=NNR^cR^c$, $=NN(R^g)C(O)NR^cR^c$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halógeno, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^c$, $-S(O)OR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)_2OR^c$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)SR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, $-C(O)N(R^g)OR^c$, $-C(NR^g)NR^cR^c$, $-C(NOH)R^c$, $-C(NOH)NR^cR^c$,

-OC(O)R^c, –OC(O)OR^c, –OC(O)SR^c, –OC(O)NR^cR^c, -OC(NR^g)NR^cR^c, –SC(O)R^c, -SC(O)OR^c, –SC(O)NR^cR^c, -SC(NR^g)NR^cR^c, -N(R^g)C(O)R^c, –N[C(O)R^c]$_2$, -N(OR^g)C(O)R^c, –N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, –N[C(O)R^c]NR^cR^c, -N(R^g)C(S)R^c, –N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)$_2R^c$, –N[S(O)$_2R^c$]$_2$, -N(R^g)S(O)$_2OR^c$, -N(R^g)S(O)$_2NR^cR^c$, –N(R^g)[S(O)$_2$]$_2R^c$, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^cR^c, –N(R^g)C(O)$NR^gNR^cR^c$, -N(R^g)N(R^g)C(O)NR^cR^c, -N(R^g)C(S)NR^cR^c, –[N(R^g)C(O)]$_2R^c$, –N(R^g)[C(O)]$_2R^c$, -N{[C(O)]$_2R^c$}$_2$, -N(R^g)[C(O)]$_2OR^c$, –N(R^g)[C(O)]$_2NR^cR^c$, –N{[C(O)]$_2OR^c$}$_2$, -N{[C(O)]$_2NR^cR^c$}$_2$, -[N(R^g)C(O)]$_2OR^c$, –N(R^g)C(NR^g)OR^c, –N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c, -N(R^g)C(NR^g)NR^cR^c y -N=C(R^g)NR^cR^c y

cada **R^c** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R^d** y/o **R^e** iguales o diferentes, seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arialquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros, y

cada **R^d** representa un grupo adecuado y se selecciona independientemente entre sí entre =O, –OR^e, haloalquiloxi C_{1-3}, –OCF_3, =S, –SR^e, =NR^e, =NOR^e, =NNR^eR^e, =NN(R^g)C(O)NR^eR^e, –NR^eR^e, –ONR^eR^e, –N(R^g)NR^eR^e, halógeno, –CF_3, –CN, -NC, -OCN, –SCN, –NO, –NO_2, =N_2, –N_3, –S(O)R^e, –S(O)OR^e, –S(O)$_2R^e$, –S(O)$_2OR^e$, -S(O)NR^eR^e, -S(O)$_2NR^eR^e$, –OS(O)R^e, –OS(O)$_2R^e$, –OS(O)$_2OR^e$, –OS(O)NR^eR^e, -OS(O)$_2NR^eR^e$, -C(O)R^e, –C(O)OR^e, –C(O)SR^e, –C(O)NR^eR^e, –C(O)N(R^g)NR^eR^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^eR^e, –C(NOH)R^e, –C(NOH)NR^eR^e, –OC(O)R^e, -OC(O)OR^e, –OC(O)SR^e, -OC(O)NR^eR^e, –OC(NR^g)NR^eR^e, –SC(O)R^e, -SC(O)OR^e, -SC(O)NR^eR^e, –SC(NR^g)NR^eR^e, –N(R^g)C(O)R^e, –N[C(O)R^e]$_2$, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, –N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^eR^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, –N(R^g)S(O)OR^e –N(R^g)S(O)$_2R^e$, -N[S(O)$_2R^e$]$_2$, -N(R^g)S(O)$_2OR^e$, -N(R^g)S(O)$_2NR^eR^e$, –N(R^g)[S(O)$_2$]$_2R^e$, –N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^eR^e, –N(R^g)C(O)$NR^gNR^eR^e$, -N(R^g)N(R^g)C(O)NR^eR^e, -N(R^g)C(S)NR^eR^e, –[N(R^g)C(O)]$_2R^e$, –N(R^g)[C(O)]$_2R^e$, -N{[C(O)]$_2R^e$}$_2$, -N(R^g)[C(O)]$_2OR^e$, –N(R^g)[C(O)]$_2NR^eR^e$, –N{[C(O)]$_2OR^e$}$_2$, -N{[C(O)]$_2NR^eR^e$}$_2$, -[N(R^g)C(O)]$_2OR^e$, –N(R^g)C(NR^g)OR^e, –N(R^g)C(NOH)R^e, -N(R^g)C(NR^g)SR^e, -N(R^g)C(NR^g)NR^eR^e y -N=C(R^g)NR^eR^e

cada **R^e** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido por uno o más **R^f** **R^g** iguales o diferentes y/o,

seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arilalquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros, y

cada **R^f** representa un grupo adecuado y en cada caso se selecciona independientemente entre sí entre =O, $-OR^g$, haloalquiloxi C_{1-3}, $-OCF_3$, =S, $-SR^g$, $=NR^g$, $=NOR^g$, $=NNR^gR^g$, $=NN(R^h)C(O)NR^gR^g$, $-NR^gR^g$, $-ONR^gR^g$, $-N(R^h)NR^gR^g$, halógeno, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^g$, $-S(O)OR^g$, $-S(O)_2R^g$, $-S(O)_2OR^g$, $-S(O)NR^gR^g$, $-S(O)_2NR^gR^g$, $-OS(O)R^g$, $-OS(O)_2R^g$, $-OS(O)_2OR^g$, $-OS(O)NR^gR^g$, $-OS(O)_2NR^gR^g$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)SR^g$, $-C(O)NR^gR^g$, $-C(O)N(R^h)NR^gR^g$, $-C(O)N(R^h)OR^g$, $-C(NR^h)NR^gR^g$, $-C(NOH)R^g$, $-C(NOH)NR^gR^g$, $-OC(O)R^g$, $-OC(O)OR^g$, $-OC(O)SR^g$, $-OC(O)NR^gR^g$, $-OC(NR^h)NR^gR^g$, $-SC(O)R^g$, $-SC(O)OR^g$, $-SC(O)NR^gR^g$, $-SC(NR^h)NR^gR^g$, $-N(R^h)C(O)R^g$, $-N[C(O)R^g]_2$, $-N(OR^h)C(O)R^g$, $-N(R^h)C(NR^h)R^g$, $-N(R^h)N(R^h)C(O)R^g$, $-N[C(O)R^g]NR^gR^g$, $-N(R^h)C(S)R^g$, $-N(R^h)S(O)R^g$, $-N(R^h)S(O)OR^g$, $-N(R^h)S(O)_2R^g$, $-N[S(O)_2R^g]_2$, $-N(R^h)S(O)_2OR^g$, $-N(R^h)S(O)_2NR^gR^g$, $-N(R^h)[S(O)_2]_2R^g$, $-N(R^h)C(O)OR^g$, $-N(R^h)C(O)SR^g$, $-N(R^h)C(O)NR^gR^g$, $-N(R^h)C(O)NR^hNR^gR^g$, $-N(R^h)N(R^h)C(O)NR^gR^g$, $-N(R^h)C(S)NR^gR^g$, $-[N(R^h)C(O)]_2R^g$, $-N(R^h)[C(O)]_2R^g$, $-N\{[C(O)]_2R^g\}_2$, $-N(R^h)[C(O)]_2OR^g$, $-N(R^h)[C(O)]_2NR^gR^g$, $-N\{[C(O)]_2OR^g\}_2$, $-N\{[C(O)]_2NR^gR^g\}_2$, $-[N(R^h)C(O)]_2OR^g$, $-N(R^h)C(NR^h)OR^g$, $-N(R^h)C(NOH)R^g$, $-N(R^h)C(NR^h)SR^g$, $-N(R^h)C(NR^h)NR^gR^g$; y $-N=C(R^h)NR^hR^h$; y

cada **R^g** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R^h** iguales o diferentes, seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arilalquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros; y

cada **R^h** se selecciona independientemente entre sí entre hidrógeno, alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arilalquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros,

opcionalmente en forma de los profármacos, los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, los profármacos y las mezclas de los mismos, y opcionalmente las sales farmacológicamente aceptables de los mismos.

Un aspecto de la invención se refiere a compuestos de fórmula general (1), en la que R^4 representa $-CH_3$ o $-CH_2CH_3$.

Otro aspecto de la invención se refiere a compuestos de fórmula general (1), en la que R^3 representa hidrógeno o $-NR^eR^e$.

Otro aspecto de la invención se refiere a compuestos de fórmula general (1), en la que R^3 representa $-NH_2$.

Otro aspecto de la invención se refiere a compuestos de fórmula general (1), en los que R^2 representa fenilo o piridilo, opcionalmente sustituidos con uno o más R^5 iguales o diferentes.

Otro aspecto de la invención se refiere a compuestos de fórmula general (1), en la que R^2 representa heterocicloalquilo opcionalmente sustituido con uno o más R^5 iguales o diferentes.

Otro aspecto de la invención se refiere a compuestos de fórmula general (1), en la que R^1 representa fenilo, piridilo o pirimidinilo, opcionalmente sustituidos con uno o más R^5 iguales o diferentes.

Un aspecto de la invención se refiere a compuestos de fórmula general (1), o a las sales farmacológicamente eficaces de los mismos, como medicamentos.

Un aspecto de la invención se refiere a compuestos de fórmula general (1), o a las sales farmacológicamente eficaces de los mismos, para preparar un medicamento con actividad antiproliferativa.

Un aspecto de la invención es una preparación farmacéutica que contiene como sustancia activa uno o más compuestos de fórmula general (1), o las sales farmacológicamente eficaces de los mismos, opcionalmente en combinación con excipientes y/o vehículos convencionales.

Un aspecto de la invención es el uso de compuestos de fórmula general (1) para preparar un medicamento para el tratamiento y/o prevención de cáncer, infecciones, enfermedades inflamatorias y autoinmunes.

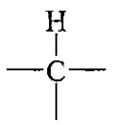
Un aspecto de la invención es una preparación farmacéutica que comprende un compuesto de fórmula general (1) y al menos otra sustancia activa citostática o citotóxica, diferente de la fórmula (1), opcionalmente en forma de los tautómeros, los racematos, los enantiómeros, los diastereómeros y las mezclas de los mismos, así como opcionalmente las sales farmacológicamente aceptables de los mismos.

Definiciones

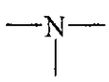
Como se usan en la presente memoria, a menos que se indique otra cosa, se aplican las siguientes definiciones.

Por sustituyentes alquilo pretenden indicarse en cada caso grupos hidrocarbonados alifáticos saturados, insaturados, de cadena lineal o ramificada (grupo alquilo), y esto incluye tanto grupos alquilo saturados como grupos alquenilo y alquinilo insaturados. Los sustituyentes alquenilo son en cada caso grupos alquilo insaturados, de cadena lineal o ramificada, que tienen al menos un doble enlace. Por sustituyentes alquinilo pretenden indicarse en cada caso grupos alquilo insaturados, de cadena lineal o ramificada, que tienen al menos un triple enlace.

El término **heteroalquilo** se refiere a grupos que pueden obtenerse a partir de alquilo como se ha definido anteriormente en su sentido más amplio reemplazando uno o más de los grupos $-CH_3$ en las cadenas hidrocarbonadas entre sí por los grupos –OH, –SH o $-NH_2$, uno o más de los grupos $-CH_2-$ independientemente entre sí por los grupos –O–, –S– o –NH–, uno o más de los grupos



por el grupo



uno o más de los grupos =CH– por el grupo =N–, uno o más de los grupos $=CH_2$ por el grupo =NH o uno o más de los grupos ≡CH por el grupo ≡N, mientras que en todos ellos sólo pueden estar presentes en un heteroalquilo un máximo de tres heteroátomos, debe existir al menos un átomo de carbono entre dos átomos de oxígeno y entre dos átomos de azufre o entre un átomo de oxígeno y un átomo de azufre, y el grupo en conjunto debe tener estabilidad química.

De la definición/derivación indirecta de alquilo se desprende que heteroalquilo está constituido por los subgrupos de cadenas hidrocarbonadas saturadas con uno o varios heteroátomos, heteroalquenilo y heteroalquinilo, aunque se puede efectuar una subdivisión adicional en los que tienen cadena lineal (sin ramificar) y los ramificados. Si se supone que un heteroalquilo está sustituido, la sustitución puede tener lugar de manera independiente entre sí, en cada caso mono- o polisustitución, en todos los átomos de oxígeno, de azufre, de nitrógeno y/o de carbono portadores de hidrógeno. El propio heteroalquilo puede estar enlazado a la molécula como sustituyente, tanto a través de un átomo de carbono como a través de un heteroátomo.

A modo de ejemplo, se enumeran los siguientes compuestos representativos:

dimetilaminometilo; dimetilaminoetilo (1-dimetilaminoetilo; 2-dimetilaminoetilo); dimetilaminopropilo (1-dimetilaminopropilo, 2-dimetilaminopropilo, 3-dimetilaminopropilo); dietilaminometilo; dietilaminoetilo (1-dietilaminoetilo, 2-dietilaminoetilo); dietilaminopropilo (1-dietilaminopropilo, 2-dietilaminopropilo, 3-dietilaminopropilo); diisopropilaminoetilo (1-diisopropilaminoetilo, 2-diisopropilaminoetilo); bis-2-metoxietilamino; [2-(dimetilamino-etil)-etil-amino]-metilo; 3-[2-(dimetilamino-etil)-etil-amino]-propilo; hidroximetilo; 2-hidroxi-etilo; 3-hidroxipropilo; metoxi; etoxi; propoxi; metoximetilo; 2-metoxietilo, etc.

Haloalquilo se refiere a grupos alquilo en los que uno o más átomos de hidrógeno se han reemplazado por átomos de halógeno. Haloalquilo incluye tanto grupos alquilo saturados como grupos alquenilo y alquinilo insaturados, tales como, por ejemplo, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$,$-CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CF=CF_2$, $-CCl=CH_2$, $-CBr=CH_2$, $-Cl=CH_2$, $-C\equiv C-CF_3$, $-CHFCH_2CH_3$ y $-CHFCH_2CF_3$.

Halógeno se refiere a átomos de flúor, cloro, bromo y/o yodo.

Por cicloalquilo pretende indicarse un anillo mono o bicíclico, mientras que el sistema de anillos puede ser un anillo saturado o bien un anillo insaturado no aromático, que opcionalmente puede contener también dobles enlaces , por ejemplo ciclopropilo, ciclopropenilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, norbornilo y norbornenilo.

Cicloalquilalquilo incluye un grupo alquilo no cíclico en el que un átomo de hidrógeno unido a un átomo de carbono, normalmente a un átomo de C terminal, se ha reemplazado por un grupo cicloalquilo.

Arilo se refiere a anillos aromáticos monocíclicos o bicíclicos con 6 - 10 átomos de carbono tales como, por ejemplo, fenilo y naftilo.

Arilalquilo incluye un grupo alquilo no cíclico en el que un átomo de hidrógeno unido a un átomo de carbono, normalmente a un átomo de C terminal, se ha reemplazado por un grupo arilo.

Por heteroarilo pretenden indicarse anillos aromáticos mono- o bicíclicos, que en lugar de uno o más átomo de carbono contienen uno más heteroátomos, iguales o diferentes, tales como, por ejemplo, átomos de nitrógeno, azufre u oxígeno. Los ejemplos incluyen furilo, tienilo, pirrolilo, oxazolilo, tiazolilo, isoxazolilo,

isotiazolilo, pirazolilo, imidazolilo, triazolilo, tetrazolilo, oxadiazolilo, tiadiazolilo, piridilo, pirimidilo, piridazinilo, pirazinilo y triazinilo. Son ejemplos de grupos heteroarilo bicíclicos los grupos indolilo, isoindolilo, benzofurilo, benzotienilo, benzoxazolilo, benzotiazolilo, benzoisoxazolilo, benzoisotiazolilo, benzoimidazolilo, benzopirazolilo, indazolilo, isoquinolinilo, quinolinilo, quinoxalinilo, cinnolinilo, ftalazinilo, quinazolinilo y benzotriazinilo, indolizinilo, oxazolopiridilo, imidazopiridilo, naftiridinilo, indolinilo, isocromanilo, cromanilo, tetrahidroisoquinolinilo, isoindolinilo, isobenzotetrahidrofurilo, isobenzotetrahidrotienilo, isobenzotienilo, benzoxazolilo, piridopiridilo, benzotetrahidrofurilo, benzotetrahidrotienilo, purinilo, benzodioxolilo, triazinilo, fenoxazinilo, fenotiazinilo, pteridinilo, benzotiazolilo, imidazopiridilo, imidazotiazolilo, dihidrobenzoisoxazinilo, benzoisoxazinilo, benzoxazinilo, dihidrobenzoisotiazinilo, benzopiranilo, benzotiopiranilo, cumarinilo, isocumarinilo, cromanilo, cromanonilo, *N*-óxido de piridilo, tetrahidroquinolinilo, dihidroquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidrocoumarinilo, dihidroisocoumarinilo, isoindolinonilo, benzodioxanilo, benzoxazolinonilo, *N*-óxido de pirrolilo, *N*-óxido de pirimidinilo, *N*-óxido de piridazinilo, *N*-óxido de pirazinilo, *N*-óxido de quinolinilo, *N*-óxido de indolilo, *N*-óxido de indolinilo, *N*-óxido de isoquinolilo, *N*-óxido de quinazolinilo, *N*-óxido de quinoxalinilo, *N*-óxido de ftalazinilo, *N*-óxido de imidazolilo, *N*-óxido de isoxazolilo, *N*-óxido de oxazolilo, *N*-óxido de tiazolilo, *N*-óxido de indolizinilo, *N*-óxido de indazolilo, *N*-óxido de benzotiazolilo, *N*-óxido de benzoimidazolilo, *N*-óxido de pirrolilo, *N*-óxido de oxadiazolilo, *N*-óxido de tiadiazolilo, *N*-óxido de triazolilo, *N*-óxido de tetrazolilo, *S*-óxido de benzotiopiranilo y *S,S*-dióxido de benzotiopiranilo.

Heteroarilalquilo incluye un grupo alquilo no cíclico en el que un átomo de hidrógeno unido a un átomo de carbono, normalmente a un átomo de C terminal, se ha reemplazado por un grupo heteroarilo.

Heterocicloalquilo se refiere a anillos mono-, bicíclicos o bicíclicos enlazados, no aromáticos, saturados o insaturados, que comprenden 3 – 12 átomos de carbono, que en lugar de uno o más átomos de carbono llevan heteroátomos tales como nitrógeno, oxígeno o azufre. Son ejemplos de tales grupos heterocicloalquilo los grupos tetrahidrofurilo, pirrolidinilo, pirrolinilo, imidazolidinilo, imidazolinilo, pirazolidinilo, pirazolinilo, piperidinilo, piperazinilo, indolinilo, isoindolinilo, morfolinilo, tiomorfolinilo, homomorfolinilo, homopiperidinilo, homopiperazinilo, homotiomorfolinilo, *S*-óxido de tiomorfolinilo, *S,S*-dióxido de tiomorfolinilo, tetrahidropiranilo, tetrahidrotienilo, *S,S*-dióxido de homotiomorfolinilo-,

oxazolidinonilo, dihidropirazolilo, dihidropirrolilo, dihidropirazinilo, dihidropiridilo, dihidropirimidinilo, dihidrofurilo, dihidropiranilo, *S*-óxido de tetrahidrotienilo, *S,S*-dióxido de tetrahidrotienilo, *S*-óxido de homotiomorfolinilo, 2-oxa-5-azabiciclo[2,2,1]heptano, 8-oxa-3-aza-biciclo[3.2.1]octano, 3,8-diaza-biciclo[3.2.1]-octano, 2,5-diaza-biciclo[2.2.1]heptano, 3,8-diaza-biciclo[3.2.1]octano, 3,9-diaza-biciclo[4.2.1]nonano y 2,6-diaza-biciclo[3.2.2]nonano.

Heterocicloalquilalquilo se refiere a un grupo alquilo no cíclico en el que un átomo de hidrógeno unido a un átomo de carbono, normalmente a un átomo de C terminal, se ha reemplazado por un grupo heterocicloalquilo.

Los siguientes Ejemplos ilustran la presente invención sin restringir su alcance.

Procedimiento General 1 (PG1): Yodación de Pirimidinas y Piridinas

Una solución de la pirimidina o piridina (1,0 equiv.) en ácido acético se enfría a 0°C y se añade en una porción *N*-yodosuccinimida (1,0 equiv.). La mezcla de reacción se agita a TA hasta que se completa la conversión del material de partida (2 - 6 h). La mezcla se vierte en agua enfriada con hielo y se trata con una mezcla de $Na_2S_2O_3$ al 5% y $NaHCO_3$ al 10%. El precipitado se retira por filtración, se lava intensamente con agua y se seca a vacío a 40°C. El producto en bruto puede usarse sin purificación adicional o se purifica adicionalmente por cromatografía sobre gel de sílice usando un gradiente de CH_2Cl_2/MeOH.

Procedimiento General 2 (PG2): Reacción de Sonogashira

El haluro (1,0 equiv.) se disuelve en DMF o THF y se añaden $PdCl_2(PPh_3)_2$ (0,1 equiv.) y CuI (0,1 equiv.). Posteriormente, se añaden trietilamina (10,0 equiv.) y finalmente el alquino (1,5 equiv.) y la mezcla de reacción se agita a 65°C. La reacción se controla por LC-MS. Si no se completa la conversión del yoduro después de 4 h, se añaden en pequeñas porciones cantidades adicionales de alquino. El producto precipita de la mezcla de reacción (y se retira por filtración y si es necesario se cristaliza de nuevo) y/o, después de la retirada del disolvente, se purifica por RP-HPLC preparativa.

Procedimiento General 3 (PG3): Desililación de Alquinos

El TMS-alquino (1,0 equiv.) se disuelve en MeOH, se añade en una porción K_2CO_3 (0,5 equiv.) y la mezcla de reacción se agita a TA hasta que se completa la conversión (3 – 16 h). El disolvente se retira al vacío, el producto en bruto se disuelve en acetato de etilo y la fase orgánica se extrae con agua. La fase orgánica se seca, se retira por filtración y el disolvente se retira al vacío. El producto se usa

sin purificación adicional o se purifica por cromatografía sobre gel de sílice usando DCM/MeOH o (ciclo-)hexano/acetato de etilo.

Procedimiento General 4 (PG4): Acoplamiento de Suzuki

La 4-cloropirimidina (1,0 equiv.) se disuelve en DME/agua (20:1 v/v), se añaden ácido borónico (1,3 equiv.), K_2CO_3 (2,0 equiv.) y $Pd(PPh_3)_4$ (0,2 equiv.) y la mezcla de reacción se agita durante 4 h a reflujo. En caso de que la conversión del material de partida no se haya completado, se añaden cantidades adicionales de ácido borónico y catalizador de Pd y se deja que la reacción se desarrolle durante una noche a la temperatura de reflujo. Después de la refrigeración a TA, se añade agua. El precipitado se retirapor filtración. En los casos en los que el producto no precipita, se extrae con éter dietílico, la fase orgánica se seca, se retira por filtración y el disolvente se retira a presión reducida. El producto obtenido puede usarse sin purificación adicional o se purifica por cromatografía.

Procedimiento General 5 (PG5): Oxidación de un Grupo Tioalquilo

La 2-metilsulfanil-pirimidina (1,0 equiv.) se recoge en DCM, se añade ácido *meta*-cloroperbenzoico (2,5 equiv.) y la mezcla de reacción se agita durante un día. La mezcla de reacción se filtra, se lava con agua y se concentra al vacío. El producto en bruto puede usarse sin purificación adicional.

Procedimiento General 6 (PG6): Sustitución Nucleófila de 2-Sulfonilpirimidinas con Aminas

El material de partida se disuelve en NMP, se añade un exceso de amina y la mezcla de reacción se calienta en el microondas a 125-150ºC. Después de la refrigeración a TA, el producto se purifica por NP-HPLC.

Procedimiento General 7 (PG7): Sustitución Nucleófila de 4-Sulfonilpirimidinas con Aminas

El material de partida se disuelve en NMP, se añade un exceso de amina y la mezcla de reacción se calienta en el microondas a 125-150ºC. Después de la refrigeración a TA, el producto se purifica por NP-HPLC.

Procedimiento General 8 (PG8): Saponificación de Ésteres

El éster se recoge en THF o dioxano, se añaden 1,1-1,5 equiv. de NaOH 1 N y la mezcla se calienta a reflujo hasta que el control de reacción muestra la conversión completa del material de partida. El producto precipita de la mezcla de reacción y se usa sin etapas de purificación adicional o puede purificarse adicionalmente por cromatografía.

Procedimiento General 9 (PG9): Formación de Amida con Aminas

La mezcla de 0,21 mmol de material de partida, 0,31 mmol de TBTU o HATUy 0,42 mmol de base de Huenig en 2 ml de DMSO se agita durante 5 min. Se añaden 0,31 mmol de amina y la mezcla resultante se agita a temperatura ambiente durante una noche. La purificación se realiza por RP-HPLC preparativa, produciendo, después de la evaporación del disolvente, el producto deseado.

Procedimiento General 10 (PG10): Formación de Amida con Cloruro de Ácido

A una mezcla de 0,13 mmol de material de partida y 67 µl de base de Huenig en 2 ml de THF se le añaden 0,26 mmol de cloruro de ácido. La mezcla de reacción se agita durante una noche a TA. El disolvente se evapora, el residuo se recoge en 1 ml de DMSO, el material insoluble se retira por filtración y la solución resultante se purifica por RP-HPLC preparativa, produciendo, después de la evaporación del disolvente, el producto deseado.

Procedimiento General 11 (PG11): Formación de Urea con Isocianatos

A una mezcla de 0,16 mmol de material de partida y 64,4 µl de base de Huenig en 2 ml de THF se le añaden 0,49 mmol de cloruro de ácido. La mezcla de reacción se agita durante una noche a TA. El disolvente se evapora, el residuo se recoge en 1 ml de DMSO, el material insoluble se retira por filtración y la solución resultante se purifica por RP-HPLC preparativa, produciendo, después de la evaporación del disolvente, el producto deseado.

Procedimiento General 12 (PG12): Formación de Urea por Pre-activación de la Amina.

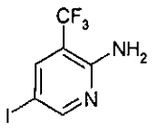
Una mezcla de 0,34 mmol de amina y 0,34 mmol de *N,N'*-carbonildiimidazol y 0,34 mmol de 1,8-diazabiciclo[5.4.0]undec-7-eno se agita durante 10 min a TA. Se añaden en una porción 0,32 mmol de material de partida. La mezcla de reacción se calienta a 100°C durante 1 h en el microondas. El disolvente se evapora, el residuo se recoge en 1 ml de DMSO, el material insoluble se retira por filtración y la solución resultante se purifica por RP-HPLC preparativa, produciendo el producto deseado.

Procedimiento General 13 (PG13): Formación de Amida con ácidos carbónicos

Una mezcla de 0,62 mmol de ácido carbónico, 0,93 mmol de TBTU y 1,2 mmol de base de Huenig en 2 ml de DMSO se agita durante 5 min. Se añaden 0,31 mmol de material de partida y la mezcla resultante se agita a TA durante una noche. La purificación se realiza por RP-HPLC preparativa, produciendo, después de la evaporación del disolvente, el producto deseado.

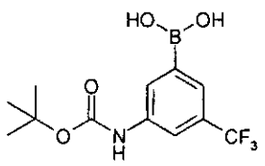
Intermedios A:

A-1) 5-Yodo-3-trifluorometil-piridin-2-ilamina



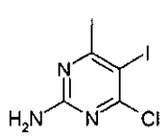
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 5,0 g (31 mmol) de 3-trifluoro-2-amino piridina y 6,9 g (31 mmol) de NIS. Rendimiento después de la precipitación de la mezcla de reacción: 6,78 g (76%).

A-2) Ácido 5-trifluorometil-3-(*terc*-butil-oxicarbonil)amino-fenilborónico



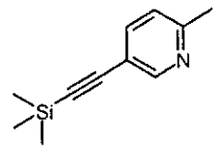
Una solución de 1,5 g (4,4 mmol) de 3-bromo-5-trifluorometil-*terc*-butil-oxicarbonil-anilina y 1,2 ml (5,3 mmol) de triisopropilborato en una mezcla de 4,5 ml de THF seco/10,5 ml de tolueno seco se enfría a -70°C en una atmósfera inerte antes de añadir gota a gota 6,9 ml de una solución de n-BuLi 1,6 M en hexanos (bomba de jeringa) durante 30 min. La mezcla de reacción se agita durante 50 min más a -70°C antes de dejar que la temperatura de reacción alcance -20°C. Después de la adición de 4,4 ml de HCl 2,2 M, la mezcla de reacción calienta a TA y las fases se separan. La fase orgánica se diluye con acetato de etilo, se lava con salmuera (pH de la fase acuosa < 3), se seca sobre Na_2SO_4, se retira por filtración y el disolvente se retira a presión reducida. El producto se purifica por PR-HPLC usando un gradiente de ACN/agua. Rendimiento: 635 mg (47%)

A-3) 4-Cloro-5-metil-6-metil-pirimidin-2-ilamina



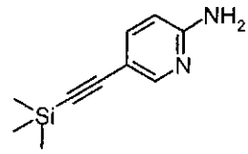
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 10 g (70 mmol) de 2-amino-4-cloro-6-metilpiridina y 16 g de NIS (70 mmol). Rendimiento: 18 g (95%). El producto en bruto se usa en las siguientes etapas sin purificación adicional.

A-4) 2-Metil-5-trimetilsilaniletinil-piridina



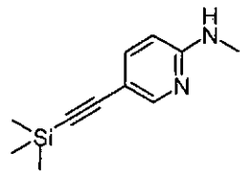
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 2,0 g (11,6 mmol) de 5-bromo-2-metil-piridina y 2,3 ml (16,3 mmol) de 1-trimetilsilil-etino usando 68 mg (0,36 mmol) de CuI, 305 mg (1,2 mmol) de trifenilfosfina, 213 mg (0,30 mmol) de $PdCl_2(PPh_3)_2$ y 18 ml (127 mmol) de trietilamina en 18 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y la fase orgánica se extrae con agua y salmuera. El producto se purifica por cromatografía sobre gel de sílice usando un gradiente de hexano/acetato de etilo. Rendimiento: 1,5 g (68%).

A-5) 5-Trimetilsilaniletinil-piridin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 5,0 g (28,9 mmol) de 5-bromo-2-amino-piridina y 5,7 ml (40,5 mmol) de 1-trimetilsilil-etino usando 168 mg (0,88 mmol) de CuI, 758 mg (2,9 mmol) de trifenilfosfina, 533 mg (0,76 mmol) de $PdCl_2(PPh_3)_2$ y 40 ml (288 mmol) de trietilamina en 40 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y pequeñas cantidades de ciclohexano y la fase orgánica se extrae con agua y salmuera. El producto se purifica por cromatografía sobre gel de sílice usando hexano/acetato de etilo (10/1 v/v). Rendimiento: 5,0 g (91%).

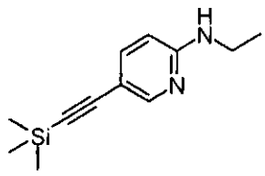
A-6) Metil-(5-trimetilsilaniletinil-piridin-2-il)-amina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 4,3 g (23,0 mmol) de 5-bromo-2-amino-piridina y 4,5 ml (32,2 mmol) de 1-trimetilsilil-etino usando 134 mg (0,71 mmol) de CuI, 601 mg (2,3 mmol) de trifenilfosfina, 420 mg (0,60 mmol) de $PdCl_2(PPh_3)_2$ y 32 ml (101 mmol) de trietilamina en 40 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y pequeñas cantidades de ciclohexano y la fase orgánica

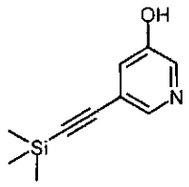
se extrae con agua y salmuera. El producto se purifica por cromatografía sobre gel de sílice usando un gradiente de hexano/acetato de etilo. Rendimiento: 4,0 g (85%).

A-7) Etil-(5-trimetilsilaniletinil-piridin-2-il)-amina



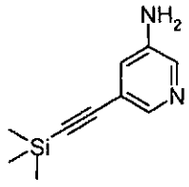
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 909 g (4,5 mmol) de 5-bromo-2-etilamino-piridina y 0,89 ml (6,3 mmol) de 1-trimetil-silil-etino usando 26 mg (0,13 mmol) de CuI, 118 mg (0,45 mmol) de trifenilfosfina, 82 mg (0,12 mmol) de $PdCl_2(PPh_3)_2$ y 6,3 ml (45,0 mmol) de trietilamina en 7 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y pequeñas cantidades de ciclohexano y la fase orgánica se extrae con agua y salmuera. El producto se purifica por cromatografía sobre gel de sílice usando un gradiente de hexano/acetato de etilo. Rendimiento: 980 mg (99%).

A-8) 5-Trimetilsilaniletinil-piridin-3-ol



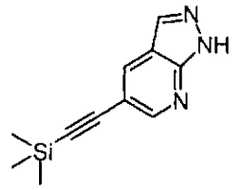
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 2,0 g (11,6 mmol) de 5-bromo-3-hidroxi-piridina y 2,3 ml (16,2 mmol) de 1-trimetilsilil-etino usando 66 mg (0,3 mmol) de CuI, 303 mg (1,2 mmol) de trifenilfosfina, 243 mg (0,3 mmol) de $PdCl_2(PPh_3)_2$ y 19 ml (139 mmol) de trietilamina en 20 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y pequeñas cantidades de ciclohexano y la fase orgánica se extrae con agua y salmuera. El producto se purifica por cromotografía sobre gel de sílice usando un gradiente de DCM/MeOH. Rendimiento: 2,0 g (91%).

A-9) 5-Trimetilsilaniletinil-piridin-3-ilamina



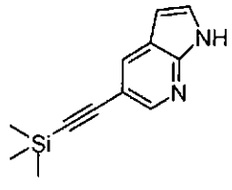
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 2,0 g (11,6 mmol) de 5-bromo-3-amino-piridina y 2,3 ml (16,2 mmol) de 1-trimetilsilil-etino usando 66 mg (0,3 mmol) de CuI, 303 mg (1,2 mmol) de trifenilfosfina, 243 mg (0,3 mmol) de $PdCl_2(PPh_3)_2$ y 19 ml (139 mmol) de trietilamina en 20 ml de THF seco. Para el tratamiento, la mezcla de reacción se diluye con acetato de etilo y pequeñas cantidades de ciclohexano y la fase orgánica se extrae con agua y salmuera. El producto se purifica por cromotografía sobre gel de sílice usando un gradiente de DCM/MeOH. El producto precipitó sobre la columna y posteriormente se extrae del gel de sílice con MeOH puro. Rendimiento: 2,0 g (91%).

A-10) 5-Trimetilsilaniletinil-1*H*-pirazolo[3,4-*b*]piridina



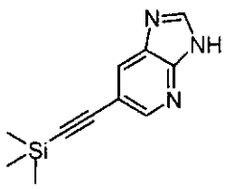
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,0 g (5,1 mmol) de 5-bromo-1H-pirazolo[4,5-b]piridina y 1,0 ml (7,1 mmol) de 1-trimetilsilil-etino usando 29 mg (0,15 mmol) de CuI, 133 mg (0,51 mmol) de trifenilfosfina, 106 mg (0,15 mmol) de $PdCl_2(PPh_3)_2$ y 8,4 ml (60,6 mmol) de trietilamina en 8 ml de THF seco. El precipitado formado se retira por filtración y el producto se purifica por RP-HPLC usando un gradiente de ACN/H_2O. Rendimiento: 542 mg (50%).

A-11) 5-Trimetilsilaniletinil-1*H*-pirrolo[2,3-*b*]piridina



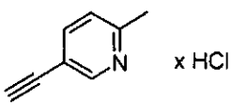
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 3,0 g (15,2 mmol) de 5-bromo-1H-pirrolo[2,3-b]piridina y 3,0 ml (21,3 mmol) de 1-trimetil-silil-etino usando 87 mg (0,46 mmol) de CuI, 400 mg (1,5 mmol) de trifenilfosfina, 312 mg (0,46 mmol) de $PdCl_2(PPh_3)_2$ y 25,4 ml (182 mmol) de trietilamina en 25 ml de THF seco. El precipitado formado se retira por filtración y el producto se purifica por cromatografía sobre gel de sílice usando un gradiente de DCM/MeOH. Rendimiento: 3,05 g (94%).

A-12) 6-Trimetilsilaniletinil-3*H*-imidazo[4,5-*b*]piridina



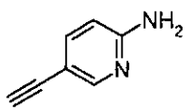
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,2 g (6,1 mmol) de 5-bromo-3H-imidazo[4,5-b]piridina y 1,2 ml (8,4 mmol) de 1-trimetilsilil-etino usando 34 mg (0,18 mmol) de CuI, 159 mg (0,61 mmol) de trifenilfosfina, 128 mg (0,18 mmol) de $PdCl_2(PPh_3)_2$ y 10,1 ml (72,7 mmol) de trietilamina en 10 ml de THF seco. El precipitado formado se retira por filtración y el producto se purifica por RP-HPLC usando un gradiente de ACN/H_2O. Rendimiento: 606 mg (46%).

A-13) 5-Etinil-2-metil-piridina



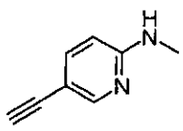
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 2,2 g (12 mmol) de 2-metil-5-trimetilsilaniletinil-piridin (A4) y 0,80 g (5,8 mmol) de K_2CO_3 en 13 ml de MeOH. El producto en bruto se purifica por cromatografía sobre gel de sílice usando un gradiente de ciclohexano/acetato de etilo. El producto se extrae de la fase orgánica con HCl 1 N y se aisla en forma del clorhidrato después de la liofilización. Rendimiento: 1,3 g (73%).

A-14) 5-Etinil-2-amino-piridina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 5,5 g (29 mmol) de 5-trimetilsilaniletinil-piridin-2-ilamina (A4) y 2,0 g (14 mmol) de K_2CO_3 en 30 ml de MeOH. El producto se purifica por cromatografía sobre gel de sílice usando un gradiente de hexano/acetato de etilo. Rendimiento: 2,9 g (85%).

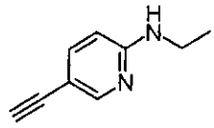
A-15) (5-Etinil-piridin-2-il)-metil-amina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 1,5 g (7,3 mmol) de metil-(5-trimetilsilaniletinil-piridin-2-il)-amina (A6) y

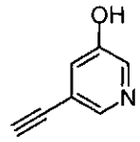
507 g (3,7 mmol) de K_2CO_3 en 10 ml de MeOH. Rendimiento: 698 mg (56%) después de la cromatografía sobre gel de sílice.

A-16) (5-Etinil-piridin-2-il)-etil-amina



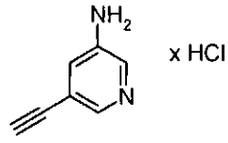
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 980 mg (4,5 mmol) de TMS-alquino y 310 mg (2,3 mmol) de K_2CO_3 en 6 ml de MeOH. Rendimiento: 388 mg (59%) después de la cromatografía sobre gel de sílice.

A-17) 5-Etinil-piridin-3-ol



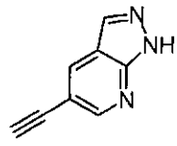
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 2,0 mg (10,5 mmol) de TMS-alquino y 722 mg (5,2 mmol) de K_2CO_3 en 10 ml de MeOH. Rendimiento: 804 mg (49%) después de la cromatografía sobre gel de sílice.

A-18) 5-Etinil-piridin-3-ilamina



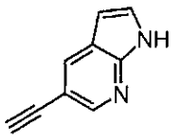
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 2,0 mg (11 mmol) de TMS-alquino y 722 mg (5,2 mmol) de K_2CO_3 en 10 ml de MeOH. Rendimiento: 1,2 g (74%) después de la cromatografía sobre gel de sílice y la precipitación en dioxano/HCl.

A-19) 5-Etinil-1*H*-pirazolo[3,4-*b*]piridina



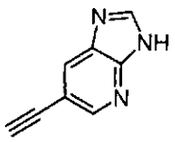
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 542 mg (2,5 mmol) de TMS-alquino y 174 mg (1,3 mmol) de K_2CO_3 en 6 ml de MeOH. Rendimiento: 330 mg (92%) después de la extracción.

A-20) 5-Etinil-1*H*-pirrolo[2,3-*b*]piridina



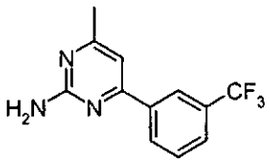
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 3,1 mg (14 mmol) de TMS-alquino y 983 mg (7,1 mmol) de K_2CO_3 en 15 ml de MeOH. Rendimiento: 1,2 mg (61%) después de la cromatografía sobre gel de sílice.

A-21) 6-Etinil-3*H*-imidazo[4,5-*b*]piridina



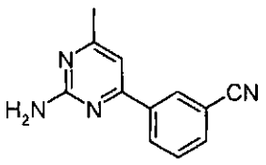
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 706 mg (3,3 mmol) de TMS-alquino y 227 mg (1,6 mmol) de K_2CO_3 en 6 ml de MeOH. Rendimiento: 491 mg (94%) después de la extracción.

A-22) 4-metil-6-(3-trifluorometil-fenil)-pirimidin-2-ilamina



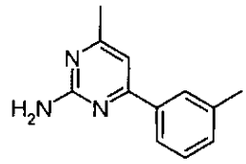
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (14 mmol) de 2-amino-4-cloro-6-metil pirimidina y 3,4 g (18 mmol) de ácido 3-trifluorometil-fenil borónico. Rendimiento después de la extracción: 5,0 g (99%).

A-23) 4-metil-6-(3-ciano-fenil)-pirimidin-2-ilamina



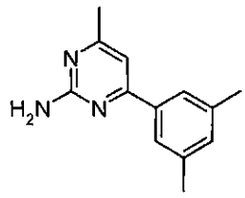
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (14 mmol) de 2-amino-4-cloro-6-metil pirimidina y 2,7 g (18 mmol) de ácido 3-ciano-fenil borónico. Rendimiento después de la extracción y la cristalización en éter dietílico: 3,2 g (100%).

A-24) 4-metil-6-(3-metil-fenil)-pirimidin-2-ilamina



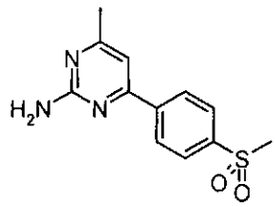
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (14 mmol) de 2-amino-4-cloro-6-metilpirimidina y 2,5 g (18 mmol) de ácido 3-ciano-fenil borónico. Rendimiento después de la extracción y la recristalización en éter dietílico: 4,1 g (al 100%, pureza de aproximadamente 70%).

A-25) 4-metil-6-(3,5-dimetil-fenil)-pirimidin-2-ilamina



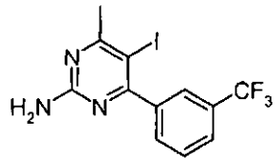
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (14 mmol) de 2-amino-4-cloro-6-metil pirimidina y 2,7 g (18 mmol) de ácido 3,5-dimetil-fenil borónico. Rendimiento después de la extracción y la cristalización en éter dietílico: 3,2 g (al 75%, pureza de aproximadamente 70%).

A-26) 4-metil-6-(4-metanosulfonil-fenil)-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 (A) partiendo de 1,5 g (10 mmol) de 2-amino-4-cloro-6-metil pirimidina y 2,7 g (14 mmol) de ácido 4-sulfonil-fenil borónico. Después del tratamiento del producto precipitado de éter dietílico, se obtienen 2,3 g (75%) del producto deseado.

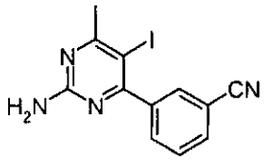
A-27) 5-Yodo-4-metil-6-(3-trifluorometil-fenil)-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 5,0 g (14 mmol) de 4-metil-6-(3-trifluorometil-fenil)-pirimidin-2-ilamina y

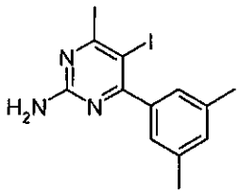
3,3 g (15 mmol) de NIS. Rendimiento después de la cromatografía sobre gel de sílice con DCM/MeOH: 3,8 g (73%).

A-28) 5-Yodo-4-metil-6-(3-ciano-fenil)-pirimidin-2-ilamina



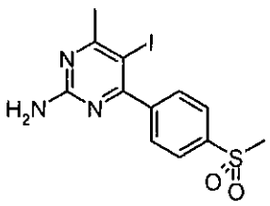
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 3,2 g (12 mmol) de 4-metil-6-(3-ciano-fenil)-pirimidin-2-ilamina y 2,8 g (13 mmol) de NIS. Rendimiento después de la cromatografía sobre gel de sílice con DCM/MeOH: 3,5 g (78%).

A-29) 5-Yodo-4-metil-6-(3,5-dimetil-fenil)-pirimidin-2-ilamina



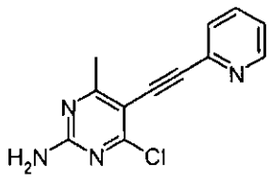
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 3,2 g (11 mmol) de 4-metil-6-(3,5-dimetil-fenil)-pirimidin-2-ilamina y 2,5 g (11 mmol) de NIS. Rendimiento después de la cromatografía sobre gel de sílice con DCM/MeOH: 1,1 g (31%).

A-30) 5-Yodo-4-metil-6-(4-metanosulfonil-fenil)-pirimidin-2-ilamina



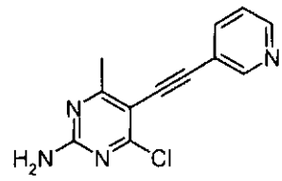
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 2,3 g (7,9 mmol) de 4-metil-6-(4-sulfonil-fenil)-pirimidin-2-ilamina y 1,8 g (7,9 mmol) de NIS. Rendimiento después de la precipitación de la mezcla de reacción con agua: 3,1 g (91%).

A-31) 4-Cloro-6-metil-5-piridin-2-iletinil-pirimidin-2-ilamina



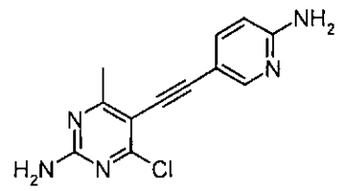
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,5 g (5,6 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 0,84 ml (8,4 mmol) de 2-etinil-piridina usando 106 mg (0,57 mmol) de CuI, 390 g (0,56 mmol) de $PdCl_2(PPh_3)_2$ y 7,8 ml (56 mmol) de trietilamina en 10 ml de DMF seca. Se añaden cantidades adicionales después de un tiempo de reacción de 24 h y 48 h, respectivamente. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por cromatografía sobre gel de sílice usando un gradiente de DCM/MeOH. Rendimiento: 2,0 g (al 100%, pureza de aproximadamente 70%).

A-32) 4-Cloro-6-metil-5-piridin-3-iletinil-pirimidin-2-ilamina



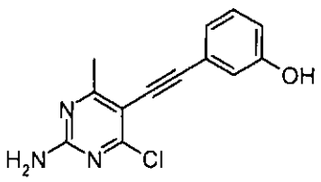
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 4,0 g (15 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 2,0 g (19 mmol) de 3-etinil-piridina usando 282 mg (1,5 mmol) de CuI, 1,0 g (1,5 mmol) de $PdCl_2(PPh_3)_2$ y 21 ml (148 mmol) de trietilamina en 200 ml de DMF seca. Para el tratamiento, la mezcla de reacción se concentra al vacío antes de que se añada agua. El precipitado se recoge, se seca a 40°C y se cristaliza en $MeOH/H_2O$. Rendimiento: 3,0 g (83%).

A-33) 5-(6-Amino-piridin-3-iletinil)-4-cloro-6-metiol-pirimidin-2-ilamina



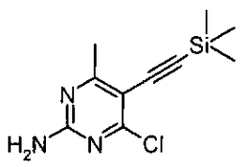
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,5 g (5,7 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 1,7 g (15 mmol) de 2-amino-5-etinil-piridina (PG15) usando 106 mg (0,56 mmol) de CuI, 390 mg (0,56 mmol) de $PdCl_2(PPh_3)_2$ y 8 ml (55 mmol) de trietilamina en 12 ml de DMF seca. Para el tratamiento, a la mezcla de reacción se le añade agua. El precipitado se recoge, se seca a 40°C y se cristaliza de nuevo en MeOH. Rendimiento: 1,5 g (al 83%, pureza de aproximadamente 80%).

A-34) 3-(2-Amino-4-cloro-6-metil-pirimidin-5-iletinil)-fenol



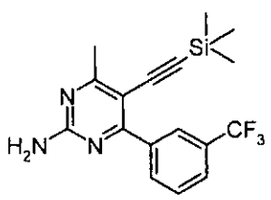
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,5 g (5,7 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 986 ml (8,4 mmol) de 3-etinil-fenol usando 106 mg (0,56 mmol) de CuI, 390 mg (0,56 mmol) de $PdCl_2(PPh_3)_2$ y 8 ml (55 mmol) de trietilamina en 12 ml de DMF seca. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por cromatografía sobre gel de sílice (gradiente de DCM/MeOH) y posteriormente RP-HPLC (gradiente de ACN/H_2O). Rendimiento: 419 mg (29%).

A-35) 4-Cloro-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina



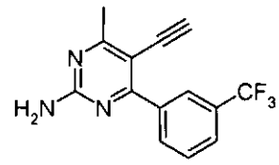
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 5,0 g (19 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 3,6 ml (26 mmol) de trimetilsililetino usando 352 mg (1,9 mmol) de CuI, 485 mg de trimetilfosfina (1,9 mmol), 1,3 g (1,9 mmol) de $PdCl_2(PPh_3)$ y 26 ml (185 mmol) de trietilamina en 100 ml de DMF seca. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por RP-MPLC (gradiente de ACN/H_2O). Rendimiento: 1,6 g (38%).

A-36) 4-(3-Trifluorometil-fenil)-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina



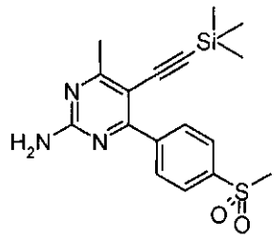
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,7 g (7,0 mmol) de 4-cloro-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina (A-35) y 2,7 g (14 mmol) de ácido 3-trifluorofenilborónico usando 571 mg (0,70 mmol) de $PdCl_2(dppf)_2$ y 3,4 g (11 mmol) de Cs_2CO_3 en una mezcla de 36 ml de THF/3,3 ml de agua. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por cromatografía sobre gel de sílice (gradiente de DCM/MeOH). Rendimiento: 1,23 g (50%).

A-37) 5-Etinil-4-(3-trifluorometil-fenil)-6-metil-pirimidin-2-ilamina



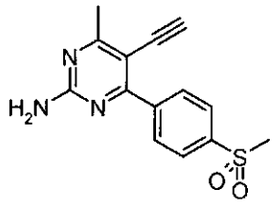
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 1,2 g (3,5 mmol) de 4-(3-trifluorometil-fenil)-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina (A-36) y 120 mg (0,87 mmol) de carbonato potásico en 5 ml de MeOH. Después de la agitación durante 2 h a TA, la mezcla de reacción se diluye con DCM y la fase orgánica se extrae con agua. La fase orgánica se seca sobre NGP_2SO_4 y el disolvente se retira al vacío. Rendimiento: 523 mg (54%).

A-38) 4-(4-Metanosulfonil-fenil)-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 3,0 g (7,7 mmol) de 5-yodo-4-metil-6-(4-metanosulfonil-fenil)-pirimidin-2-ilamina (A-33) y 1,6 ml (12 mmol) de trimetilsililetino usando 147 mg (0,77 mmol) de CuI, 541 mg (0,77 mmol) de $PdCl_2(PPh_3)_2$ y 11 ml (7,7 mmol) de trietilamina en 18 ml de DMF seca. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por cromatografía sobre gel de sílice (gradiente de DCM/MeOH). Rendimiento: 2,45 g (al 71%, pureza de aproximadamente 80%).

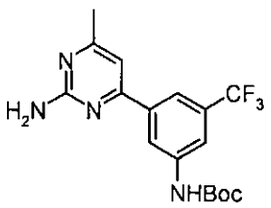
A-39) 5-Etinil-4-(4-metanosulfonil-fenil)-6-metil-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG3 partiendo de 2,7 g (6,0 mmol) de 4-(4-metanosulfonil-fenil)-6-metil-5-trimetilsilaniletinil-pirimidin-2-ilamina (A-36) y 415 mg (3,0 mmol) de carbonato potásico en 40 ml de MeOH. Después de la agitación durante 2 h a 0°C, el producto precipitado se retira por filtración y se seca durante una noche a 40°C. El producto

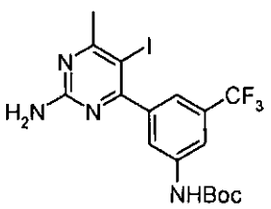
se trata con agua, se retira por filtración y se seca de nuevo. Rendimiento: 1,8 g (83%).

A-40) Éster *terc*-butílico del ácido [3-(2-amino-6-metil-pirimidin-4-il)-5-trifluorometil-fenil]-carbámico



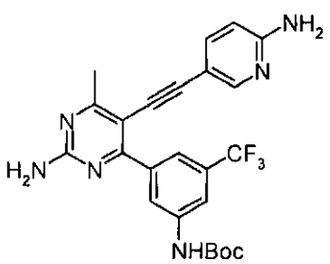
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 (A) partiendo de 215 mg (1,5 mmol) de 2-amino-4-cloro-6-metil pirimidina y 2,7 g (14 mmol) de ácido 5-trifluorometil-3-(*terc*-butil-oxicarbonil)aminofenil borónico (PG2). El producto se precipita de la mezcla de reacción por adición de agua. Rendimiento después del secado a 40°C: 550 mg (100%).

A-41) Éster *terc*-butílico del ácido [3-(2-amino-5-yodo-6-metil-pirimidin-4-il)-5-trifluorometil-fenil]-carbámico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 550 mg (1,5 mmol) de éster *terc*-butílico del ácido [3-(2-amino-6-metil-pirimidin-4-il)-5-trifluorometil-fenil]-carbámico (PG40) y 336 mg (1,5 mmol) de NIS. Rendimiento: 733 mg (99%).

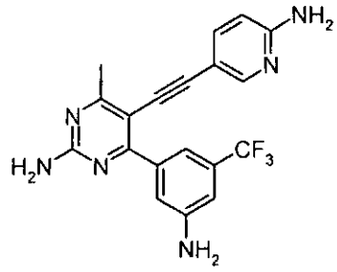
A-42) Éster *terc*-butílico del ácido {3-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-5-trifluorometil-fenil}-carbámico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 733 mg (1,5 mmol) de éster *terc*-butílico del ácido [3-(2-amino-5-yodo-6-metil-pirimidin-4-il)-5-trifluorometil-fenil]-carbámico (A-41) y 262 mg (2,2 mmol) de

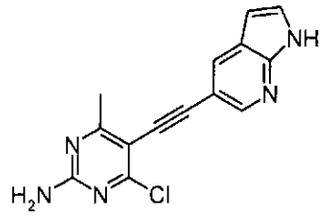
2-amino-5-etinil-piridina (A-15) usando 28 mg (0,15 mmol) de CuI, 104 mg (0,15 mmol) de $PdCl_2(PPh_3)_2$ y 2 ml (15 mmol) de trietilamina en 14 ml de DMF seca. Para el tratamiento, el disolvente se retira al vacío y el producto se purifica por cromatografía sobre gel de sílice (gradiente de DCM/MeOH). Rendimiento: 632 mg (88%).

A-43) 5-(6-Amino-piridin-3-iletinil)-4-(3-amino-5-trifluorometil-fenil)-6-metil-pirimidin-2-ilamina



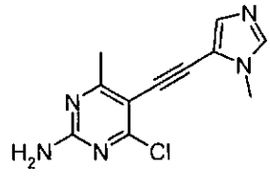
El compuesto del título se sintetiza partiendo de 632 mg (1,3 mmol) de éster *terc*-butílico del ácido {3-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-5-trifluorometil-fenil}-carbámico (A-42) por tratamiento con una solución de HCl 4 M en dioxano. Después de que se complete la reacción, el disolvente se retira al vacío seguido de extracción con DCM y una solución acuosa saturada de $NaHCO_3$. Rendimiento: 310 mg (62%).

A-44) 3-(2-Amino-4-cloro-6-metil-pirimidin-5-iletinil)-fenol



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 500 mg (1,9 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (PG3) y 396 mg (2,8 mmol) de 5-etinil-1*H*-pirrolo[2,3-*b*]piridina (A-20) usando 35 mg (0,19 mmol) de CuI, 130 mg (0,19 mmol) de $PdCl_2(PPh_3)_2$ y 2,6 ml (19 mmol) de trietilamina en 6 ml de DMF seca. El producto precipita de la mezcla de reacción, se retira por filtración y se lava con DMF. Rendimiento: 436 mg (75%).

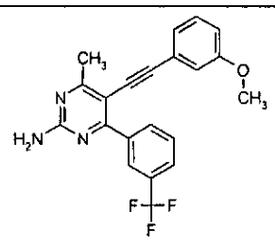
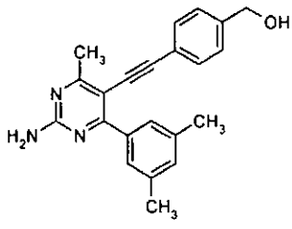
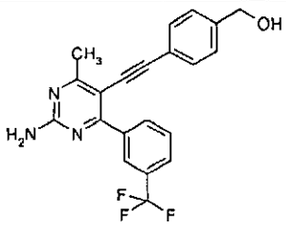
A-45) 4-Cloro-6-metil-5-(3-metil-3*H*-imidazol-4-iletinil)-pirimidin-2-ilamina

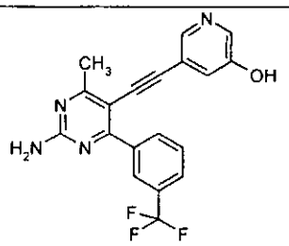
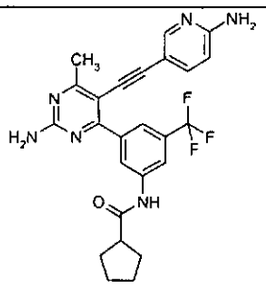
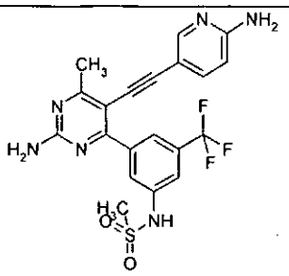
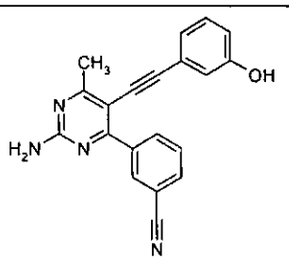
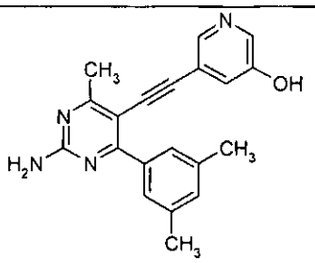


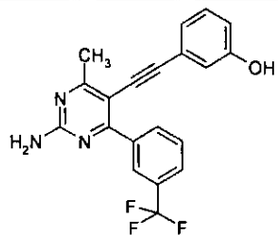
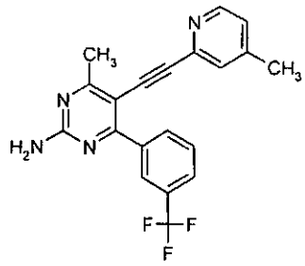
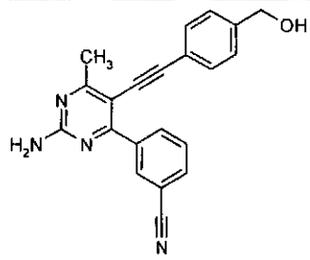
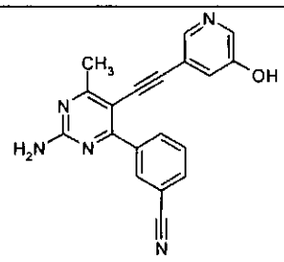
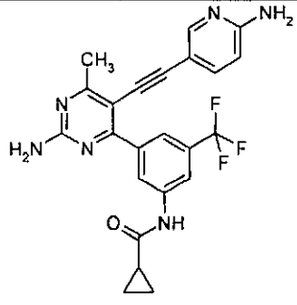
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,4 g (5,3 mmol) de 4-cloro-5-yodo-6-metil-pirimidin-2-ilamina (A-3) y 900 mg (8,5 mmol) de 5-etinil-1-metil-1H-imidazol usando 10 mg (0,05 mmol) de CuI, 112 mg (0,03 mmol) de $PdCl_2(PPh_3)_2$, 5,3 ml (5,3 mmol) de 9-metoxi-9-BBN y 1,3 ml (9,5 mmol) de trietilamina en 125 ml de acetonitrilo desgasificado y seco. El producto precipita de la mezcla de reacción y se retira por filtración. Rendimiento: 780 mg (54%).

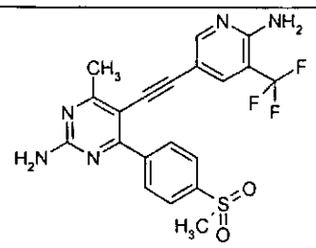
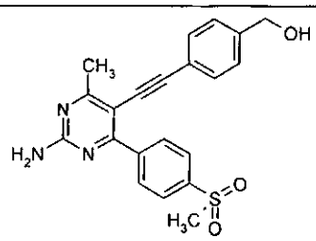
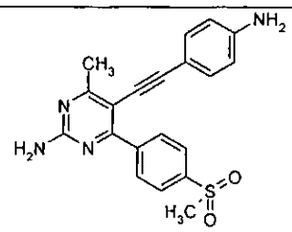
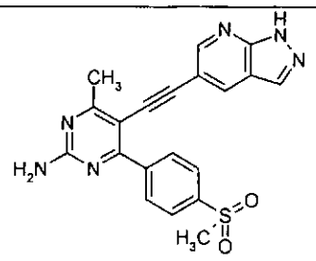
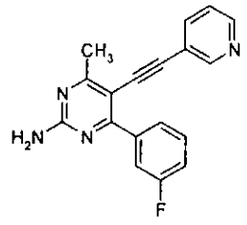
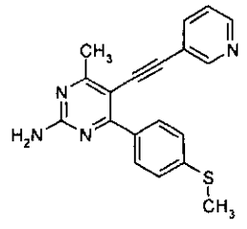
Ejemplos 1-86

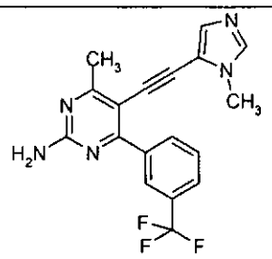
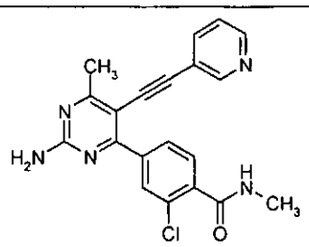
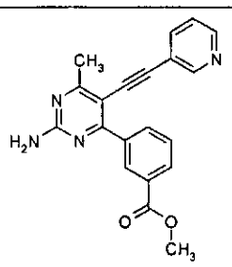
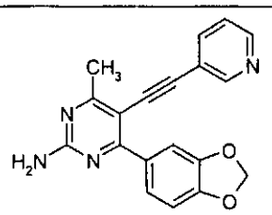
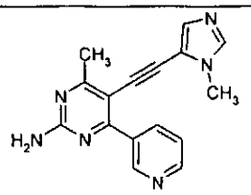
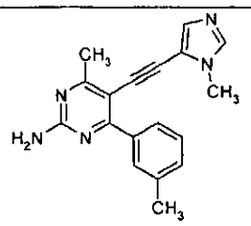
Los Ejemplos 1 a 86 se sintetizan de acuerdo con los procedimientos generales PG2 (reacción Sonogashira), PG4 (acoplamiento de Suzuki) o PG6 (desplazamiento nucleófilo) como se ha indicado anteriormente. Los haluros apropiados requeridos para la síntesis pueden deducirse a partir de la tabla de los ejemplos.

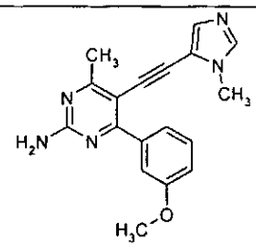
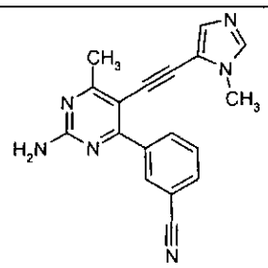
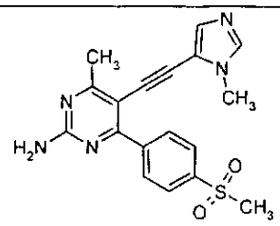
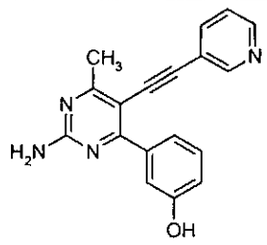
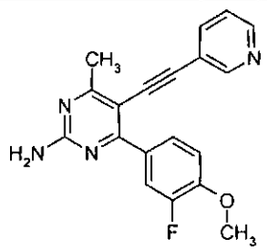
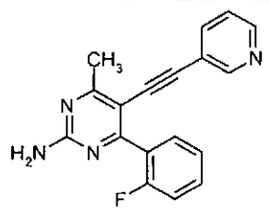
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
1	A-37		384	2,40
2	A-29		344	1,98
3	A-27		384	2,06

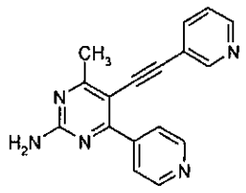
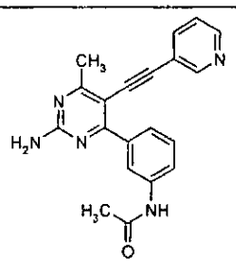
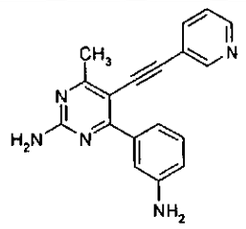
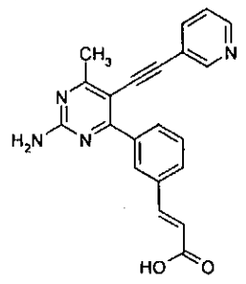
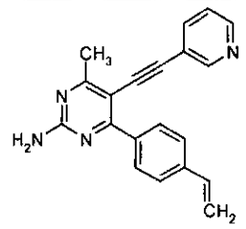
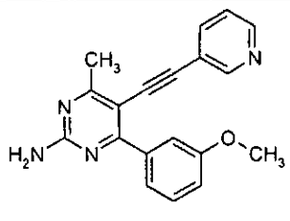
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
4	A-27		371	1,32
5	A-43		481	1,04
6	A-43		463	1,36
7	A-28		327	1,67
8	A-29		331	1,22

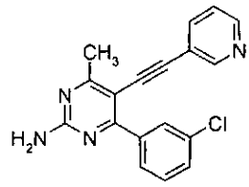
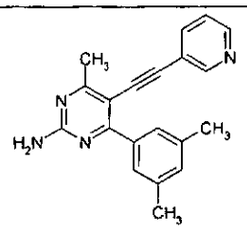
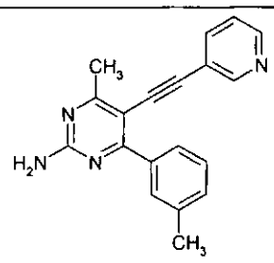
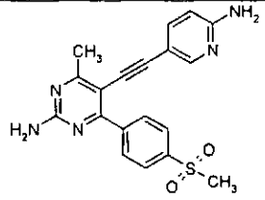
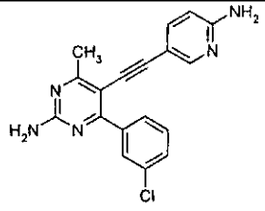
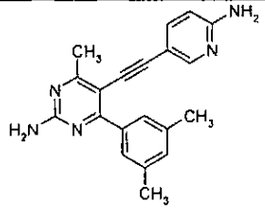
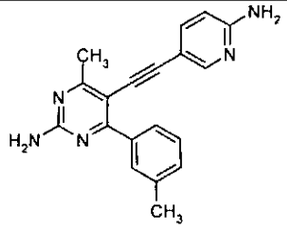
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
9	A-27		370	1,90
10	A-37		369	2,14
11	A-28		341	1,79
12	A-28		328	1,11
13	A-43		453	1,87

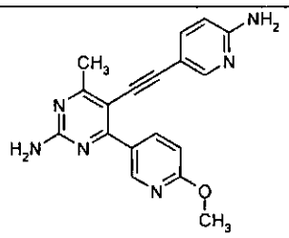
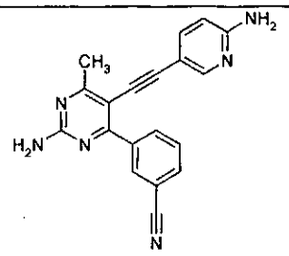
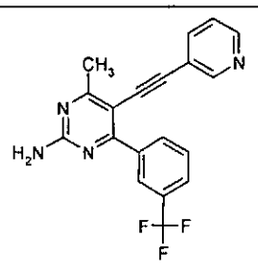
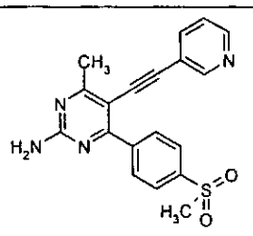
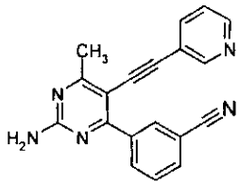
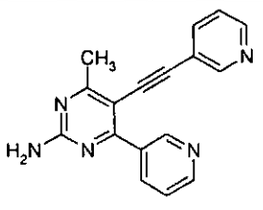
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
14	A-39		448	1,84
15	A-30		394	1,66
16	A-39		379	1,69
17	A-30		405	1,59
18	A-32		305	1,06
19	A-32		333	1,10

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
20	A-45		358	1,04
21	A-32		378/379	0,94
22	A-32		345	1,05
23	A-32		331	1,03
24	A-45		291	0,80
25	A-45		304	0,98

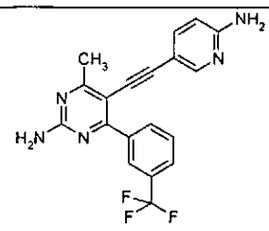
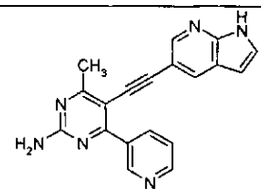
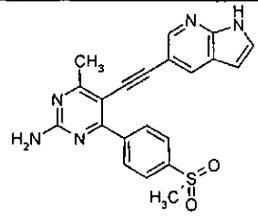
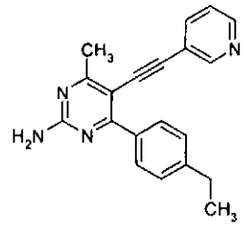
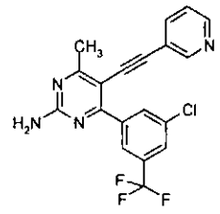
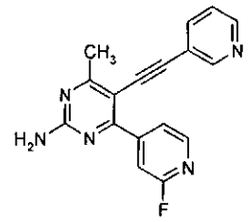
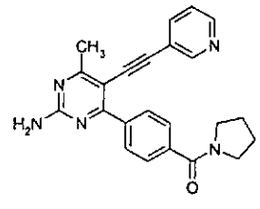
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
26	A-45		320	0,94
27	A-45		315	0,92
28	A-45		368	0,86
29	A-32		303	0,81
30	A-32		335	1,06
31	A-32		305	1,01

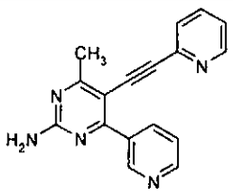
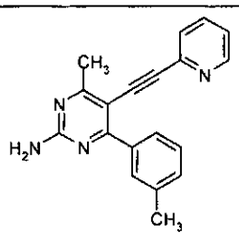
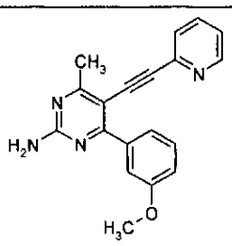
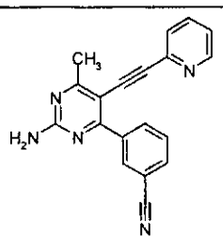
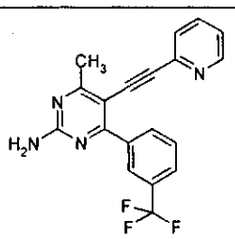
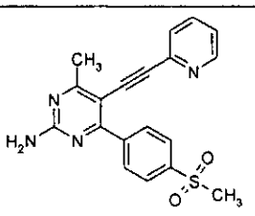
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
32	A-32		288	0,89
33	A-32		344	0,92
34	A-32		302	0,92
35	A-32		357	0,73
36	A-32		313	1,11
37	A-32		317	1,80

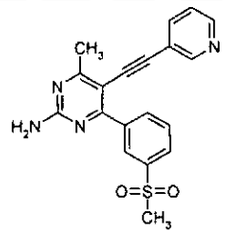
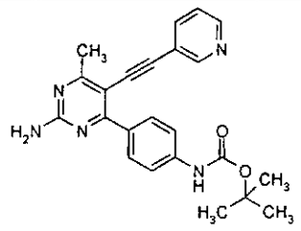
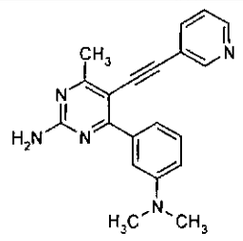
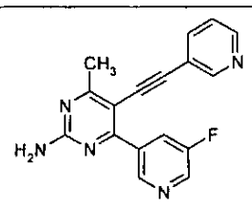
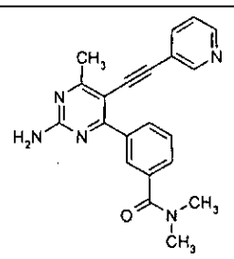
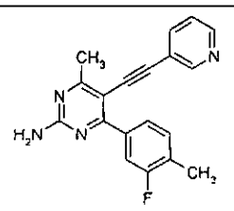
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
38	A-32		321	1,96
39	A-32		315	1,99
40	A-32		301	1,89
41	A-30		380	1,52
42	A-33		336/338	1,83
43	A-33		330	1,85
44	A-33		316	1,74

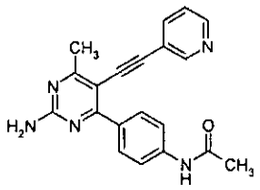
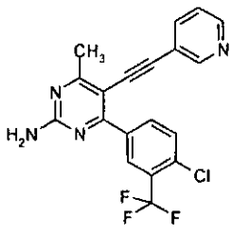
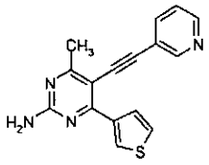
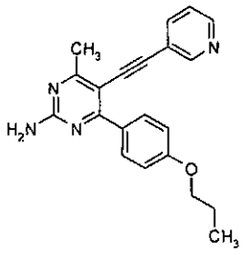
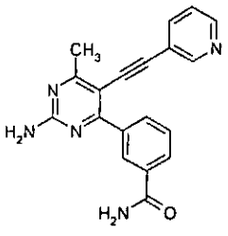
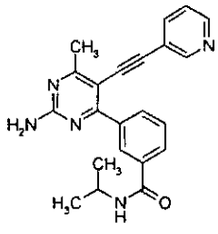
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
45	A-33		333	1,59
46	A-28		327	1,65
47	A-27		355	2,04
48	A-30		365	1,60
49	A-32		312	1,77
50	A-32		288	1,50

103

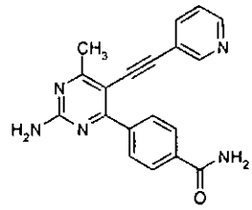
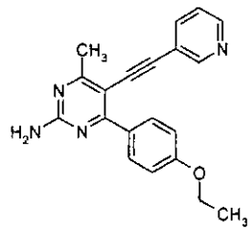
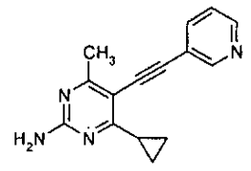
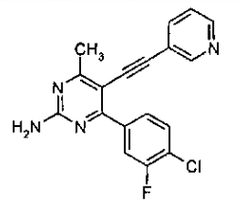
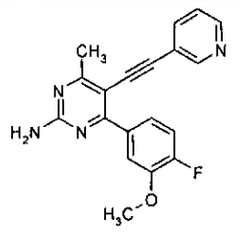
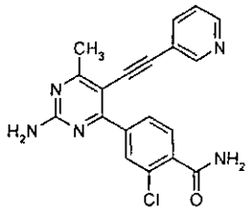
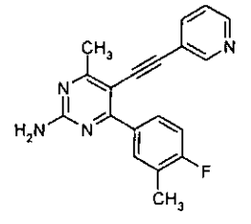
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
51	A-33		370	1,90
52	A-44		327	1,63
53	A-44		404	1,72
54	A-32		315	1,15
55	A-32		389/391	1,23
56	A-32		306	0,96
57	A-32		384	0,97

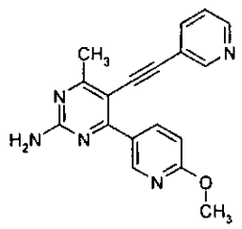
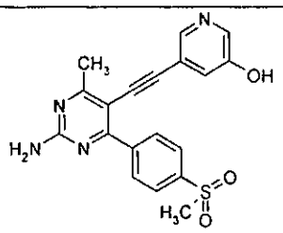
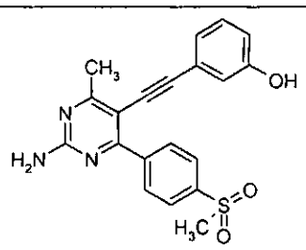
N°	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
58	A-31		288	0,89
59	A-31		301	1,09
60	A-31		317	1,04
61	A-31		312	1,02
62	A-31		355	1,14
63	A-31		365	2,92

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
64	A-32		365	0,95
65	A-32		402	1,12
66	A-32		330	1,06
67	A-32		306	0,95
68	A-32		358	0,93
69	A-32		319	1,11

N°	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
70	A-32		344	0,91
71	A-32		389/391	1,20
72	A-32		293	1,03
73	A-32		345	1,15
74	A-32		330	0,88
75	A-32		372	0,98

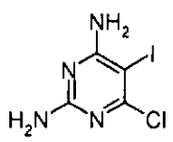
105

N°	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
76	A-32		330	0,87
77	A-32		331	1,09
78	A-32		251	1,00
79	A-32		339/341	1,14
80	A-32		335	1,06
81	A-32		364/366	0,90
82	A-32		319	1,10

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
83	A-32		318	0,99
84	A-30		381	0
85	A-30		380	1,50

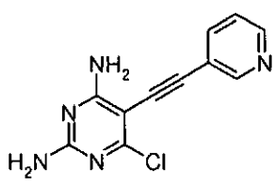
Intermedios B

B-1) 6-Cloro-5-yodo-pirimidina-2,4-diamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 25 g (173 mmol) de 6-cloro-pirimidina-2,4-diamino y 39 g (173 mmol) de NIS. Rendimiento después de la precipitación del producto en agua: 38,8 g (83%).

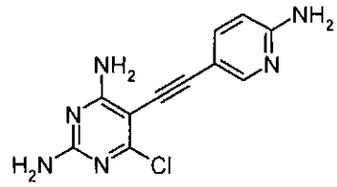
B-2) 6-Cloro-5-piridin-3-iletinil-pirimidina-2,4-diamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,0 g (3,7 mmol) de 6-cloro-5-yodo-pirimidina-2,4-diamina, 494 g (4,79 mmol) 3-etinilpiridina, 70 mg (0,37 mmol) de CuI, 259 mg (0,37 mmol) de

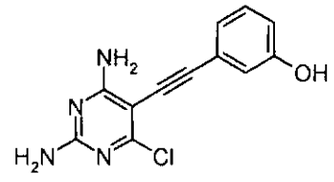
$PdCl_2(PPh_3)_2$ y 85 ml de trietilamina 60 ml de DMF seca. Rendimiento después de la purificación por cromatografía sobre gel de sílice: 800 mg (88%).

B-3) 5-(6-Amino-piridin-3-iletinil)-6-cloro-pirimidina-2,4-diamina



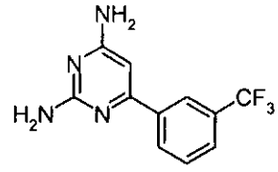
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 850 mg (3,1 mmol) de 6-cloro-5-yodo-pirimidina-2,4-diamina, 2,2 g (19 mmol) de 5-etinil-2-amino-piridina, 59 mg (0,31 mmol) de CuI, 218 mg (0,31 mmol) de $PdCl_2(PPh_3)_2$ y 21 ml de trietilamina en 25 ml de DMF seca. Rendimiento después de la purificación por RP-HPLC: 720 mg (88%).

B-4) 3-(2,4-Diamino-6-cloro-pirimidin-5-iletinil)-fenol



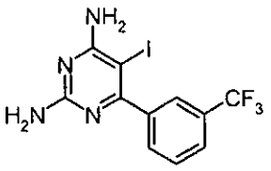
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 500 mg (1,8 mmol) de 6-cloro-5-yodo-pirimidina-2,4-diamina, 827 mg (7,0 mmol) de 3-etinil-fenol, 35 mg (0,19 mmol) de CuI, 129 mg (0,19 mmol) de $PdCl_2(PPh_3)_2$ y 4,1 ml de trietilamina en 4 ml de DMF seca. Rendimiento después de la purificación por RP-HPLC: 511 mg (100%).

B-5) 6-(3-Trifluorometil-fenil)-pirimidina-2,4-diamina



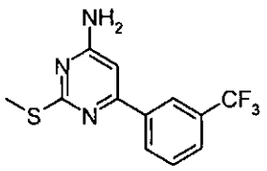
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 (A) partiendo de 1,3 g (9,0 mmol) de 6-cloro-pirimidina-2,4-diamina, 2,2 g (12 mmol) de ácido 3-trifluorofenil borónico, 260 mg de $Pd(PPh_3)_4$ y 7,7 ml de una solución acuosa de K_2CO_3 2 M y 26 ml de dimetoxietano. Rendimiento después de la cromatografía por RP-HPLC: 1,25 g (55%).

B-6) 5-Yodo-6-(3-trifluorometil-fenil)-pirimidina-2,4-diamina



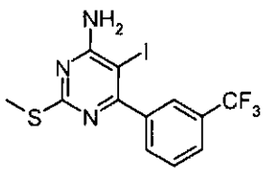
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 1,8 g (7,1 mmol) de 6-(3-trifluorometil-fenil)-piridimidina-2,4-diamina y 1,8 g (7,8 mmol) de NIS. Rendimiento: 2,0 g (74%).

B-7) 2-Metilsulfanil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina



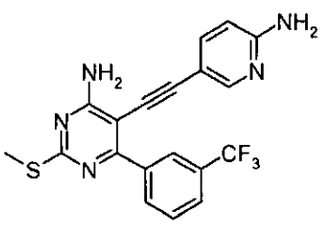
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 (C) partiendo de 1,0 g (5,7 mmol) de 6-cloro-2-metilsulfanil-pirimidin-4-ilamina, 1,4 g (7,4 mmol) de ácido 3-trifluorofenilborónico, 164 mg de $Pd(PPh_3)_4$ y 1,6 g (11 mmol) de K_2CO_3 en una mezcla de DME/agua (16/5 v/v). El disolvente se retira a presión reducida y el producto en bruto se separa entre agua y acetato de etilo. La fase orgánica se separa, se seca sobre NGP_2SO_4 y se retira por filtración. El disolvente se separa a presión reducida. El producto en bruto se emplea sin purificación adicional. Rendimiento: 2,14 g (100%).

B-8) 5-Yodo-2-metilsulfanil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina



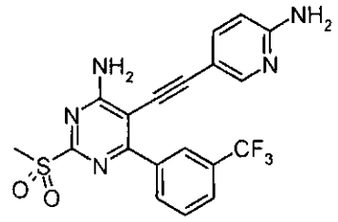
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 2,0 g (7,0 mmol) de 2-metilsulfanil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina y 1,6 g (7,0 mmol) de NIS. Rendimiento después de la precipitación: 1,9 g (66%).

B-9) 5-(6-Amino-piridin-3-iletinil)-2-metilsulfonil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 850 mg (2,1 mmol) de 5-yodo-2-metilsulfanil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina, 1,5 g (12,4 mmol) de 5-etinil-2-amino-piridina, 39 mg (0,21 mmol) de CuI, 145 mg (0,21 mmol) de $PdCl_2(PPh_3)_2$ y 2,9 ml de trietilamina en 15 ml de DMF seca. Rendimiento después de la purificación por RP-HPLC: 427 mg (52%).

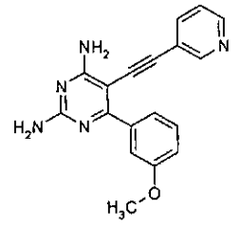
B-10) 5-(6-Amino-piridin-3-iletinil)-2-metanosulfonil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina

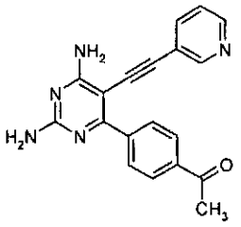
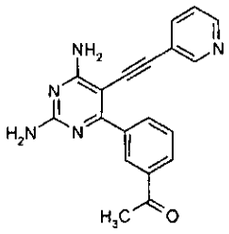
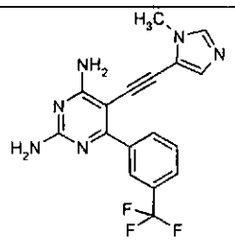
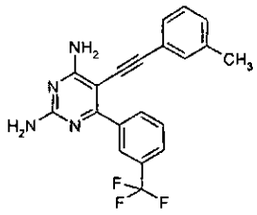
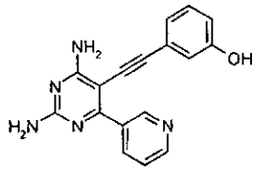
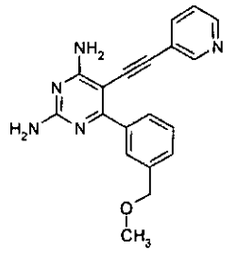


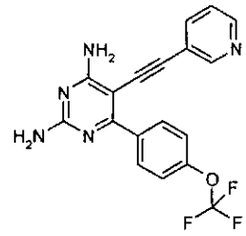
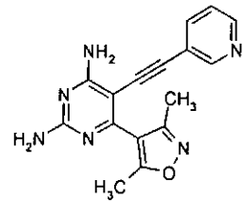
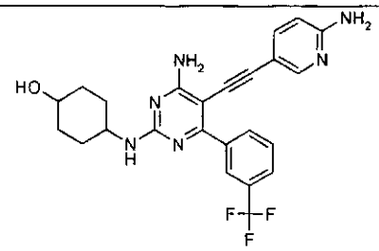
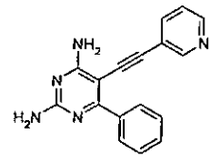
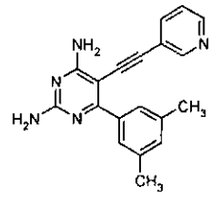
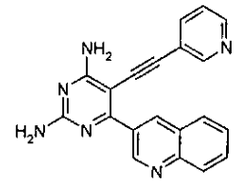
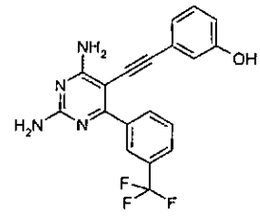
Se añade m-CPBA (859 mg, 5,0 mmol) a una solución de 1,0 g (2,5 mmol) de 5-(6-amino-piridin-3-iletinil)-2-metilsulfanil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina en 100 ml de DCM. Después de la agitación durante 48 h a TA, se añaden 215 mg más de m-CPBA y la mezcla se agita durante 24 h más. Se forma una mezcla de sulfona y sulfóxido. El precipitado se retira por filtración y se lava con DCM (510 mg). Se aísla más cantidad de producto a partir de la fase líquida después de la extracción con agua y la retirada del disolvente de la fase orgánica. Rendimiento: 1,1 g (100%).

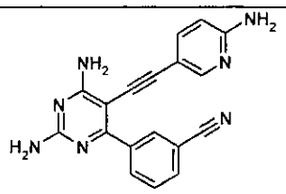
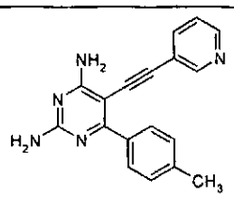
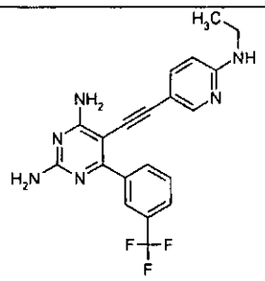
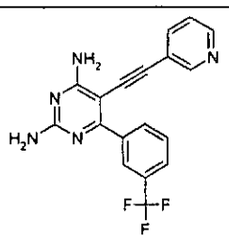
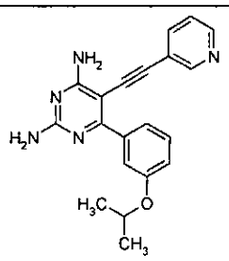
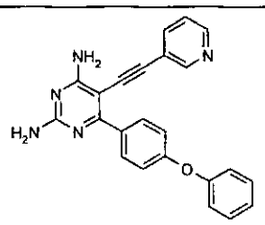
Ejemplos 86-139

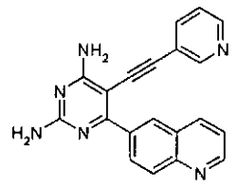
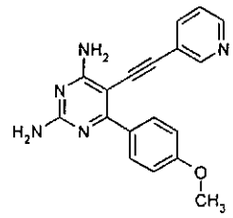
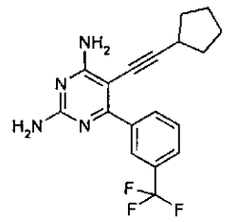
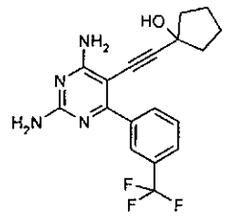
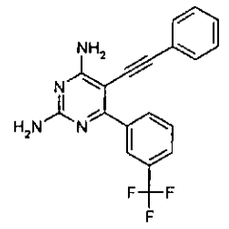
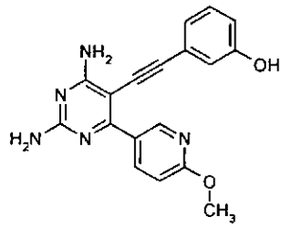
Los Ejemplos 86-139 se sintetizan de acuerdo con los procedimientos generales PG2 (reacción Sonogashira), PG4 (acoplamiento de Suzuki) o PG6 (desplazamiento nucleófilo) como se ha indicado anteriormente. Los haluros apropiados requeridos para la síntesis pueden deducirse a partir de la tabla de ejemplos.

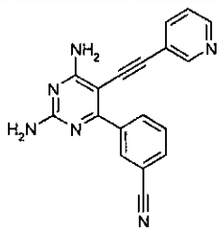
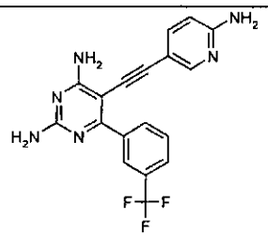
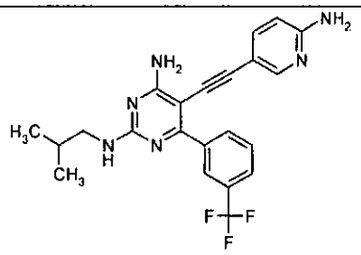
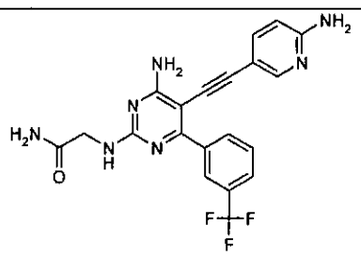
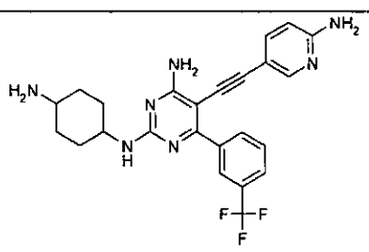
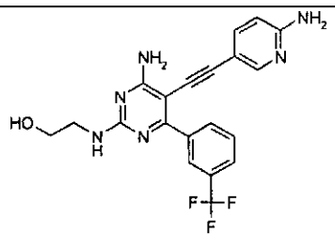
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
86	B-2		318	0,96

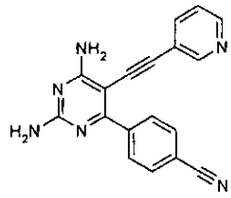
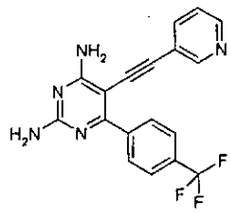
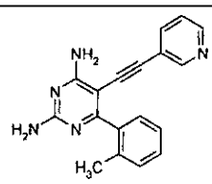
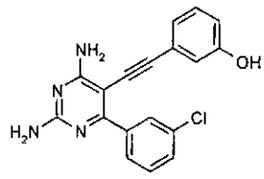
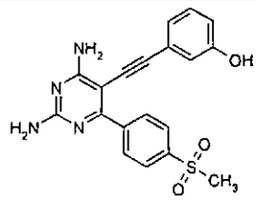
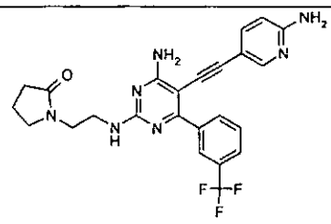
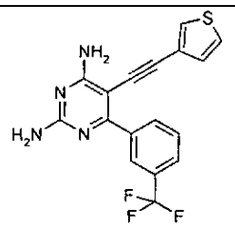
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
87	B-2		330	0,91
88	B-2		330	0,91
89	B-6		359	0,97
90	B-6		369	1,25
91	B-4		304	1,41
92	B-2		332	0,92

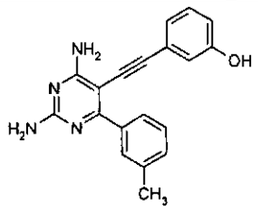
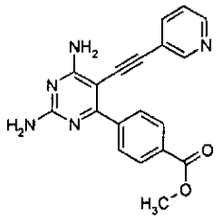
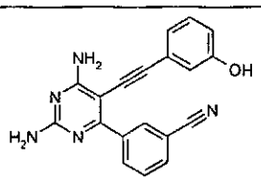
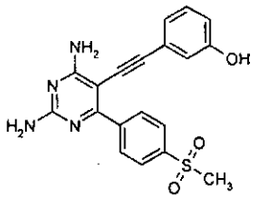
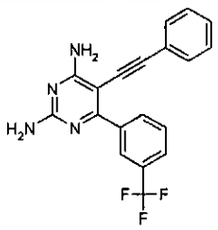
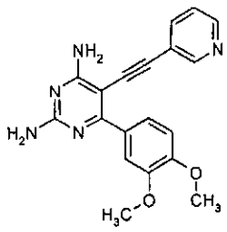
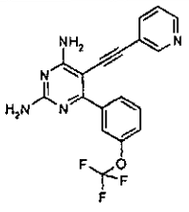
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
93	B-2		372	1,09
94	B-2		307	0,85
95	B-10		469	1,89
96	B-2		288	1,55
97	B-2		316	1,04
98	B-2		339	0,94
99	B-4		371	1,93

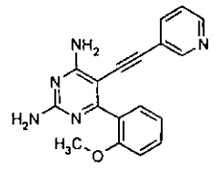
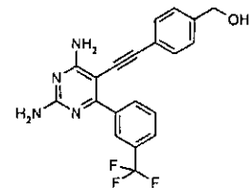
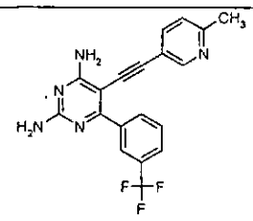
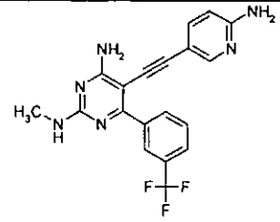
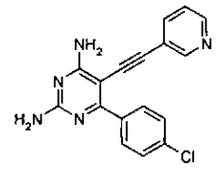
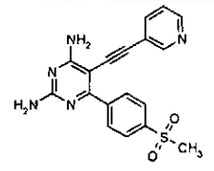
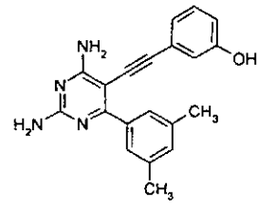
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
100	B-3		328	1,49
101	B-2		302	1,00
102	B-6		399	2,00
103	B-6		356	1,86
104	B-2		346	1,05
105	B-2		380	1,12

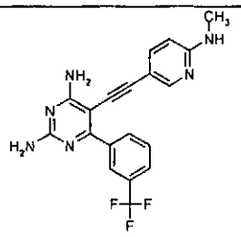
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
106	B-2		339	0,88
107	B-2		318	0,96
108	B-6		347	1,24
109	B-6		363	1,11
110	B-6		355	2,50
111	B-4		334	1,62

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
112	B-2		313	1,60
113	B-6		371	1,76
114	B-10		427	2,28
115	B-10		428	1,68
116	B-10		468	1,91
117	B-10		415	1,76

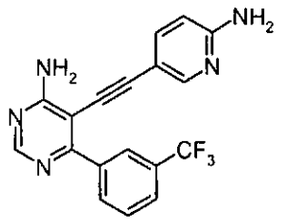
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
118	B-2		313	0,94
129	B-2		356	1,08
120	B-2		302	0,95
121	B-4		337	1,85
122	B-4		381	1,52
123	B-10		482	1,85
124	B-6		361	1,19

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
125	B-4		317	1,79
126	B-2		346	0,96
127	B-4		328	1,68
128	B-4		381	1,31
129	B-6		355	2,10
130	B-2		348	0,91
131	B-2		372	1,08

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
132	B-2		318	0,91
133	B-6		385	1,06
134	B-6		370	1,94
135	B-10		385	1,94
136	B-2		322/324	1,03
137	B-2		366	0,86
138	B-4		331	1,88

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
139	B-6		385	1,88

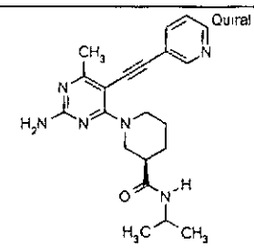
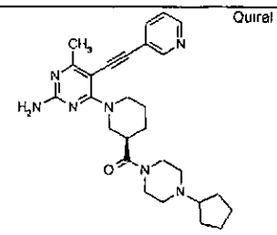
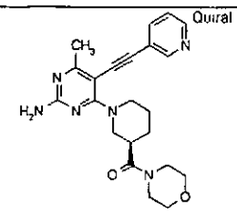
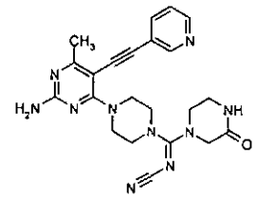
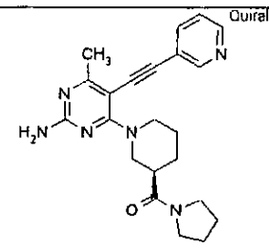
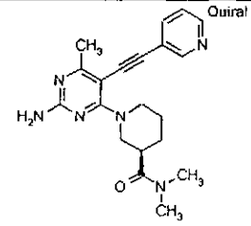
140) 5-(6-Amino-piridin-3-iletinil)-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina

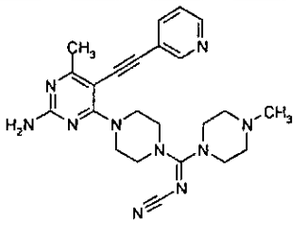
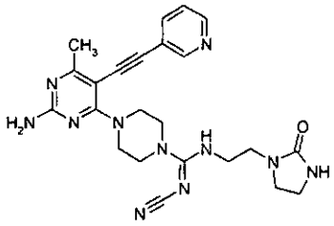
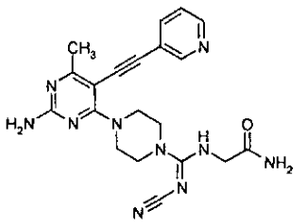
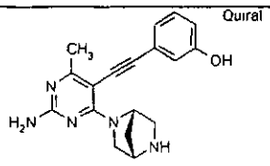
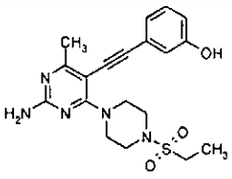
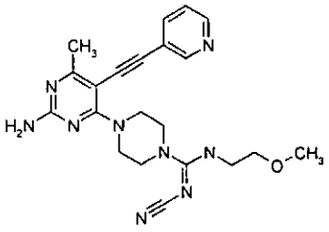
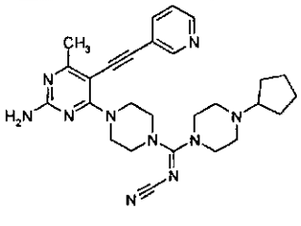


Una solución de 60 mg (0,080 mmol) de 5-(6-amino-piridin-3-iletinil)-2-metanosulfonil-6-(3-trifluorometil-fenil)-pirimidin-4-ilamina (B-10) y 15,7 mg (0,42 mmol) de borohidruro sódico en 1 ml de EtOH se agita a 80ºC durante 60 minutos. El compuesto del título se purifica a partir de la mezcla de reacción en bruto por RP-HPLC (gradiente de ACN/H_2O). Rendimiento: 1,4 mg (5%).

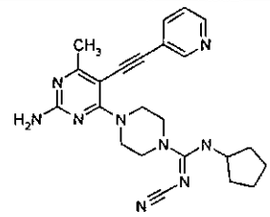
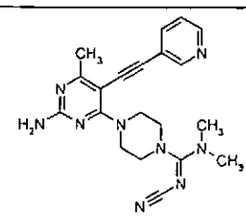
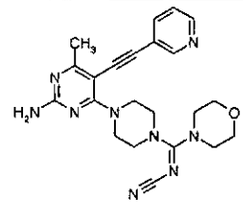
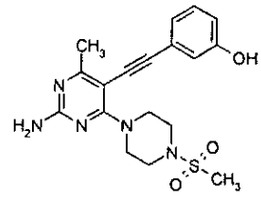
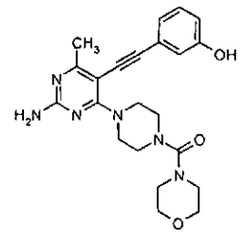
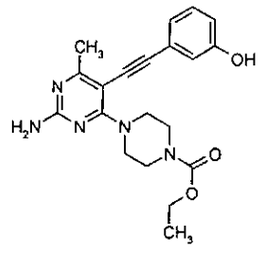
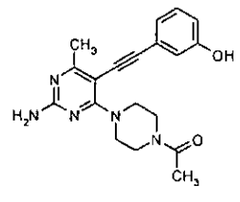
Ejemplos 141-212

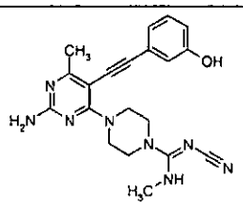
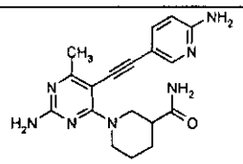
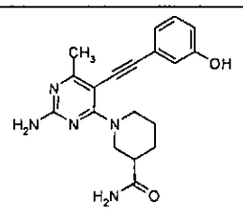
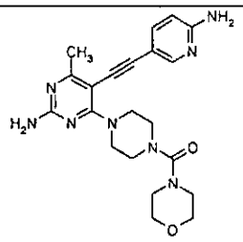
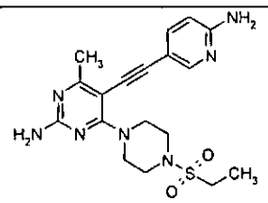
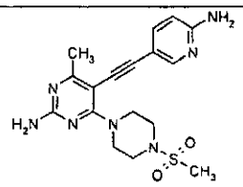
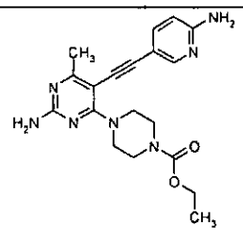
Los Ejemplos 141 a 212 se sintetizan de acuerdo con los procedimientos generales PG2 (reacción de Sonogashira) y PG6 (desplazamiento nucleófilo) que se han indicado anteriormente. Los haluros apropiados requeridos para la síntesis pueden deducirse a partir de la tabla de ejemplos.

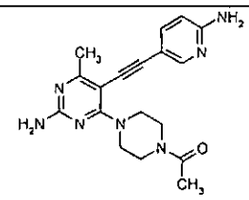
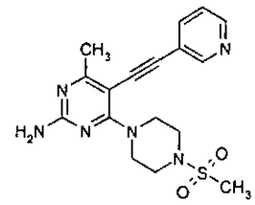
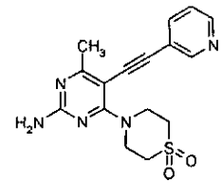
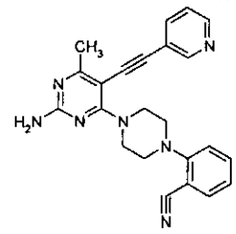
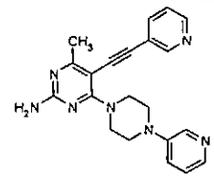
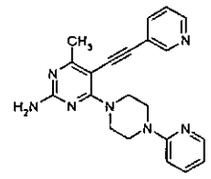
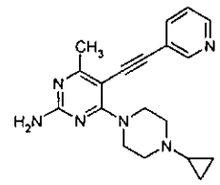
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
141	A-32		379	1,63
142	A-32		474	1,84
143	A-32		407	1,56
144	A-32		445	1,42
145	A-32		391	1,67
146	A-32		365	1,57

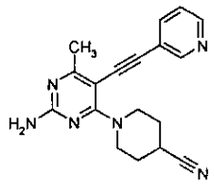
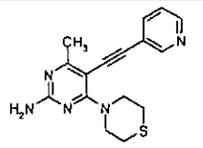
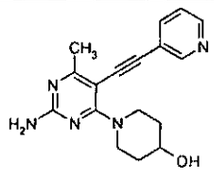
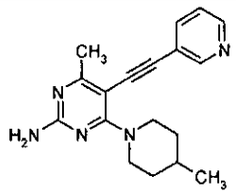
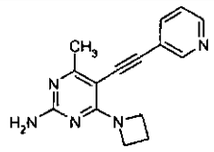
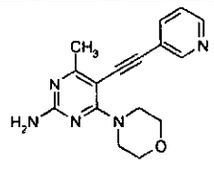
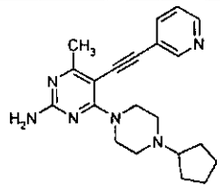
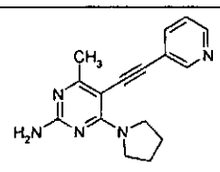
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
147	A-32		445	1,53
148	A-32		474	1,44
149	A-32		419	1,37
150	A-34		322	1,2-1,4
151	A-34		402	1,63
152	A-32		420	1,54
153	A-32		499	1,80

113

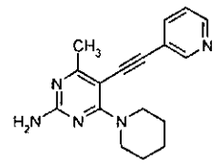
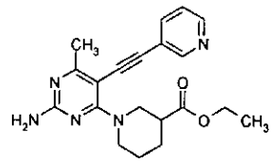
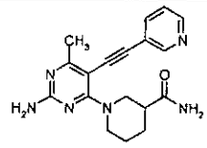
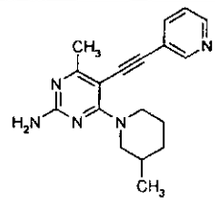
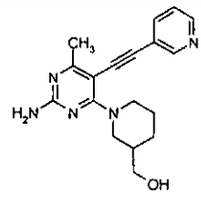
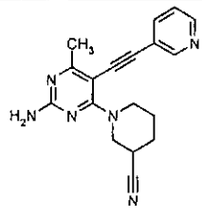
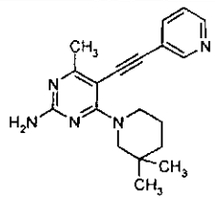
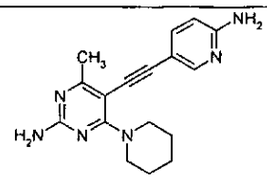
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
154	A-32		402	1,57
155	A-32		390	1,54
156	A-32		432	1,53
157	A-34		388	1,53
158	A-34		423	
159	A-34		382	1,74
160	A-34		352	1,42

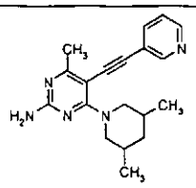
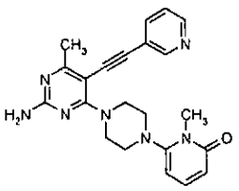
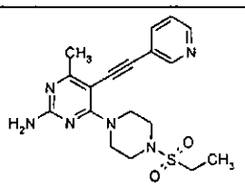
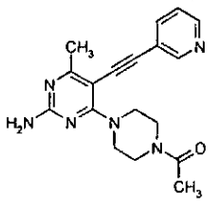
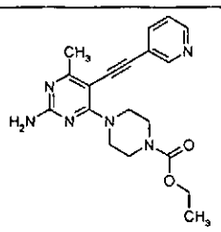
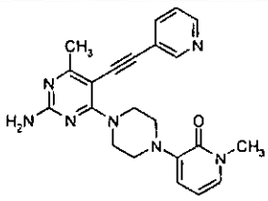
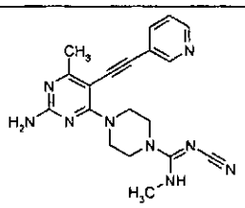
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
161	A-34		391	1,45
162	A-33		352	1,33
163	A-34		352	1,38
164	A-33		423	1,47
165	A-33		402	1,54
166	A-33		388	1,49
167	A-33		382	1,65

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
168	A-33		352	1,41
169	A-32		373	1,56
170	A-32		344	1,69
171	A-32		396	2,24
172	A-32		372	1,61
173	A-32		372	1,63
174	A-32		335	1,42

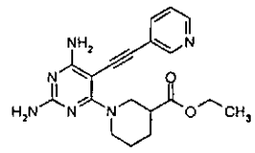
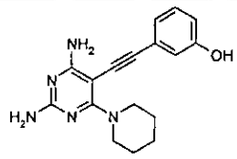
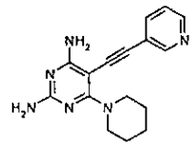
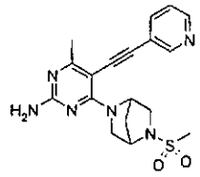
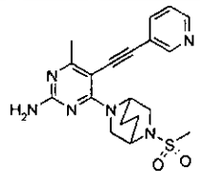
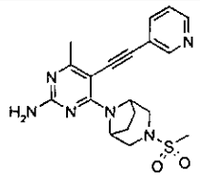
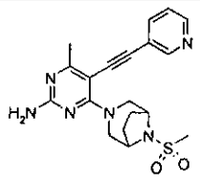
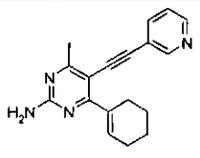
Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
175	A-32		319	2,34
176	A-32		312	2,45
177	A-32		310	2,13
178	A-32		308	2,69
179	A-32		266	2,25
180	A-32		296	2,21
181	A-32		363	2,02
182	A-32		280	1,91

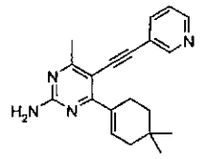
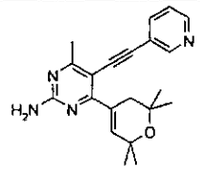
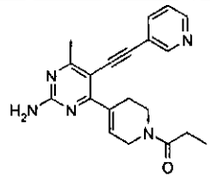
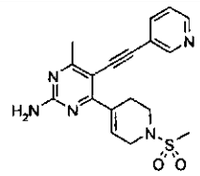
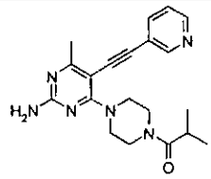
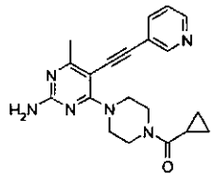
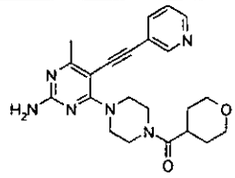
115

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
183	A-32		294	1,86
184	A-32		366	1,88
185	A-32		337	1,39
186	A-32		308	1,98
187	A-32		324	1,57
188	A-32		319	1,64
189	A-32		322	2,04
190	A-33		309	1,72

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
191	A-32		322	2,06/2,09
192	A-32		402	1,63
193	A-32		387	1,66
194	A-32		337	1,47
195	A-32		367	1,76
196	A-32		402	1,64
197	A-32		376	1,49

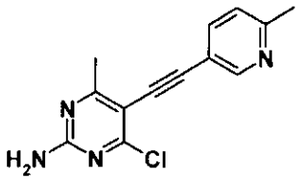
116

Nº	Educto	Estructura	$[M+H]^+$	t_{Ret} [min]
198	B-2		367	1,74
199	B-4		310	1,81
200	B-2		295	1,71
201	A-32		385	
202	A-32		399	
203	A-32		399	
204	A-32		399	
205	A-32		291	

N°	Educto	Estructura	$[M+H]^+$	t_{Rct} [min]
206	A-32		319	
207	A-32		349	
208	A-32		348	
209	A-32		370	
210	A-32		365	
211	A-32		363	
212	A-32		407	

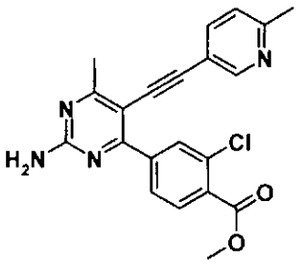
Intermedios C

C-46) 4-Cloro-6-metil-5-(6-metil-piridin-3-iletinil)-pirimidin-2-ilamina



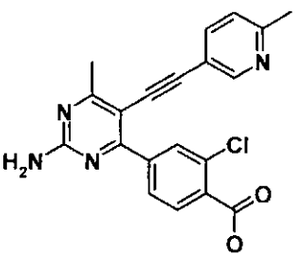
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 1,0 g (3,7 mmol) de 4-cloro-6-metil-5-yodo-pirimidin-2-ilamina usando 570 mg (3,7 mmol) de 5-etinil-2-metil-piridina, 71 mg (0,37 mmol) de CuI, 260 mg (0,37 mmol) de cloruro de bis-(trifenilfosfina)paladio (II) y 5,1 ml (27 mmol) de trietilamina en 40 ml de DMF. La mezcla de reacción se agita durante una noche a 55°C. Después de la retirada del disolvente a presión reducida, el producto se purifica por cromatografía sobre gel de sílice usando un gradiente de DCM/MeOH (100:0 -> 85:15, 30 min). Rendimiento: 270 mg (28%).

C-47) Éster metílico del ácido 4-[2-amino-6-metil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico



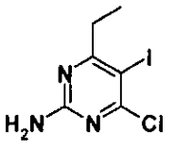
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 200 mg (0,77 mmol) de 4-cloro-6-metil-5-(6-metil-piridin-3-iletinil)-pirimidin-2-ilamina usando 249 mg (1,16 mmol) de ácido 3-cloro-4-metoxicarbonilfenil borónico, 24 mg (0,16 mmol) de $Pd(PPh_3)_4$ y 205 mg (1,47 mmol) de K_2CO_3 en 3 ml de DME/H_2O (3:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y puede usarse sin purificación adicional. Rendimiento: 235 mg (77%).

C-48) Ácido 4-[2-amino-6-metil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico



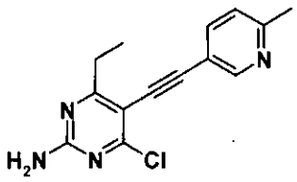
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 235 mg (0,6 mmol) de ácido 4-[2-amino-6-metil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-cloro benzoico usando 0,9 ml (0,9 mmol) de NaOH 1 N en THF. Rendimiento: 130 mg (57%).

C-49) 4-Cloro-6-etil-5-yodo-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG1 partiendo de 2,5 g (16 mmol) de 4-cloro-6-etil-pirimidin-2-ilamina y 3,7 g (16 mmol) de NIS. Rendimiento después de la precipitación de la mezcla de reacción: 3,83 g (85%).

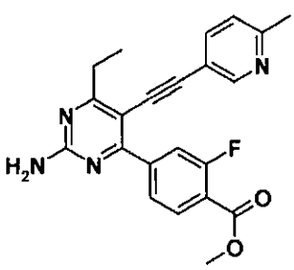
C-50) 4-Cloro-6-etil-5-(6-metil-piridin-3-iletinil)-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 300 g (1,1 mmol) de 4-cloro-6-etil-5-yodo-pirimidin-2-ilamina usando 160 mg (1,1 mmol) de clorhidrato de 5-etinil-2-metil-piridina, 20 mg (0,11 mmol) de CuI, 74 mg (0,11 mmol) de cloruro de bis-(trifenilfosfina)paladio (II) y 1,5 ml (10,6 mmol) de trietilamina en 11 ml de DMF. La mezcla de reacción se agita durante una noche a 60°C. Después de la retirada del disolvente a presión reducida, el producto se purifica por PR-HPLC.

Rendimiento: 130 mg (45%).

C-51) Éster metílico del ácido 4-[2-amino-6-etil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico

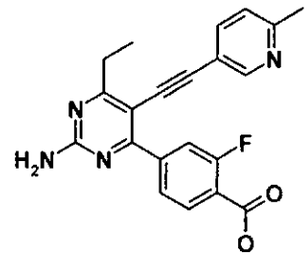


El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 130 mg (0,48 mmol) de 4-cloro-6-etil-5-(6-metil-piridin-3-iletinil)-

118

pirimidin-2-ilamina usando 142 mg (0,7 mmol) de ácido 3-fluoro-4-metoxicarbonilfenil borónico, 14 mg (0,01 mmol) de $Pd(PPh_3)_4$ y 133 mg (1,0 mmol) de K_2CO_3 en 2,25 ml de DME/H_2O (10:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y puede usarse sin purificación adicional. Rendimiento: 125 mg (67%).

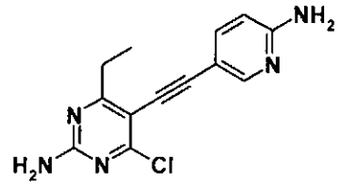
C-52) Ácido 4-[2-amino-6-etil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 130 mg (0,47 mmol) de éster metílico del ácido 4-[2-amino-6-etil-5-(6-metil-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico usando 470 µl (0,47 mmol) de NaOH 1 N en 3 ml de THF. El producto precipita de la mezcla de reacción y se aísla por filtración.

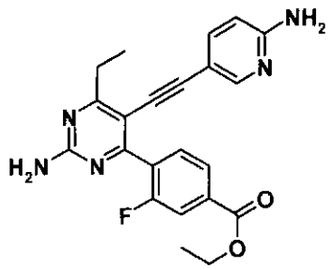
Rendimiento: 77 mg (62%).

C-) 5-(6-Amino-piridin-3-iletinil)-4-cloro-6-etil-pirimidin-2-ilamina53



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 3,0 g (10,6 mmol) de 4-cloro-6-etil-5-yodo-pirimidin-2-ilamina usando 1,37 mg (12 mmol) de 5-etinil-2-amino-piridina, 200 mg (1,1 mmol) de CuI, 740 mg (1,1 mmol) de cloruro de bis-(trifenilfosfina)paladio (II) y 15 ml (106 mmol) de trietilamina en 60 ml de DMF. La mezcla de reacción se agita durante una noche a 65ºC. A la mezcla de reacción se le añaden pequeñas cantidades de agua y el producto precipitado se retira por filtración y se lava posteriormente con DMF, H_2O y éter dietílico. El producto en bruto se cristaliza de nuevo en DMF (Rendimiento: 1,65 g). Se aísla más cantidad de producto a partir de las aguas madre por RP-HPLC. (Rendimiento: 325 mg). Rendimiento global: 1,97 g (68%).

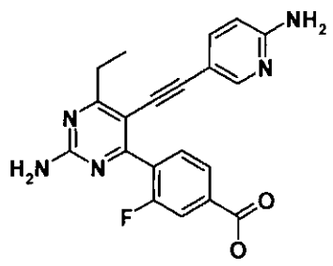
C-54) Éster etílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-3-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 300 mg (1,1 mmol) de 4-cloro-6-etil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 349 mg (1,6 mmol) de ácido 2-fluoro-4-etoxicarbonilfenil borónico, 34 mg (0,22 mmol) de $Pd(PPh_3)_4$ y 291 mg (2,1 mmol) de K_2CO_3 en 5 ml de DME/H_2O (5:2 v/v). Después de agitar dos veces durante 60 min a 130°C con irradiación con microondas, la conversión del material de partida es de aproximadamente 75% y se forma una mezcla de aproximadamente 1:1 del producto deseado y el éster saponificado. El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico. Rendimiento: 155 mg (35%).

Las aguas madre contienen el ácido carboxílico correspondiente que puede aislarse junto con el ácido obtenido de la saponificación del éster.

C-55) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-3-fluoro-benzoico

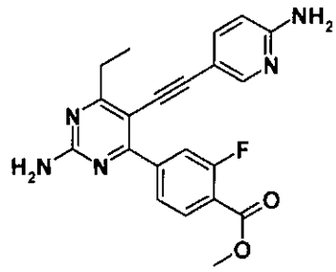


El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 200 mg (0,54 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-3-fluoro-benzoico usando 0,81 ml (0,81 mmol) de NaOH 1 N en 4 ml de THF.

Después de que se complete la reacción, la mezcla de reacción se combina con las aguas madre del acoplamiento de Suzuki anterior. El pH se ajusta a 4-5 (usando HCl 1 N), después de lo cual el producto precipita de la mezcla de reacción y se aísla por filtración.

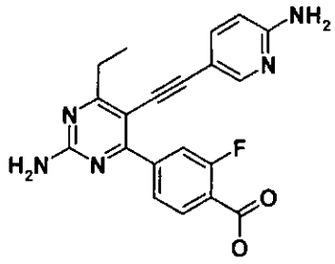
Rendimiento: 240 mg (al 58% en dos etapas).

C-56) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-fluoro-benzoico



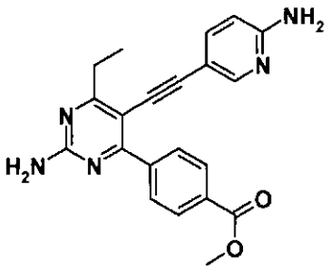
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 500 mg (1,8 mmol) de 4-cloro-6-etil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 542 mg (2,7 mmol) de ácido 3-fluoro-4-metoxicarbonilfenil borónico, 56 mg (0,37 mmol) de $Pd(PPh_3)_4$ y 611 mg (4,4 mmol) de K_2CO_3 en 10 ml de DME/H_2O (9:1 v/v). Después de agitar dos veces durante 60 min a 130°C con irradiación con microondas, la conversión del material de partida es de aproximadamente 75% y se forma una mezcla de aproximadamente 1:4 del producto deseado y el éster saponificado. El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico. Rendimiento: 537 mg (75%).

C-57) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 630 mg (1,6 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-fluoro-benzoico usando 1,6 ml (1,6 mmol) de NaOH 1 N en 10 ml de THF. El precipitado se recoge por filtración y se lava con THF. Rendimiento: 580 mg (96%).

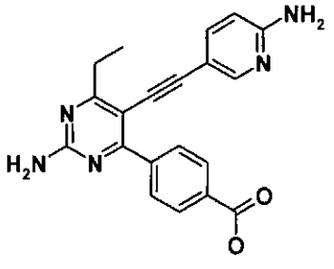
C-58) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 300 mg (1,1 mmol) de 4-cloro-6-etil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 296 mg (1,6 mmol) de ácido 4-metoxicarbonilfenil borónico, 34 mg (0,22 mmol) de $Pd(PPh_3)_4$ y 290 mg (2,1 mmol) de K_2CO_3 en 5 ml de DME/H_2O (5:2 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico. Rendimiento: 120 mg (29%).

Las aguas madre contienen el ácido carboxílico correspondiente que puede aislarse junto con el ácido obtenido de la saponificación del éster.

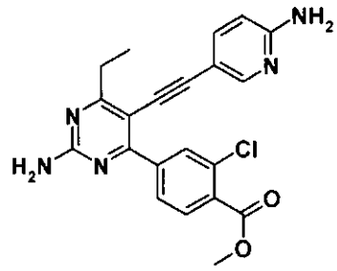
C-59) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 120 mg (0,32 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-benzoico usando 0,48 ml (0,48 mmol) de NaOH 1 N en 3 ml de THF.

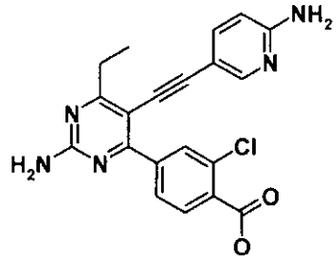
Durante el tratamiento, la mezcla de reacción se combina con las aguas madre del acoplamiento de Suzuki anterior (que contienen cantidades adicionales del producto), el pH se ajusta a pH 4-5 (usando HCl 1 N), después de lo cual el producto precipita y se aísla por filtración. El producto se lava con agua y éter dietílico. Rendimiento: 400 mg (>100% en 2 etapas).

C-60) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-cloro-benzoico



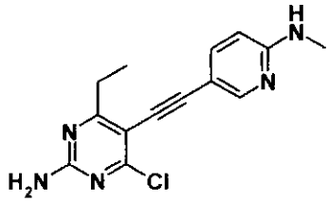
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 700 mg (2,6 mmol) de 4-cloro-6-etil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 822 mg (3,8 mmol) de ácido 3-cloro-4-metoxicarbonilfenil borónico, 80 mg (0,37 mmol) de $Pd(PPh_3)_4$ y 678 mg (4,8 mmol) de K_2CO_3 en 9 ml de DME/H_2O (7:2 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua, éter dietílico, isopropanol y éter dietílico de nuevo. Rendimiento: 951 mg (91%).

C-61) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-cloro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 951 mg (2,3 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-etil-pirimidin-4-il]-2-cloro-benzoico usando 3,5 ml (3,5 mmol) de NaOH 1 N en 16 ml de THF. El producto precipita de la mezcla de reacción y se aísla por filtración. El producto se lava con THF y éter dietílico. Rendimiento: 345 mg (38%).

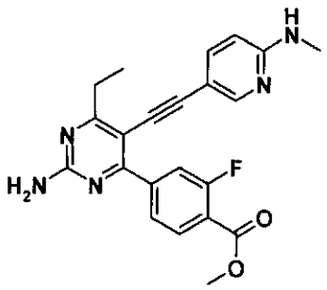
C-62) 4-Cloro-6-etil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-2-ilamina



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 3,0 g (10,6 mmol) de 4-cloro-6-etil-5-yodo-pirimidin-2-ilamina usando 1,5 g (11,6 mmol) de 5-etinil-2-aminometil-piridina, 201 mg (1,1 mmol) de CuI, 743

mg (1,1 mmol) de cloruro bis-(trifenilfosfina)paladio (II) y 15 ml (106 mmol) de trietilamina en 25 ml de DMF. La mezcla de reacción se agita durante 3 días a 50ºC. La mezcla de reacción se concentra a presión reducida y el producto se aísla por cromatografía sobre gel de sílice. Rendimiento: 1,54 g (51%).

C-63) Éster metílico del ácido 4-[2-amino-6-etil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico

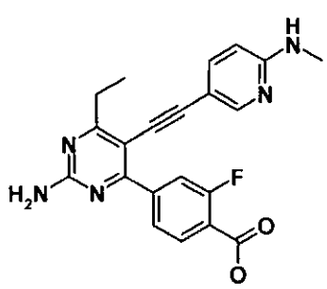


El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 330 mg (1,2 mmol) de 4-cloro-6-etil-5-(6-aminometil-piridin-3-iletinil)-pirimidin-2-ilamina usando 344 mg (1,7 mmol) de ácido 3-fluoro-4-metoxicarbonilfenil borónico, 36 mg (0,23 mmol) de $Pd(PPh_3)_4$ y 307 mg (2,2 mmol) de K_2CO_3 en 7 ml de DME/H_2O (5:2 v/v). Después de agitar durante 60 min a 130ºC con irradiación con microondas, se forma una mezcla de aproximadamente 1:1 del producto deseado y el éster saponificado. El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico.

Rendimiento: 238 mg (51%).

Las aguas madre contienen el ácido carboxílico correspondiente que puede aislarse junto con el ácido obtenido de la saponificación del éster.

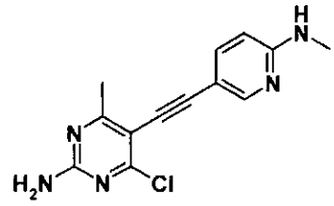
C-64) Ácido 4-[2-amino-6-etil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 238 mg (0,59 mmol) de éster etílico del ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-fluoro-benzoico usando 0,88 ml (0,88 mmol) de NaOH 1 N en 3 ml de THF.

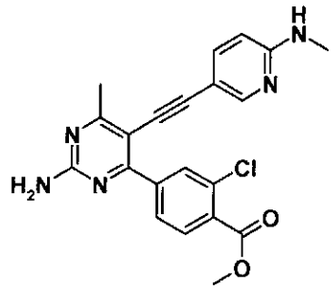
Durante el tratamiento, la mezcla de reacción se combina con las aguas madre del acoplamiento de Suzuki anterior (que contienen cantidades adicionales del producto), el pH se ajusta a pH 4-5 (usando HCl 1 N), después de lo cual el producto precipita y se aísla por filtración. El producto se lava con agua y éter dietílico. Rendimiento: 517 mg (114% en 2 etapas).

C-65) 4-Cloro-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-2-ilamina



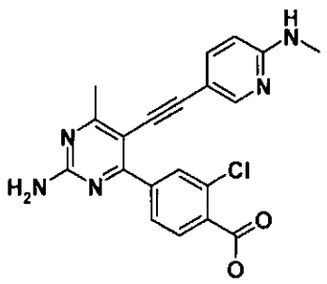
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG2 partiendo de 3,0 g (10,6 mmol) de 4-cloro-6-etil-5-yodo-pirimidin-2-ilamina usando 1,5 g (11,6 mmol) de 5-etinil-2-aminometil-piridina, 201 mg (1,1 mmol) de CuI, 743 mg (1,1 mmol) de cloruro de bis-(trifenilfosfina)paladio (II), 15 ml (106 mmol) de trietilamina en 25 ml de DMF. La mezcla de reacción se agita durante 3 días a 50°C. La mezcla de reacción se concentra a presión reducida y el producto se aísla por cromatografía sobre gel de sílice. Rendimiento: 1,54 g (51%).

C-66) Éster metílico del ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico



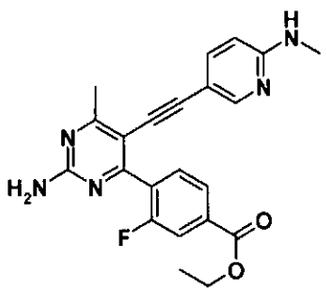
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 500 mg (1,8 mmol) de 4-cloro-6-metil-5-(6-aminometil-piridin-3-iletinil)-pirimidin-2-ilamina usando 587 mg (2,7 mmol) de ácido 3-cloro-4-metoxicarbonilfenil borónico, 56 mg (0,23 mmol) de $Pd(PPh_3)_4$ y 5100 mg (3,7 mmol) de K_2CO_3 en 6 ml de DME/H_2O (5:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua. Rendimiento: 740 mg (99%).

C-67) Ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico



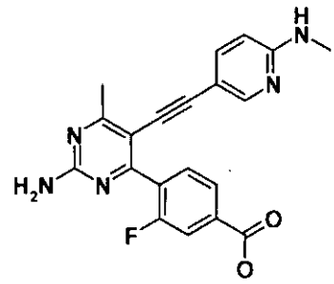
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 700 mg (1,7 mmol) de éster metílico del ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico usando 2,6 ml (2,6 mmol) de NaOH 1 N en 10 ml de THF. El producto precipita y se aísla por filtración. El producto se lava con agua y se usa sin purificación adicional. Rendimiento: 370 mg (55%).

C-68) Éster metílico del ácido 4-[2-amino-6-etil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-3-fluoro-benzoico



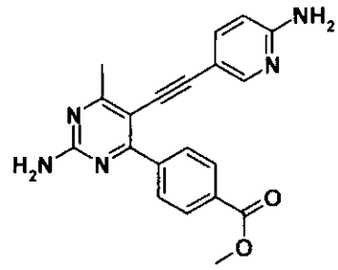
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 500 mg (1,8 mmol) de 4-cloro-6-metil-5-(6-aminometil-piridin-3-iletinil)-pirimidin-2-ilamina usando 581 mg (2,7 mmol) de ácido 2-fluoro-4-etoxicarbonilfenil borónico, 56 mg (0,37 mol) de $Pd(PPh_3)_4$ y 510 mg (3,7 mmol) de K_2CO_3 en 6 ml de DME/H_2O (5:1 v/v). Después de la agitación durante 2 x 30 min a 120°C con irradiación con microondas, el producto precipita de la mezcla de reacción, se retira por filtración y se lava con DMF, MeOH, agua y éter dietílico. Rendimiento: 637 mg (86%).

C-69) Ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-3-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 640 mg (1,6 mmol) de éster etílico del ácido 4-[2-amino-6-metil-5-(6-metilamino-piridin-3-iletinil)-pirimidin-4-il]-2-cloro-benzoico usando 2,4 ml (2,4 mmol) de NaOH 1 N en 10 ml de THF. El producto precipita y se aísla por filtración. El producto se lava con agua. Rendimiento: 620 mg (104%, contiene una pequeña cantidad de material de partida del acoplamiento de Suzuki anterior).

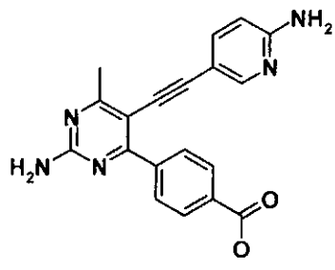
C-70) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (7,7 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 2,1 g (11,6 mmol) de ácido 4-metoxicarbonilfenil borónico, 240 mg (1,5 mmol) de $Pd(PPh_3)_4$, 2,2 g (15,4 mmol) de K_2CO_3 en 20 ml de DME/H_2O (4:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico.

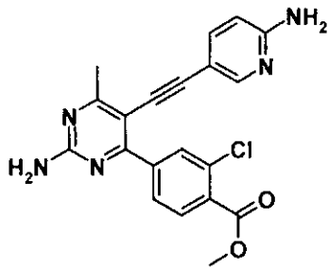
Rendimiento: 2,3 g (98%).

C-71) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-benzoico



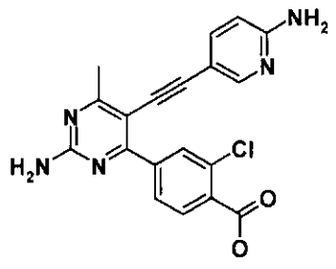
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 2,3 g (6,4 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-benzoico usando 9,6 ml (9,6 mmol) de NaOH 1 N en 20 ml de THF. El producto precipita, se aísla por filtración y se lava con agua. Rendimiento: 2,2 g (99%).

C-72) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro benzoico



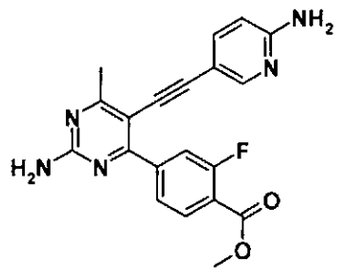
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 1,0 mg (3,9 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 1,2 g (5,8 mmol) de ácido 2-cloro-4-metoxicarbonilfenil borónico, 120 mg (0,77 mmol) de $Pd(PPh_3)_4$ y 1,0 g (7,3 mmol) de K_2CO_3 en 12 ml de DME/H_2O (5:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico. Rendimiento: 1,24 g (82%).

C-73) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro benzoico



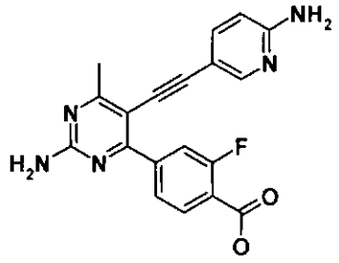
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 1,24 g (3,1 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro-benzoico usando 4,7 ml (4,7 mmol) de NaOH 1 N en 22 ml de THF. El producto precipita y se aísla por filtración. El producto se lava con THF y éter dietílico. Rendimiento: 1,13 g (95%).

C-74) Éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 2,0 g (7,7 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 2,3 g (11,6 mmol) de ácido 2-fluoro-4-metoxicarbonilfenil borónico, 240 mg (1,5 mmol) de $Pd(PPh_3)_4$ y 2,6 g (18,5 mmol) de K_2CO_3 en 24 ml de DME/H_2O (5:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico. Rendimiento: 2,9 g (100%).

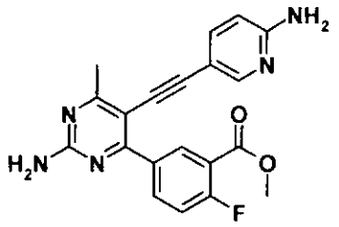
C-75) Ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluoro benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 3,0 g (8,0 mmol) de éster metílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluorobenzoico usando 12 ml (12 mmol) de NaOH 1 N en 30 ml de THF. El producto precipita y se aísla por filtración. El producto se lava con agua.

Rendimiento: 2,2 g (76%).

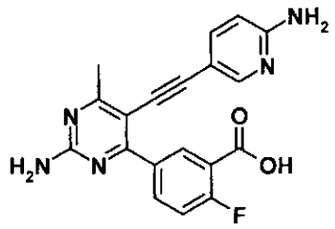
C-76) Éster metílico del ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluoro-benzoico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 1,5 g (5,8 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 1,7 g (8,7 mmol) de ácido (4-fluoro-3-metoxicarbonil)fenil

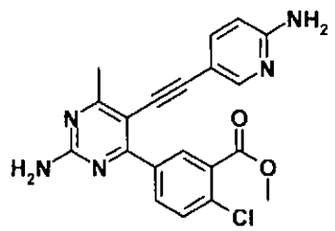
borónico, 67 mg (0,58 mmol) de $Pd(PPh_3)_4$ y 2,6 g (18,5 mmol) de K_2CO_3 en 18 ml de DME/H_2O/etanol (10:5:1 v/v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico, produciendo 1,95 g (5,2 mmol) del producto deseado, que se usa sin purificación adicional.

C-77) Ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluoro-benzoico



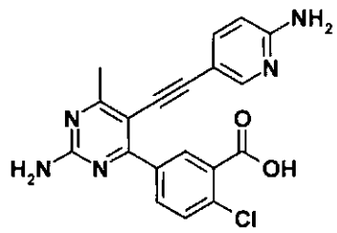
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 1,95 g (5,1 mmol) de éster metílico del ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-fluoro-benzoico usando 500 mg (11,9 mmol) de LiOH en 40 ml de THF y 10 ml de agua. El producto precipita y se aísla por filtración. El producto se lava con MeOH, produciendo 1,76 g (4,48 mmol) del producto deseado.

C-78) Éster metílico del ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro benzoico



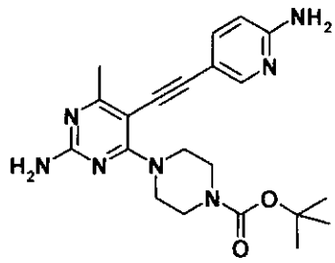
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG4 partiendo de 1,5 g (5,8 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina usando 1,36 g (6,35 mmol) de ácido 4-cloro-3-metoxicarbonil)fenil borónico, 202 mg (0,29 mmol) de $Pd(PPh_3)_4$, 2,6 g (18,5 mmol) de K_2CO_3 en 16 ml de DME/H_2O (5:1 v/v). El producto precipita de la mezcla de reacción, se retira por filtración y se lava con agua y éter dietílico, produciendo 1,76 g (4,4 mmol) del producto deseado, que se usa sin purificación adicional.

C-79) Ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro-benzoico



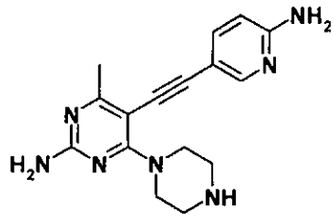
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 2,28 g (5,78 mmol) de éster metílico del ácido 5-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-2-cloro-benzoico usando 347 mg (14,4 mmol) de LiOH en 20 ml de THF y 1 ml de agua. El producto precipita y se aísla por filtración. El producto se lava con agua/acetonitrilo (1:1 v/v), produciendo 1,30 g (3,44 mmol) del producto deseado, que se usa sin purificación adicional.

C-84) Éster *terc*-butílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperazina-1-carboxílico



El compuesto del título se sintetiza de acuerdo con el procedimiento general PG7 partiendo de 5,0 g (19,3 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina y 3,94 g (21,2 mmol) de *N*-Boc-piperazina usando 2,94 ml (21,2 mmol) de trietilamina en 30 ml de NMP. El tratamiento se realiza por adición de 500 ml de agua a la mezcla de reacción y agitación durante 30 min. El material solido se retira por filtración y se lava con agua (50 ml, tres veces), produciendo 7,25 g (17,7 mmol) del producto deseado con suficiente pureza.

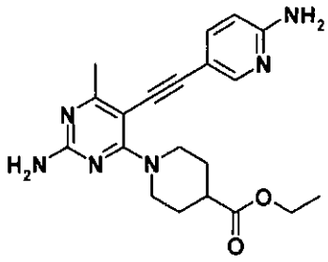
C-85) 5-(6-Amino-piridin-3-iletinil)-4-metil-6-piperazin-1-il-pirimidin-2-ilamina



Se disuelven 7,1 g (17,3 mmol) de éster *terc*-butílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperazina-1-carboxílico en DCM (400 ml) y se añaden 40 ml de TFA. La mezcla de reacción se agita durante una noche a TA. La mezcla de reacción se ajusta a pH neutro usando una solución acuosa

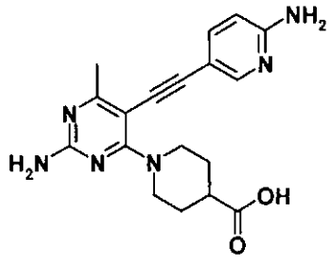
concentrada de Na_2CO_3 y el DCM se evapora a presión reducida. El residuo se lava con agua, se recoge en acetonitrilo y se liofiliza, produciendo 4,0 g (13,0 mmol) del producto deseado que se usa en la siguiente etapa sin purificación adicional.

C-86) Éster etílico del ácido 1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidina-4-carboxílico



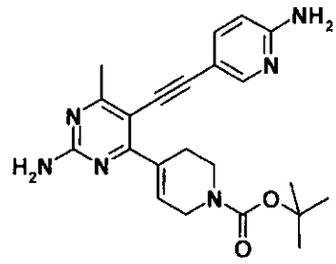
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG7 partiendo de 2,0 g (7,7 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina y 1,33 g (8,47 mmol) de éster etílico del ácido piperidina-4-carboxílico usando 1,18 ml (8,5 mmol) de trietilamina en 12 ml de NMP. El tratamiento se realiza por adición de 50 ml de agua a la mezcla de reacción y agitación durante 30 min. El material solido se retira por filtración y se lava con agua (50 ml, tres veces), produciendo 1,58 g (4,15 mmol) del producto deseado con suficiente pureza.

C-87) Ácido 1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidina-4-carboxílico



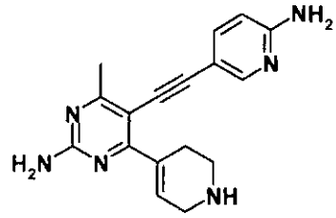
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG8 partiendo de 1,0 g (2,63 mmol) de éster etílico del ácido 1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidina-4-carboxílico y 126 mg (5,26 mmol) de LiOH en 80 ml de THF y 20 ml de agua. Produciendo 772 mg (2,19 mmol) del producto deseado.

C-88) Éster *terc*-butílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-3,6-dihidro-2*H*-piridina-1-carboxílico



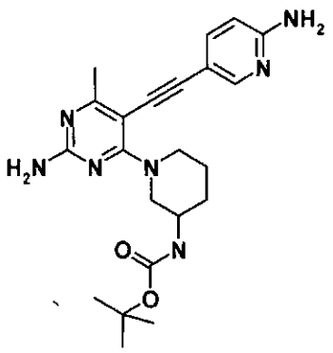
Una mezcla de 500 mg (1,9 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina, 1,2 g (3,9 mmol) de éster *terc*-butílico del ácido 4-(4,4,5,5-tetrametil-[1,3,2]-dioxaborolan-2-il)-3,6-dihidro-2*H*-piridina-1-carboxílico, 135 mg (1,9 mmol) de $Pd(PPh_3)_2Cl_2$, 40 ml de una solución acuosa de Na_2CO_3 1 N y 244 mg de LiCl (5,78 mmol) en 100 ml de tolueno/etanol (4:1 v/v) se mantiene durante 2 días a la temperatura de reflujo. Después de la refrigeración, el disolvente se evapora, se añade agua y la suspensión acuosa se extrae 4 veces con acetato de etilo (200 ml cada vez). La fase orgánica se seca sobre $MgSO_4$ y el disolvente se retira bajo presión reducida. El residuo se purifica usando cromatografía en columna ultrarrápida, produciendo 635 mg (1,56 mmol) del producto deseado que se usa sin purificación adicional en la siguiente etapa.

C-89) 5-(6-amino-piridin-3-iletinil)-4-metil-6-(1,2,3,6-tetrahidro-piridin-4-il)-pirimidin-2-ilamina



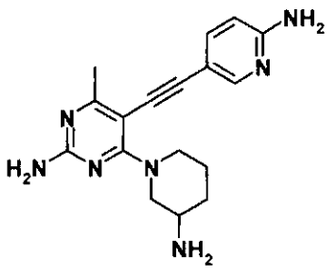
Se disuelven 630 mg (1,5 mmol) de éster *terc*-butílico del ácido 4-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-3,6-dihidro-2*H*-piridina-1-carboxílico en DCM (40 ml) y se añaden 2 ml de TFA. La mezcla de reacción se agita durante 3 h, se añade una solución acuosa concentrada de Na_2CO_3 hasta que se alcanza un valor de pH de 7 y el DCM se evapora a presión reducida. El residuo se lava con agua, se recoge en acetonitrilo y se liofiliza, produciendo 253 mg (0,83 mmol) del producto deseado que se usa en la siguiente etapa sin purificación adicional.

C-90) Éster *terc*-butílico del ácido {1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidin-3-il}-carbámico



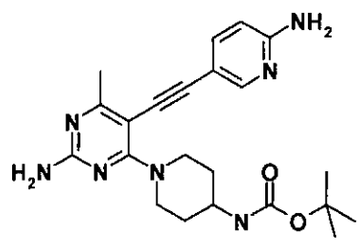
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG7 partiendo de 2,0 g (7,7 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina y 2,0 g (10,0 mmol) de éster *terc*-butílico del ácido piperidin-3-il-carbámico usando 1,29 ml (9,2 mmol) de trietilamina en 5 ml de NMP y 5 ml de DMSO. Se añaden 200 ml de acetato de etilo y 100 ml de una solución acuosa semi-concentrada de Na_2CO_3 y las fases se separan. La fase acuosa se extrae 2 veces con acetato de etilo (100 ml cada una). Las fases orgánicas combinadas se secan sobre sulfato sódico y el disolvente se retira a presión reducida. El producto en bruto se usa sin purificación adicional en la siguiente etapa.

C-91) 4-(3-Amino-piperidin-1-il)-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-2-ilamina



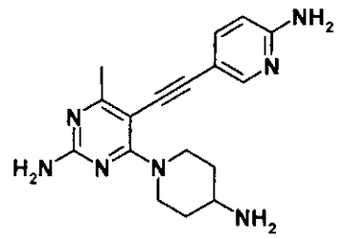
Se disuelven 3,3 g (7,8 mmol) de éster terc-butílico del ácido {1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidin-3-il}-carbámico en DCM (50 ml) y se añaden 26 ml de TFA. La mezcla de reacción se agita durante una noche a TA. La mezcla de reacción se ajusta a pH neutro usando una solución acuosa concentrada de Na_2CO_3 y el DCM se evapora a presión reducida. El residuo se lava con agua, se recoge en acetonitrilo y se liofiliza. El producto en bruto se usa sin purificación adicional en la siguiente etapa.

C-92) Éster *terc*-butílico del ácido {1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidin-4-il}-carbámico



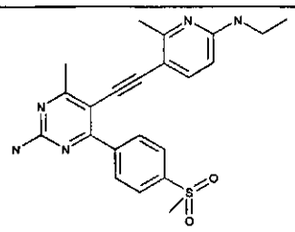
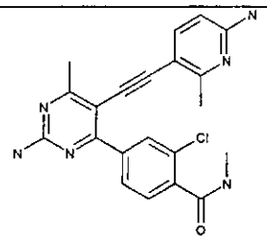
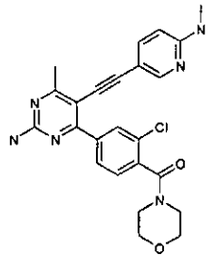
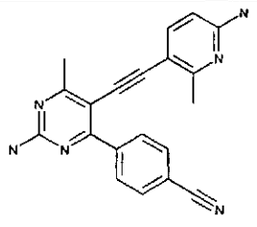
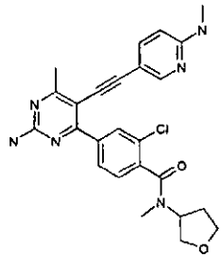
El compuesto del título se sintetiza de acuerdo con el procedimiento general PG7 partiendo de 2,0 g (7,7 mmol) de 4-cloro-6-metil-5-(6-amino-piridin-3-iletinil)-pirimidin-2-ilamina y 1,7 g (8,47 mmol) de éster *terc*-butílico del ácido piperidin-4-il-carbámico usando 1,07 ml (7,7 mmol) de trietilamina en 3 ml de NMP y 12 ml de DMSO. Se añaden 200 ml de acetato de etilo y 100 ml de una solución acuosa semi-concentrada de Na_2CO_3 y las fases se separan. La fase acuosa se extrae 2 veces con acetato de etilo (100 ml cada una). Las fases orgánicas combinadas se secan sobre sulfato sódico y el disolvente se retira a presión reducida. El producto en bruto se usa sin purificación adicional en la siguiente etapa.

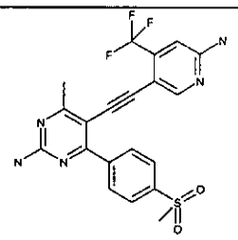
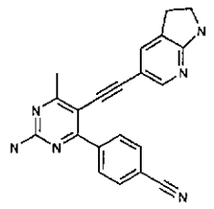
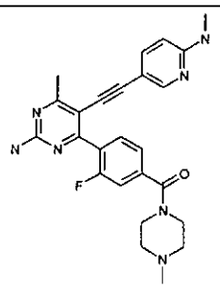
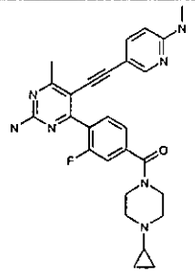
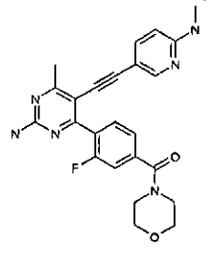
C-93) 4-(4-Amino-piperidin-1-il)-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-2-ilamina

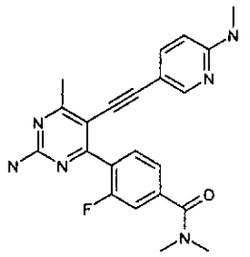
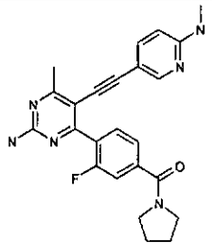
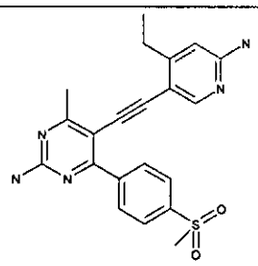
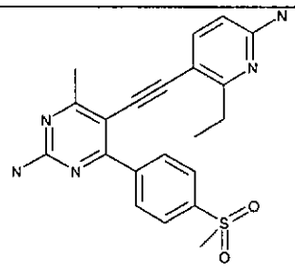
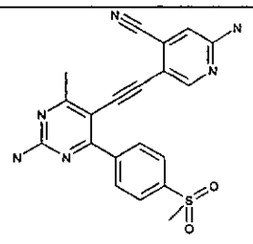


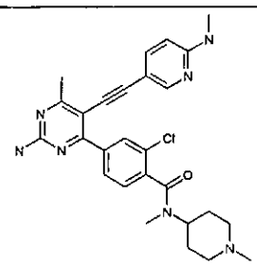
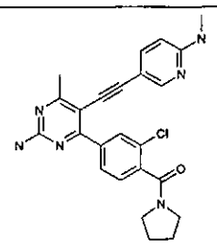
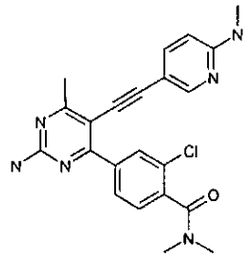
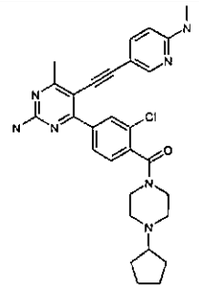
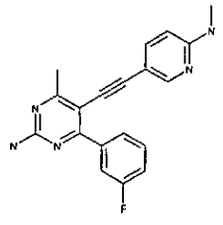
Se disuelven 3,2 g (7,6 mmol) de éster terc-butílico del ácido {1-[2-amino-5-(6-amino-piridin-3-iletinil)-6-metil-pirimidin-4-il]-piperidin-4-il}-carbámico en DCM (50 ml) y se añaden 26 ml de TFA. La mezcla de reacción se agita durante una noche a TA. La mezcla de reacción se ajusta a pH neutro usando una solución acuosa concentrada de Na_2CO_3 y el DCM se evapora a presión reducida. El residuo se lava con agua, se recoge en acetonitrilo y se liofiliza. El producto en bruto se usa sin purificación adicional en la siguiente etapa.

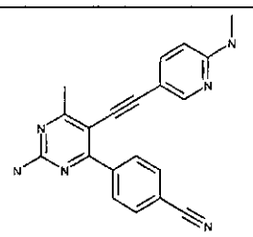
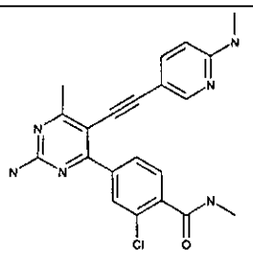
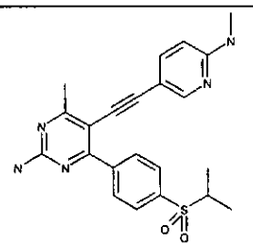
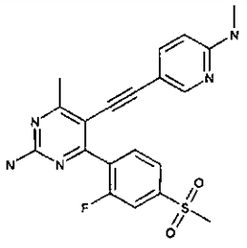
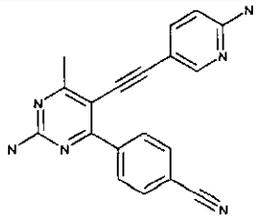
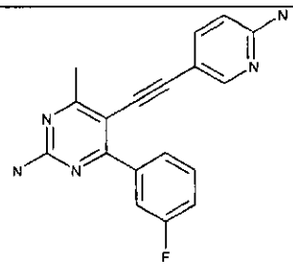
Ejemplos 213-418

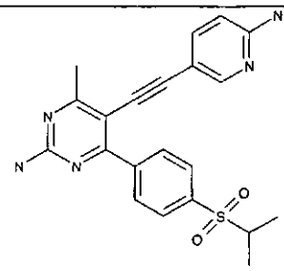
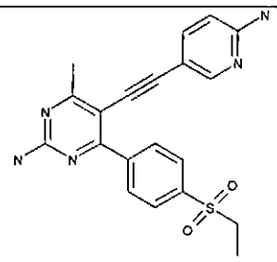
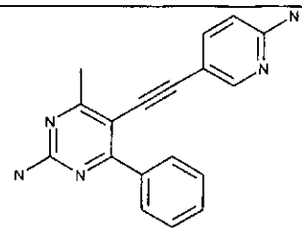
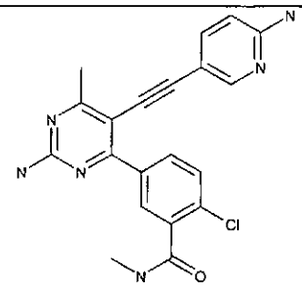
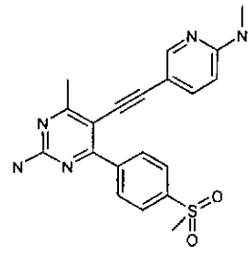
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
213		A-39	421,5	422	1,58
214			406,9	407	1,19
215			462,9	463	1,45
216			340,4	341	1,39
217		C-67	477	477/479	1,50

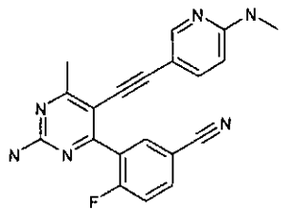
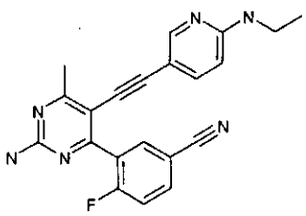
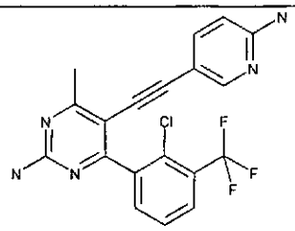
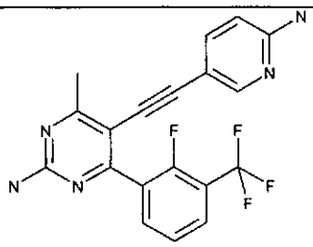
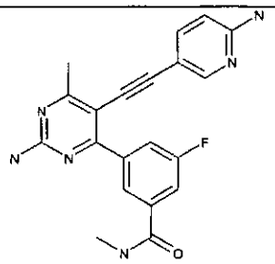
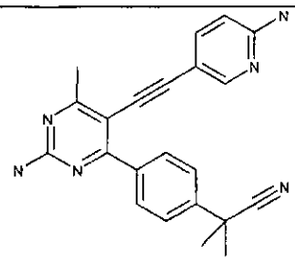
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
218		A-39	447,4	448	1,47
219			352,4	353	1,49
220		C-69	459,5	460	1,33
221		C-69	485,6	486	1,67
222		C-69	446,5	447	1,37

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
223		C-69	404,4	405	1,34
224		C-69	430,5	431	1,60
225		A-39	407,5	408	1,43
226		A-39	407,5	408	1,47
227		A-39	404,5	M-H = 403	

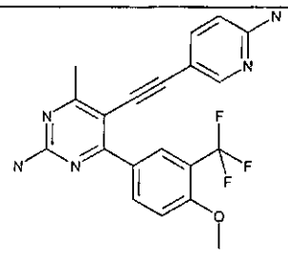
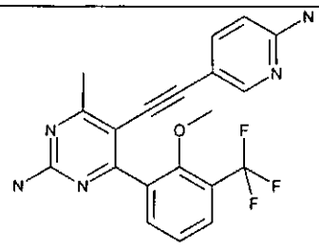
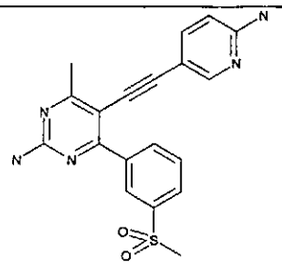
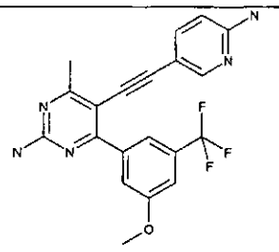
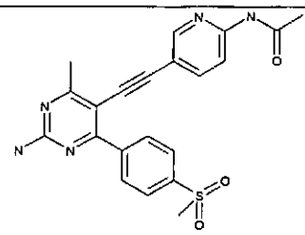
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
228		C-67	504	504/506	1,48
229		C-67	446,9	447/449	1,56
230		C-67	420,9	421	1,49
231		C-67	530,1	530/532	1,75
232		C-65	333,4	334	1,61

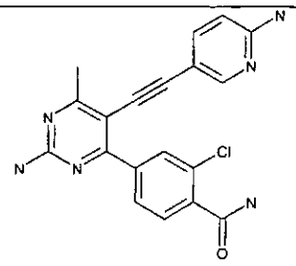
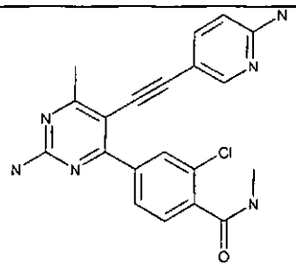
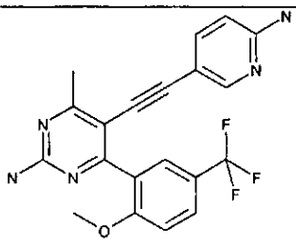
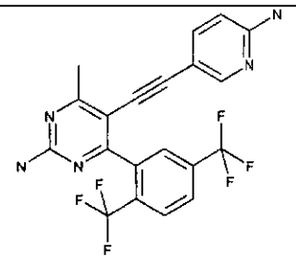
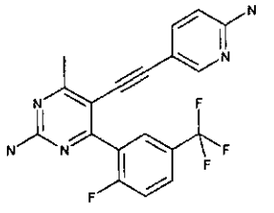
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
233		C-65	340,4	341	1,55
234		C-65	406,9	407	1,40
235		C-65	421,5	422	1,55
236		C-65	411,5	412	
237		A-33	326,4	327	1,40
238		A-33	319,3	320	1,26

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
239		A-33	407,5	408	1,42
240		A-33	393,5	394	1,34
241		A-33	301,4	302	1,39
242		A-33	392,8	393	1,27
243		A-30	393,5	394	1,50

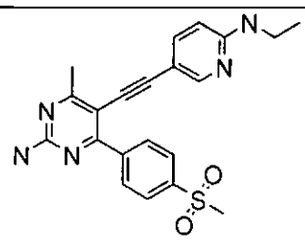
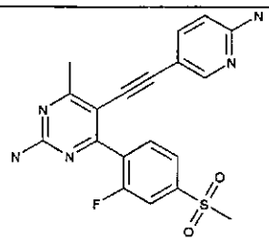
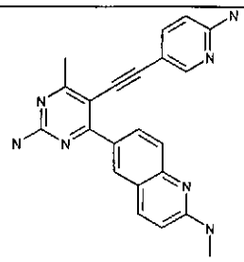
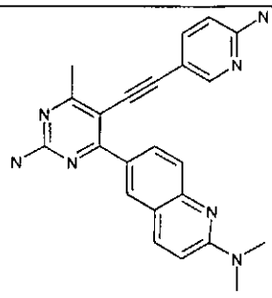
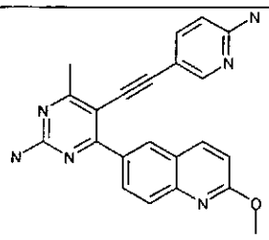
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
244		A-30	358,4	359	1,52
245			372,4	373	1,64
246		A-33	403,8	404	1,59
247		A-33	387,3	388	1,56
248		A-33	376,4	377	1,28
249		A-33	368,4	369	1,51

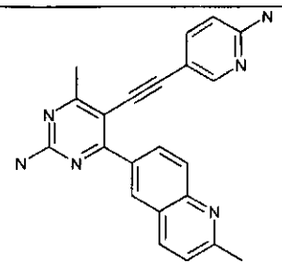
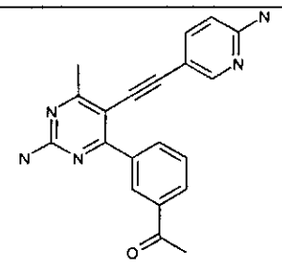
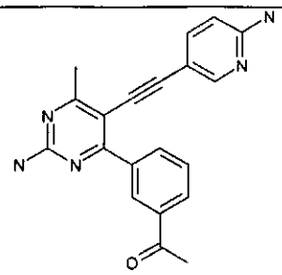
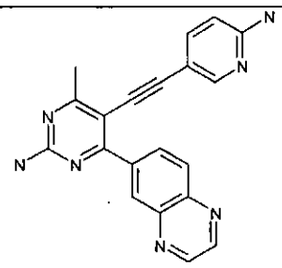
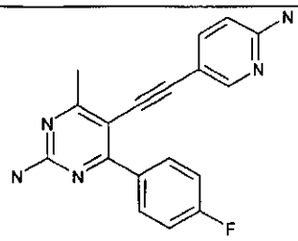
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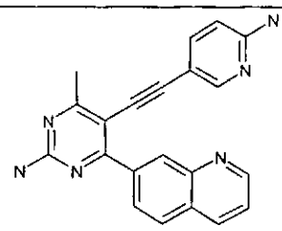
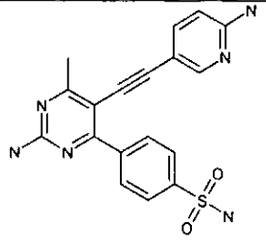
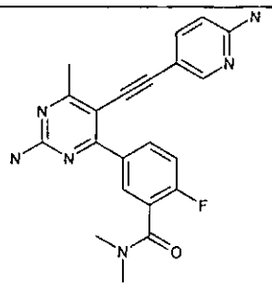
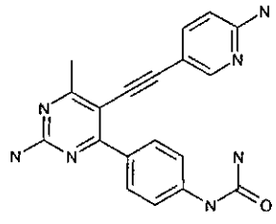
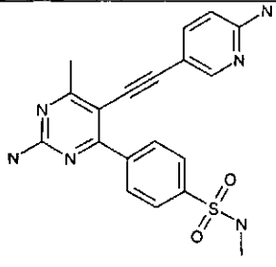
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
250		A-33	399,4	400	1,64
251		A-33	399,4	400	1,63
252		A-33	379,4	380	1,26
253		A-33	399,4	400	1,68
254		A-39	421,5	422	

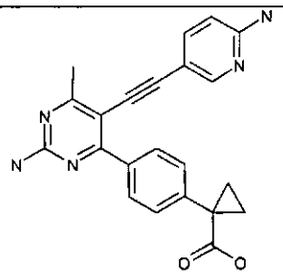
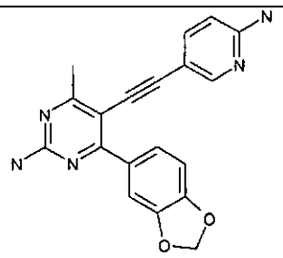
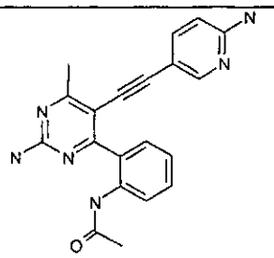
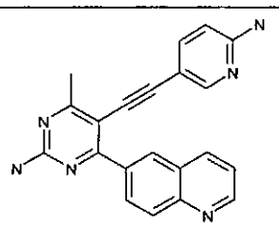
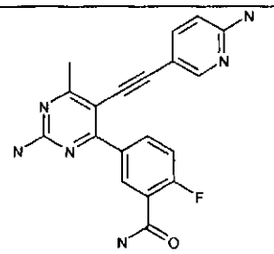
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
255		A-33	378,8	379	
256		A-33	392,8	393	
257		A-33	399,4	400	1,54
258		A-33	437,3	438	1,65
259		A-33	387,3	388	1,60

131

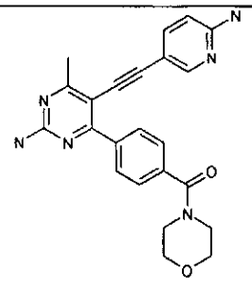
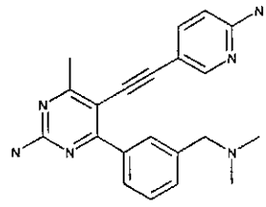
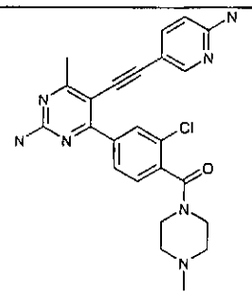
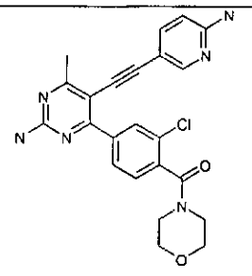
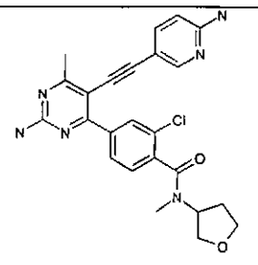
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
260		A-39	407,5	408	1,53
261		A-33	397,4	398	1,29
262		A-33	381,4	382	1,42
263		A-33	395,5	396	1,62
264		A-33	382,4	383	1,65

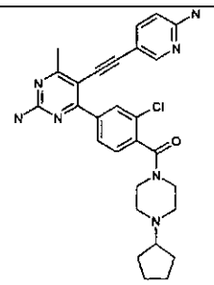
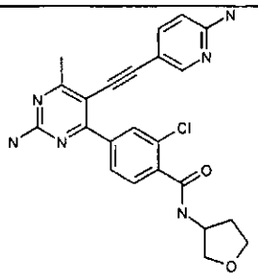
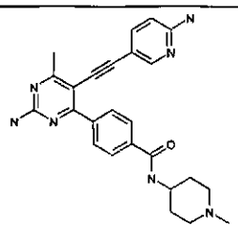
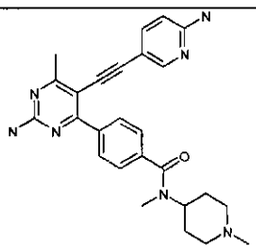
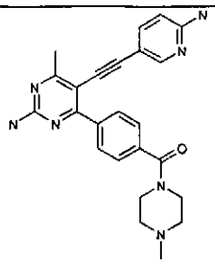
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
265		A-33	366,4	367	1,48
266		A-33	343,4	344	1,29
267		A-33	343,4	344	
268		A-33	353,4	354	1,21
269		A-33	319,3	320	

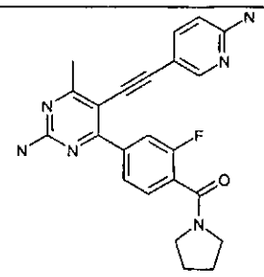
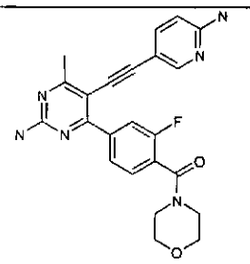
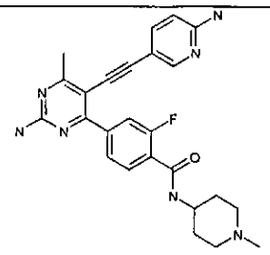
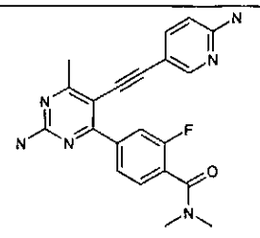
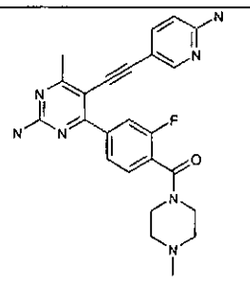
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
270		A-33	352,4	353	1,28
271		A-33	380,4		
272		A-33	390,4	391	1,23
273		A-33	359,4	360	1,01
274		A-33	394,5	395	

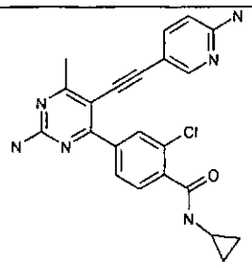
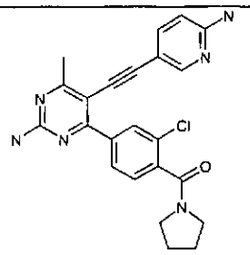
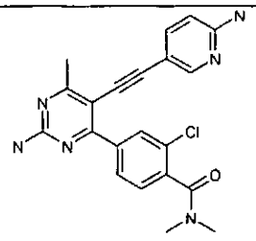
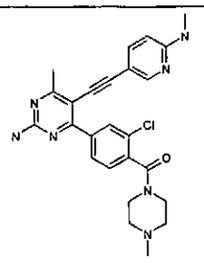
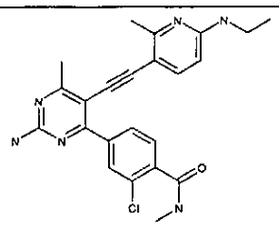
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
275		A-33	385,4	386	
276		A-33	345,4	346	
278		A-33	358,4	359	
279		A-33	352,4	353	1,25
280		A-33	362,4	363	1,08

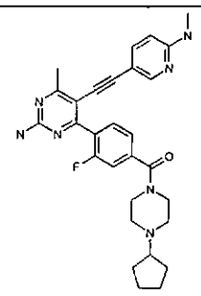
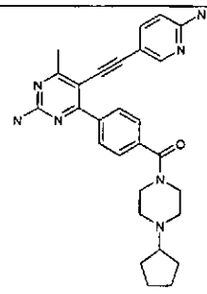
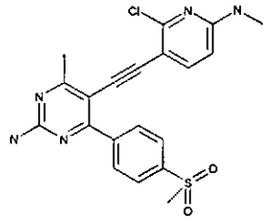
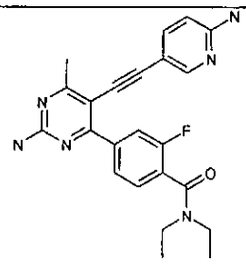
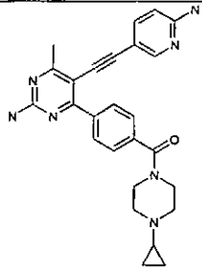
123

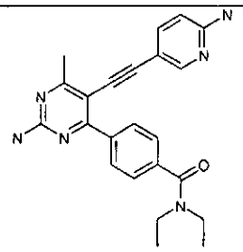
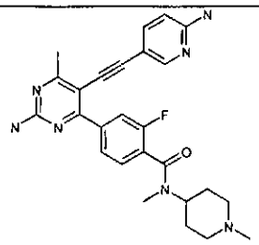
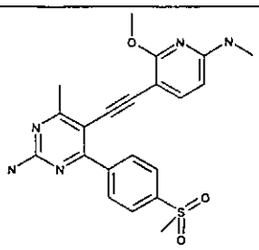
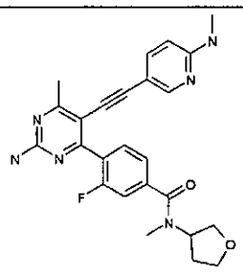
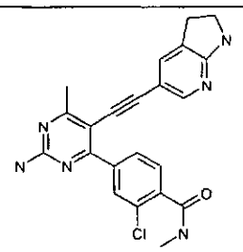
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
281		C-71	414,5	415	1,39
282		A-33	358,4	359	
283		C-73	462	462/464	1,44
284		C-73	448,9	449	1,42
285		C-73	462,9	463/465	1,47

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
286		C-73	516	516/518	1,76
287		C-73	448,9	449	1,40
288		C-71	441,5	442	1,36
289		C-71	455,6	456	1,40
290		C-71	427,5	428	1,35

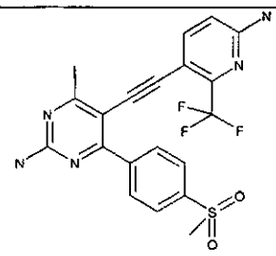
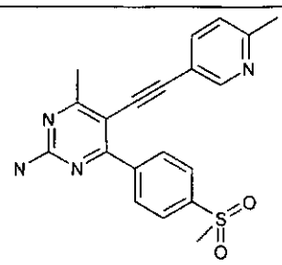
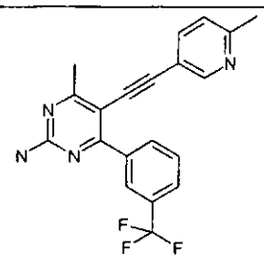
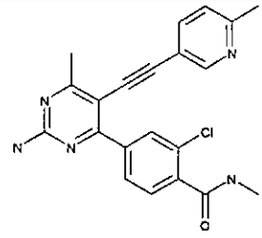
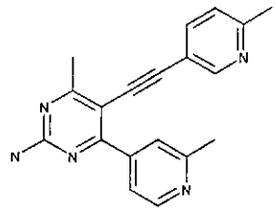
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
291		C-75	416,5	417	1,49
292		C-75	432,5	433	1,38
293		C-75	459,5	460	1,45
294		C-75	390,4	391	1,40
295		C-75	445,5	446	1,40

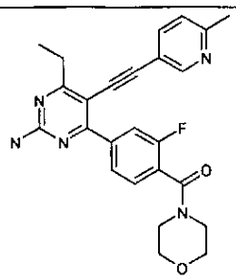
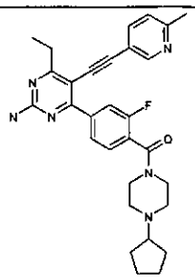
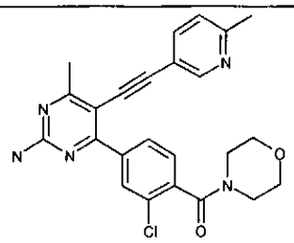
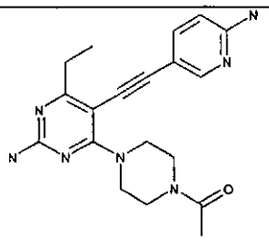
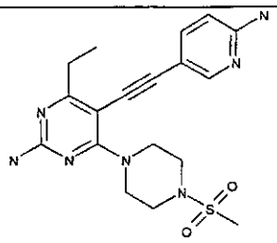
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
296		C-73	418,9	419	
297		C-73	432,9	433/435	1,55
298		C-73	406,9	407/409	1,45
299		C-67	476	476	1,58
300			434,9	435/437	1,71

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
301		C-69	513,6	514	1,79
302		C-71	481,6	482	1,65
303		A-39	427,9	428/430	1,86
304		C-75	418,5	419	1,58
305		C-71	453,5	454	1,54

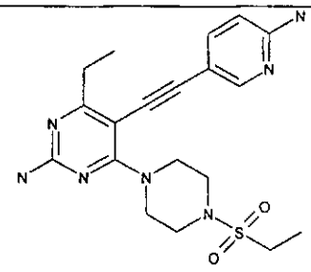
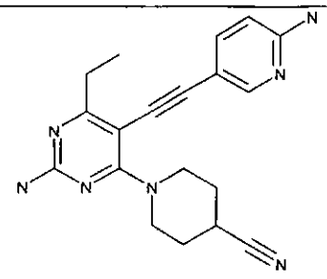
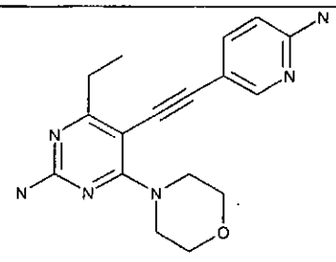
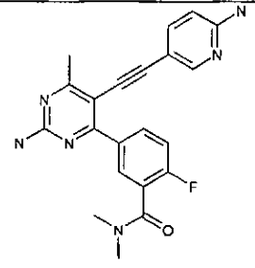
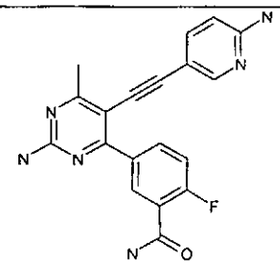
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
306		C-71	400,5	401	1,52
307		C-75	473,6	474	1,46
308		A-39	423,5	424	1,92
309		C-69	460,1	461	
310			418,9	419	1,53

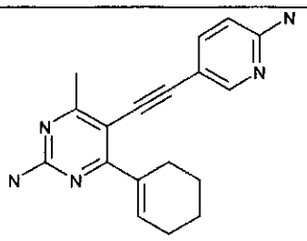
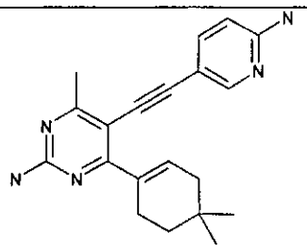
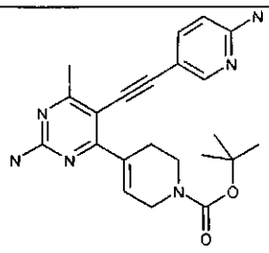
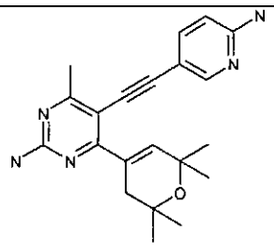
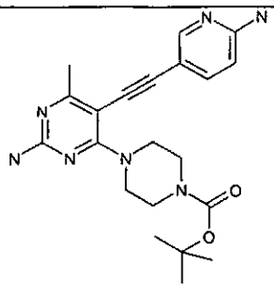
136

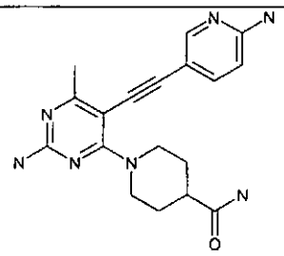
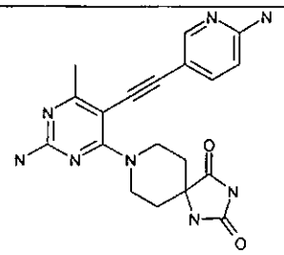
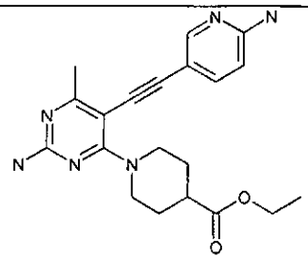
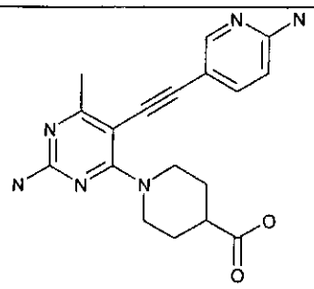
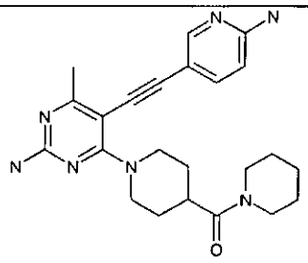
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
311		A-39	447,4	M-H = 446 (571)	1,61
312		A-30	378,5	379	1,72
313		A-27	368,4	369	2,13
314		C-46	391,9	392/394	1,51
315		C-46	315,4	316	1,46

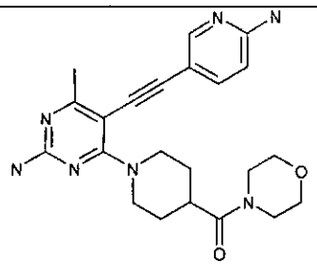
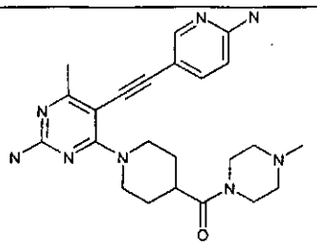
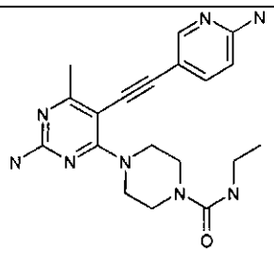
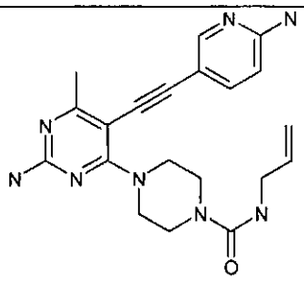
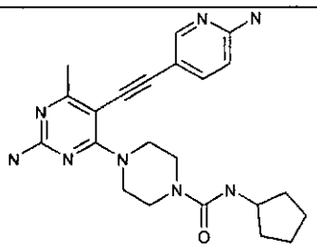
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
316		C-52	445,5	446	1,65
317		C-52	512,6	513	1,95
318		C-48	447,9	448/450	1,57
319		C-53	365,4	366	
320		C-53	401,5	402	1,33

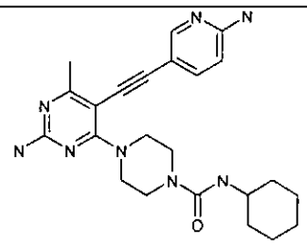
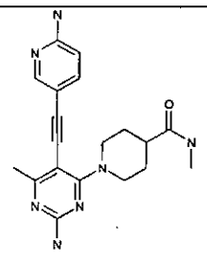
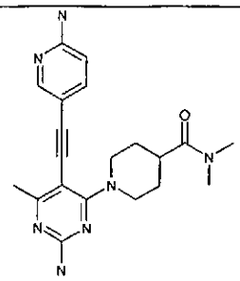
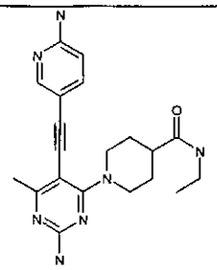
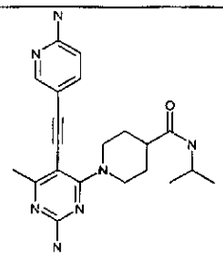
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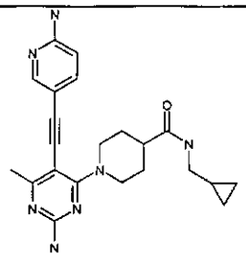
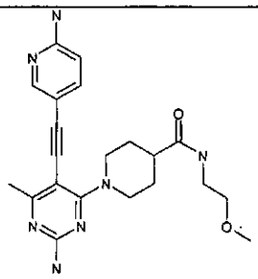
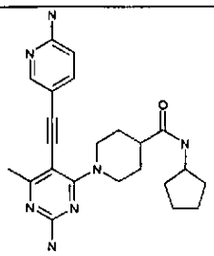
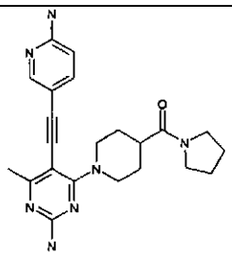
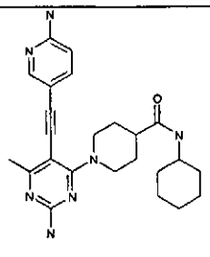
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
321		C-53	415,5	416	
322		C-53	347,4	348	1,39
323		C-53	324,4	325	1,32
324		A-33	390,4	391	1,23
325		A-33	362,4	363	1,08

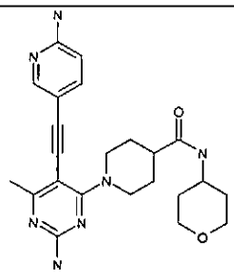
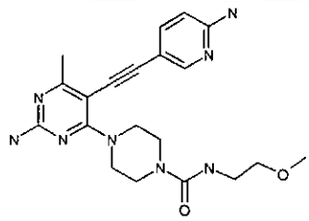
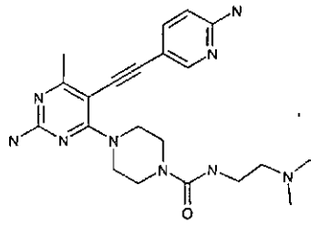
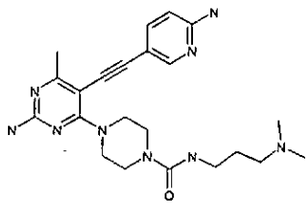
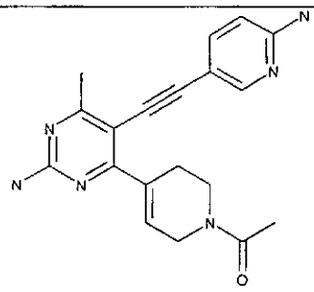
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
326		A-33	305,4	306	1,58
327		A-33	333,4	334	1,78
328			406,5	407	1,69
329		A-33	363,5	364	1,61
330			409,5	410	1,70

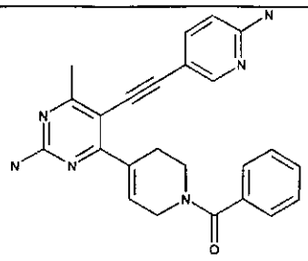
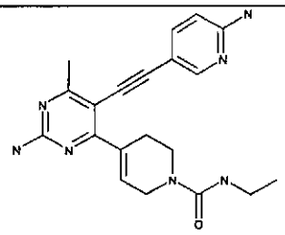
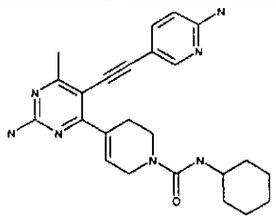
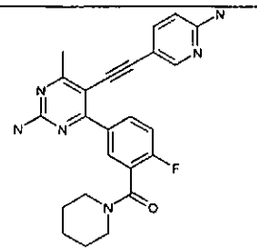
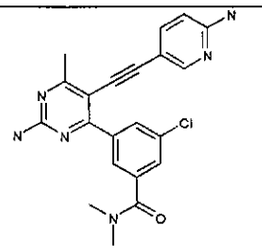
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
331		A-33	351,4	352	
332		A-33	392,4	393	
333		A-33	380,4	381	
334			352,4	353	0,62
335		C-87	419,5	420	

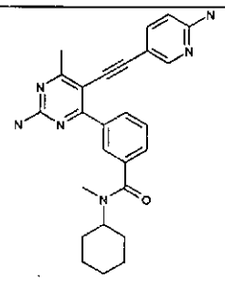
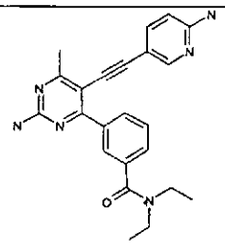
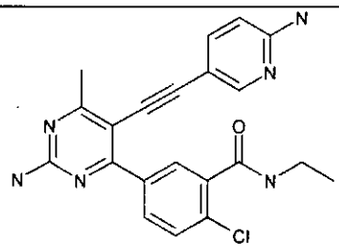
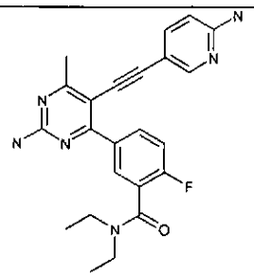
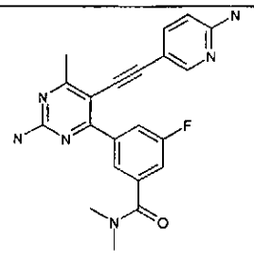
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
336		C-87	421,5	422	
337		C-87	434,6	435	
338		C-85	380,5	381	
339		C-85	392,5	393	0,15
340		C-85	420,5	421	1,28

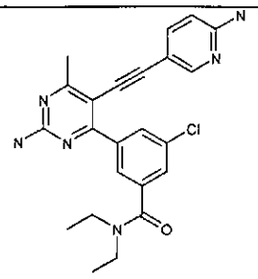
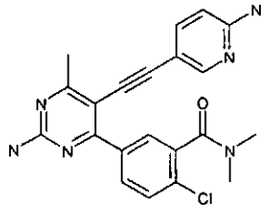
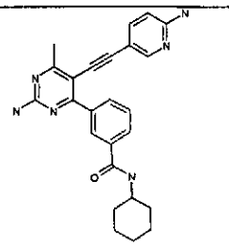
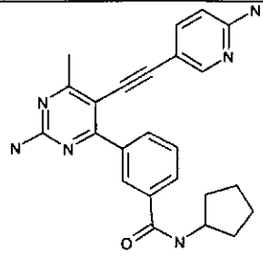
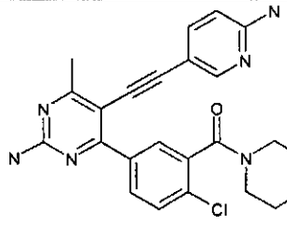
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
341		C-85	434,6	435	1,43
342		C-87	365,4	366	1,18
343		C-87	379,5	380	
344		C-87	379,5	380	1,26
345		C-87	393,5	394	1,35

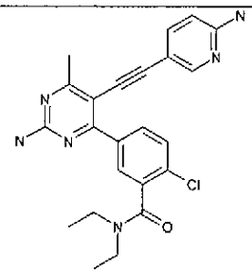
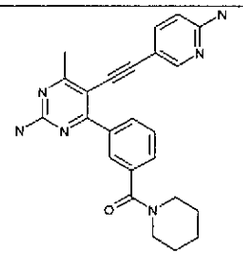
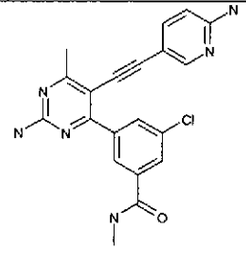
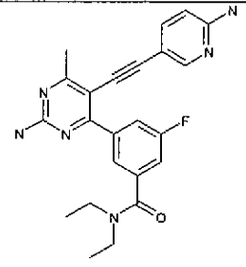
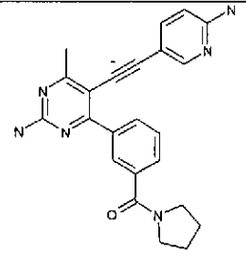
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
346		C-87	405,5	406	
347		C-87	409,5	410	
348		C-87	419,5	420	
349		C-87	405,5	406	1,41
350		C-87	433,6	434	1,58

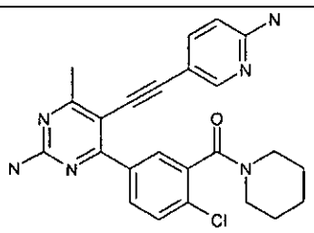
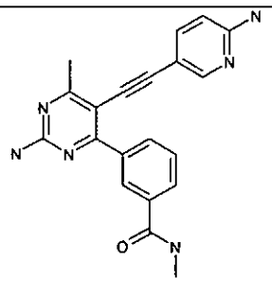
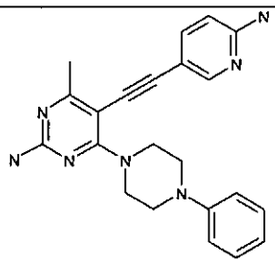
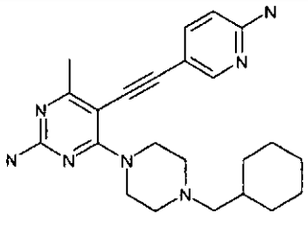
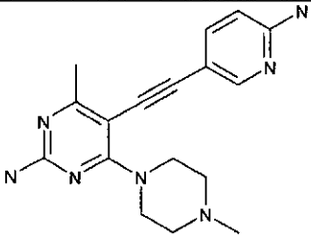
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
351		C-87	435,5	436	1,26
352		C-85	410,5	411	1,23
353		C-85	423,5	424	1,28
354		C-85	437,5	438	1,35
355		C-89	348,4	349	

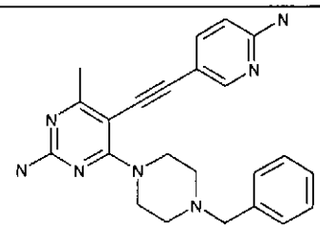
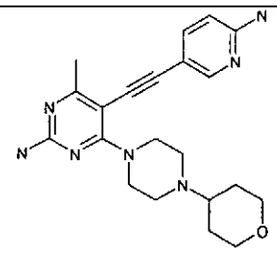
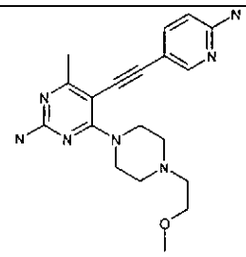
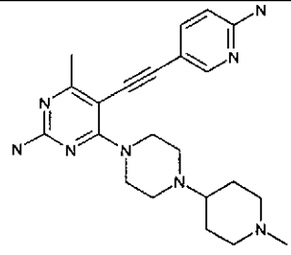
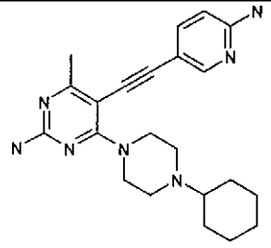
N°	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
356		C-89	410,5	411	1,44
357		C-89	377,4	378	
358		C-89	431,5	432	
359		A-33	430,5	431	
360		A-33	406,9	407	

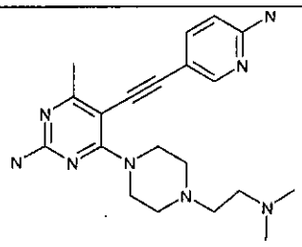
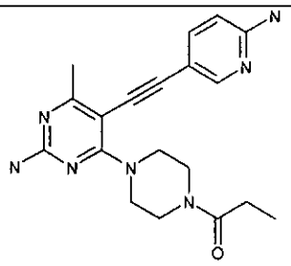
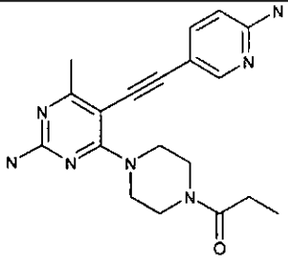
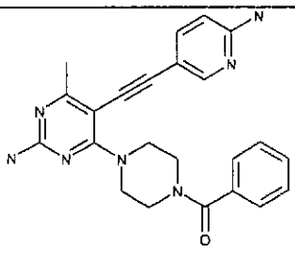
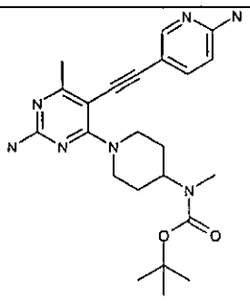
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
361		A-33	440,5	441	
362		A-33	400,5	401	
363		A-33	406,9	407	
364		A-33	418,5	419	
365		A-33	390,4	391	

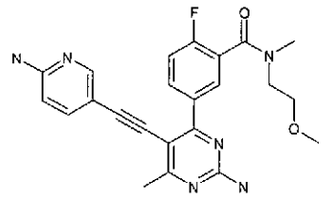
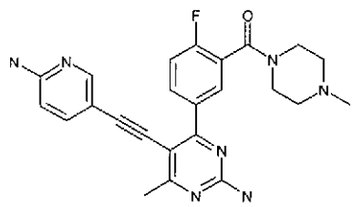
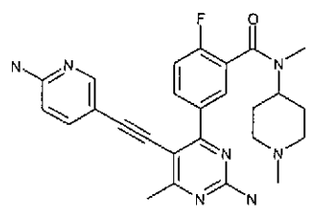
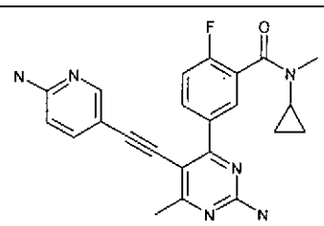
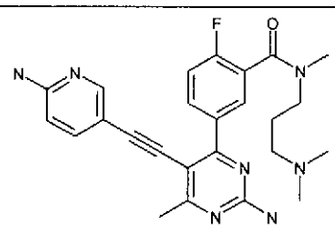
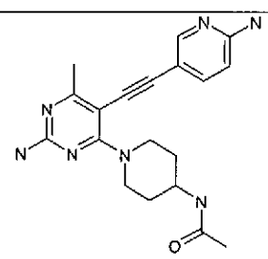
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
366		A-33	434,9	435	
367		A-33	406,9	407	
368		A-33	426,5	427	
369		A-33	412,5	414	
370		A-33	448,9	449	

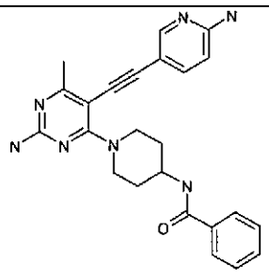
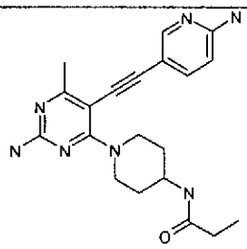
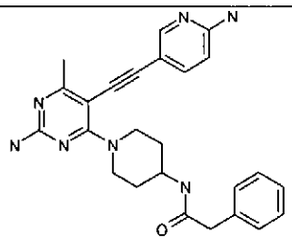
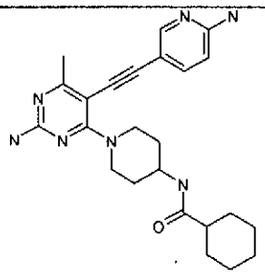
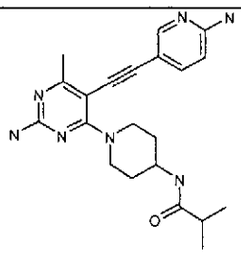
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
371		A-33	434,9	435	
372		A-33	412,5	413	1,48
373		A-33	392,8	393	
374		A-33	418,5	419	1,53
375		A-33	398,5	399	1,37

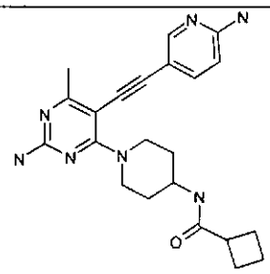
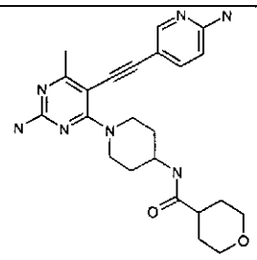
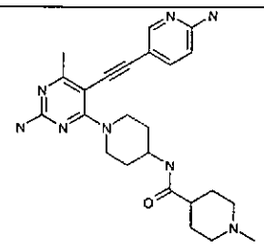
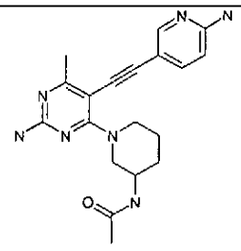
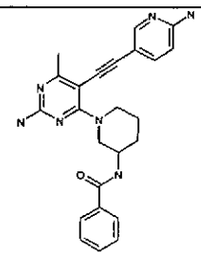
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
376		A-33	446,9	447	
377		A-33	358,4	359	
378		A-33	385,5	386	1,66
379		A-33	405,5	406	1,91
380		A-33	323,4	324	1,22

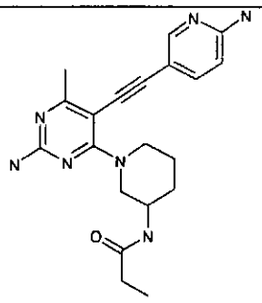
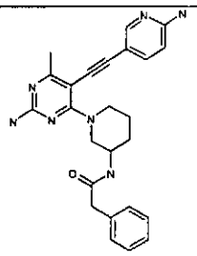
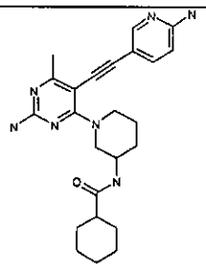
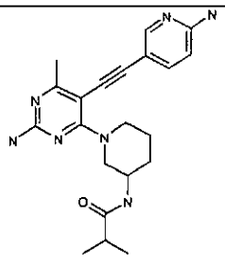
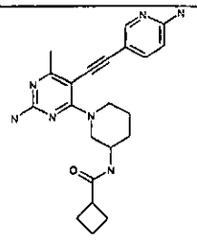
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
381		A-33	399,5	400	1,64
382		A-33	393,5	394	1,28
383		A-33	367,5	368	1,27
384		A-33	406,5	407	1,36
385		A-33	391,5	392	1,68

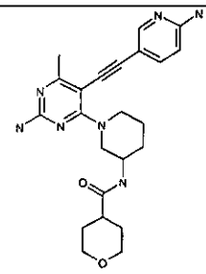
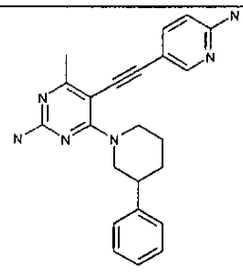
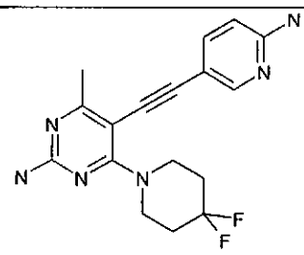
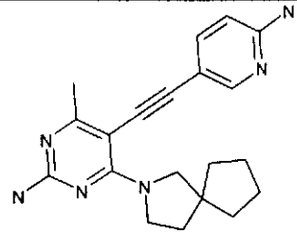
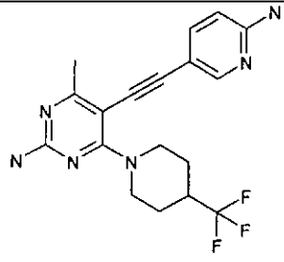
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
386		A-33	380,5	381	1,30
387		A-33	365,4	366	1,25
388		A-33	419,5	420	1,57
389		A-33	413,5	414	1,42
390			437,5	438	1,71

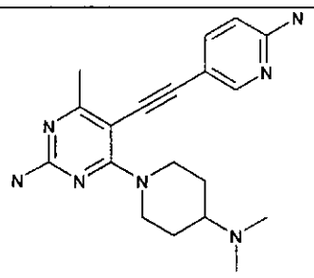
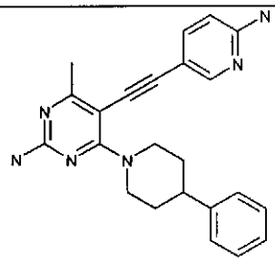
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
391		C-77	434,5	435	1,38
392		C-77	445,5	446	1,33
393		C-77	473,6	474	1,40
394		C-77	416,5	417	1,46
395		C-77	461,5	462	1,43
396		C-93	365,4	366	1,14

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
397		C-93	427,5	428	1,45
398		C-93	379,5	380	1,22
399		C-93	441,5	442	1,45
400		C-93	433,6	434	1,54
401		C-93	393,5	394	1,31

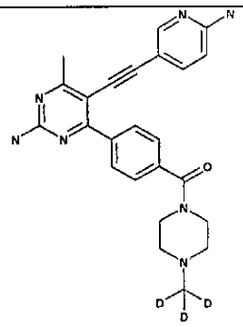
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
402		C-93	405,5	406	1,36
403		C-93	435,5	436	1,23
404		C-93	448,6	449	1,29
405		C-91	365,4	366	1,17
406		C-91	427,5	428	1,44

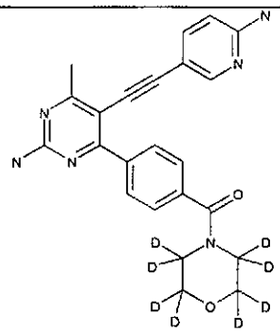
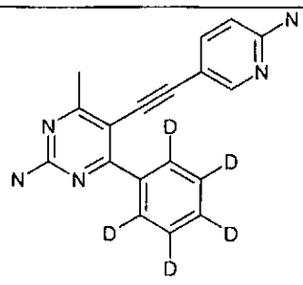
Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
407		C-91	379,5	380	1,24
408		C-91	441,5	442	1,44
409		C-91	433,6	434	1,54
410		C-91	393,5	394	1,33
411		C-91	405,5	406	1,37

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
412		C-91	435,5	436	1,25
413		A-33	384,5	385	1,78
414		A-33	344,4	345	1,49
415		A-33	348,5	349	1,72
416		A-33	376,4	377	1,60

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
417		A-33	351,5	352	1,35
418		A-33	384,5	385	

Los compuestos que llevan uno o más deuterios en vez de hidrógeno pueden prepararse como se ha indicado anteriormente. Los siguientes ejemplos se han preparado usando componentes básicos de vendedores comerciales (identificados, por ejemplo, por ACD-Finder o SciFinder) usando PG4 (acoplamiento de Suzuki) o PG9 (Formación de amidas):

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
419		C-71	430,5	431	1,24

Nº	Estructura	Material de Partida	PM	MS $[M+H]^+$	HPLC t_{Ret}
420		C-71	422,5	423	1,22
421		A-33	306,4	307	

Método analítico 1

HPLC: Agilent 1100 Series

MS: Agilent LC/MSD SL

columna: Phenomenex, Mercury Gemini C18, 3 µm, 2,0 x 20 mm, Pieza número 00M-4439-B0-CE

Disolvente A: NH_4HCO_3 5 mM/NH_3 20 mM

B: acetonitrilo de calidad HPLC

Detección:		
	MS:	positiva y negativa
	Intervalo de masas:	120 - 700 m/z
	fragmentador:	70
	ganancia EMV:	1
	umbral:	150
	tamaño de escalón:	0,25
	UV:	315 nm
	ancho de banda:	170 nm
	Referencia:	apagado
	intervalo:	210 - 400 nm
	escalón de intervalo:	2,00 nm
	anchura de pico:	< 0,01 min

rendija: 2 nm

inyección: 5 µl

Flujo: 1,00 ml/min

temperatura de la columna: 40°C

gradiente:

0,00 min	B al 5%
0,00 – 2,50 min	B al 5% -> 95%
2,50 – 2,80 min	B al 95%
2,81 – 3,10 min	B al 95% -> 5%

Método analítico 2

Instrumento: Agilent 1100-SL: incl. ELSD/DAD/MSD

Cromatografía:

Columna: Phenomenex Gemini® C18, 50 x 2,0 mm, 3 µ

Método "Ácido"

Eluyente A: ácido fórmico en acetonitrilo al 0,1%

Eluyente B: ácido fórmico en agua al 0,1%

Programa de gradiente lineal: t_0 = A al 2%, $t_{3,5min}$ = A al 98%, t_{6min} = A al 98%

Flujo: 1 ml/min

Temperatura del horno de la columna: 35°C

Método "Base"

Eluyente A: amoniaco 10 mM en acetonitrilo

Eluyente B: amoniaco 10 mM en agua

Programa de gradiente lineal: t_0 = A al 2%, $t_{3,5min}$ = A al 98%, t_{6min} = A al 98%

Flujo: 1 ml/min

Temperatura del horno de la columna: 35°C

Detector de Dispersión de Luz Evaporativa (ELSD):

Instrumento: Polymer Laboratories PL-ELS 2100

Flujo de gas de nebulización: 1,1 l/min N_2

Temp. de nebulización: 50°C

Temp. de evaporación: 80°C

Lámpara: LED Azul de 480 nm

Detector de matriz de diodos (DAD):

Instrumento: Agilent G1316A

Longitud de onda para la muestra: 220-320 nm

Longitud de onda de referencia: apagado

Espectroscopía de masas (MSD):

Instrumento: Agilent LC/MSD-SL

Ionización: ESI (positiva y negativa)

Intervalo de masas: 100-800

Abreviaturas utilizadas

ACN	acetonitrilo	ml	mililitro
bu	butilo	EM	espectrometría de masas
CDI	carbonildiimidazol	N	normal
d	día(s)	NIS	*N*-yodosuccinimida
DC	cromatografía de capa fina.	NMP	N-metilpirrolidininona
DCM	diclorometano	NMR	espectroscopía de resonancia nuclear
DIPEA	diisopropiletilamina	NP	fase normal
DMF	*N,N*-dimetilformamida	ppm	partes por millón
DMSO	dimetilsulfóxido	Rf	factor de retención
Et	etilo	RP	fase invertida
h	hora(s)	prep.	preparativa
HPLC	cromatografía líquida de alto rendimiento	TA	temperatura ambiente
iPr	isopropilo	*terc.*	terciario
LC	Cromatografía líquida	t_{Ret}	tiempo de retención
M	molar	THF	tetrahidrofurano
Me	metilo	TMS	tetrametilsilanilo
min	minuto(s)		

Los siguientes ejemplos describen la actividad biológica de los compuestos de acuerdo con la invención, sin restringir la invención a estos Ejemplos.

Ensayo de proliferación de PC3

El ensayo se basa en la medición del contenido de ADN celular a través de la unión de colorante fluorescente. Puesto que el contenido de ADN celular está altamente regulado y es estrechamente proporcional al número de células. El grado

de proliferación se determina comparando el recuento de células para muestras tratadas con fármacos y con controles sin tratar.

Se siembran células PC3 (línea celular de carcinoma de próstata humano) en placas de microtitulación, y se incuban durante una noche en medio de cultivo a 37 °C y 5% de CO_2. Se diluyen escalonadamente las sustancias de ensayo y se añaden a las células de manera que el volumen total es 200 µL por pocillo. Sirven como controles células a las que se añade diluyente, pero no sustancia. Después de un tiempo de incubación de 3 días, se reemplaza el medio por 100 µL/pocillo de solución de unión a colorante, y se incuban las células a 37 °C en la oscuridad, durante 60 minutos más. Para medir la fluorescencia, la excitación tiene lugar a una longitud de onda de 485 nm y la emisión se mide a 530 nm.

Los valores de CE_{50} se calculan mediante el programa GraphPad Prism.

La mayoría de los compuestos de los Ejemplos citados tienen una CE_{50} (Proliferación de PC3) inferior a 1 µM.

Medición de P-AKT en células PC3

Los niveles de P-AKT en células PC3 se detectan mediante ELISA basado en células. Se cultivan las células en placas de 96 pocillos y se tratan con diluciones en serie de las sustancias de ensayo durante 2 horas. Sirven como controles células a las que se añade diluyente, pero no sustancia. Después se fijan rápidamente las células para preservar las modificaciones proteicas. Después se incuba cada pocillo con un anticuerpo primario específico para AKT fosforilado en Ser473. La posterior incubación con anticuerpo secundario conjugado con HRP y solución de revelado proporcionan una lectura colorimétrica a 450 nm. Los valores de CE_{50} se calculan mediante el programa GraphPad Prism.

La mayoría de los compuestos de los Ejemplos citados tienen una CE_{50} (P-AKT de PC3) inferior a 1 µM.

Las sustancias de la presente invención son inhibidores de PI3 quinasa. En virtud de sus propiedades biológicas, los nuevos compuestos de la fórmula general (1) y sus isómeros y sus sales fisiológicamente toleradas son adecuados para el tratamiento de enfermedades que se caracterizan por una proliferación celular excesiva o anómala.

Estas enfermedades incluyen, por ejemplo: infecciones víricas (por ejemplo VIH y sarcoma de Kaposi); enfermedades inflamatorias y autoinmunitarias (por ejemplo colitis, artritis, enfermedad de Alzheimer, glomerulonefritis y cicatrización de heridas); infecciones bacterianas, fúngicas y/o parasitarias; leucemias, linfomas

y tumores sólidos; enfermedades de la piel (por ejemplo psoriasis); enfermedades óseas; enfermedades cardiovasculares (por ejemplo reestenosis e hipertrofia). Además, los compuestos son útiles para proteger a las células proliferantes (por ejemplo células pilosas, células intestinales, células sanguíneas y células progenitoras) del daño al ADN causado por irradiación, tratamientos con UV y/o tratamiento citostático (Davis y otros, 2001).

Por ejemplo, las siguientes enfermedades cancerosas se pueden tratar con compuestos de acuerdo con la invención, aunque sin limitarse a las mismas: tumores cerebrales tales como neurinoma del acústico, astrocitomas tales como astrocitomas piloides, astrocitoma fibrilar, astrocitoma protoplásmico, astrocitoma gemistocítico, astrocitoma anaplásico y glioblastomas, linfomas cerebrales, metástasis cerebrales, tumor hipofisario tal como prolactinoma, tumor productor de HGH (hormona del crecimiento humana) y tumor productor de ACTH (hormona adenocorticotrófica), craneofaringiomas, meduloblastomas, meningiomas y oligodendrogliomas; tumores nerviosos (neoplasmas) tales como tumores del sistema nervioso vegetativo tales como neuroblastoma simpático, ganglioneuroma, paraganglioma (feocromocitoma y cromafinoma) y tumor del cuerpo carotídeo, tumores del sistema nervioso periférico tales como neuroma de amputación, neurofibroma, neurinoma (neurilemoma, schwannoma) y schwannoma maligno, así como tumores del sistema nervioso central tales como tumores cerebrales y de la médula espinal; cáncer intestinal tal como carcinoma rectal, carcinoma de colon, carcinoma anal, tumores del intestino delgado y tumores duodenales; tumores de párpado tales como basalioma o carcinoma de células basales; cáncer de la glándula pancreática o carcinoma pancreático; cáncer de vejiga o carcinoma de vejiga; cáncer de pulmón (carcinoma bronquial) tal como carcinomas bronquiales de células pequeñas (carcinomas de células en avena) y carcinomas bronquiales de células no pequeñas tales como carcinomas del epitelio escamoso, adenocarcinomas y carcinomas bronquiales de células grandes; cáncer de mama tal como carcinoma mamario, tal como carcinoma ductal infiltrante, carcinoma coloide, carcinoma lobular invasivo, carcinoma tubular, carcinoma adenoide quístico, y carcinoma papilar; linfomas no Hodgkin (NHL) tales como linfoma de Burkitt, linfomas no Hodgkin (NHL) de bajo grado de malignidad y micosis fungoides; cáncer de útero o carcinoma de endometrio o carcinoma de cuerpo; síndrome CUP (cáncer de origen primario desconocido); cáncer de ovario o carcinoma de ovario tal como cáncer mucinoso, de endometrio o seroso; cáncer de

la vesícula biliar; cáncer del conducto biliar tal como tumor de Klatskin; cáncer testicular tal como seminomas y no seminomas; linfoma (linfosarcoma) tal como linfoma maligno, enfermedad de Hodgkin, linfomas no Hodgkin (NHL) tales como leucemia linfática crónica, leucemia de células pilosas, inmunocitoma, plasmocitoma (mieloma múltiple), inmunoblastoma, linfoma de Burkitt, micosis fungoides de zona T, linfoblastoma anaplásico de células grandes y linfoblastoma; cáncer de laringe tal como tumor de cuerdas vocales, tumores laríngeos supraglótico, glótico y subglótico; cáncer óseo tal como osteocondroma, condroma, condroblastoma, fibroma condromixoide, osteoma, osteoma osteoide, osteoblastoma, granuloma eosinófilo, tumor de células gigantes, condrosarcoma, osteosarcoma, sarcoma de Ewing, reticulosarcoma, plasmocitoma, displasia fibrosa, quiste óseo juvenil y quiste óseo aneurismático; tumores de cabeza y cuello tales como tumores de los labios, de la lengua, del suelo de la boca, de la cavidad oral, de las encías, del paladar, de las glándulas salivares, de la faringe, de las cavidades nasales, de los senos paranasales, de la laringe y del oído medio; cáncer de hígado tal como carcinoma de células hepáticas o carcinoma hepatocelular (HCC); leucemias, tales como leucemias agudas, tal como leucemia linfática/linfoblástica aguda (ALL), leucemia mieloide aguda (AML); leucemias crónicas tales como leucemia linfática crónica (CLL), leucemia mieloide crónica (CML); cánceres de estómago o carcinoma de estómago tal como adenocarcinoma papilar, tubular y mucinoso, carcinoma de células en anillo de sello, carcinoma adenoide de células escamosas, carcinoma de células pequeñas y carcinoma indiferenciado; melanomas tales como de extensión superficial, lentigo maligno nodular y melanoma acrolentiginoso; cáncer renal tal como carcinoma de células renales o hipernefroma o tumor de Grawitz; cáncer de esófago o carcinoma esofágico; cáncer del pene; cáncer de próstata; cáncer de faringe o carcinoma faríngeo tal como carcinomas nasofaríngeos, carcinomas orofaríngeos y carcinomas hipofaríngeos; retinoblastoma; cáncer vaginal o carcinoma vaginal; carcinomas del epitelio escamoso, adenocarcinomas, carcinomas in situ, melanomas malignos y sarcomas; carcinomas de la glándula tiroides tales como carcinoma papilar, folicular y medular de la glándula tiroides, y también carcinomas anaplásicos; espinalioma, carcinoma de células espinosas y carcinoma del epitelio escamoso de la piel; timomas, cáncer de uretra y cáncer de vulva.

Los nuevos compuestos se pueden utilizar para la prevención o el tratamiento a corto plazo o a largo plazo de las enfermedades antes mencionadas,

también, cuando sea apropiado, en combinación con otros compuestos del estado de la técnica tales como otras sustancias antitumorales, sustancias citotóxicas, inhibidores de la proliferación celular, sustancias antiangiogénicas, esteroides o anticuerpos.

Los compuestos de la fórmula general (1) pueden usarse, por sí solos o en combinación con otros compuestos activos de acuerdo con la invención y, cuando sea apropiado, también en combinación con otros compuestos farmacológicamente activos. Los agentes quimioterapéuticos que pueden administrarse en combinación con los compuestos de acuerdo con la invención incluyen, aunque sin similtarse a los mismos, hormonas, análogos de hormonas y antihormonas (por ejemplo tamoxifeno, toremifeno, raloxifeno, fulvestrant, acetato de megestrol, flutamida, nilutamida, bicalutamida, aminoglutetimida, acetato de ciproterona, finasterida, acetato de buserelina, fludrocortisona, fluoximesterona, medroxiprogesterona y octreótida), inhibidores de aromatasa (por ejemplo anastrozol, letrozol, liarozol, vorozol, exemestano y atamestano), agonistas y antagonistas de LHRH (por ejemplo acetato de goserelina y luprolida), inhibidores de factores de crecimiento (factores de crecimiento tales como factor de crecimiento derivado de plaquetas y factor de crecimiento de hepatocitos, son ejemplos de inhibidores los anticuerpos contra factores de crecimiento, anticuerpos contra receptores de factores de crecimiento e inhibidores de tirosina-quinasas, tales como gefitinib, imatinib, lapatinib, Erbitux® y trastuzumab); antimetabolitos (por ejemplo antifolatos tales como metotrexato y raltitrexed, análogos de pirimidina tales como 5-fluorouracilo, capecitabina y gemcitabina, análogos de purina y de adenosina tales como mercaptopurina, tioguanina, cladribina y pentostatina, citarabina y fludarabina); antibióticos antitumorales (por ejemplo antraciclinas tales como doxorrubicina, daunorrubicina, epirrubicina e idarrubicina, mitomicina C, bleomicina, dactinomicina, plicamicina y estreptozocina); derivados de platino (por ejemplo cisplatino, oxaliplatino y carboplatino); agentes alquilantes (por ejemplo, estramustina, mecloretamina, melfalán, clorambucilo, busulfán, dacarbazina, ciclofosfamida, ifosfamida y temozolomida, nitrosoureas tales como carmustina y lomustina y tiotepa); agentes antimitóticos (por ejemplo alcaloides de la vinca tales como vinblastina, vindesina, vinorrelbina y vincristina; y taxanos tales como paclitaxel y docetaxel); inhibidores de la topoisomerasa (por ejemplo epipodofilotoxinas tales como etopósido y etopofos, tenipósido, amsacrina, topotecán, irinotecán y mitoxantrona) y diversos agentes quimioterapéuticos tales como amifostina,

anagrelida, clodronato, filgrastina, interferón alfa, leucovorina, rituximab, procarbazina, levamisol, mesna, mitotán, pamidronato y porfímero.

Son ejemplos de formas adecuadas para el uso comprimidos, cápsulas, supositorios, soluciones, en particular soluciones para inyección (s.c., i.v., i.m.) e infusión, jarabes, emulsiones o polvos dispersables. A este respecto, la proporción del compuesto o compuestos farmacéuticamente activos debe situarse en cada caso en el intervalo de 0,1-90% en peso, preferiblemente 0,5-50% en peso, de la composición total, es decir, en cantidades que sean suficientes para conseguir el intervalo de dosificación que se especifica más adelante. Si fuera necesario, las dosis mencionadas se pueden administrar varias veces al día.

Los comprimidos adecuados se pueden obtener, por ejemplo, mezclando el compuesto o compuestos activos con sustancias auxiliares conocidas, por ejemplo diluyentes inertes tales como carbonato cálcico, fosfato cálcico o lactosa, disgregantes tales como almidón de maíz o ácido algínico, aglutinantes tales como almidón o gelatina, lubricantes tales como estearato de magnesio o talco y/o agentes para conseguir un efecto de liberación prolongada, tales como carboximetil celulosa, acetato ftalato de celulosa o acetato de polivinilo. Los comprimidos también pueden comprender varias capas.

De acuerdo con esto, se pueden introducir comprimidos recubiertos de azúcar revistiendo núcleos, que se han preparado de manera análoga a los comprimidos, con agentes que se utilizan habitualmente en revestimientos de azúcar, por ejemplo colidona o goma laca, goma arábiga, talco, dióxido de titanio o azúcar. El núcleo puede comprender también varias capas con el fin de lograr un efecto de liberación prolongada o para evitar incompatibilidades. Del mismo modo, el revestimiento de azúcar puede comprender también varias capas con el fin de lograr un efecto de liberación prolongada, siendo posible utilizar las sustancias auxiliares que se han mencionado antes en el caso de los comprimidos.

Los jarabes de los compuestos activos o combinaciones de compuestos activos de acuerdo con la invención pueden comprender, además, un agente edulcorante, tal como sacarina, ciclamato, glicerol o azúcar, así como un agente mejorador del sabor, por ejemplo agentes saporíferos tales como vainillina o extracto de naranja. También pueden comprender adyuvantes de suspensión o espesantes tales como carboximetilcelulosa sódica, agentes humectantes tales como, por ejemplo, productos de condensación de alcoholes grasos con óxido de etileno o protectores tales como p-hidroxibenzoatos.

Las soluciones para inyección e infusión se producen de la manera habitual, por ejemplo añadiendo agentes isotonizantes, conservantes tales como p-hidroxibenzoatos, o estabilizantes, tales como sales de metales alcalinos del ácido etilendiaminotetraacético, usando cuando sea apropiado emulsionantes y/o dispersantes, siendo posible, por ejemplo, emplear cuando sea apropiado disolventes orgánicos como agentes solubilizantes o disolventes auxiliares cuando se emplea agua como diluyente, y se dividen en alícuotas en frascos o ampollas para inyección o frascos para infusión.

Las cápsulas que comprenden uno o más compuestos activos o combinaciones de compuestos activos se pueden producir, por ejemplo, mezclando los compuestos activos con vehículos inertes tales como lactosa o sorbitol, y encapsulando la mezcla en cápsulas de gelatina. Se pueden producir supositorios adecuados, por ejemplo, mezclando con excipientes adaptados a este fin, tales como grasas neutras o polietilenglicol o sus derivados.

Son sustancias auxiliares que se pueden mencionar a modo de ejemplo, el agua, disolventes orgánicos farmacéuticamente inofensivos tales como parafinas (por ejemplo, fracciones del petróleo), aceites de origen vegetal (por ejemplo, aceite de cacahuete o aceite de sésamo), alcoholes monofuncionales o polifuncionales (por ejemplo, EtOH o glicerol), sustancias de vehículo tales como polvos de minerales naturales (por ejemplo, caolines, tierras arcillosas, talco y creta), polvos de minerales sintéticos (por ejemplo, ácido silícico altamente disperso y silicatos), azúcares (por ejemplo, azúcar de caña, lactosa y azúcar de uva), emulsionantes (por ejemplo, lignina, aguas del tratamiento con sulfito, metilcelulosa, almidón y polivinilpirrolidona) y lubricantes (por ejemplo, estearato de magnesio, talco, ácido esteárico y laurilsulfato sódico).

La administración se efectúa de manera habitual, preferiblemente por vía oral o transdérmica, en particular y preferiblemente por vía oral. En el caso del uso oral, los comprimidos también pueden comprender como es natural, además de las sustancias de vehículo antes mencionadas, aditivos tales como citrato sódico, carbonato cálcico y fosfato dicálcico, junto con otras diversas sustancias tales como almidón, preferiblemente almidón de patata, gelatina y similares. Además, también es posible emplear lubricantes tales como estearato de magnesio, laurilsulfato sódico y talco, durante la compresión. En el caso de las suspensiones acuosas, también se pueden añadir a los compuestos activos diversos mejoradores del sabor o colorantes, además de las sustancias auxiliares antes mencionadas.

Para la administración parenteral, es posible emplear soluciones de los compuestos activos, utilizando materiales de vehículo líquidos adecuados. La dosificación para administración intravenosa es de 1-1000 mg por hora, preferiblemente entre 5 y 500 mg por hora.

A pesar de esto, puede ser necesario, cuando sea apropiado, desviarse de las cantidades antes mencionadas, en función del peso corporal o de la naturaleza de la vía de administración, de la respuesta individual al medicamento, de la naturaleza de su formulación, y del momento o del intervalo de tiempo en el que se realiza la administración. Así, en algunos casos puede ser suficiente administrar cantidades inferiores a las mínimas antes mencionadas, mientras que en otros casos hay que sobrepasar el límite superior antes mencionado. Cuando se estén administrando cantidades relativamente grandes, puede ser conveniente dividirlas en varias dosis individuales, que se administran a lo largo del día.

Los siguientes ejemplos de formulación ilustran la presente invención, aunque sin limitar su alcance:

Ejemplos de formulación farmacéutica

A) Comprimidos	por comprimido
Compuesto activo según la fórmula (1)	100 mg
Lactosa	140 mg
Almidón de maíz	240 mg
Polivinilpirrolidona	15 mg
Estearato de magnesio	5 mg
	500 mg

Se mezclan entre sí el compuesto activo finamente molido, lactosa y una parte del almidón de maíz. Se tamiza la mezcla, después se humedece con una solución de polivinilpirrolidona en agua, se amasa, se granula en húmedo y se seca. Se tamizan el material granular, el resto del almidón de maíz y el estearato de magnesio y se mezclan entre sí. La mezcla se comprime en comprimidos de forma y tamaño adecuados.

B) Comprimidos	por comprimido
Compuesto activo según la fórmula (1)	80 mg
Lactosa	55 mg
Almidón de maíz	190 mg
celulosa microcristalina	35 mg

Polivinilpirrolidona	15 mg
carboximetilalmidón sódico	23 mg
Estearato de magnesio	2 mg
	400 mg

Se mezclan entre sí el compuesto activo finamente molido, una parte del almidón de maíz, la lactosa, la celulosa microcristalina y la polivinilpirrolidona, después de lo cual se tamiza la mezcla y se elabora, junto con el resto del almidón de maíz y agua, para dar un material granular, que se seca y se tamiza. Después se añaden al material granular el carboximetilalmidón sódico y el estearato de magnesio, y se mezclan con el mismo, y se comprime la mezcla para dar comprimidos de tamaño adecuado.

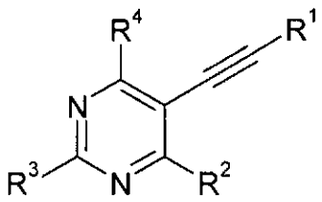
C) Solución en ampolla

Compuesto activo según la fórmula (1)	50 mg
Cloruro sódico	50 mg
Agua para inyección	5 ml

Se disuelve en agua el compuesto activo, sea a su pH intrínseco o, cuando sea apropiado, a un valor de pH de 5,5-6,5, después de lo cual se añade cloruro sódico como agente isotonizante. Se libera de pirógenos por filtración la solución resultante, y el filtrado se divide en alícuotas, en condiciones asépticas, en ampollas, que después se esterilizan y se cierran herméticamente por fundido. Las ampollas contienen 5 mg, 25 mg y 50 mg de compuesto activo.

REIVINDICACIONES

1. Compuestos de fórmula general (1),



(1),

en la que

R^1 representa un grupo seleccionado entre cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, arilo C_{6-10} y heteroarilo de 5-12 miembros, opcionalmente sustituido con uno o más R^5 iguales o diferentes; y

R^2 representa un grupo seleccionado entre cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, arilo C_{6-10} y heteroarilo de 5-12 miembros, opcionalmente sustituido con uno o más R^5 iguales o diferentes y

R^3 representa hidrógeno o un grupo seleccionado entre halógeno, $-OR^e$, $-NR^eR^e$, $-CF_3$, -CN, -NC, $-NO_2$ y alquilo C_{1-6}; y

R^4 representa un grupo seleccionado entre alquilo C_{1-3}, cicloalquilo C_{3-8}, heterocicloalquilo de 3-8 miembros, $-OR^e$, $-NR^eR^e$, $-CF_3$, $-CN$, -NC y $-NO_2$, y

cada **R^5** representa un grupo seleccionado entre R^a, R^b y R^a sustituido con uno o más R^b y/o R^c iguales o diferentes; y

cada **R^a** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R^b** y/o **R^c** iguales o diferentes, seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arialquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros;

cada **R^b** representa un grupo adecuado y se selecciona independientemente entre sí entre =O, $-OR^c$, haloalquiloxi C_{1-3}, $-OCF_3$, =S, $-SR^c$, $=NR^c$, $=NOR^c$, $=NNR^cR^c$, $=NN(R^g)C(O)NR^cR^c$, $-NR^cR^c$, $-ONR^cR^c$, $-N(OR^c)R^c$, $-N(R^g)NR^cR^c$, halógeno, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^c$, $-S(O)OR^c$, $-S(O)_2R^c$, $-S(O)_2OR^c$, $-S(O)NR^cR^c$, $-S(O)_2NR^cR^c$, $-OS(O)R^c$, $-OS(O)_2R^c$, $-OS(O)_2OR^c$, $-OS(O)NR^cR^c$, $-OS(O)_2NR^cR^c$, $-C(O)R^c$, $-C(O)OR^c$, $-C(O)SR^c$, $-C(O)NR^cR^c$, $-C(O)N(R^g)NR^cR^c$, $-C(O)N(R^g)OR^c$, $-C(NR^g)NR^cR^c$, $-C(NOH)R^c$, $-C(NOH)NR^cR^c$, $-OC(O)R^c$, $-OC(O)OR^c$, $-OC(O)SR^c$, $-OC(O)NR^cR^c$, $-OC(NR^g)NR^cR^c$, $-SC(O)R^c$,

-SC(O)OR^c, –SC(O)NR^{c}R^c, –SC(NR^g)NR^{c}R^c, -N(R^g)C(O)R^c, –N[C(O)R^c]$_2$, -N(OR^g)C(O)R^c, –N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, –N[C(O)R^c]NR^{c}R^c, -N(R^g)C(S)R^c, –N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, –N(R^g)S(O)$_2$R^c, –N[S(O)$_2$R^c]$_2$, -N(R^g)S(O)$_2$OR^c, -N(R^g)S(O)$_2$NR^{c}R^c, –N(R^g)[S(O)$_2$]$_2$R^c, –N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^{c}R^c, –N(R^g)C(O)NR^{g}NR^{c}R^c, –N(R^g)N(R^g)C(O)NR^{c}R^c, -N(R^g)C(S)NR^{c}R^c, –[N(R^g)C(O)]$_2$R^c, –N(R^g)[C(O)]$_2$R^c, –N{[C(O)]$_2$R^c}$_2$, -N(R^g)[C(O)]$_2$OR^c, –N(R^g)[C(O)]$_2$NR^{c}R^c, –N{[C(O)]$_2$OR^c}$_2$, –N{[C(O)]$_2$NR^{c}R^c}$_2$, -[N(R^g)C(O)]$_2$OR^c, –N(R^g)C(NR^g)OR^c, –N(R^g)C(NOH)R^c, –N(R^g)C(NR^g)SR^c, -N(R^g)C(NR^g)NR^{c}R^c y -N=C(R^g)NR^{c}R^c y

cada **R^c** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R$_d$** y/o **R$_e$** iguales o diferentes, seleccionados entre alquilo C$_{1-6}$, heteroalquilo de 2-6 miembros, haloalquilo C$_{1-6}$, cicloalquilo C$_{3-10}$, cicloalquilalquilo C$_{4-16}$, arilo C$_{6-10}$, arialquilo C$_{7-16}$, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros, y

cada **R^d** representa un grupo adecuado y se selecciona independientemente entre sí entre =O, –OR^e, haloalquiloxi C$_{1-3}$, –OCF$_3$, =S, –SR^e, =NR^e, =NOR^e, =NNR^{e}R^e, =NN(R^g)C(O)NR^{e}R^e, –NR^{e}R^e, –ONR^{e}R^e, –N(R^g)NR^{e}R^e, halógeno, –CF$_3$, –CN, -NC, -OCN, –SCN, –NO, –NO$_2$, =N$_2$, –N$_3$, –S(O)R^e, –S(O)OR^e, –S(O)$_2$R^e, –S(O)$_2$OR^e, -S(O)NR^{e}R^e, –S(O)$_2$NR^{e}R^e, –OS(O)R^e, –OS(O)$_2$R^e, –OS(O)$_2$OR^e, –OS(O)NR^{e}R^e, -OS(O)$_2$NR^{e}R^e, –C(O)R^e, –C(O)OR^e, –C(O)SR^e, –C(O)NR^{e}R^e, –C(O)N(R^g)NR^{e}R^e, -C(O)N(R^g)OR^e, –C(NR^g)NR^{e}R^e, –C(NOH)R^e, –C(NOH)NR^{e}R^e, –OC(O)R^e, -OC(O)OR^e, –OC(O)SR^e, –OC(O)NR^{e}R^e, –OC(NR^g)NR^{e}R^e, –SC(O)R^e, -SC(O)OR^e, -SC(O)NR^{e}R^e, –SC(NR^g)NR^{e}R^e, –N(R^g)C(O)R^e, –N[C(O)R^e]$_2$, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, –N(R^g)N(R^g)C(O)R^e, –N[C(O)R^e]NR^{e}R^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, –N(R^g)S(O)OR^e –N(R^g)S(O)$_2$R^e, –N[S(O)$_2$R^e]$_2$, -N(R^g)S(O)$_2$OR^e, -N(R^g)S(O)$_2$NR^{e}R^e, –N(R^g)[S(O)$_2$]$_2$R^e, –N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^{e}R^e, –N(R^g)C(O)NR^{g}NR^{e}R^e, -N(R^g)N(R^g)C(O)NR^{e}R^e, -N(R^g)C(S)NR^{e}R^e, –[N(R^g)C(O)]$_2$R^e, –N(R^g)[C(O)]$_2$R^e, -N{[C(O)]$_2$R^e}$_2$, -N(R^g)[C(O)]$_2$OR^e, –N(R^g)[C(O)]$_2$NR^{e}R^e, –N{[C(O)]$_2$OR^e}$_2$, -N{[C(O)]$_2$NR^{e}R^e}$_2$, -[N(R^g)C(O)]$_2$OR^e, –N(R^g)C(NR^g)OR^e, –N(R^g)C(NOH)R^e, -N(R^g)C(NR^g)SR^e, -N(R^g)C(NR^g)NR^{e}R^e y -N=C(R^g)NR^{e}R^e

cada **R^e** independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más **R^f** y/o **R^g**, iguales o similares, seleccionados entre alquilo C$_{1-6}$, heteroalquilo de 2-6 miembros, haloalquilo C$_{1-6}$,

cicloalquilo C_{3-6}, cicloalquilalquilo C_{4-16}, arilo $C_{6,10}$, arialquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros, y

cada $\mathbf{R^f}$ representa un grupo adecuado y en cada caso se selecciona independientemente entre sí entre =O, $-OR^g$, haloalquiloxi C_{1-3}, $-OCF_3$, =S, $-SR^g$, $=NR^g$, $=NOR^g$, $=NNR^gR^g$, $=NN(R^h)C(O)NR^gR^g$, $-NR^gR^g$, $-ONR^gR^g$, $-N(R^h)NR^gR^g$, halógeno, $-CF_3$, -CN, -NC, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^g$, $-S(O)OR^g$, $-S(O)_2R^g$, $-S(O)_2OR^g$, $-S(O)NR^gR^g$, $-S(O)_2NR^gR^g$, $-OS(O)R^g$, $-OS(O)_2R^g$, $-OS(O)_2OR^g$, $-OS(O)NR^gR^g$, $-OS(O)_2NR^gR^g$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)SR^g$, $-C(O)NR^gR^g$, $-C(O)N(R^h)NR^gR^g$, $-C(O)N(R^h)OR^g$, $-C(NR^h)NR^gR^g$, $-C(NOH)R^g$, $-C(NOH)NR^gR^g$, $-OC(O)R^g$, $-OC(O)OR^g$, $-OC(O)SR^g$, $-OC(O)NR^gR^g$, $-OC(NR^h)NR^gR^g$, $-SC(O)R^g$, $-SC(O)OR^g$, $-SC(O)NR^gR^g$, $-SC(NR^h)NR^gR^g$, $-N(R^h)C(O)R^g$, $-N[C(O)R^g]_2$, $-N(OR^h)C(O)R^g$, $-N(R^h)C(NR^h)R^g$, $-N(R^h)N(R^h)C(O)R^g$, $-N[C(O)R^g]NR^gR^g$, $-N(R^h)C(S)R^g$, $-N(R^h)S(O)R^g$, $-N(R^h)S(O)OR^g$, $-N(R^h)S(O)_2R^g$, $-N[S(O)_2R^g]_2$, $-N(R^h)S(O)_2OR^g$, $-N(R^h)S(O)_2NR^gR^g$, $-N(R^h)[S(O)_2]_2R^g$, $-N(R^h)C(O)OR^g$, $-N(R^h)C(O)SR^g$, $-N(R^h)C(O)NR^gR^g$, $-N(R^h)C(O)NR^hNR^gR^g$, $-N(R^h)N(R^h)C(O)NR^gR^g$, $-N(R^h)C(S)NR^gR^g$, $-[N(R^h)C(O)]_2R^g$, $-N(R^h)[C(O)]_2R^g$, $-N\{[C(O)]_2R^g\}_2$, $-N(R^h)[C(O)]_2OR^g$, $-N(R^h)[C(O)]_2NR^gR^g$, $-N\{[C(O)]_2OR^g\}_2$, $-N\{[C(O)]_2NR^gR^g\}_2$, $-[N(R^h)C(O)]_2OR^g$, $-N(R^h)C(NR^h)OR^g$, $-N(R^h)C(NOH)R^g$, $-N(R^h)C(NR^h)SR^g$, $-N(R^h)C(NR^h)NR^gR^g$; y $-N=C(R^h)NR^hR^h$; y

cada $\mathbf{R^g}$ independientemente entre sí representa hidrógeno o un grupo opcionalmente sustituido con uno o más $\mathbf{R^h}$, iguales o diferentes, seleccionados entre alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arilalquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros; y

cada $\mathbf{R^h}$ se selecciona independientemente entre sí entre hidrógeno, alquilo C_{1-6}, heteroalquilo de 2-6 miembros, haloalquilo C_{1-6}, cicloalquilo C_{3-10}, cicloalquilalquilo C_{4-16}, arilo C_{6-10}, arilalquilo C_{7-16}, heteroarilo de 5-12 miembros, heteroarilalquilo de 6-18 miembros, heterocicloalquilo de 3-14 miembros y heterocicloalquilalquilo de 4-14 miembros,

opcionalmente en forma de los profármacos, los tautómeros, los racematos, los enantiómeros, los diastereoisómeros, los profármacos y las mezclas de los mismos y opcionalmente las sales farmacológicamente aceptables de los mismos.

2. Compuestos de acuerdo con la reivindicación 1, en los que $\mathbf{R^4}$ representa $-CH_3$ o $-C_2H_5$.

3. Compuestos de acuerdo con las reivindicaciones 1 a 2, en los que $\mathbf{R^3}$ representa hidrógeno o $-NR^eR^e$.

4. Compuestos de acuerdo con la reivindicación 3, en los que $\mathbf{R^3}$ representa $-NH_2$.

5. Compuestos de acuerdo con las reivindicaciones 1 a 4, en los que $\mathbf{R^2}$ representa fenilo o piridilo, opcionalmente sustituidos con uno o más R^5 iguales o diferentes.

6. Compuestos de acuerdo con las reivindicaciones 1 a 4, en los que $\mathbf{R^2}$ representa heterocicloalquilo, opcionalmente sustituido con uno o más R^5 iguales o diferentes.

7. Compuestos de acuerdo con la reivindicación 1 a 6, en los que $\mathbf{R^1}$ representa fenilo, piridilo o pirimidinilo, opcionalmente sustituidos con uno o más R^5 iguales o diferentes.

8. Compuestos, o sales farmacológicamente eficaces de los mismos, de acuerdo con una de las reivindicaciones 1 a 7, como medicamentos.

9. Compuestos, o sales farmacológicamente eficaces de los mismos, de acuerdo con una de las reivindicaciones 1 a 7, para preparar un medicamento con actividad antiproliferativa.

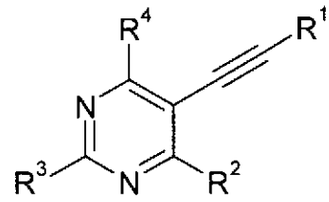
10. Preparaciones farmacéuticas que contienen como sustancia activa uno o más compuestos de fórmula general (1) de acuerdo con una de las reivindicaciones 1 a 7 o las sales farmacológicamente aceptables de los mismos, opcionalmente en combinación con excipientes y/o vehículos convencionales.

11. Uso de compuestos de fórmula general (1) de acuerdo con una de las reivindicaciones 1 a 7 para preparar un medicamento para el tratamiento y/o prevención de cáncer, infecciones, enfermedades inflamatorias y autoinmunes.

12. Preparación farmacéutica que comprende un compuesto de fórmula general (1) de acuerdo con una de las reivindicaciones 1 a 7 y al menos otra sustancia activa citostática o citotóxica, diferente de la fórmula (1), opcionalmente en forma de los tautómeros, los racematos, los enantiómeros, los diastereómeros y las mezclas de los mismos, así como opcionalmente las sales farmacológicamente aceptables de los mismos.

RESUMEN

La presente invención comprende compuestos de fórmula general (1)



(1),

en la que

R^1 a R^4 se definen como en la reivindicación 1, que son adecuados para el tratamiento adecuado de enfermedades caracterizadas por proliferación celular excesiva o anormal, y el uso de los mismos para preparar un medicamento que tiene las propiedades mencionadas anteriormente.

GESCANNT

PATENT COOPERATION TRE

Case: P12-0284/WO/1 Anwalt: Gassner
Frist: 02.12.2009 Erinn: 02.10.2009
Fristart: OA
AKZ: PCT/EP2009059763
Text: R 44.1

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BOEHRINGER INGELHEIM GMBH
Attn. Hammann, Heinz
CD Patents
Binger Straße 173
D-55216 Ingelheim am Rhein
ALLEMAGNE

RECEIVED
09. Okt. 2009
FEP / Patents

Eingang CD Patents
02. Okt. 2009
SdT | No: | Yes:
SB | gesehen | erledigt

NOTIFICATION OF THE INTERNATIONAL SEARCH REPORT, THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 12-0284-WO	Date of mailing *(day/month/year)* 02/10/2009
International application No. PCT/EP2009/059763	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH	International filing date *(day/month/year)* 28/07/2009

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are 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, Fascimile No.: (41-22) 338.82.70

   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 and the written opinion of the International Searching Authority are 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 the expiration of **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.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   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 International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chantal Gottar

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

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

Where not to file the amendments?

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

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

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

NOTES TO FORM PCT/ISA/220 (continued)

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

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

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

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

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

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

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

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

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

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

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
12-0284-WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2009/059763	28/07/2009	29/07/2008
Applicant		
BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

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 3 sheets.

[X] 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:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] 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**,
   [X] 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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/059763

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/48 C07D401/04 C07D401/06 C07D403/06 C07D403/14
C07D409/06 C07D413/14 A61K31/495

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)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/044823 A (AMGEN INC [US]; CHAFFEE STUART C [US]; ALBRECHT BRIAN K [US]; HODOUS B) 27 April 2006 (2006-04-27) cited in the application claims, compounds I and II; description p. 1ff	1-12

[ ] Further documents are listed in the continuation of Box C.

[X] 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 document but published on or after the international filing date

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

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

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

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

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

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

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2009	02/10/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/059763

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006044823 A	27-04-2006	AU 2005295414 A1	27-04-2006
		CA 2583907 A1	27-04-2006
		EP 1802586 A2	04-07-2007
		US 2006217380 A1	28-09-2006

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-009242- -00000-0000

Fecha: 2011-01-27 16:39:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 158

159

PATENTE DE INVENCIÓN ☐ MODELO

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☒ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

160

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

REFERENCIA	Radicación No.	11 009242
	Solicitud internacional	PCT/EP2009/059763
	Fecha inicio fase nacional	28/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 0 5 7 1 6

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

31 MAR. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11

Industria y Comercio
SUPERINTENDENCIA

161

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

REFERENCIA	Radicación No.	11 009242
	Solicitud internacional	PCT/EP2009/059763
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	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 0 5 7 1 7

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAR 2011
adpa11