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Organizacion y Digitalizacion CSA Ltda

PCT

Organizacion y Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

10-110021

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

1/2

# SOLICITUD DE PATENTE DE INVENCIÓN

OK

**TITULO:** PIRROLO [2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA

**SOLICITANTE:** NOVARTIS AG

**DIRECCIÓN:** Lichtstrasse 35, CH- 4056 Basel, Suiza

**APODERADO:** CARLOS R. OLARTE

**BOGOTÁ:** 06 de Septiembre de 2010

**P2010/000115**

Traducir Anexo
06-09-2010
No Exclusiva

# OLARTE RAISBECK

OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-110021- -00000-0000
Fecha: 2010-09-06 17:06:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 432

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** **P2010/000115**

**SOLICITUD DE:**

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

[ ] Capítulo I. [X] Capítulo II.

| | | |
|---|---|---|
| (2) **SOLICITANTE (71)** | **Nombre:** NOVARTIS AG<br>**Dirección:** Lichtstrasse 35, CH-4056 Basel<br>**Nacionalidad o Domicilio:** Suiza<br>**Lugar de Constitución:** Suiza<br>**Teléfono:** **Fax:**<br>**E-mail:** | **IDENTIFICACIÓN**<br>**C.C.** [ ] **NIT** [ ]<br>**C.E.** [ ] **Otro** [ ]<br>**Cual**<br>**Número** |
| **REPRESENTANTE O APODERADO** | **Nombre:** CARLOS R. OLARTE<br>**Dirección:** Diagonal 34 No 5-28 Bogotá D.C.<br>**Teléfono:** 601-7700 **Fax:** 601-7799<br>**E-mail:** office@olarteraisbeck.com | **IDENTIFICACIÓN**<br>**C.C.** [X] **NIT** [ ]<br>**C.E.** [ ] **Otro** [ ]<br>**Cual**<br>**Número** 79782747Bta<br>**TP** 74.295 |
| **INVENTOR (ES) (72)** | **Nombre:** **1)** CHRISTOPH GAUL; **2)** MARC GERSPACHER; **3)** PHILIPP HOLZER **4)** Carole PISSOT SOLDERMANN<br>**Dirección:** Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Suiza<br>**Nacionalidad o Domicilio:** 1) Alemana, 2 y 3) Suiza 4) Francesa | |

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2009/051281 Fecha Febrero 4, 2009

Publicación Internacional No. WO 2009/098236 Fecha Agosto 13, 2009

(6) **Título (54)** **PIRROLO[2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA**

**Clasificación Internacional (51)** C07D 487/04, A61K 31/519

| **Prioridad** SI [X] NO [ ] | (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|---|
| | EP | Febrero 6, 2008 | 08151137.0 |

(9) **Comprobante de pago No.** 10- **Fecha** Septiembre de 2010

(10) **ANEXOS**

2

[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. 08-102.832

[ ] 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.

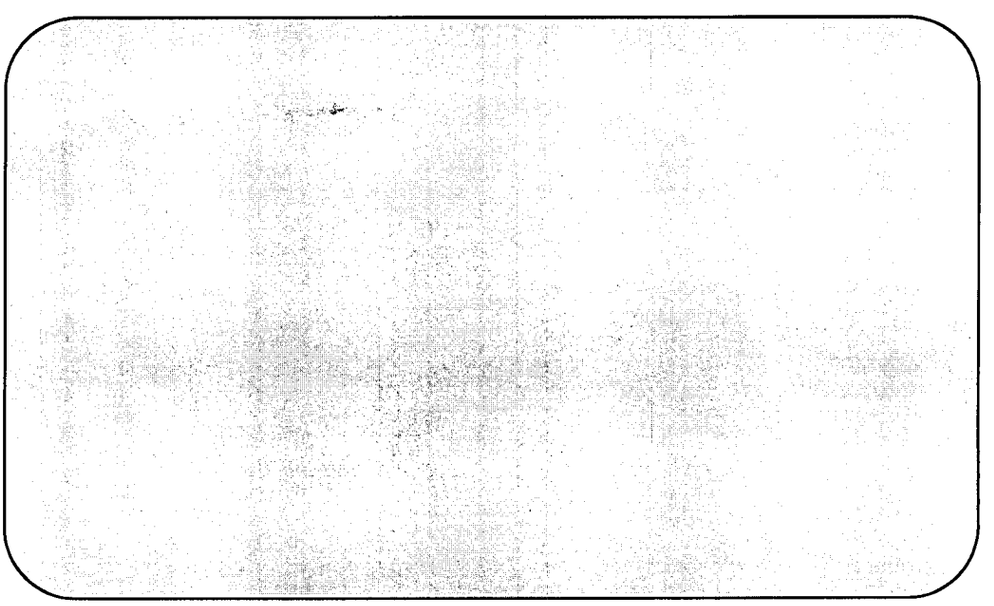
[ ] Arte final 12 x 12.

[ ] 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.

[x] 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.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 10-110021- -00000-0000**

Fecha: 2010-09-06 17:06:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 432

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 74,034
FECHA : SEPTIEMBRE 6 DE 2010

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| OLARTE RAISBEK | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 379391311 | 06/09/2010 | 3,979,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 554,000.00 |
| | | TOTAL : $ | 554,000.00 |

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

*Nota del traductor:*

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor C
JORGE E. SIERR
Licencia [illegible]

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4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.,

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

*Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.*

Traductor Ofic
JORGE E. SERRA
Licencia 276 - 1993

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*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"*

*Fecha: 12 de Septiembre de 2006.*

*Traductor: Jorge Enrique Sierra Reyes.*

*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 2182308, (57-1) 6232925.*

*E-mail: treseser1@yahoo.com. No. 8346*

Traductor Ofi
JORGE E. SIERRA
Licencia 376 - 1993

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olar
J. Ian Raisbe
Ana María Frie
Juan Guillermo Mou
Natalia Cast

Zayde Chab
Jacqueline Chapar
José Luis Londoñ
Felipe Mejdo
Simón Salin

Of Coun
Guillermo Chah
Graciela Me

# Power of Attorney

# Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Albin Cannici

Pascal Haub

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 10, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

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## Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975/2006

115-9

Caso de Patente: 52213

**CESIÓN**

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

| | | |
|---|---|---|
| Christoph GAUL | Ciudadano de Alemania | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basilea<br>CH |
| Marc GERSPACHER | Ciudadano de Suiza | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basilea<br>CH |
| Philipp HOLZER | Ciudadano de Suiza | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basilea<br>CH |
| Carole PISSOT SOLDERMANN | Ciudadano de Francia | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basilea<br>CH |

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo (Novartis AG, llamados de ahora en adelante colectivamente los CESIONARIOS) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

**COMPUESTOS HETEROCICLICOS**

* archivada en el **RO/EP de 20** y acuerdo con numero de patente internacional **PCT/** , (2) la solicitud de Patente identificada en , (3) todas las fases nacionales de dicha solicitud de patente internacional, (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la solicitud de patente provisional presentada en la oficina de Marcas y Patentes Europeas el **6 de febrero de 2008** y de acuerdo con las solicitud número **08151137.0**, (5) todas las continuaciones y divisiones de todas las solicitudes de patentes mencionadas (Incluyendo además continuaciones y divisiones como tal, sin límites de continuaciones de continuaciones y continuaciones de divisiones), ((2)-(5) llamados de ahora en

...PRODUCTOR NT... E OFICI...
...ES ESPA... ...PAÑOL - INGLES
...ES.

adelante colectivamente "solicitudes de patentes" ), (6) todas las patentes que sean concedidas de cualquiera de las solicitudes de patentes mencionadas, (7) todos los registros y confirmaciones y certificados de importación basados en una o mas de las patentes mencionadas y (8) todos los re-otorgamientos, renovaciones, y extensiones de dichas patentes, emisión de certificados de reexaminación para dichas patentes y certificados de protección adicional basados en dichas patentes incluyendo el derecho a presentar las solicitudes de patentes de dichos inventos y descubrimientos en nombre del CESIONARIO, sus diseños en cualquier o en todos nuestros nombres, en todas las regiones y países para todas las solicitudes de patentes mencionadas bajo el Convenio Internacional para la Protección de la Propiedad Industrial, y todos los demás acuerdos internacionales similares que sean aplicables) así mismo para se conservada y disfrutada por dichos cesionarios, sus sucesores, cesionarios y representantes legales, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo harían si esta cesión no hubiera sido vendida y transferida.

*Nosotros por medio del presente autorizamos al CESIONARIO y sus representantes para incorporar en este instrumento el Número de la Solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos y entregaremos cualquier y todos los documentos necesarios o deseables para perfeccionar el título de los anteriores inventos o descubrimientos, solicitudes de patente, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones certificados de reexaminación, certificados de protección adicional a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes u otra oficina de propiedad industrial, agencia o de cualquier región o país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos cualquier solicitud de patente adicional, solicitudes para registros y/o confirmaciones de una o más de las patentes mencionadas, solicitudes de certificados de importación basada en una o más de las patentes mencionada, solicitudes de re-otorgamientos renovaciones y extensiones de una o más de las patentes mencionadas y certificados de protección adicional basados en una o más de las patentes mencionadas y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 15 de diciembre de 2008.
Christoph-GAUL (firma ilegible) L.S.

Ejecutado el 15 de diciembre de 2008.
Marc GERSPACHER (firma ilegible) L.S.

Ejecutado el 15 de diciembre de 2008

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1790 - 1988

Philipp HOLZER (firma ilegible) L.S.

Ejecutado el 15 de diciembre de 2009
Carole PISSOT SOLDERMANN (firma ilegible) L.S.

## ACEPTACION DE LA CESION

En referencia con la cesión realizada a **NOVARTIS AG** de la invención titulada "**COMPUESTOS HETEROCICLICOS**" firmado por **Christoph GAUL, Marc GERSPACHER, Philipp HOLZER y Carole PISSOT SOLDERMANN**; esta certificara que **NOVARTIS AG** acepta dicha cesión.

**NOVARTIS AG**

| | | |
|---|---|---|
| Por: | [Firma llegible] | [Firma llegible] |
| Nombre: | Ella Rutschmann | Reto Halreisen |
| Cargo: | Administrador Profesional de PS | Administrador Profesional de PS |
| Fecha: | 17 de diciembre de 2008 | |

## TESTIFICACION

Yo, el suscrito notario público de Basilea, Suiza, **Dr. Mathias Staehelin**, certifico por medio del presente la autenticidad de las firmas del **Sr. Christoph Gaul**, ciudadano Aleman, residente en Aesch/BL, Suiza; el **Sr. Marc Gerpacher**, ciudadano de Aeschi/SO, Suiza, residente en Hâgendorf/SO, Suiza; el **Sr. Philipp Holzer,** ciudadano de Riehen/BS, Suiza, residente en Sissach, Suiza; y la **Sra Carole Pissot Soldermann** , ciudadano Frances, residente en Rosenau, Francia.

Además, certifico que lo anterior son las firmas autenticas de firmas de **la Sra. Ella Rutschmann,** ciudadana de Lotzwil, Suiza, residente en Basilea, Suiza, y el Sr., **Reto Halbeisen,** ciudadano de Wahlen/BE, Suiza, residente en Laufen/BL, Suiza, ambas actuando por **Novartis AG**, en Basilea, Suiza, como residentes, ambas con firmas conjunta poseedoras.

La autenticidad de la firma fue demostrada bajo comparación.

BASILEA, Suiza, a los 22 días del mes de diciembre de 2008

(Firma) Notario Dr. M. Staehelin.

Leg.Prot.Nr. 3099/2008

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. JUSTICIA 1780 - 1983

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## POR COPIA CERTIFICADA

Yo, El firmante Notario Civil, de Basilea, Suiza, Dr. Mark Eichner, por este medio certifico que el documento aquí adjunto es una copia fiel del documento original.

Basilea, Suiza, este 30 de julio de 2010

(Firma) Notario Dr. M. Staehelin

Leg. Prot. 434 /2010

## APOSTILLA

## (CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: SUIZA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR: Dr Mark Eichner
3. EN CALIDAD DE: NOTARIO PÚBLICO OFICIAL
4. CERTIFICADO CON EL SELLO DE: NOTARIO PÚBLICO

CERTIFICO

5. EN BASILEA
6. EL 30 DE JULIO DE 2010
7. POR: LA CANCILLERÌA DEL ESTADO DE CANTON DE BASILEA
8. No. 5156/410731
9. SELLO: DE LA CANCILLERÌA DE ESTADO CIUDAD DE BASILEA
10. FIRMA: (ILEGIBLE)

Hanna Lauener

MAURICIO URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
ES. 1790 - 1983

MINISTERIO DE
RELACIONES
EXTERIORES

266446
Mauricio Umaña
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO ASUME
RESPONSABILIDAD
DEL TEXTO

2010 AUG 28 A 10:22

JEFE DE LEGALIZACIONES
BOGOTA D.C.

RECIBO [illegible]

No pago

10/115 842 CO

13

Case 52213

## ASSIGNMENT

For good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, we

| | | |
|---|---|---|
| Christoph GAUL | citizen of Germany | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basel<br>CH |
| Marc GERSPACHER | citizen of Switzerland | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basel<br>CH |
| Philipp HOLZER | citizen of Switzerland | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basel<br>CH |
| Carole PISSOT SOLDERMANN | citizen of France | Novartis Pharma AG<br>Werk Klybeck<br>Postfach<br>4002 Basel<br>CH |

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, 4056 Basel, Switzerland, and its successors, assigns and legal representatives, all our right, title and interest for all countries of the world (Novartis AG hereinafter referred to as the "**ASSIGNEE**") in and to (1) all of our inventions and discoveries described in the patent application(s) entitled

HETEROCYCLIC COMPOUNDS

filed* in the RO/ on _____, 20____, and accorded International Patent Application Number PCT _____, (2) said patent application(s), (3) all national stages of said international patent application, (4) all other patent applications in all countries and regions claiming the priority of the European Procedure, patent application filed on February 06, 2008 and accorded Application Number 08151137.0 (5) all continuations and divisions of all of said patent applications (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(5) hereinafter referred to collectively as "patent applications"), (6) all patents that are granted on any of said patent applications, (7) all registrations and confirmations of, and importation certificates based on, one or more of said patents and (8) all reissues, renewals and extensions of said patents, reexamination certificates issued for said patents and supplementary protection certificates based on said patents (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEE**, their designees or in any or all of our names, at their election and in accordance with applicable law in all countries and regions and all rights of priority in all countries and regions for all of said patent applications under the International Convention for the Protection of Industrial Property, and all other applicable similar international agreements), the same to be held and enjoyed by said **ASSIGNEE**, their successors, assigns and legal representatives, to the full ends of the terms for which all patents therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

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*We hereby authorize **ASSIGNEE** and their representatives to insert in this instrument the Application Number and the filing date of said patent application when notified thereof.

And we hereby covenant and agree that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates and supplementary protection certificates in **ASSIGNEE**, their successors, assigns or other legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute all additional patent applications, applications for registration and/or confirmation of one or more of said patents, applications for certificates of importation based on one or more of said patents, applications for reissues, renewals and extensions of one or more of said patents and supplemental protection certificates based upon one or more of said patents, and that we will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEE**, the successors, assigns or other legal representatives.

Executed this 15 day of December, 2008.

_____ L.S.
**Christoph GAUL**

Executed this 15 day of December, 2008.

_____ L.S.
**Marc GERSPACHER**

Executed this 15 day of December, 2008.

_____ L.S.
**Philipp HOLZER**

Executed this 15 day of December, 2008.

_____ L.S.
**Carole PISSOT SOLDERMANN**

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## ACCEPTANCE OF ASSIGNMENT

With reference to the Assignment to **NOVARTIS AG** of an invention entitled **"HETEROCYCLIC COMPOUNDS"** signed by **Christoph GAUL, Marc GERSPACHER, Philipp HOLZER** and **Carole PISSOT SOLDERMANN**; this will certify that **NOVARTIS AG** accepts such Assignment.

**NOVARTIS AG**

| | | |
|---|---|---|
| By : | E. Rutschmann | R. Halbeisen |
| Name : | Ella Rutschmann | Reto Halbeisen |
| Function : | Administrative Professional PS | Administrative Professional PS |
| Date: | 17.12.2008 | |

**Attestation**

I, the undersigned notary public of Basel, Switzerland, Dr. Matthias Staehelin, certify herewith the authenticity of the signature of **Mr. Christoph Gaul**, German citizen, residing in Aesch/BL, Switzerland; of **Mr. Marc Gerspacher**, citizen of Aeschi/SO, Switzerland, residing in Hägendorf/SO, Switzerland; of **Mr. Philipp Holzer**, citizen of Riehen/BS, Switzerland, residing in Sissach, Switzerland; and of **Ms. Carole Pissot Soldermann**, French citizen, residing in Rosenau, France.

I further certify that the above signatures are the genuine signatures of **Ms. Ella Rutschmann**, citizen of Lotzwil, Switzerland, residing in Basel, Switzerland, and of **Mr. Reto Halbeisen**, citizen of Wahlen (BL), Switzerland, residing in Laufen, Switzerland, both acting for **Novartis AG**, in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 22nd (twenty-second) day of December 2008 (two thousand and eight).

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 3099 /2008

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**FOR CERTIFIED COPY**

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Mark Eichner, hereby certify that the document attached heretofore is a true and authentic photocopy of the original document.

BASEL, Switzerland, this 30th (thirtieth) day of July 2010 (two thousand and ten)

M. Eichner
Notar

Leg.Prot.Nr. 434 / 2010

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by Dr. iur. M. Eichner
3. in his/her function as notary public
4. and certified by the seal of the above mentioned

Certified

5. in Basel (Bâle) 6. on 30. Juli 2010
7. by the State Chancery of the Canton of Basel-Stadt
8. no. 5156/10731
9. Seal/stamp: STATE CHANCERY * BASLE-CITY *
10. Signature: H. Lauener
Hanna Lauener

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(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GAUL, Christoph** [DE/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **GERSPACHER, Marc** [CH/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **HOLZER, Philipp** [CH/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **PISSOT SOLDERMANN, Carole** [FR/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH).

(74) Agent: **DYER, James**; Novartis Pharma Ag, Patent Department, CH-4002 Basel (CH).

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**Declarations under Rule 4.17**:

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

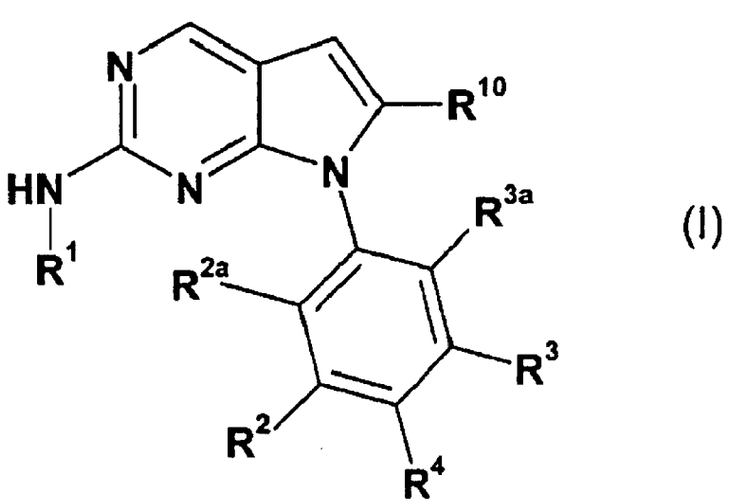
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(54) **Title**: PYRROLO [2, 3-D] PYRIDINES AND USE THEREOF AS TYROSINE KINASE INHIBITORS




(I)

(57) **Abstract**: The invention relates to compounds of formula (I) and salts thereof formula (I), wherein the substituens are as defined in the specification, processes for the preparation thereof; to pharmaceuticals containing such compounds, in particular for the use in one or more Protein tyrosine kinase mediated diseases.

WO 2009/098236 A1

# PYRROLO[2,3-D]PYRIDINES AND USE THEREOF AS TYROSINE KINASE INHIBITORS

The invention relates to 7-phenyl-7H-pyrrolo[2,3d]pyrimidin-2yl-amino derivatives of the formula I given below, as well as salts thereof; processes for the preparation thereof; pharamaceutical compositions comprising a compound of the formula (I), optionally in the presence of a combination partner; the application of a compound of formula (I) in a process for the treatment of the human or animal body, (in particular with regard to a proliferative disease); the use of a compound of formula (I) for manufacturing a medicament for the treatment of such diseases.

Janus kinases (JAKs) form a family of intracellular protein tyrosine kinases with four members, JAK1, JAK2, JAK3 and TYK2. These kinases are important in the mediation of cytokine receptor signaling which induces various biological responses including cell proliferation, differentiation and apoptosis. Knock-out experiments in mice have shown that JAKs are inter alia important in hematopoiesis. In addition, JAK2 was shown to be implicated in myeloproliferative diseases and cancers. JAK2 activation by chromosome re-arrangements and/or loss of negative JAK/STAT (STAT = signal transducing and activating factor(s)) pathway regulators has been observed in hematological malignancies as well as in certain solid tumors.

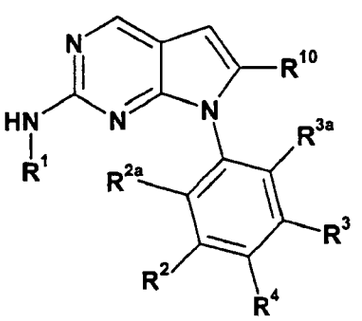
WO 2005/080393 dicsloses inter alia 7H-pyrrolo[2,3d]pyrimidin-2yl-amino derivatives which are useful in the treatment of disorders associated with abnormal or deregulated kinase activity.

Bioorganic & Medical Chemistry Letters 16 (2006), 2689 discloses design and synthesis of certain 7H-pyrrolo[2,3d]pyrimidines as focal adhesion kinase inhibitors.

It has now been found that the 7-phenyl-7H-pyrrolo[2,3d]pyrimidin-2yl-amino derivatives of the formula I given below, have advantageous pharmacological properties and inhibit, for example, the tyrosine kinase activity of Janus kinases, such as JAK2 kinase and/or JAK3- (but also JAK-1-) kinase. Hence, the compounds of formula I are suitable, for example, to be used in the treatment of diseases depending on the tyrosine kinase activity of JAK2 (and/or JAK3) kinase, especially proliferative diseases such as tumor diseases, leukaemias, polycythemia vera, essential thrombocythemia, and myelofibrosis with myeloid metaplasia. Through the inhibition of JAK-3 kinase, compounds of the invention also have utility as

immunosuppressive agents, for example for the treatment of diseases such as organ transplant rejection, lupus erythematodes, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes.

In a first aspect, the invention relates to compounds of the formula I,



(I)

wherein

$R^1$ represents unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl;

$R^2$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

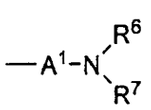
$R^3$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

or $R^2$ and/or $R^3$ are connected to $R^5$ or $R^7$ to form a cyclic moiety fused to the phenyl ring to which $R^2$/$R^3$ are attached;

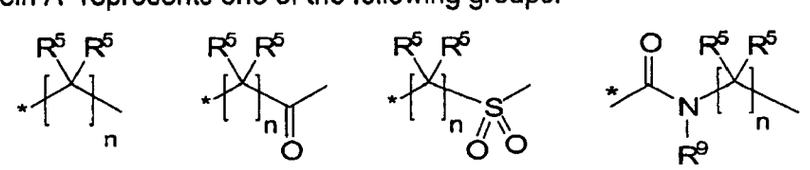
$R^{2a}$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^{3a}$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^4$ represents a group:



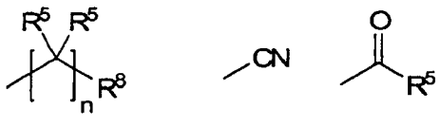
wherein $A^1$ represents one of the following groups:



in which the atom marked * is bond to the phenyl ring;

or

$R^4$ represents one of the following groups:



$R^5$ represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle

or

$R^6$ represents hydrogen or optionally substituted alkyl and

$R^7$ represents optionally substituted alkyl;

$R^8$ represents alkyl, hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;

$R^9$ represents H or lower alkyl;

$R^{10}$ represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;

n represens 0, 1 or 2;

or salts thereof.

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications cited in this specification are herein incorporated by reference. As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. If at least one asymmetrical carbon atom is present in a compound of the formula I, such a compound may exist in optically active form or in the form of a mixture of optical isomers, e. g. in the form of a racemic mixture. All optical isomers and their mixtures, including the racemic mixtures, are part of the present invention. Thus, any given formula given herein is intended to represent a racemate, one or more enantiomeric forms,

one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (i.e. cis and trans isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}F$ $^{31}P$, $^{32}P$, $^{35}S$, $^{36}Cl$, $^{125}I$ respectively. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as $^{3}H$, $^{13}C$, and $^{14}C$ are incorporated. Such isotopically labelled compounds are useful in metabolic studies (preferably with $^{14}C$), reaction kinetic studies (with, for example $^{2}H$ or $^{3}H$), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{18}F$ or labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., $^{2}H$) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a. readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the moiety for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula (where one or more up to all more general expressions in embodiments characterized as preferred above or below can be replaced with a more specific definition, thus leading to a more preferred embodiment of the invention, respectively).

Where the plural form (e.g. compounds, salts) is used, this includes the singular (e.g. a single compound, a single salt). "A compound" does not exclude that (e.g. in a pharmaceutical formulation) more than one compound of the formula I (or a salt thereof) is present.

The acid addition salt of compounds of formula I are preferably pharmaceutically acceptable salts. Such salts are known in the field.

The following general definitions shall apply in this specification, unless otherwise specified:

**Halogen** (or halo) denotes fluorine, bromine, chlorine or iodine, in particular fluorine, chlorine. Halogen-substituted groups and moieties, such as alkyl substituted by halogen (halogenalkyl) can be mono-, poly- or per-halogenated.

**Hetero atoms** are atoms other than Carbon and Hydrogen, preferably nitrogen (N), oxygen (O) or sulfur (S).

**Carbon containing groups**, moieties or molecules contain 1 to 8, preferably 1 to 6, more preferably 1 to 4, most preferably 1 or 2, carbon atoms. Any non-cyclic carbon containing group or moiety with more than 1 carbon atom is straight-chain or branched.

The prefix "**lower**" or "$C_1$-$C_7$" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

"**Alkyl**" refers to a straight-chain or branched-chain alkyl group, preferably represents a straight-chain or branched-chain $C_{1-12}$alkyl, particularly preferably represents a straight-chain or branched-chain $C_{1-7}$alkyl; for example, methyl, ethyl, n- or iso-propyl, n-, iso-, sec- or tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, with particular preference given to methyl, ethyl, n-propyl, iso-propyl and n-butyl and iso-butyl. Alkyl may be unsubstituted or substituted. Exemplary substituents include, but are not limited to hydroxyl, alkoxy, oxo (i.e. =O), halogen and amino. An example of a substituted alkyl is trifluoromethyl. Cycloalkyl may also be a substituent to alkyl. An example of such a case is the moiety (alkyl)-cyclopropyl or alkandiyl-cyclopropyl, e.g. $-CH_2$-cyclopropyl. $C_1$-$C_7$-alkyl is preferably alkyl with from and including 1 up to and including 7, preferably from and including

1 up to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or preferably methyl.

Each alkyl part of other groups like "alkoxy", "alkoxyalkyl", "alkoxycarbonyl", "alkoxycarbonylalkyl", "alkylsulfonyl", "alkylsulfinyl", "alkylamino", "halogenalkyl" shall have the same meaning as described in the above-mentioned definition of "alkyl".

"**Alkandiyl**" refers to a straight-chain or branched-chain alkandiyl group bound by two different Carbon atoms to the moiety, it preferably represents a straight-chain or branched-chain $C_{1-12}$ alkandiyl, particularly preferably represents a straight-chain or branched-chain $C_{1-6}$ alkandiyl; for example, methandiyl ($-CH_2-$), 1,2-ethanediyl ($-CH_2-CH_2-$), 1,1-ethanediyl ($-CH(CH_3)-$), 1,1-, 1,2-, 1,3-propanediyl and 1,1-, 1,2-, 1,3-, 1,4-butanediyl, with particular preference given to methandiyl, 1,1-ethanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl.

"**Alkendiyl**" refers to a straight-chain or branched-chain alkendiyl group bound by two different Carbon atoms to the molecule, it preferably represents a straight-chain or branched-chain $C_{2-6}$ alkandiyl; for example, $-CH=CH-$, $-CH=C(CH_3)-$, $-CH=CH-CH_2-$, $-C(CH_3)=CH-CH_2-$, $-CH=C(CH_3)-CH_2-$, $-CH=CH-C(CH_3)H-$, $-CH=CH-CH=CH-$, $-C(CH_3)=CH-CH=CH-$, $-CH=C(CH_3)-CH=CH-$, with particular preference given to $-CH=CH-CH_2-$, $-CH=CH-CH=CH-$. Alkendiyl may be substituted or unsubstituted

"**Cycloalkyl**" refers to a saturated or partially saturated, monocyclic, fused polycyclic, or Spiro polycyclic, carbocycle having from 3 to 12 ring atoms per carbocycle. Illustrative examples of cycloalkyl groups include the following moieties: cyclopropyl, cyclobutyl, cyclpentyl and cylclohexyl. Cycloalkyl may be unsubstituted or substituted; exemplary substituents are provided in the definition for alkyl.

"**Aryl**" refers to an aromatic homocyclic ring system with 6 or mor carbon atoms; aryl is preferably an aromatic moiety with 6 to 14 ring carbon atoms, more preferably with 6 to 10 ring carbon atoms, such as phenyl or naphthyl, preferably phenyl. Aryl may be unsubstituted or substituted by one or more, preferably up to three, more preferably up to two substituents independently selected from the group consisting of unsubstituted or substituted heterocyclyl as described below, especially pyrrolidinyl, such as pyrrolidino, oxopyrrolidinyl, such as oxo-

pyrrolidino, $C_1$-$C_7$-alkyl-pyrrolidinyl, 2,5-di-($C_1$-$C_7$alkyl)pyrrolidinyl, such as 2,5-di-($C_1$-$C_7$alkyl)-pyrrolidino, tetrahydrofuranyl, thiophenyl, $C_1$-$C_7$-alkylpyrazolidinyl, pyridinyl, $C_1$-$C_7$-alkylpiperidinyl, piperidino, piperidino substituted by amino or N-mono- or N,N-di-[lower alkyl, phenyl, $C_1$-$C_7$-alkanoyl and/or phenyl-lower alkyl)-amino, unsubstituted or N-lower alkyl substituted piperidinyl bound via a ring carbon atom, piperazino, lower alkylpiperazino, morpholino, thiomorpholino, S-oxo-thiomorpholino or S,S-dioxothiomorpholino; $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, phenyl, naphthyl, mono- to tri-[$C_1$-$C_7$-alkyl, halo and/or cyano]-phenyl or mono- to tri-[$C_1$-$C_7$-alkyl, halo and/or cyano]-naphthyl; $C_3$-$C_8$-cycloalkyl, mono- to tri-[$C_1$-$C_7$-alkyl and/or hydroxy]-$C_3$-$C_8$-cycloalkyl; halo, hydroxy, lower alkoxy, lower-alkoxy-lower alkoxy, (lower-alkoxy)-lower alkoxy-lower alkoxy, halo-$C_1$-$C_7$-alkoxy, phenoxy, naphthyloxy, phenyl- or naphthyl-lower alkoxy; amino-$C_1$-$C_7$-alkoxy, lower-alkanoyloxy, benzoyloxy, naphthoyloxy, formyl (CHO), amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, $C_1$-$C_7$-alkanesulfonylamino, carboxy, lower alkoxy carbonyl, e.g.; phenyl- or naphthyl-lower alkoxycarbonyl, such as benzyloxycarbonyl; $C_1$-$C_7$-alkanoyl, such as acetyl, benzoyl, naphthoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-mono- or N,N-di-substituted carbamoyl wherein the substitutents are selected from lower alkyl, (lower-alkoxy)-lower alkyl and hydroxy-lower alkyl; amidino, guanidino, ureido, mercapto, lower alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-lower alkylthio, lower alkyl-phenylthio, lower alkyl-naphthylthio, halogen-lower alkylmercapto, sulfo (-$SO_3H$), lower alkanesulfonyl, phenyl- or naphthyl-sulfonyl, phenyl- or naphthyl-lower alkylsulfonyl, alkylphenylsulfonyl, halogen-lower alkylsulfonyl, such as trifluoromethanesulfonyl; sulfonamido, benzosulfonamido, azido, azido-$C_1$-$C_7$-alkyl, especially azidomethyl, $C_1$-$C_7$-alkanesulfonyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, cyano and nitro; where each phenyl or naphthyl (also in phenoxy or naphthoxy) mentioned above as substituent or part of a substituent of substituted alkyl (or also of substituted aryl, heterocyclyl etc. mentioned herein) is itself unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from halo, halo-lower alkyl, such as trifluoromethyl, hydroxy, lower alkoxy, azido, amino, N-mono- or N,N-di-(lower alkyl and/or $C_1$-$C_7$-alkanoyl)-amino, nitro, carboxy, lower-alkoxycarbonyl, carbamoyl, cyano and/or sulfamoyl.

"**Heterocyclyl**" refers to a heterocyclic radical that is unsaturated (= carrying the highest possible number of conjugated double bonds in the ring(s) i.e. heteroaryl), saturated or

partially saturated and is preferably a monocyclic or in a broader aspect of the invention bicyclic, tricyclic or spirocyclic ring; and has 3 to 24, more preferably 4 to 16, most preferably 5 to 10 and most preferably 5 or 6 ring atoms; wherein one or more, preferably one to four, especially one or two carbon ring atoms are replaced by a heteroatom, the bonding ring preferably having 4 to 12, especially 5 to 7 ring atoms. The heterocyclic radical (heterocyclyl) may be unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected from the group consisting of the substituents defined above for substituted alkyl and / or from one or more of the following substituents: oxo (=O), thiocarbonyl (=S), imino(=NH), imino-lower alkyl. Further, heterocyclyl is especially a heterocyclyl radical selected from the group consisting of oxiranyl, azirinyl, aziridinyl, 1,2-oxathiolanyl, thienyl (= thiophenyl), furanyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, (S-oxo or S,S-dioxo)-thiomorpholinyl, indolizinyl, azepanyl, diazepanyl, especially 1,4-diazepanyl, isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl, chromanyl, benzo[1,3]dioxol-5-yl and 2,3-dihydro-benzo[1,4]dioxin-6-yl, each of these radicals being unsubstituted or substituted by one or more, preferably up to three, substituents selected from those mentioned above for substituted aryl and/or from one or more of the following substituents: oxo (=O), thiocarbonyl (=S), imino(=NH), imino-lower alkyl.

**"Arylalkyl"** refers to an aryl group bound to the molecule via an alkyl group, such as a methyl or ethyl group, preferably phenethyl or benzyl, in particular benzyl. Similarly, **cycloalkylalkyl** and **heterocyclylalkyl** represents a cycloalkyl group bound to the molecule via an alkyl group or a heterocyclyl group bound to the molecule via an alkyl group. In each instance, aryl, heterocyclyl, cycloalkyl and alkyl may be substituted as defined above.

"**Treatment**" includes prophylactic (preventive) and therapeutic treatment as well as the delay of progression of a disease or disorter.

"**Protein tyrosine kinase mediated diseases**" (especially JAK2 and/or JAK3 kinase mediated diseases) are especially such disorders that respond in a beneficial way (e.g. amelioration of one or more symptoms, delay of the onset of a disease, up to temporary or complete cure from a disease) to the inhibition of a protein tyrosine kinase, especially inhibition of a JAK (preferably JAK2 and/or JAK3) kinase or TYK2, more especially inhibition of JAK2 kinase (where among the diseases to be treated, especially proliferative diseases such as tumor diseases, leukaemias, polycythemia vera, essential thrombocythemia, and myelofibrosis with myeloid metaplasia may be mentioned) and/or of JAK3 kinase (where preferably the treatment (e.g. by immunosuppression) of diseases such as organ transplant rejection, lupus erythematodes, multiple sclerosis, rheumatoid arthritis, psoriasis, dermatitis, Crohn's disease, type-1 diabetes and complications from type-1 diabetes are to be mentioned as preferred.

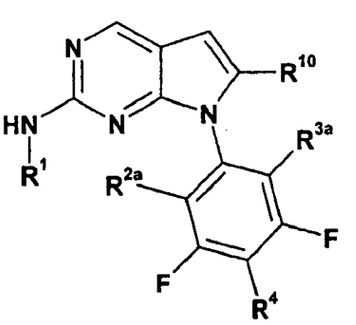
"**Salts**" (which, what is meant by "or salts thereof" or "or a salt thereof", can be present alone or in mixture with free compound of the formula I) are preferably pharmaceutically acceptable salts. Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, e.g., carboxylic acids or sulfonic acids, such as fumaric acid or methansulfonic acid. For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred. In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

**Combination** refers to either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula I and a combination partner (e.g. an other drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a coope-

rative, e.g. synergistic effect. The terms "**co-administration**" or "**combined administration**" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "**pharmaceutical combination**" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "**fixed combination**" means that the active ingredients, e.g. a compound of formula I and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "**non-fixed combination**" means that the active ingredients, e.g. a compound of formula I and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

In preferred embodiments, which are preferred independently, collectively or in any combination or sub-combination, the invention relates to a compound of the formula I, in free base form or in acid addition salt form, wherein the substituents are as defined herein.

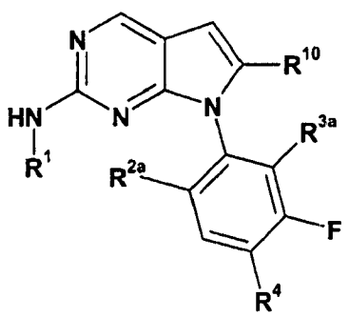
In an embodiment, the invention relates to a compound of formula IA




IA

wherein the substituents are as defined for a compound of formula I.

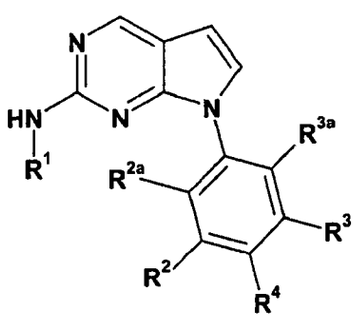
In a further embodiment, the invention relates to a compound of formula IB



IB

wherein the substituents are as defined for a compound of formula I.

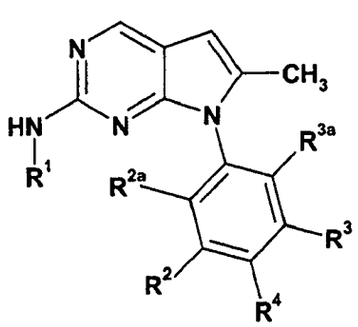
In a further embodiment, the invention relates to a compound of formula IC



IC

wherein the substituents are as defined for a compound of formula I.

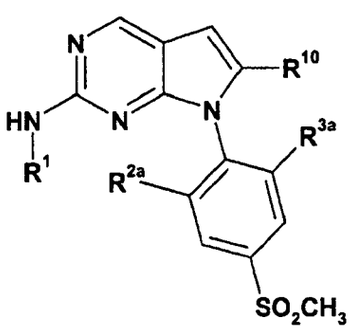
In a further embodiment, the invention relates to a compound of formula ID



ID

wherein the substituents are as defined for a compound of formula I.

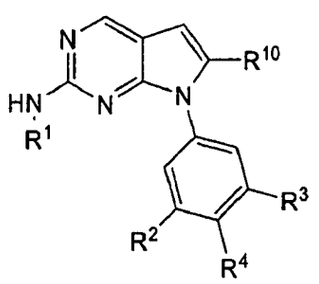
In a further embodiment, the invention relates to a compound of formula IE



IE

wherein the substituents are as defined for a compound of formula I.

In a futher embodiment, the invention relates to compounds of the formula (I) wherein $R^{2a}$ and $R^{3a}$ are both H, that is, this embodiment relates to compounds of the formula I':



(I')

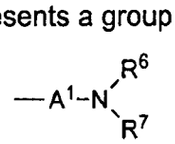
wherein

$R^1$ represents unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl;

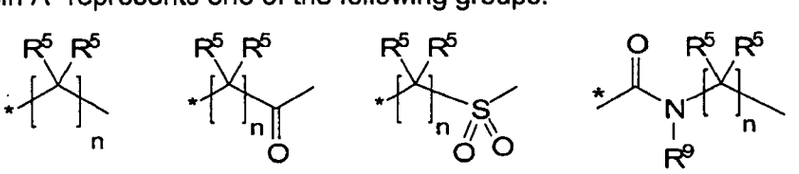
$R^2$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^3$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^4$ represents a group:



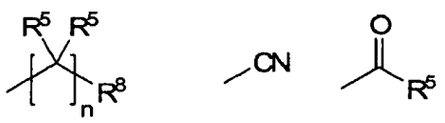
wherein $A^1$ represents one of the following groups:



in which the atom marked * is bond to the phenyl ring;

or

$R^4$ represents one of the following groups:



$R^5$ represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle

or

$R^6$ represents hydrogen or optionally substituted alkyl and

$R^7$ represents optionally substituted alkyl;

$R^8$ represents hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;

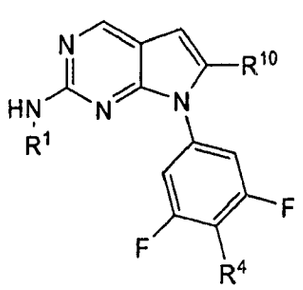
$R^9$ represents H or lower alkyl;

$R^{10}$ represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;

n represens 0, 1 or 2;

or salts thereof.

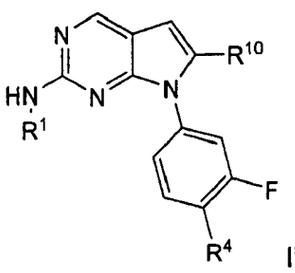
In a further embodiment, the invention relates to a compound of formula I'A



I'A

wherein the substituents are as defined for a compound of formula I.

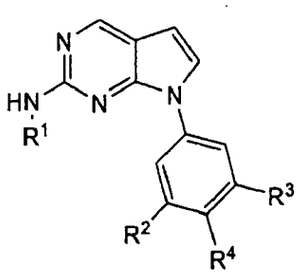
In a further embodiment, the invention relates to a compound of formula I'B



I'B

wherein the substituents are as defined for a compound of formula I.

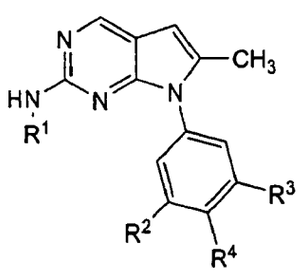
In a further embodiment, the invention relates to a compound of formula I'C



I'C

wherein the substituents are as defined for a compound of formula I.

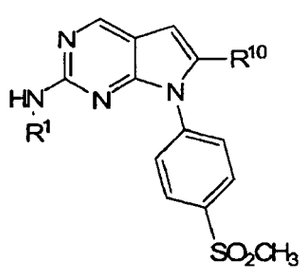
In a further embodiment, the invention relates to a compound of formula I'D



I'D

wherein the substituents are as defined for a compound of formula I.

In a further embodiment, the invention relates to a compound of formula I'E



I'E

wherein the substituents are as defined for a compound of formula I.

$A^1$ preferably represents a direct bond, carbonyl (-C(=O)-) or methandiyl ($-CH_2-$).

The following definitions apply to any of the formulae described herein.

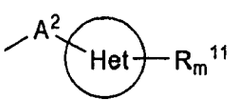
$R^1$ preferably represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl
wherein said heterocyclyl is selected from unsaturated, saturated or partially saturated heterocycles which are monocyclic, bicyclic, tricyclic or spirocyclic and have 4 to 16, ring atoms wherein one to four heteroatoms are present;
wherein said aryl is selected from aromatic moieties with 6 to 14 ring carbon atoms;
wherein said substiutents are independently selected from one or more, preferably one to four of the following moieties: $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl-$C_1$-$C_7$-alkyl, morpholino-$C_1$-$C_7$-alkyl, thiomorpholino-$C_1$-$C_7$-alkyl, S-mono- or S,S-dioxo-thiomorpholino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, pyrrolidino, oxo-pyrrolidino, piperidino, piperazin-1-yl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl, morpholino, thiomorpholino, S-oxo- or S,S-dioxothiomorpholino, $C_1$-$C_7$-alkanesulfonylamino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl and/or (N'-mono- or N',N'-di-($C_1$-$C_7$-alkyl)-amino-$C_1$-$C_7$-alkyl)-carbamoyl, pyrrolidin-1-carbonyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-($C_1$-$C_7$-alkyl)piperazin-1-carbonyl, morpholin-1-carbonyl, thiomorpholin-1-carbonyl, S-oxo- or S,S-dioxothiomorpholin-1-carbonyl, sulfo, $C_1$-$C_7$-alkanesulfonyl, $C_1$-$C_7$-alkanesulfinyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, cyano and nitro.

$R^1$ particular preferably represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl

wherein said heterocyclyl or aryl is selected from the group consisting of phenyl, naphthyl, indanyl, pyrrole, pyrroline, pyrrolidine, pyrazole, pyrazoline, pyrazolidine, imidazole, imidazoline, imidazolidine, triazole, triazoline, triazolidine, tetrazole, furane, dihydrofurane, tetrahydrofurane, furazane (oxadiazole), dioxolane, thiophene, dihydrothiophene, tetrahydrothiophene, oxazole, oxazoline, oxazolidine, isoxazole, isoxazoline, isoxazolidine, thiazole, thiazoline, thiazlolidine, isothiazole, istothiazoline, isothiazolidine, thiadiazole, thiadiazoline, thiadiazolidine, pyridine, piperidine, pyridazine, pyrazine, piperazine, triazine, pyrane, tetrahydropyrane, thiopyrane, tetrahydrothiopyrane, oxazine, thiazine, dioxine, morpholine, purine, pterine, and the corresponding benz-annelated heterocycles, e.g. indole, isoindole, cumarine, cumaronecinoline, isochinoline, cinnoline and

wherein said heterocyclyl or aryl is substituted by one or more, preferably one to three moieties independently selected from the group consisting of $C_1$-$C_7$-alkyl, (amino, $C_1$-$C_7$-alkyl-amino, $C_1$-$C_7$-dialkyl-amino) -$C_1$-$C_7$-alkyl, (amino, $C_1$-$C_7$-alkyl-amino, $C_1$-$C_7$-dialkyl-amino) -$C_1$-$C_7$-alkyloxy, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl-$C_1$-$C_7$-alkyl, morpholino-$C_1$-$C_7$-alkyl, thiomorpholino-$C_1$-$C_7$-alkyl, S-mono- or S,S-dioxo-thiomorpholino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, pyrrolidino, oxo-pyrrolidino, piperidino, piperazin-1-yl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl, morpholino, thiomorpholino, S-oxo- or S,S-dioxothiomorpholino, $C_1$-$C_7$-alkanesulfonylamino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl and/or (N'-mono- or N',N'-di-($C_1$-$C_7$-alkyl)-amino-$C_1$-$C_7$-alkyl)-carbamoyl, pyrrolidin-1-carbonyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-($C_1$-$C_7$-alkyl)piperazin-1-carbonyl, morpholin-1-carbonyl, thiomorpholin-1-carbonyl, S-oxo- or S,S-dioxothiomorpholin-1-carbonyl, sulfo, $C_1$-$C_7$-alkanesulfonyl, $C_1$-$C_7$-alkanesulfinyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, cyano and nitro.

$R^1$ very particular preferably represents heterocyclyl, heteroaryl or aryl in each case unsubstituted or substituted by one or more (preferably 0, 1 or 2 substituents), wherein said heterocyclyl, heteroaryl or aryl is selected from the group consisting of phenyl, 2-, 3-, 4-pyridyl, 2-, 4-, 5-pyrimidinyl, pyrazinyl, 3-, 4-pyridanzinyl, 3-, 4-, 5-pyrazolyl, 2-, 4-, 5-imidazolyl, 2-, 4-, 5-thiazolyl, 3-, 4-, 5-isothiazolyl and
wherein said substituent is selected from the group consisting of fluoro, chloro, cyano, $C_1$-$C_4$-alkyl (in particular methyl, ethyl), $C_1$-$C_4$-alkyloxy (in particular methoxy), hydroxyl-$C_1$-$C_4$-alkyl (in particular 2-hydroxyethyl), halo-$C_1$-$C_4$-alkyl (in particular $CF_3$), $C_1$-$C_4$-alkyloxy-$C_1$-$C_4$-alkyl (in particular methoxymethyl), cyclopropyl, cyclopentyl, cyclopropyloxy, cyclopentyloxy or a group




in which

$A^2$ represents a single bond, carbonyl, methandiyl, 1,1-ethandiyl, 1,2-ethandiyl

Het represents a saturated heteroycycle with 5 or 6 ring atoms (in particular piperidinyl, piperazinyl, morpholinyl

m represents 0, 1 or 2

$R^{11}$ represents $C_1$-$C_4$-alkyl (in particular methyl, ethyl), $C_1$-$C_4$-alkyloxy (in particular methoxy), $C_1$-$C_4$-alkyloxycarbonyl (in particular tert-Butoxycarbonyl), hydroxyl-$C_1$-$C_4$-alkyl (in particular 2-hydroxyethyl), halo-$C_1$-$C_4$-alkyl (in particular $CF_3$), $C_1$-$C_4$-alkyloxy-$C_1$-$C_4$-alkyl (in particular methoxymethyl), cyclopropyl, cyclopropyloxy.

In any of the formulae herein, $R^1$ is preferably aryl or heteroaryl, each being unsubstituted or substituted as defined herein.

$R^2$ preferably represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy.

$R^2$ particular preferably represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro.

$R^2$ very particular preferably represents hydrogen, fluoro, chloro, methyl.

$R^3$ preferably represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy.

$R^3$ particular preferably represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro.

$R^3$ very particular preferably represents hydrogen, fluoro, chloro, methyl.

When $R^2$ and/or $R^3$ are connected to $R^5$ or $R^7$ to form a cyclic moiety fused to the phenyl ring to which $R^2$/$R^3$ are attached, the resultant fused ring system is preferably a 1,3-dihydro-indol-2-one, optionally substituted in the 1-position with lower alkyl such as methyl, or a 3,4-dihydro-1H-quinolin-2-one.

$R^{2a}$ preferably represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy.

$R^{2a}$ particular preferably represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro.

$R^{2a}$ very particular preferably represents hydrogen, fluoro, chloro, methyl.

$R^{2a}$ more preferably represents hydrogen or methyl, even more preferably hydrogen.

$R^{3a}$ preferably represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy.

$R^{3a}$ particular preferably represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro.

$R^{3a}$ very particular preferably represents hydrogen, fluoro, chloro, methyl.

$R^{3a}$ more preferably represents hydrogen or methyl, even more preferably hydrogen.

$R^5$ preferably represents hydrogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-haloalkyl, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-halocycloalkyl or both R5 form together with the carbon to which they are attached a cyclopropyl.

$R^5$ particular preferably represents hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_2$-haloalkyl, cyclopropyl.

$R^5$ very particular preferably represents hydrogen, methyl or cyclopropyl.

$R^6$ and $R^7$ preferably represent together with the nitrogen to which they are attached an optionally substituted heterocycle substituted by one or more substituents,
wherein said heterocycle is saturated, contains 5 or 6 ring atoms, and 1, 2 or 3 heteroatoms selected from the group of N, O and S, and
wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or SO2), hydroxy, halo, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy hydroxy- $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkylamino, di- $C_1$-$C_7$-alkylamino.

$R^6$ and $R^7$ very preferably represent together with the nitrogen to which they are attached an optionally substituted heterocycle optionally substituted by one to three substituents, wherein said heterocycle is selected from the group of morpholinyl, piperazinyl, thiazidinyl, pyrrolidinyl and
wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopropyloxy, hydroxy-$C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkylamino, di-$C_1$-$C_4$-alkylamino.

$R^6$ preferably represents hydrogen, optionally substituted $C_1$-$C_7$-alkyl, and

$R^7$ represents hydrogen, optionally substituted $C_1$-$C_7$-alkyl, wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), hydroxy, halo, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy hydroxy- $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkylamino, di- $C_1$-$C_7$-alkylamino.

$R^6$ very preferably represents hydrogen and

$R^7$ very preferably represents n-butyl, sec-butyl, iso-butyl, tert-butyl, n-propyl, iso-propyl, ethyl or methyl in particular tert.-butyl each being optionally substituted, wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), hydroxy, halo, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy hydroxy-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkylamino, di- $C_1$-$C_7$-alkylamino.

$R^8$ preferably represents hydroxy, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyloxy, $C_1$-$C_7$-alkyl- sulfonyl, $C_1$-$C_7$-haloalkyl- sulfonyl, $C_3$-$C_6$-cycloalkyl- sulfonyl, $C_3$-$C_6$-halocycloalkyl- sulfonyl, $C_1$-$C_7$-alkyl- sulfinyl, $C_1$-$C_7$-haloalkyl-sulfinyl, $C_3$-$C_6$-cycloalkyl- sulfinyl, $C_3$-$C_6$-halocycloalkyl- sulfinyl.

$R^8$ particular preferably represents hydroxy, methoxy, ethoxy, iso-propoxy, halomethoxy, methylcarbonyl, methylsulfonyl ($H_3CSO_2$-), cyclopropylsulfonyl.

$R^8$ very particular preferably represents hydroxy, methoxy or methylsulfonyl.

$R^9$ preferably represents hydrogen, $C_1$-$C_7$-alkyl.

$R^9$ particular preferably represents hydrogen, $C_1$-$C_4$-alkyl.

$R^9$ very particular preferably represents hydrogen.

$R^{10}$ preferably represents hydrogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-haloalkyl, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-halocycloalkyl.

$R^{10}$ particular preferably represents hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_2$-haloalkyl, cyclopropyl.

$R^{10}$ very particular preferably represents hydrogen or methyl.

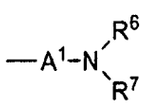
n preferably represents 0 or 1.

n particular preferably represents 0.

n further particular preferably represents 1.

In a further advantageous embodiment, n represents 0 and $R^8$ represents $-SO_2CH_3$.

In a yet further advantageous embodiment, n represents 0 or 1 and $R^4$ represents the group:



as defined above, more preferably wherein the group is as defined above and $R^6$ and $R^7$ together with the nitrogen atom to which they are attached form a morpholinyl, piperazinyl, thiazidinyl or pyrrolidinyl group, each being optionally substituted, most preferably $R^6$ and $R^7$ together with the nitrogen atom to which they are attached form an optionally substituted morpholinyl group, wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), hydroxy, halo, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy hydroxy- $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkylamino, di- $C_1$-$C_7$-alkylamino

In a further advantageous embodiment, at least one of $R^2$ and $R^3$ does not represent hydrogen.

In a further advantageous embodiment, $R^1$ is optionally substituted aryl selected from the group consisting of phenyl, naphthyl, each of which is unsubstituted or substituted by one to three moieties independently selected from the group consisting of $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl-$C_1$-$C_7$-alkyl, morpholino-$C_1$-$C_7$-alkyl, thiomorpholino-$C_1$-$C_7$-alkyl, S-mono- or S,S-dioxo-thiomorpholino-$C_1$-$C_7$-alkyl,

carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, pyrrolidino, oxo-pyrrolidino, piperidino, piperazin-1-yl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl, morpholino, thiomorpholino, S-oxo- or S,S-dioxothiomorpholino, $C_1$-$C_7$-alkanesulfonylamino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl and/or (N'-mono- or N',N'-di-($C_1$-$C_7$-alkyl)-amino-$C_1$-$C_7$-alkyl)-carbamoyl, pyrrolidin-1-carbonyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-($C_1$-$C_7$-alkyl)piperazin-1-carbonyl, morpholin-1-carbonyl, thiomorpholin-1-carbonyl, S-oxo- or S,S-dioxothiomorpholin-1-carbonyl, sulfo, $C_1$-$C_7$-alkanesulfonyl, $C_1$-$C_7$-alkanesulfinyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, cyano and nitro; for example, it can bpreferably be phenyl or naphthyl that is substituted by one or more, especially one to four substituents independently selected from the group consisting of $C_1$-$C_7$-alkoxy, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl and/or $C_1$-$C_7$-alkyloxy-$C_1$-$C_7$-alkyl)-carbamoyl, N-mono- or N,N-di-{[unsubstituted, N'-mono- or N',N'-di-($C_1$-$C_7$-alkyl)-substituted]-carbamoyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, piperidino, piperazino, N-$C_1$-$C_7$-alkylpiperazino, morpholino, thiomorpholino, S-oxothiomorpholino and S,S-dioxothiomorpholino, in the case of $R^2$, unsubstituted or substituted aryl is preferably phenyl or naphthyl that is unsubstituted or substituted by one or more, especially up to three, more especially up to two, substituents, preferably not in ortho-position, more preferably with not more than one substituent in meta-position, most preferably with one substituent in meta- and/or one substituent in para position, most preferably with one substituent in meta-position or especially one in para-position, where the substituents are independently selected from the group consisting of $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, $C_1$-$C_7$-alkanesulfonyl-amino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl, $C_1$-$C_7$-alkanesulfonyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholino-sulfonyl, cyano and nitro.

In a further advantageous embodiment, $R^1$ is optionally substituted aryl selected from the group consisting of phenyl, (especially 3,4,5-)trimethoxyphenyl*, (especially 3,4- or 3,5-

)dimethoxyphenyl*, (especially 4-)morpholinophenyl, (especially 4-) N-(2-methoxyethyl)-carbamoylphenyl*, or (especially 4-)N,N-(2-dimethylamino-ethyl)-carbamoylphenyl*, (especially 4-)dimethylaminocarbonyl-(especially 3-)methyl-phenyl*, (especially 4-)-(preferably 4-)-(2-methoxy-ethyl-piperazin-(especially 1-)yl-(especially 3-)-methyl-phenyl, (especially 4-)pyrrolidin-1-carbonyl-(especially 3-)methyl-phenyl*, (especially 3-)methyl-(especially 4-)-4-methylpiperazin-1-carbonyl-phenyl, (especially 3- or 4-)4-methyl-piperazin-1-yl-phenyl*, (especially 4-)-4-ethyl-piperazin-1-yl-(especially 3-)methyl-phenyl*, (especially 4-)-4-methyl-piperazin-1-yl-(especially 3-)cyano-phenyl, (especially 4-)-piperazin-1-yl-phenyl, (especially 4-)-4-cyclopropyl-piperazin-1-yl-phenyl, (especially 4-)-4-(2-dimethylaminoethyl)-piperazin-1-yl-(especially 3-)methyl-phenyl*, (especially 4-)4-isopropyl-piperazin-1-yl)-(especially 3-)methyl-phenyl*, (especially 4-)N,N-diethylaminocarbonyl-(especially 3-)methyl-phenyl*, (especially 4-)4-ethylpiperazin-1-carbonyl-(especially 3-)methyl-phenyl, (especially 4-)-(4-ethylpiperazin-1-ylmethyl)-(especially 3-)methyl-phenyl, (especially 4-)N-methylaminocarbonyl-(especially 3-)methylphenyl, (especially 4-)-4-(3,3,3-trifluoropropyl)-piperazin-1-yl-(especially 3-)methyl-phenyl, (especially 4-)-4-(2-(N',N'-dimethylamino)ethyl-aminocarbonyl-(especially 3-)methyl-phenyl, (especially 4-)-methanesulfonyl-phenyl*, (especially 4-)[(especially 2-)-oxo-pyrrolidin-1-yl]-phenyl, (especially 4-)N,N-diethylaminocarbonyl-(especially 3-)methoxyphenyl, (especially 3-)-4-methylpiperazin-1-yl-(especially 4-)methyl-phenyl, (especially 3-)-4-methylpiperazin-1-yl-(especially 4-)methoxy-phenyl*, (especially 3- or 4-)-morpholinomethyl-(especially 4- or 3-)methyl-phenyl, (especially 2-)acetylamino-indan-(especially 5-)yl, (especially 2-)oxo-2,3-dihydroindol-(especially 5-)yl, (especially 4-)methylsulfinylphenyl, (especially 4-)methoxyphenyl, (especially 4-)methyl-(especially 3-)methoxyphenyl, (especially 4-)-N-(2-methoxyethyl)-aminocarbonyl-phenyl, (especially 4-)N,N-dimethylcarbamoyl-phenyl, (especially 3-)methanesulfonylamino-phenyl, (especially 4-)methoxycarbonyl-(especially 3-)methoxy-phenyl, (especially 4-)N,N-dimethylcarbamoyl-(especially 3-)methoxy-phenyl, (especially 4-)-(4-cyclopropyl-piperazin-1-yl)-(especially 3-)methyl-phenyl*, (especially 4-)-N-(2-(N',N'-dimethylaminoethyl)-N-methyl-carbamoyl-(especially 3-)methyl-phenyl*, 1,3-dimethyl-oxo-1H-pyridine-5-yl, (especially 3- or 4-)morpholino-(especially 4- or 3-)methyl-phenyl*, (especially 4-)morpholinomethyl-(especially 3-)methyl-phenyl, (especially 4-)morpholin-1-carbonyl-(especially 3-)methyl-phenyl, (especially 4-)-N-2-(methoxyethyl)aminocarbonyl-(especially 3-)methyl-phenyl, (especially 4-)-N-(3-N'.N'-dimethylaminopropyl)amino-carbonyl-(especially 3-)methyl-phenyl, (especially 5-)-methyl-(especially 6-)methoxy-pyridin-3-yl, (especially 4-)dimethylcarbamoyl-(especially 3,5-)dimethyl-phenyl, (especially 4-)dimethylcarbamoyl-(especially 3-)ethyl-phenyl, (especially 4-(4-)N,N-dimethylcarbamoyl-(especially 3-)methyl-phenyl or (especially

4-)morpholino-(especially 3-)cyano-phenyl; where the moieties marked with an asterisk (*) are especially preferred, as are the moieties where the position after "especially" is given).

In a further andvantageous embodiment, $R^1$ is optionally substituted heterocyclyl selected from the group consisting of preferably pyridyl, pyrimidyl, pyrazolyl, thiophenyl, pyrrolyl imidazolyl, or *1H*-benzoimidazolyl, each of which is unsubstituted or substituted by one to three moieties independently selected from those mentioned above as substituents for aryl $R^1$, or especially from the group consisting of $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, $C_1$-$C_7$-alkanesulfonylamino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl, $C_1$-$C_7$-alkanesulfonyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, thiomorpholinosulfinyl, cyano and nitro.

In a further andvantageous embodiment, $R^1$ represents phenyl or pyridiyl in each case optionally substituted by one or two substitutents, the substituents being selected from the group consisting of $C_1$-$C_4$-alkyl (in particular methyl), $C_1$-$C_4$-alkoxy (in particular methoxy), halo ( in particular fluoro), N-methyl-N-piperazinyl-methyl, N-methyl-N-piperazinyl-carbonyl, 3,5-dimethyl-N-piperazinyl.

The invention further relates to pharmaceutically acceptable prodrugs of a compound of formula (I).

The invention further relates to pharmaceutically acceptable metabolites of a compound of formula (I).

The invention relates especially to the compounds of the formula I given in the Examples, as well as the methods of manufacture described therein.

The compounds of formula I thereof have valuable pharmacological properties, as described hereinbefore and hereinafter. They inhibit various protein tyrosine kinases, and especially JAK2 and/or JAK3-receptor tyrosine kinase. Preferably, the compounds of formula I exhibit selectivity for JAK2 and JAK3 over JAK1 and TYK2 kinases. Most preferably, the

compounds of formula I exhibit selectivity for JAK2 over the other JAK family kinases, i.e. preferably, selectivity is exhibited for JAK2 over JAK1, JAK3 and TYK2 kinases.

Preferably, the compounds of formula I exhibit selectively for JAK2 inhibition when compared to other kinases, for example cMet, cKit, ALK and/or PDGFRa.

The compounds of formula I typically show IC50 values for JAK2 inhibition in the range < 0.003 to 2 umol l-1, preferably < 0.003 to 1 umol l-1, more preferably < 0.003 to 0.100 umol l-1, even more preferably < 0.003 to 0.050 umol l-1.

The efficacy of the compounds of the invention as inhibitors of JAK/TYK kinase activity can be demonstrated as follows (Results are given at the end of the specification):

All four kinases of the JAK/TYK-kinase family were used as purified recombinant GST-fusion proteins, containing the active kinase domains. GST-JAK1(866-1154), GST-JAK3(811-1124), and GST-TYK2(888-1187) were expressed and purified by affinity chromatography at the EPK biology unit. GST-JAK2(808-1132) was purchased from Invitrogen (Carlsbad, USA, #4288).

The kinase assays were based on the Caliper mobility shift assay using the LabChip 3000 systems. This technology is similar to capillary electrophoresis and uses charge driven separation of substrate and product in a microfluidic chip.

All kinase reactions were performed in 384 well microtiter plates in a total reaction volume of 18 µl. The assay plates were prepared with 0.1 µl per well of test compound in the appropriate test concentration, as described under the section "preparation of compound dilutions". The reactions were started by combining 9 µl of substrate mix (consisting of peptide and ATP) with 9 µl of kinase dilution. The reactions were incubated for 60 minutes at 30°C and stopped by adding 70 µl of stop buffer (100 mM Hepes, 5% DMSO, 0.1% Coating reagent, 10 mM EDTA, 0.015% Brij 35).

Fluorescently labeled synthetic peptides were used as substrates in all reactions. A peptide derived from the sequence of IRS-1 (IRS-1 peptide, FITC-Ahx-KKSRGDYMTMQIG-NH2) was used for JAK1 and TYK2 and a peptide named JAK3tide (FITC-GGEEEEYFELVKKKK-NH2) for JAK2 and JAK3. Specific assay conditions are described in Table1:

Table1: Assay conditions of individual kinase assays

| Kinase | JAK1 | JAK2 | JAK3 | TYK2 |
|---|---|---|---|---|
| Buffer | 50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 12 mM MgCl2 | 50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2 | 50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 1.5 mM $MgCl_2$ | 50 mM Hepes pH 7.5, 0.02% Tween 20, 1 mM DTT, 0.02% BSA, 9 mM MgCl2 |
| DMSO | 0.6 % | 0.6 % | 0.6 % | 0.6 % |
| Kinase conc. | 50 nM | 1.8 nM | 6 nM | 40 nM |
| Substrate peptide conc. | 5 µM | 2 µM | 2 µM | 5 µM |
| ATP conc. | 40 µM | 20 µM | 80 or 18 µM | 30 µM |

The terminated reactions were transferred to the Caliper LabChip 3000 reader and the turnover of each reaction was measured by determining the substrate/product ratio.

*Preparation of compound dilutions*

Test compounds were dissolved in DMSO (10 mM) and transferred into 1.4mL flat bottom or V-shaped Matrix tubes carrying a unique 2D matrix chip by individual compound hubs. The numbers of these chips were distinctively linked to the individual compound identification numbers. The stock solutions were stored at –20°C if not used immediately. For the test procedure the vials were defrosted and identified by a scanner whereby a working sheet was generated that guided the subsequent working steps.

Compound dilutions were made in 96 well plates. This format enabled the assay of maximally 40 individual test compounds at 8 concentrations (single points) including 4 reference compounds. The dilution protocol included the production of pre-dilution plates, master plates and assay plates:

Pre-dilution plates: 96 polypropylene well plates were used as pre-dilution plates. A total of 4 pre-dilution plates were prepared including 10 test compounds each on the plate positions A1-A10, one standard compound at A11 and one DMSO control at A12. All dilution steps were done on a HamiltonSTAR robot.

Master plates: 100µL of individual compound dilutions including standard compound and controls of the 4 "pre-dilution plates" were transferred into a 384 "master plate" including the

following concentrations 1'820, 564, 182, 54.6, 18.2, 5.46, 1.82 and 0.546µM, respectively in 90 % of DMSO.

Assay plates: Identical assay plates were then prepared by pipetting 100 nL each of compound dilutions of the master plates into 384-well "assay plates". In the following the compounds were mixed with 9µL of assays components plus 9µL enzyme corresponding to a 1:181 dilution steps enabling the final concentration of 10, 3.0, 1.0, 0.3, 0.1, 0.03, 0.01 and 0.003µM, respectively. The preparation of the master plates were handled by the Matrix PlateMate Plus robot and replication of assay plates by the HummingBird robot.

On the basis of these studies, a compound of the invention shows therapeutic efficacy especially against disorders dependent on protein kinase, especially proliferative diseases mediated by JAK/TYK kinase activity.

*STAT nuclear translocation assays:*
Alternatively, the activity of the compounds of the invention as inhibitors of the JAK/STAT pathway can be demonstrated as follows (Results are given at the end of the specification):

The medium-throughput (96-well format) cellular automated fluorescence microscopy Cellomics assay can be routinely used to assess the functional activation of Janus Kinases (JAKs), based on the nuclear translocation of their substrate, Signal Transducer and Activator of Transcription (STAT). Nuclear translocation can be monitored either in HT1080 fibrosarcoma cells stably transfected with STAT1 fused to Green Fluorescence Protein (GFP) or in U-2 OS osteosarcoma cells stably transfected with STAT5 fused to Green Fluorescence Protein (GFP). Stimulation of HT1080 cells with interferon-γ (IFN-γ) results in JAK1/JAK2-dependent nuclear translocation of STAT1-GFP, whereas stimulation of U-2 OS cells with recombinant human erythropoietin (rhEpo) results in JAK2-dependent nuclear translocation of STAT5-GFP, both of which can be quantified using the Cellomics Cyto/NucTrans software package. This assay may be used to provide an assessment of the nuclear-cytoplasmic differential (NCD) of STAT-GFP using Hoechst dye to define the boundaries of the nucleus.

*Generation of HT1080 Fibrosarcoma Cells stably expressing GFP-STAT1:*
HT1080 fibrosarcoma cells may be obtained from ATCC and can be cultured in alpha Modified Eagle Medium with 10 % FCS. Cells can be transfected with pEGFP-N2 STAT1

using Fugene 6 Transfection Reagent following the manufacturers' protocol. 24 hours after transfection the medium can be replaced and selected in 1 mg/ml Geneticin.

*Generation of U2OS cells stably expressing STAT5a-GFP and EpoR:*

U-2 OS osteosarcoma cells may be obtained from ATCC and can be cultured in standard RPMI medium supplemented with 10 % FCS and 2 mM L-glutamine. Cells can be stably transfected with STAT5a-GFP using Lipofectamine following the manufacturers' protocol. 24 hours after transfection the medium can be replaced and selected in 400 µg/ml Geneticin. Subsequently, cells can be stably transfected with EpoR using Lipofectamine following the manufacturers' protocol. 24 hours after transfection the medium can be replaced and cells selected in 100 µg/ml Hygromycin B.

*Preparation of compound stocks:*

Compounds can be dissolved in DMSO to a final stock concentration of 10 mM and stored as aliquots at 4 °C. Compounds may be pre-diluted in 100 % DMSO at 10 mM, 3 mM 1 mM, 0.3 mM, 0.1 mM, 0.03 mM, 0.01 mM and 0.003 mM. Subsequently, compounds may be diluted in medium and added in 50 µl to the cells. The final compound concentrations tested may be 10 $\mu$M, 3 $\mu$M 1 $\mu$M, 0.3 $\mu$M, 0.1 $\mu$M, 0.03 $\mu$M, 0.01 $\mu$M and 0.003 $\mu$M and the final DMSO concentration can be 0.1 %.

*Cellomics Nuclear STAT-GFP Translocation Assays:*

HT1080 STAT1-GFP cells may be seeded at a density of 10'000 cells per well in clear-bottom black 96-well Packard View-Plates™. 16-24 hours later, the cells can be treated for 2 hours with 100 ng/ml IFN-$\gamma$, washed twice in pre-warmed PBS and fixed in 200 $\mu$l of pre-warmed fixation solution (PBS, 3.7% Formaldehyde) for 10 minutes. The plates may be washed twice in 200 $\mu$l PBS and incubated, protected from light, in 100 $\mu$l of DNA-staining solution (PBS, 0.5 $\mu$g/ml Hoechst-33342) for 1 minute. The plates may then be washed once in PBS, and 200 $\mu$l PBS finally added per well. The plates, being finally covered with a black adhesive, may be either read directly or stored at 4°C for later imaging. Where appropriate, the compounds may be added 30 min before stimulation with IFN-$\gamma$.

U-2 OS may be seeded at a cell density of 12'000 cells per well in clear-bottom black 96-well Packard View-Plates™. The following day, medium can be removed and replaced with medium containing either the vehicle (DMSO) or increasing concentrations of test compounds for 30 minutes at 37 °C. Cells can then be stimulated for 1 hour by adding 10 µl

per well of 50 U/ml rhEpo to obtain 5 U/ml of rhEpo as the final concentration. Following treatments, cells can fixed and processed as described above.

*STAT-GFP nuclear translocation measurement by Cellomics automated fluorescence microcopy imaging and analysis:*

The plates can be read on a Cellomics® ArrayscanII automated fluorescence microscope plate reader equipped with a Mercury-Xenon white light illumination source and a Zeiss Axiovert inverted microscope, using the XF100 dichroic/emission filter cube and matching excitation filters, 10x magnification, and a 0.3 numerical aperture objective. Image acquisition and analysis can be performed using a customized protocol based on the 'NuclearTranslocation' Bioapplication. For each well, multiple images (fields) can be acquired until a minimum of 1000 cells are counted using two 2 channels: Channel 1 (Hoechst) = focus + nuclear mask, Channel 2 (GFP) = signal quantification in mask areas as outlined below. Nuclei may be first identified based on the Hoechst staining and a mask generated for each nucleus that then serves as a template to generate a circle (eroded inwards by 1 pixel) and a 3 pixel-wide collar-like ring (off-set outwards by 1 pixel), in which the nuclear and cytoplasmic intensity of GFP, respectively, are quantified in the corresponding channel. High content analysis yields numerous measurements per cell and the GFP intensity differential between the nuclear and the cytoplasmic masks may be chosen as a measure of sub-cellular STAT-GFP relocation. The resulting values may be averaged for all cells in the well to return a single measurement plus standard deviation.

To generate $IC_{50}$ values, the nuclear-cytoplasmic STAT-GFP differential of untreated cells may be used as a baseline and the following equation used to determine the percentage increase in nuclear translocation: Percentage = 100 * (NCD Compound pre-treated and stimulated - NCD Untreated)/(NCD DMSO-pretreated and stimulated – NCD Untreated).
In these assays, compounds of formula (I) generally inhibit JAK2 kinases in the range of 1 – 10 000 nM.

The activity of the compounds of the formula I can also be determined *in vivo:*

<u>JAK-2 in vivo</u>

The assay can be performed as described by G. Wernig, T. Mercher, R. Okabe, R.L. Levine, B. H. Lee, D.G. Gilliland, Blood First Edition paper, published online February 14, 2006; DOI 10, 1182/blood-2005-12-4824.

On the basis of these studies, a compound of formula I according to the invention shows therapeutic efficacy especially against disorders dependent on protein kinase, especially proliferative diseases mediated JAK2 kinase activity.

In addition, further protein kinases can be inhibited by compounds of this invention, such as Tyk2, c-src, Flt-3, KDR and others, for each of which test systems are known in the art.

A compound of formula I can be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. A compound of formula I can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

Thus, a compound of the formula I may be used to advantage in combination with other antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozo-

lomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer, leucovorin, EDG binders, antileukemia compounds, ribonucleotide reductase inhibitors, S-adenosylmethionine decarboxylase inhibitors, antiproliferative antibodies or other chemotherapeutic compounds. Further, alternatively or in addition they may be used in combination with other tumor treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radiosensitizers. Also, in anti-inflammatory and/or antiproliferative treatment, combination with anti-inflammatory drugs is included. Combination is also possible with antihistamine drug substances, bronchodilatatory drugs, NSAID or antagonists of chemokine receptors.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be

administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505. The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHOS. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to

taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR..

The term "platin compound" as used herein includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is

marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, e.g. imatinib;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825)

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds

which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.
Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

The term "Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase" includes, but is not limited to inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.

The term "Compounds which induce cell differentiation processes" includes, but is not limited to e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

The term "cyclooxygenase inhibitor" as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.
The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.
The term " biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).
The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomid (Velcade™)and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1,erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in

US 6,552,065, in particular, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof and *N*-hydroxy-3-[4-[(2-hydroxyethyl){2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

"Somatostatin receptor antagonists" as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230.

"Tumor cell damaging approaches" refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology*, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

The term "ribonucleotide reductase inhibitors" includes, but is not limited to to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1*H*-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica*, Vol. 33, No. 8, pp. 953-961 (1994).

The term "*S*-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U S A*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-

3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell*, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

"Photodynamic therapy" as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.

"Angiostatic steroids" as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone. hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

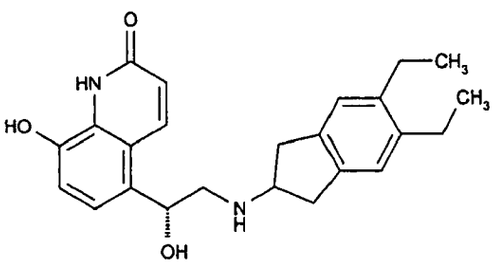
"Implants containing corticosteroids" as used herein includes, but is not limited to compounds, such as e.g. fluocinolone, dexamethasone.

"Other chemotherapeutic compounds" include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of inflammatory diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a com-

pound of the invention as hereinbefore described with an anti-inflammator or antihistamine drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, non-steroidal glucocorticoid receptor agonists such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229; LTB4 antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in US 5451700; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; A2a agonists such as those disclosed in EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083; A2b antagonists such as those described in WO 02/42298; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula I of WO 04/16601, and also compounds of WO 04/033412.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, US 5171744, US 3714357, WO 03/33495 and WO 04/018422.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-amin-ium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

Therapeutic agents for possible combination are especially one or more antiproliferative, cytostatic or cytotoxic compounds, for example one or several agents selected from the group which includes, but is not limited to, an inhibitor of polyamine biosynthesis, an inhibitor of a protein kinase, especially of a serine/threonine protein kinase, such as protein kinase C, or of a tyrosine protein kinase, such as the EGF receptor tyrosine kinase, e.g. Iressa®, the

VEGF receptor tyrosine kinase, e.g. PTK787 or Avastin®, or the PDGF receptor tyrosine kinase, e.g. STI571 (Glivec®), a cytokine, a negative growth regulator, such as TGF-ß or IFN-ß, an aromatase inhibitor, e.g. letrozole (Femara®) or anastrozole, an inhibitor of the interaction of an SH2 domain with a phosphorylated protein, antiestrogens, topoisomerase I inhibitors, such as irinotecan, topoisomerase II inhibitors, microtubule active agents, e.g. paclitaxel or an epothilone, alkylating agents, antiproliferative antimetabolites, such as gemcitabine or capecitabine, platin compounds, such as carboplatin or cis-platin, bisphosphonates, e.g. AREDIA® or ZOMETA®, and monoclonal antibodies, e.g. against HER2, such as trastuzumab.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The above-mentioned compounds, which can be used in combination with a compound of the formula I, can be prepared and administered as described in the art, such as in the documents cited above.

Thus, the invention relates in a further aspect to a combination comprising a therapeutically effective amount of a compound of formula I in free form or in pharmaceutically acceptable salt form and a second drug substance, for simultaneous or sequential administration.

The invention also provides, in a further aspect, a pharmaceutical preparation (composition), comprising a compound of formula I as defined herein, or a pharmaceutically acceptable salt of such a compound, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier and / or diluents and optionally one or more further drug substances.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Topical administration is e.g. to the skin. A further form of topical administration is to the eye. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical

acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The invention relates also to pharmaceutical compositions comprising an effective amount, especially an amount effective in the treatment of one of the above-mentioned diseases (= disorders), of a compound of formula I or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration and that may be inorganic or organic, solid or liquid. There can be used for oral administration especially tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, mannitol, and/or glycerol, and/or lubricants and/or polyethylene glycol. Tablets may also comprise binders, for example magnesium aluminum silicate, starches, such as corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, dyes, flavorings and sweeteners. It is also possible to use the pharmacologically active compounds of the present invention in the form of parenterally administrable compositions or in the form of infusion solutions. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilisers, wetting compounds and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions, which may, if desired, comprise other pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectionning, dissolving or lyophilising processes, and comprise approximately from 1% to 99%, especially from approx. 1% to approx. 20%, active ingredient(s).

The dosage of the active ingredient to be applied to a warm-blooded animal depends upon a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. The dose of a compound of the formula I or a pharmaceutically acceptable salt thereof to be administered to warm-

blooded animals, for example humans of approximately 70 kg body weight, is preferably from approximately 3 mg to approximately 5 g, more preferably from approximately 10 mg to approximately 1.5 g per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

In a further aspect, the invention relates to a compound of formula I or a pharmaceutically acceptable salt, as a medicament / for use as a medicament, in particular for the treatment of one or more Protein tyrosine kinase mediated diseases.

In a further aspect, the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt,as active ingredient in a medicament, in particular for the treatment of one or more Protein tyrosine kinase mediated diseases.

In a further aspect, the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt, as medicament, in particular for the treatment of one or more Protein tyrosine kinase mediated diseases.

In a further aspect, the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt, for the manufacture of a medicament for the treatment of one or more Protein tyrosine kinase mediated diseases.

In a further aspect, the invention relates to a compound of formula I or a pharmaceutically acceptable salt of such a compound, for use in a method for the treatment of a subject in need thereof, especially for the treatment of a Protein tyrosine kinase mediated disease, most especially in a patient requiring such treatment.

In a further aspect, the invention relates to a method for the treatment of a disease which responds to an inhibition of JAK-2 and/or Jak-3 kinase, which comprises administering a compound of formula I or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above, especially in a quantity effective against said disease, to a warm-blooded animal requiring such treatment.

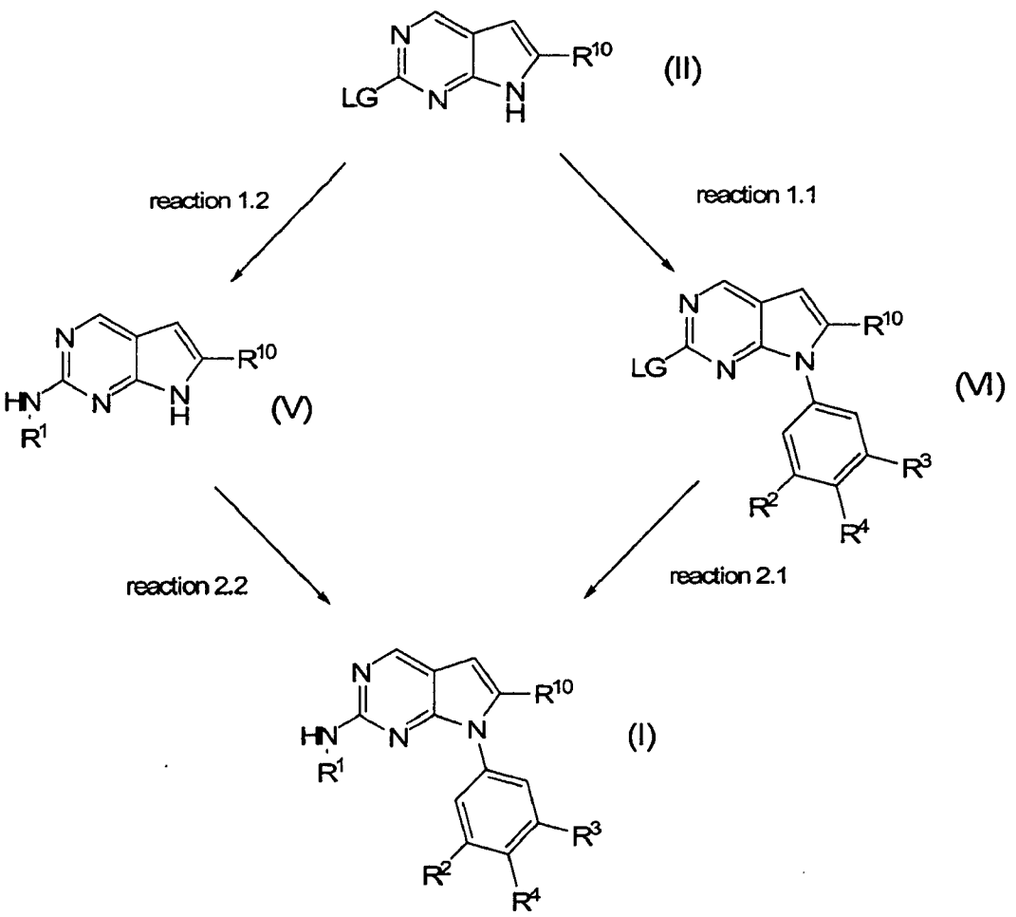
In a further aspect, the invention relates to a pharmaceutical composition comprising a compound of formula I as active ingredient in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner.

In a further aspect, the invention relates to a method of treatment of one or more Protein tyrosine kinase mediated diseases, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of compound of formula I.

In a further aspect, the invention relates to pharmaceutical compositions comprising: (a) an effective amount of compound of formula I and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites thereof; and (b) one or more pharmaceutically acceptable excipients and / or diluents.

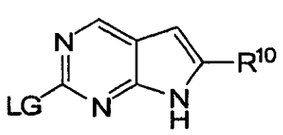
In a further aspect, the invention relates to a pharmaceutical composition for treatment of a disease, e.g. of solid or liquid tumours in warm-blooded animals, including humans, comprising a dose effective in the treatment of said disease of a compound of the formula I as described above or a pharmaceutically acceptable salt of such a compound together with a pharmaceutically acceptable carrier (= carrier material).

A compound of the formula I or I' may be prepared by processes that, though not applied hitherto for the new compounds of the present invention where they thus form new processes, are known *per se*, the following scheme illustrates methods for such preparation.



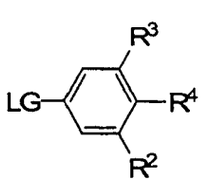

Preferably, a process for the manufacture of a compound of the formula I comprises either

Method a) reacting in a first step a compound of the formula II,

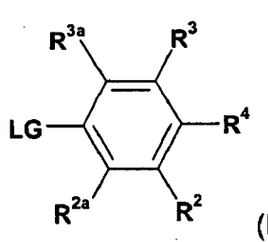


(II)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group (such as tosylate, mesylate or halo, in particular chloride) with a compound of the formula IV or IV',

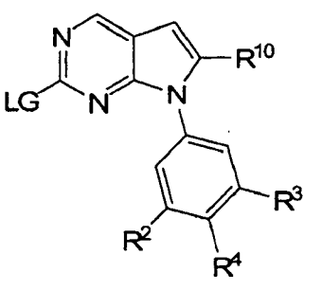


(IV')

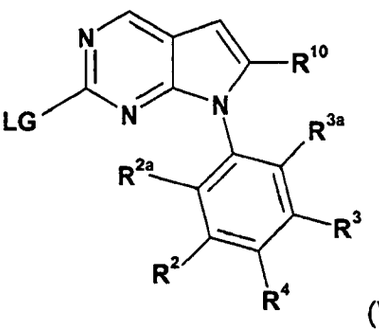


(IV)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group (such as tosylate, mesylate or halo, in particular bromide) in a Cu-catalyzed Buchwald reaction to obtain a compound of formula (VI) or (VI')

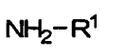


(VI')



(VI)

wherein the substituents are as defined above with a compound of formula I and reacting in a second step the obtained compound of formula VI with a compound of formula (III)

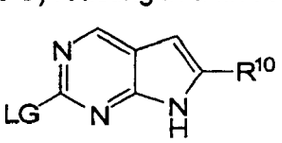


(III)

wherein R1 is as defined in formula I to obtain a compound of formula I;

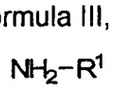
or

method B) reacting in a first step a compound of the formula II,



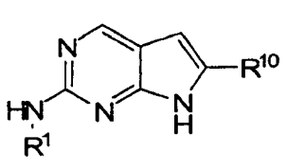
(II)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group (such as tosylate, mesylate or halo, in particular chloride) with a compound of the formula III,



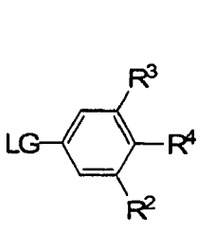
(III)

wherein $R^1$ is as defined in formula I either in a Pd-catalyzed Buchwald reaction or under acidic conditions to obtain a compound of formula (V)

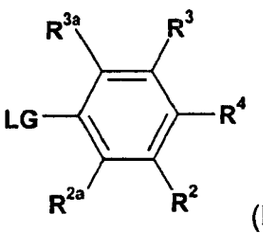


(V)

wherein the substituents are as defined above for a compound of formula I and reacting in a second step the obtained compound of formula V with a compound of formula IV




(IV')




(IV)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group (such as tosylate, mesylate or halo, in particular bromide) to obtain a compound of formula I;

and, if desired, converting a compound of the formula I obtained according to method A) or method B) into a different compound of the formula I, and/or converting an obtainable salt of a compound of the formula I into a different salt thereof, and/or converting an obtainable free compound of the formula I into a salt thereof, and/or separating an obtainable isomer of a compound of the formula I from one or more different obtainable isomers of the formula I.

Reaction conditions

Where temperatures are given hereinbefore or hereinafter, "about" has to be added, as minor deviations from the numeric values given, e.g. variations of ±10 %, are tolerable. All reactions may take place in the presence of one or more diluents and/or solvents. The starting materials may be used in equimolar amounts; alternatively, a compound may be used in excess, e.g. to function as a solvent or to shift equilibrium or to generally accelerate reation rates. Reaction aids, such as acids, bases or catalysts may be added in suitable amounts, as known in the field, required by a reation and in line with generally known procedures.

Buchwald reaction

This reaction, also known as Buchwald amination or Buchwald-Hartwig reaction is generally known in the field. This reaction is catalyzed by transition metals, in particular Cu or Pd complexes or salts; takes place in the presence of one or more basic compounds (such as an amine or an alkalialkoxide) and one or more diluents (such as polar aprotic diluents). Further details may be found in the examples.

Protecting groups

If one or more other functional groups, for example carboxy, hydroxy, amino, sulfhydryl or the like are or need to be protected in a starting material as described herein or any other

precursor, because they should not take part in the reaction or disturb the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars. Protecting groups are such groups that are no longer present in the final compounds once they are removed, while groups that remain as substituents are not protecting groups in the sense used here which are groups that are added at a starting material or intermediate stage and removed to obtain a final compound. Also in the case of conversions of a compound of the formula I into a different compound of the formula I, protecting groups may be introduced and removed, if useful or required.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by acetolysis, protonolysis, solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and below.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

Optional Reactions and Conversions

A compound of the formula I may be converted into a different compound of the formula I.

For example, in a compound of the formula I wherein $R^1$ or especially $R^4$ carries an amino or amino-$C_1$-$C_7$-alkyl substituent, the amino can be converted into acylamino, e.g. $C_1$-$C_7$-alkanoylamino or $C_1$-$C_7$-alkanesulfonylamino, by reaction with a corresponding $C_1$-$C_7$-alkanoylhalogenide or $C_1$-$C_7$-alkanesulfonylhalogenide, e.g. a corresponding chloride, in the presence of a tertiary nitrogen base, such as triethylamine or pyridine, in the absence or presence of an appropriate solvent, such a methylene chloride, for example at temperatures in the range from –20 to 50 °C, e.g. at about room temperature.

In a compound of the formula I wherein $R^1$ or especially $R^4$ carries a cyano substituent, the cyano may be converted to an aminomethyl group, e.g. by hydrogenation in the presence of an appropriate metal catalyst, such as Raney Nickel or Raney Cobalt, in an appropriate solvent, e.g. a lower alkanol, such as methanol and/or ethanol, for example at temperatures in the range from –20 to 50 °C, e.g. at about room temperature.

In a compound of the formula I wherein $R^1$ or especially $R^4$ carries a carboxyl (COOH) substituent, the latter can be converted into an amide group, e.g. an N-$C_1$-$C_7$-alkyl-carbamoyl group, by reaction with the corresponding amine, e.g. in the presence of a coupling agent, that forms a preferred reactive derivative of the carboxyl group *in situ*, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/ HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl); *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole or/1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* (1972), 453-463. The reaction mixture is preferably stirred at a temperature of between approximately -20 and 50 °C, especially between 0 °C and 30 °C, e.g. at room temperature.

In a compound of the formula I wherein $R^1$ or especially $R^4$ carries two vicinal amino groups, the two nitrogen atoms of the two amino groups can be bridged by a –CH= group (thus forming, together with the two carbon atoms that bind the original amino groups and the bond between them, an *1H*-imidazolo ring annelated to $R^1$ or $R^4$; for example, (vicinal diamino)-phenyl can be converted into benzoimidazolyl according to this method. The reaction prefer-

ably takes place by first reacting the compound of the formula I carrying the two vicinal amino groups with formic acid, e.g. in the presence of a coupling agent as mentioned in the preceding paragraph, such as EDC hydrochloride, a base, such as N,N-dimethylaminopyridine (DMAP) and preferably an appropriate solvent, such as methylene chloride, e.g. at temperatures in the range from –20 to 50 °C, e.g. at about room temperature, thus converting one (especially a para-positioned) of the vicinal amino groups into a formylamino group. In a second step, the amino and formylamino group are then reacted to –N=C-N- by heating in the presence of an acid, especially acetic acid, e.g. at temperatures in the range from 50 to 110 °C, for example at about 100 °C.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formula I) may also be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from 130 to 170°C, one molecule of the acid being expelled per molecule of a compound of formula I. Salts can usually be converted to free compounds, e.g. by treating with suitable basic compounds, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates (and are thus useful in the preparation of corresponding starting materials).

Starting materials:

The starting materials of the formulae II, III and IV, as well as other starting materials mentioned herein, e.g. below, can be prepared according to or in analogy to methods that are known in the art, are known in the art and/or are commercially available. Novel starting materials, as well as processes for the preparation thereof, are likewise an embodiment of the present invention. In the preferred embodiments, such starting materials are used and the reaction chosen are selected so as to enable the preferred compounds to be obtained.

In the starting materials (including intermediates), which may also be used and/or obtained as salts where appropriate and expedient, the substituents are preferably as defined for a compound of the formula I.

The following examples illustrate the invention without limiting the scope thereof.

Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at rt.

The $R_f$ values in TLC indicate the ratio of the distance moved by each substance to the distance moved by the eluent front. $R_f$ values for TLC are measured on 5 x 10 cm TLC plates, silica gel $F_{254}$, Merck, Darmstadt, Germany; the solvent systems are marked in the examples as follows:

* 10% methanol / 90% methylene chloride ($CH_2Cl_2$)

** 5% methanol / 95% methylene chloride

*** 2% methanol / 98% methylene chloride

‡ 50% hexane / 50% ethyl acetate

† 66% hexane / 33% ethyl acetate

If not indicated otherwise, the analytical HPLC conditions are as follows:

**Method A**

| | |
|---|---|
| Column | SunFire C18 20x4.6 mm, 3.5 µm |
| Column Temperature | 40 °C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 3.0 mL/min |

| | |
|---|---|
| Gradient | 5-100% B in 4.0 min |

**Method B**

| | |
|---|---|
| Column | Column Engineering, Inc., Matrix, 3µm C18 150x4.6 mm (Lot # 205). Detection by UV absorption at 215 and 254nm. |
| Column Temperature | 35°C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 1 mL/min |
| Gradient | water (0.1% TFA)/acetonitrile (0.1% TFA) = 98/2 for 1 min. To 100% acetonitrile (0.1% TFA) in 10 min. Stay at 100% for 2 min (total run time: 13 min.) |

**Method C**

| | |
|---|---|
| Column | Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD |
| Column Temperature | 30 °C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 1.0 mL/min |
| Gradient | 2-100% B in 7.0 min |

**Method D**

| | |
|---|---|
| Column | Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD |
| Column Temperature | 30 °C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 1.0 mL/min |
| Gradient | 20-100% B in 7.0 min |

**Method E**

| | |
|---|---|
| System | Agilent 1100 Series with Waters Micromass ZQ |
| Column | XBridge C18, 3 x 30 mm, 2.5 micron |
| Eluents | A: H2O, containing 5% acetonitril and 0.8% HCOOH B: acetonitrile, containing 0.6% HCOOH |
| Flow Rate | 1.4-2.4 mL/min |
| Gradient | 10-95% B in 2.4 min (E1) or 1-95% B in 2.9 min (E2) |

**Method F**

| | |
|---|---|
| Column | Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD |

| | |
|---|---|
| Column Temperature | 30 °C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 1.0 mL/min |
| Gradient | 2-100% B in 7.0 min then 2 min by 100% B |

**Method G**

| | |
|---|---|
| Column | Acquity UPLC BEH C18 / 2.1*50mm / 1.7µm |
| Column Temperature | 40 °C |
| Eluents | A: $H_2O$, B: acetonitrile, both containing 0.1% TFA |
| Flow Rate | 1.0 mL/min |
| Gradient | 0.1min 2% B; 2 to 100% B in 1.5min; 0.4min 100% B |

**Abbreviations**

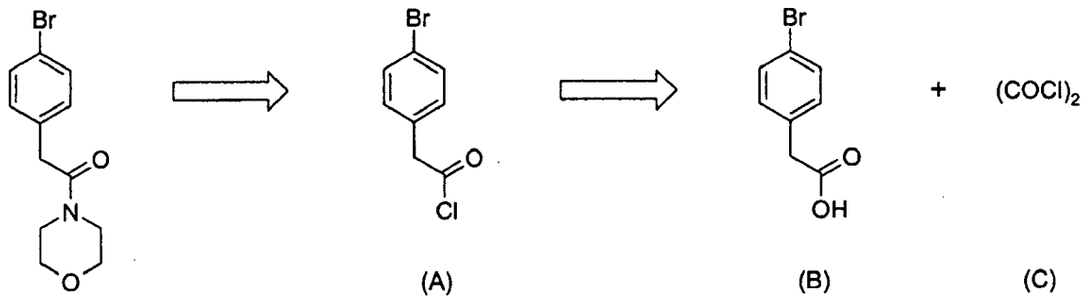
| | |
|---|---|
| AIBN | α,α'-azo-isobutyronitrile |
| Ar | Argon |
| Bn | benzyl |
| Boc | tert-butoxycarbonyl |
| DCM | dichloromethane |
| DIPEA | diisopropyl- ethyl-amine |
| DME | 1,2-dimethoxyethane |
| DMF | N,N-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| h | hour(s) |
| HATU | 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HPLC | High Performance Liquid Chromatography |
| HV | high vacuum |
| Isolute | Isolute® HM-N by International Solvent Technology Ltd., U.K. |
| LAH | lithium aluminium hydride |
| mL | millilitre(s) |
| min | minute(s) |
| MS-ES | electrospray mass spectrometry |

| | |
|---|---|
| MW | microwave |
| $R_f$ | ratio of fronts in TLC |
| rt | room temperature |
| TBTU | [(Benzotriazol-1-yloxy)-dimethylamino-methylene]-dimethyl-ammonium tetrafluoro borate |
| TBDPS | tert-butyldiphenylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| $t_R$ | retention time |
| UV | Ultraviolet |

Starting Materials:

Several aryl bromides and anilines as used according to Scheme 1-3 have been purchased from commercial sources where practicable. Otherwise, the aryl bromides and anilines/aminoheterocycles are being prepared according to the exemplified general procedures:

General procedure I for the synthesis of aryl bromide building blocks (in the following formula exemplified for 2-(4-bromo-phenyl)-1-morpholin-4-yl-ethanone):




2-(4-Bromo-phenyl)-1-morpholin-4-yl-ethanone

(A) (B) (C)

The compound shown on the left above, 2-(4-bromo-phenyl)-1-morpholin-4-yl-ethanone, is obtained by reaction of the corresponding acid chloride (A), (4-bromo-phenyl)-acetyl chloride, with morpholine and $Et_3N$ in DCM at rt. The product is obtained in high yield. The intermediate acid chloride (A) is obtained by reaction of (4-bromo-phenyl)-acetic acid (B) and oxalyl chloride (C) in DCM at rt and using DMF as reaction initiator. The intermediate (A) is obtained in good yield.

Alternatively, amide bond formation can be achieved by coupling of the appropriate carboxylic acid (B) and the appropriate amine in the presence of HATU and N-methyl morpholine in DMF at rt.

The following aryl bromides used in the examples below are synthesized analogously, using the appropriate starting materials:

2-(4-Bromo-phenyl)-1-(4-methyl-piperazin-1-yl)-ethanone

(4-Bromo-2-fluoro-phenyl)-morpholin-4-yl-methanone

(4-Bromo-2-fluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone

2-(4-Bromo-2-fluoro-phenyl)-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone

[1-(4-Bromo-phenyl)-cyclopropyl]-(4-ethyl-piperazin-1-yl)-methanone

(4-Bromo-phenyl)-morpholin-4-yl-methanone

(4-Bromo-phenyl)-(4-methyl-piperazin-1-yl)-methanone

(4-Bromo-phenyl)-pyrrolidin-1-yl-methanone

4-Bromo-N-(2-morpholin-4-yl-ethyl)-benzamide

4-Bromo-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide

(4-Bromo-phenyl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone

(5-Bromo-pyridin-2-yl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone

(6-Bromo-pyridin-3-yl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone

(4-Bromo-2,6-difluoro-phenyl)-(1,1-dioxido-thiomorpholin-4-yl)-methanone

(4-Bromo-2,6-difluoro-phenyl)-morpholin-4-yl-methanone

(4-Bromo-2,6-difluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone

(4-Bromo-2-chloro-phenyl)-morpholin-4-yl-methanone

(4-Bromo-2-methyl-phenyl)-morpholin-4-yl-methanone

(4-Bromo-3-fluoro-phenyl)-morpholin-4-yl-methanone

(6-Bromo-pyridin-3-yl)-morpholin-4-yl-methanone

(5-Bromo-pyridin-2-yl)-morpholin-4-yl-methanone

(3-Bromo-phenyl)-(4-methyl-piperazin-1-yl)-methanone

2-(4-Bromo-phenyl)-2-methyl-1-morpholin-4-yl-propan-1-one

[1-(4-Bromo-phenyl)-cyclopropyl]-morpholin-4-yl-methanone

[1-(4-Bromo-phenyl)-cyclopropyl]-(4-methyl-piperazin-1-yl)-methanone

(5-Bromo-pyridin-2-yl)-morpholin-4-yl-methanone

(5-Bromo-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone

2-(4-Bromo-phenyl)-1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethanone

4-Bromo-2-fluoro-N-(2-morpholin-4-yl-ethyl)-benzamide

4-Bromo-2-fluoro-N-[2-(4-methyl-piperazin-1-yl)-ethyl]-benzamide

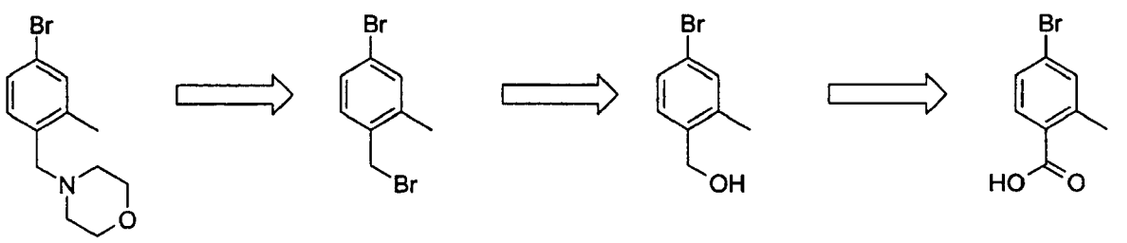
(4-Bromo-2-fluoro-phenyl)-(4-dimethylamino-piperidin-1-yl)-methanone

(4-Bromo-phenyl)-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone

(4-Bromo-2-fluoro-phenyl)-(1,1-Dioxido-thiomorpholin-4-yl)-methanone

(4-Bromo-3-fluoro-phenyl)-morpholin-4-yl-methanone

General procedure II for the synthesis of aryl bromide building blocks (in the following formula exemplified for 4-(4-bromo-2-methyl-benzyl)-morpholine):




4-(4-Bromo-2-methyl-benzyl)-morpholine (A) (B) (C)

The compound shown on the left above, 4-(4-Bromo-2-methyl-benzyl)-morpholine, is obtained by reaction of the corresponding benzyl bromide (A), 4-bromo-1-bromomethyl-2-methyl-benzene, with morpholine in DMF at rt. The product is obtained in high yield. The intermediate benzyl bromide (A) is obtained by reaction of (4-bromo-2-methyl-phenyl)-methanol (B) with $PPh_3$ and $CBr_4$ in DCM at rt. The intermediate (A) is obtained in high yield. The intermediate benzyl alcohol B is obtained by reduction of the corresponding carboxylic acid (C), 4-bromo-2-methyl-benzoic acid with LAH in THF. The intermediate (B) is obtained in good yield.

The following aryl bromides used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

4-(4-Bromo-2-fluoro-benzyl)-morpholine

4-(4-Bromo-2-chloro-benzyl)-morpholine

4-(4-Bromo-2-methyl-benzyl)-morpholine

4-(4-Bromo-2,6-difluoro-benzyl)-morpholine

4-[1-(4-Bromo-phenyl)-ethyl]-morpholine

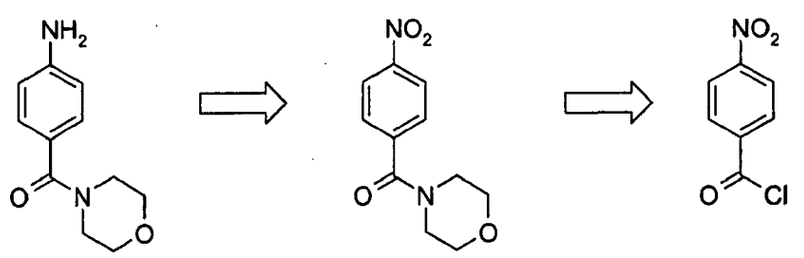
4-(6-Bromo-pyridin-3-ylmethyl)-morpholine

4-(5-Bromo-pyridin-2-ylmethyl)-morpholine

4-[2-(4-Bromo-phenyl)-ethyl]-morpholine

1-(4-Bromo-2-fluoro-benzyl)-4-ethyl-piperazine
1-(4-Bromo-2,6-difluoro-benzyl)-4-ethyl-piperazine
4-(4-Bromo-2,6-difluoro-benzyl)-1-ethyl-piperazin-2-one
1-[4-(4-Bromo-2,6-difluoro-benzyl)-piperazin-1-yl]-ethanone
4-(4-Bromo-2,6-difluoro-benzyl)-thiomorpholine 1,1-dioxide
4-(4-Bromo-2-fluoro-benzyl)-thiomorpholine 1,1-dioxide
4-(4-Bromo-2-chloro-benzyl)-thiomorpholine 1,1-dioxide
1-(4-Bromo-2,6-difluoro-benzyl)-4-methyl-piperazine
1-(4-Bromo-2,6-difluoro-benzyl)-4-isopropyl-piperazine
1-(4-Bromo-2,6-difluoro-benzyl)-4-cyclopropyl-piperazine
4-(4-Bromo-2,6-difluoro-benzyl)-3,3-dimethyl-morpholine
4-(4-Bromo-2,6-difluoro-benzyl)-1-methyl-piperazin-2-one
4-(4-Bromo-2,6-difluoro-benzyl)-piperazin-2-one
8-(4-Bromo-2,6-difluoro-benzyl)-2,5-dioxa-8-aza-spiro[3.5]nonane
4-(4-Bromo-2,6-difluoro-benzyl)-cis-2,6-dimethyl-morpholine
1-(4-Bromo-2,6-difluoro-benzyl)-pyrrolidin-2-one
1-(4-Bromo-2,6-difluoro-benzyl)-3-methoxy-azetidine
4-(4-Bromo-2,6-difluoro-benzyl)-morpholin-3-one

General procedure **III** for the synthesis of aniline building blocks (in the following formula exemplified for (4-amino-phenyl)-morpholin-4-yl-methanone):




(4-Amino-phenyl)-morpholin-4-yl-methanone (A) (B)

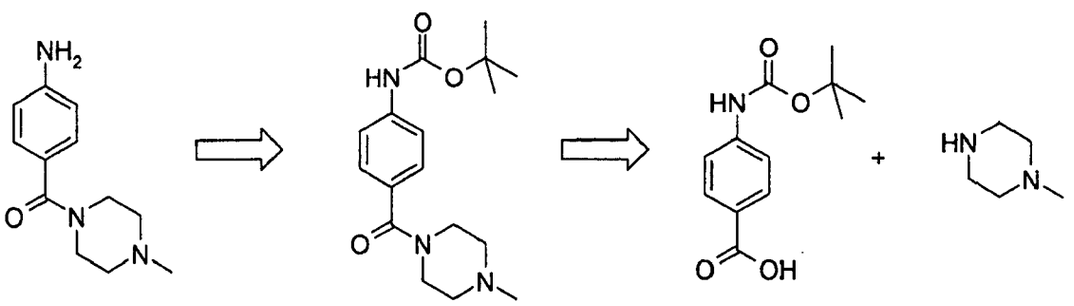
The compound shown on the left above, (4-amino-phenyl)-morpholin-4-yl-methanone, is obtained by hydrogenation of the corresponding nitro-compound (A), morpholin-4-yl-(4-nitro-phenyl)-methanone, with Pd/C or Raney-Nickel and $H_2$ or $NH_4CO_2H$ in MeOH at rt. Alternatively, the nitro group reduction can be achieved with $SnCl_2$ in EtOH at 90 °C. The intermediate nitro compound (A) is obtained by the reaction of 4-nitro-benzoyl chloride (B)

and morpholine and $Et_3N$ in DCM at rt. The intermediate (A) is obtained in good yield. When needed, analogs of (B) are obtained from the corresponding carboxylic acid derivatives heated to reflux for 2 hrs with thionylchloride or oxalylchloride in DCM or dichloroethane.

Alternatively, amide bond formation can be achieved by coupling of the appropriate carboxylic acid derivative (B) and the appropriate amine in the presence of TBTU and $Et_3N$ in THF at 0 °C to rt.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:
4-Amino-N-(1-methyl-piperidin-4-yl)-benzamide
(4-Amino-phenyl)-(4-dimethylamino-piperidin-1-yl)-methanone
4-Amino-N-(2-morpholin-4-yl-ethyl)-benzamide
4-Amino-N-(1-ethyl-pyrrolidin-2-ylmethyl)-benzamide
(4-Amino-2-fluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(4-Amino-2-chloro-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(4-Amino-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(4-Amino-2-trifluoromethyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(4-Amino-2-methyl-phenyl)-morpholin-4-yl-methanone
(4-Amino-2-methyl-phenyl)-pyrrolidin-1-yl-methanone
(5-Amino-2-fluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(5-Amino-2-fluoro-phenyl)-morpholin-4-yl-methanone
5-Amino-N-(1-ethyl-pyrrolidin-2-ylmethyl)-2-fluoro-benzamide
4-(4-Amino-benzoyl)-piperazine-1-carboxylic acid tert-butyl ester
(4-Amino-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone
(4-Amino-pyridin-2-yl)-(2,5-dioxa-8-aza-spiro[3.5]non-8-yl)-methanone
4-Amino-pyridin-2-yl)-(cis-3,5-dimethyl-piperazin-1-yl)-methanone
4-(4-Amino-pyridine-2-carbonyl)-piperazine-1-carboxylic acid tert-butyl ester
(5-Amino-2-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone
(5-Amino-2-methyl-phenyl)-(cis-3,5-dimethyl-piperazin-1-yl)-methanone

General procedure **IV** for the synthesis of aniline building blocks (in the following formula exemplified for (4-amino-phenyl)-(4-methyl-piperazin-1-yl)-methanone):



(4-Amino-phenyl)-(4-methyl-piperazin-1-yl)-methanone (A) (B) (C)

The compound shown on the left above, (4-amino-phenyl)-(4-methyl-piperazin-1-yl)-methanone, is obtained by treatment of intermediate (A), [4-(4-methyl-piperazine-1-carbonyl)-phenyl]-carbamic acid tert-butyl ester, with TFA in DCM at rt. The intermediate compound (A) is obtained by coupling of 4-tert-butoxycarbonylamino-benzoic acid (B) and N-methyl piperazine (C) in the presence of HATU and N-methyl morpholine in DCM at rt. The intermediate (A) is obtained in good yield.

The use of the Boc protecting group is not necessary for the preparation of certain aniline building blocks.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

4-Amino-N-(2-dimethylamino-ethyl)-N-methyl-benzamide

4-Amino-N-(2-dimethylamino-ethyl)-benzamide

4-Amino-N-(2-hydroxy-ethyl)-benzamide

(5-Amino-pyridin-2-yl)-morpholin-4-yl-methanone

(3-Amino-phenyl)-morpholin-4-yl-methanone

(3-Amino-phenyl)-(4-methyl-piperazin-1-yl)-methanone

3-Amino-N-(2-dimethylamino-ethyl)-benzamide

2-(3-Amino-phenyl)-1-(4-methyl-piperazin-1-yl)-ethanone

2-(3-Amino-phenyl)-1-(4-ethyl-piperazin-1-yl)-ethanone

(4-Amino-phenyl)-(4-ethyl-piperazin-1-yl)-methanone

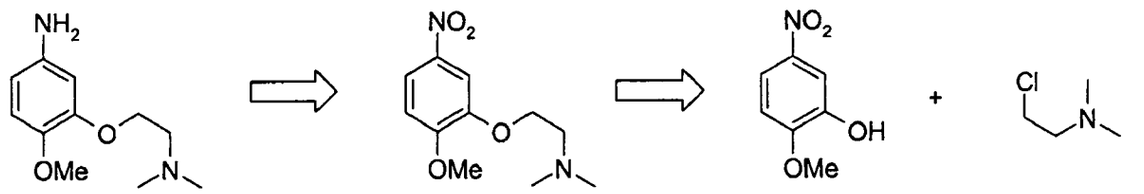
(5-Amino-pyridin-3-yl)-morpholin-4-yl-methanone

(3-Amino-phenyl)-(cis-3,5-dimethyl-piperazin-1-yl)-methanone

(3-Amino-phenyl)-(4-cyclopropyl-piperazin-1-yl)-methanone

(5-Amino-pyridin-2-yl)-(4-methyl-piperazin-1-yl)-methanone

General procedure **V** for the synthesis of aniline building blocks (in the following formula exemplified for 3-(2-dimethylamino-ethoxy)-4-methoxy-phenylamine):




3-(2-Dimethylamino-ethoxy)-4-methoxy-phenylamine (A) (B) (C)

The compound shown on the left above, 3-(2-dimethylamino-ethoxy)-4-methoxy-phenylamine, is obtained by treatment of intermediate (A), [2-(2-methoxy-5-nitro-phenoxy)-ethyl]-dimethyl-amine, with Pd/C and $NH_4CO_2H$ in MeOH/THF at rt. The intermediate compound (A) is obtained by alkylation of 2-methoxy-5-nitro-phenol (B) with (2-chloro-ethyl)-dimethyl-amine (C) in the presence of NaH in DMF at 150 °C.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

3-(3-Dimethylamino-propoxy)-4-methoxy-phenylamine

4-Methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenylamine

4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamine

3-(2-Morpholin-4-yl-ethoxy)-phenylamine

3-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-phenylamine

3-(2-Diethylamino-ethoxy)-phenylamine

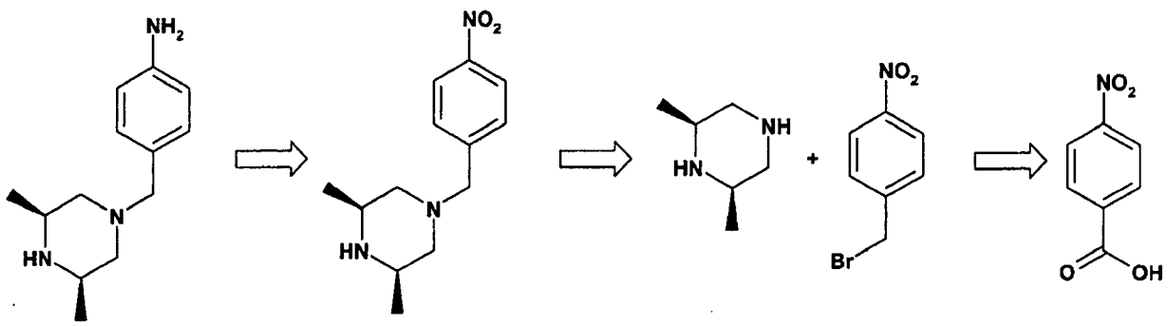
4-(2-Diethylamino-ethoxy)-phenylamine

4-(2-Morpholin-4-yl-ethoxy)-phenylamine

4-(2-Pyrrolidin-1-yl-ethoxy)-phenylamine

3,5-Dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenylamine

General procedure **VI** for the synthesis of aniline building blocks (in the following formula exemplified for 4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenylamine):




4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamine (A) (B) (C) (D)

The compound shown on the left above, 4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenylamine, is obtained by treatment of intermediate (A), cis-3,5-dimethyl-1-(4-nitro-benzyl)-piperazine, with $SnCl_2$ hydrate in MeOH at rt. Alternatively, the nitro group reduction can be achieved with Pd/C or Raney-Nickel and $H_2$ or $NH_4CO_2H$ in MeOH at rt. The intermediate compound (A) is obtained by reaction of cis-2,6-dimethyl-piperazine (B) with 1-bromomethyl-4-nitro-benzene (C) in the presence of $Et_3N$ or DIPEA in DMF at rt. Where needed, the (substituted) benzyl bromide (C) is synthesized from the corresponding carboxylic acid (D) via reduction to the alcohol and conversion to the halogen compound.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

4-((2R,5S)-2,5-Dimethyl-piperazin-1-ylmethyl)-phenylamine (racemic)
4-(4-Amino-benzyl)-piperazin-2-one
4-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-phenylamine
4-(4-Amino-benzyl)-piperazine-1-carboxylic acid tert-butyl ester
1-[4-(4-Amino-benzyl)-piperazin-1-yl]-ethanone
4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenylamine
4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamine
4-Methyl-3-morpholin-4-ylmethyl-phenylamine
5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-ylamine
4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamine
4-(5-Amino-2-methyl-benzyl)-piperazine-1-carboxylic acid tert-butyl ester
4-(5-Amino-2-methyl-benzyl)-piperazin-2-one
4-(4-Amino-benzyl)-1-methyl-piperazin-2-one

4-(4-Methyl-piperazin-1-ylmethyl)-phenylamine
3-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamine
3-(2,5-Dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-4-methyl-phenylamine
3-(4-Cyclopropyl-piperazin-1-ylmethyl)-4-methyl-phenylamine
4-(4-Amino-pyridin-2-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester
3-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-4-methyl-phenylamine
3-((2R,5S)-2,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamine (racemic)
3-(3,3-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamine
3-(3,3-Difluoro-pyrrolidin-1-ylmethyl)-4-methyl-phenylamine
1-(5-Amino-2-methyl-benzyl)-azetidin-3-ol
4-(5-Amino-2-methyl-benzyl)-1-methyl-piperazin-2-one
3-[4-(2-Dimethylamino-ethyl)-piperazin-1-ylmethyl]-4-methyl-phenylamine
4-(5-Amino-2-methyl-benzyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester
1-(5-Amino-2-chloro-benzyl)-azetidin-3-ol
4-(5-Amino-2-chloro-benzyl)-piperazine-1-carboxylic acid tert-butyl ester
4-Methyl-3-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenylamine (racemic)
3-(3-Methoxy-azetidin-1-ylmethyl)-4-methyl-phenylamine
1-(5-Amino-2-methyl-benzyl)-pyrrolidin-3-ol
3-Imidazol-1-ylmethyl-4-methyl-phenylamine
4-Methyl-3-pyrazol-1-ylmethyl-phenylamine
4-Methyl-3-[1,2,4]triazol-4-ylmethyl-phenylamine
3-(3-Methoxy-pyrrolidin-1-ylmethyl)-4-methyl-phenylamine
3-(5-Amino-2-methyl-benzyloxy)-azetidine-1-carboxylic acid tert-butyl ester
[1-(5-Amino-2-methyl-benzyl)-pyrrolidin-3-yl]-dimethyl-amine
3-(7-Aza-bicyclo[2.2.1]hept-7-ylmethyl)-4-methyl-phenylamine
4-(4-Amino-2-methyl-benzyl)-piperazine-1-carboxylic acid tert-butyl ester
4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-3-methyl-phenylamine
4-(3,3-Difluoro-pyrrolidin-1-ylmethyl)-phenylamine
6-(4-Methyl-piperazin-1-ylmethyl)-pyridin-3-ylamine
4-(3,3-Dimethyl-piperazin-1-ylmethyl)-phenylamine
4-(3-Trifluoromethyl-piperazin-1-ylmethyl)-phenylamine (racemic)
4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-2-fluoro-phenylamine
1-(4-Amino-benzyl)-azetidin-3-ol
6-Morpholin-4-ylmethyl-pyridin-3-ylamine
6-Piperazin-1-ylmethyl-pyridin-3-ylamine

4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenylamine

4-(4-Amino-benzyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

4-(5-Amino-pyridin-2-ylmethyl)-1-methyl-piperazin-2-one

4-(3-Methoxy-pyrrolidin-1-ylmethyl)-phenylamine

1-(5-Amino-pyridin-2-ylmethyl)-pyrrolidin-3-ol (racemic)

4-Methyl-3-(7-methyl-2,7-diaza-spiro[4.4]non-2-ylmethyl)-phenylamine

4-Methyl-3-(4-methyl-pyrazol-1-ylmethyl)-phenylamine

2-[1-(5-Amino-2-methyl-benzyl)-1H-pyrazol-4-yl]-ethanol

Alternatively, (A) is obtained by the reaction of 2-bromomethyl-1-methyl-4-nitro-benzene (C) with sodium azide in ethanol / water 1:2 at rt overnight, followed by triazole formation with dimethyl-prop-2-ynyl-amine in tert-butanol / water 1:1 in presence of cupper (I) sulfate (0.15 eq.) and L-(+)-sodium ascorbate (0.3 eq.).

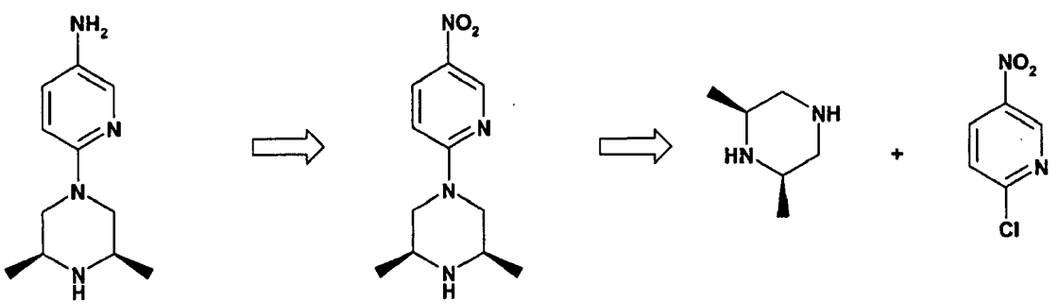
3-(4-Dimethylaminomethyl-[1,2,3]triazol-1-ylmethyl)-4-methyl-phenylamine

[1-(5-Amino-2-methyl-benzyl)-1H-[1,2,3]triazol-4-yl]-methanol

Alternatively, (B) is obtained from the reaction of 3-oxo-piperazine-1-carboxylic acid tert-butyl ester activated with sodium hydride with (2-bromo-ethyl)-dimethyl-amine in DMF. The resulting material is then Boc-deprotected in dioxane with HCl to give (B) as HCl salt.

4-(5-Amino-2-methyl-benzyl)-1-(2-dimethylamino-ethyl)-piperazin-2-one

General procedure **VII** for the synthesis of aniline building blocks (in the following formula exemplified for 6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamine):




6-(cis-3,5-Dimethyl-piperazin-1-yl) -pyridin-3-ylamine (A) (B) (C)

The compound shown on the left above, 6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamine, is obtained by treatment of intermediate (A), cis-3,5-dimethyl-1-(5-nitro-pyridin-2-yl)-

piperazine, with $H_2$ (or ammonium formate) and Pd/C (or Raney-Nickel) in MeOH (and THF) at rt. The intermediate compound (A) is obtained by reaction of cis-2,6-dimethyl-piperazine (B) with 2-chloro-5-nitro-pyridine (C) in the presence of $Et_3N$ in THF at rt to 70 °C.

Alternatively, in case (B) is an alcohol, 2-bromo-5-nitro-pyridine, or 2-chloro-4-nitro-pyridine-1-oxide for some of the meta-substituted derivatives, is used as (C) in presence of KOtBu or $Cs_2CO_3$ or NaH in DMA or THF at rt to 80 °C.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamine (racemic)

6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-ylamine

2-[4-(5-Amino-pyridin-2-yl)-piperazin-1-yl]-ethanol

2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-ylamine

2-(4-Methyl-piperazin-1-yl)-pyrimidin-5-ylamine

6-Isopropoxy-pyridin-3-ylamine

4-(4-Amino-pyridin-2-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester

6-(cis-3,5-dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-ylamine

5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamine

2-(4-Cyclopropyl-piperazin-1-yl)-pyridin-4-ylamine

6-(4-Cyclopropyl-piperazin-1-yl)-pyridin-3-ylamine

6-[4-(2-Dimethylamino-ethyl)-piperazin-1-yl]-pyridin-3-ylamine

6-(3-Trifluoromethyl-piperazin-1-yl)-pyridin-3-ylamine (racemic)

4-(5-Amino-pyridin-2-yl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

4-(5-Amino-3-methyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

6-(3,3-Dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-ylamine

5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamine

5-Amino-2-(cis-3,5-dimethyl-piperazin-1-yl)-nicotinonitrile

4-(5-Amino-3-chloro-pyridin-2-yl)-piperazin-2-one

1-(5-Amino-pyridin-2-yl)-3,3-dimethyl-piperazin-2-one

1-(5-Amino-3-methyl-pyridin-2-yl)-3,3-dimethyl-piperazin-2-one

4-(5-Amino-3-methyl-pyridin-2-yl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-trifluoromethyl-pyridin-3-ylamine

6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-methoxy-pyridin-3-ylamine

4-(4-Amino-pyridin-2-yl)-piperazin-2-one

4-(5-Amino-3-chloro-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

1-(4-Amino-pyridin-2-yl)-3,3-dimethyl-piperazin-2-one

4-(4-Amino-pyridin-2-yl)-1-methyl-piperazin-2-one

6-(6,6-Difluoro-[1,4]diazepan-1-yl)-5-methyl-pyridin-3-ylamine (B obtained from WO2003042172 p.51)

6-(2-Morpholin-4-yl-ethoxy)-pyridin-3-ylamine

3-(5-Amino-pyridin-2-yloxy)-azetidine-1-carboxylic acid tert-butyl ester

6-(Tetrahydro-pyran-4-yloxy)-pyridin-3-ylamine

6-(2-Methoxy-ethoxy)-pyridin-3-ylamine

6-(Tetrahydro-pyran-4-ylmethoxy)-pyridin-3-ylamine

6-[2-(tert-Butyl-diphenyl-silanyloxy)-ethoxy]-pyridin-3-ylamine

3-(5-Amino-pyridin-2-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

6-[3-(tert-Butyl-diphenyl-silanyloxy)-pyrrolidin-1-yl]-pyridin-3-ylamine

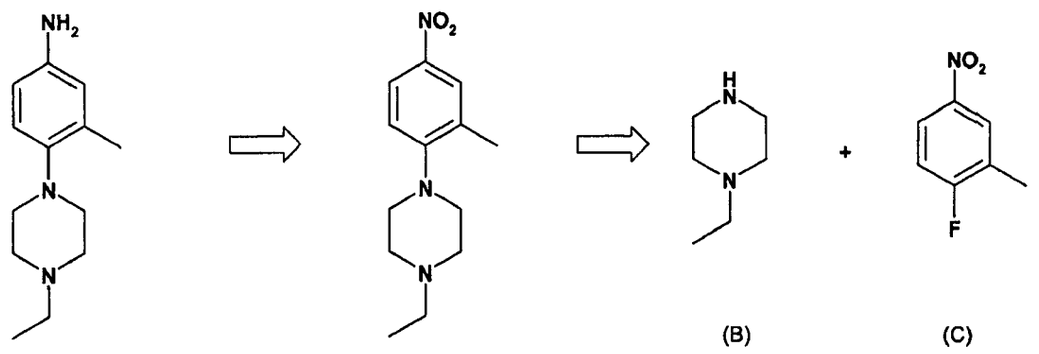
2-(Tetrahydro-pyran-4-yloxy)-pyridin-4-ylamine

2-(2-Morpholin-4-yl-ethoxy)-pyridin-4-ylamine

2-(3-Trifluoromethyl-piperazin-1-yl)-pyridin-4-ylamine (racemic)

5-(4-Methyl-piperazin-1-yl)-pyridin-2-ylamine

<u>General procedure **VIII** for the synthesis of aniline building blocks (in the following formula exemplified for 4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamine):</u>




4-(4-Ethyl-piperazin-1-yl)-3-methyl -phenylamine

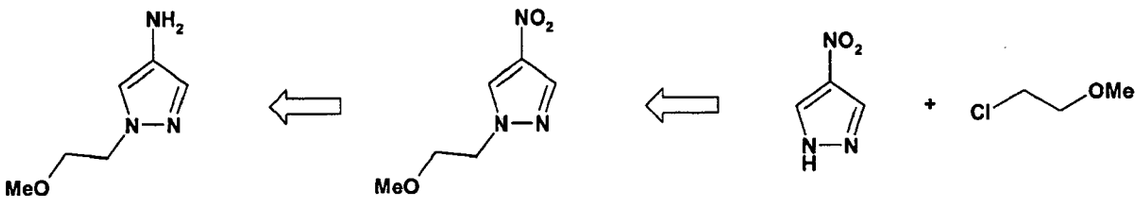
(A)

(B)

(C)

The compound shown on the left above, 4-(4-ethyl-piperazin-1-yl)-3-methyl-phenylamine, is obtained by treatment of intermediate (A), 1-ethyl-4-(2-methyl-4-nitro-phenyl)-piperazine, with $H_2$ (or ammonium formate) and Pd/C in MeOH (and THF) at rt. The intermediate compound (A) is obtained by reaction of N-ethyl-piperazine (B) with 1-fluoro-2-methyl-4-nitro-benzene (C) in dimethylacetamide (DMA) at 110 °C for 20 hours.

General procedure **IX** for the synthesis of aminopyrazole building blocks (in the following formula exemplified for 1-(2-methoxy-ethyl)-1H-pyrazol-4-ylamine):



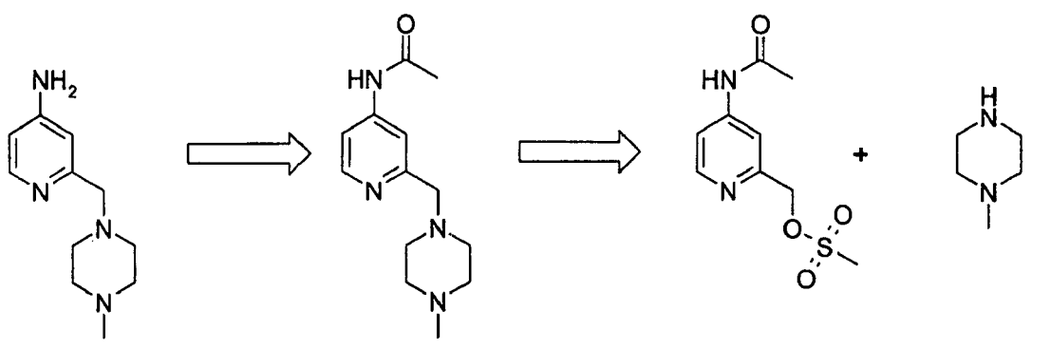

1-(2-methoxy-ethyl)-1H-pyrazol-4-ylamine (A) (B) (C)

The compound shown on the left above, 1-(2-methoxy-ethyl)-1H-pyrazol-4-ylamine, is obtained by treatment of intermediate (A), 1-(2-methoxy-ethyl)-4-nitro-1H-pyrazole, with ammonium formate and Pd/C in MeOH at rt. The intermediate compound (A) is obtained by alkylation of 4-nitro-1H-pyrazole (B) with 1-chloro-2-methoxy-ethane (C) in the presence of NaH in DMF at 95 °C.

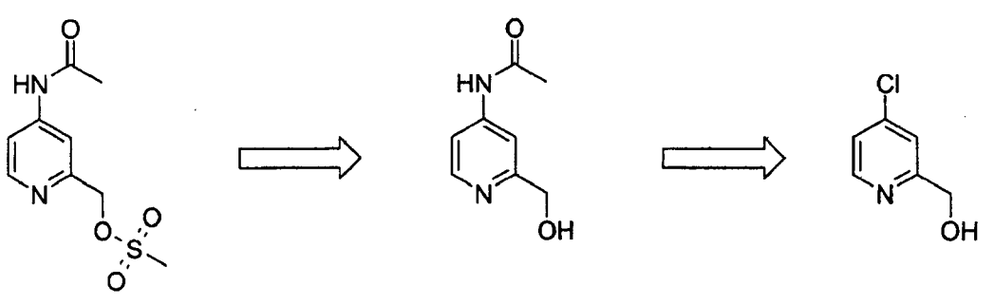
The following aminopyrazole used in the examples below is synthesized analogously, using the appropriate corresponding starting materials:

4-(4-Amino-pyrazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

General procedure **X** for the synthesis of aniline building blocks (in the following formula exemplified for 2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-ylamine):



2-(4-Methyl-piperazin-1-ylmethyl)-pyridin-4-ylamine (A) (B) (C)



(B) (D) (E)

The compound shown on the left above, 2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-ylamine), is obtained by treatment of intermediate (A), N-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-yl]-acetamide, with KOH in EtOH / water 2:1 at 100 °C for 4 h. The intermediate compound (A) is obtained by reaction of N-methyl-piperazine (C) with methanesulfonic acid 4-acetylamino-pyridin-2-ylmethyl ester (B) in DCM at rt in the presence of DIPEA. The intermediate compound (B) is obtained from the reaction of N-(2-hydroxymethyl-pyridin-4-yl)-acetamide (D) with methanesulfonyl chloride in the presence of $Et_3N$ in DCM (or with $SOCl_2$ in 1,2-dichloroethane with a small amount of DMF for the chloride analog of (B)). Intermediate (D) is obtained from the treatment of (4-chloro-pyridin-2-yl)-methanol with acetamide in presence of $Pd(OAc)_2$, 4,5-bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene and cesium carbonate in dioxane and DMF at 130 °C in the microwave oven for 1 h.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

2-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-pyridin-4-ylamine

2-[4-(2-Dimethylamino-ethyl)-piperazin-1-ylmethyl]-pyridin-4-ylamine

4-(4-Amino-pyridin-2-ylmethyl)-1-methyl-piperazin-2-one

2-(3,3-Difluoro-pyrrolidin-1-ylmethyl)-pyridin-4-ylamine

2-(4-Cyclopropyl-piperazin-1-ylmethyl)-pyridin-4-ylamine

2-(3-Trifluoromethyl-piperazin-1-ylmethyl)-pyridin-4-ylamine (racemic)

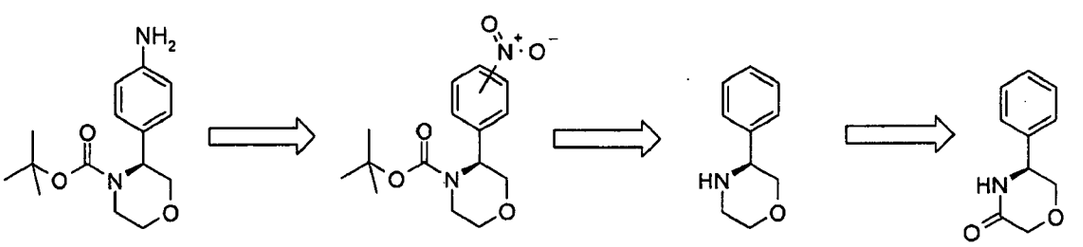
4-(4-Amino-pyridin-2-ylmethyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester

1-(4-Amino-pyridin-2-ylmethyl)-pyrrolidin-3-ol

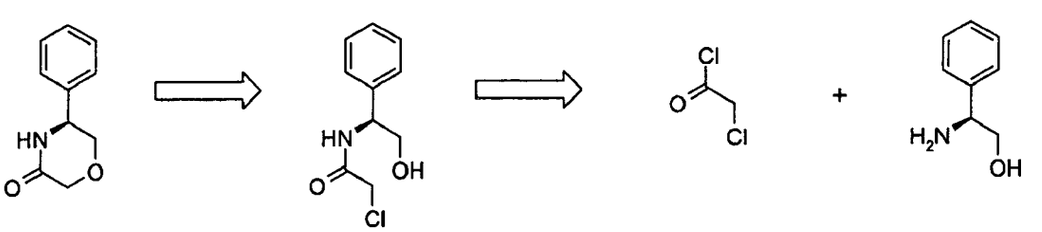
2-(3-Methoxy-pyrrolidin-1-ylmethyl)-pyridin-4-ylamine

2-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-pyridin-4-ylamine

General procedure **XI** for the synthesis of aniline building blocks (in the following formula exemplified for (S)-3-(4-Amino-phenyl)-morpholine-4-carboxylic acid tert-butyl ester):



(S)-3-(4-Amino-phenyl)-morpholine-4-carboxylic acid tert-butyl ester (A) (B) (C)



(C) (D) (F) (E)

The compound shown on the left above, (S)-3-(4-amino-phenyl)-morpholine-4-carboxylic acid tert-butyl ester, is obtained from the hydrogenation of intermediate (A) with hydrazine hydrate in ethanol in presence of Raney-Nickel under argon atmosphere at rt, followed by separation of the $NO_2$-regioisomers. To obtain the intermediate compound (A) (mixture of regioisomers), a solution of (S)-3-phenyl-morpholine (B) in DCM is slowly dropped into

fuming nitric acid in DCM at -45°C. After 1h, the reaction is quenched slowly with an aq. sol. of NaOH followed by a DCM / aq. bicarbonate work-up. The resulting material is purified on silica column chromatography and then Boc protected with Boc-anhydride in DCM at rt.

The intermediate compound (B) is obtained from the reduction of (S)-5-phenyl-morpholin-3-one (C) with LAH in THF at rt. The morpholine derivative compound (C) is obtained from the ring closing of 2-chloro-N-((S)-2-hydroxy-1-phenyl-ethyl)-acetamide (D) in presence of sodium hydride in THF / toluene 1:1 at 0 °C to rt. The intermediate compound (D) results from the slow addition of chloro-acetyl chloride (F) dissolved in DCM to (S)-2-amino-2-phenyl-ethanol (E) in THF in presence of $Et_3N$ at 0 °C to rt.

The following anilines used in the examples below are synthesized analogously, using the appropriate corresponding starting materials:

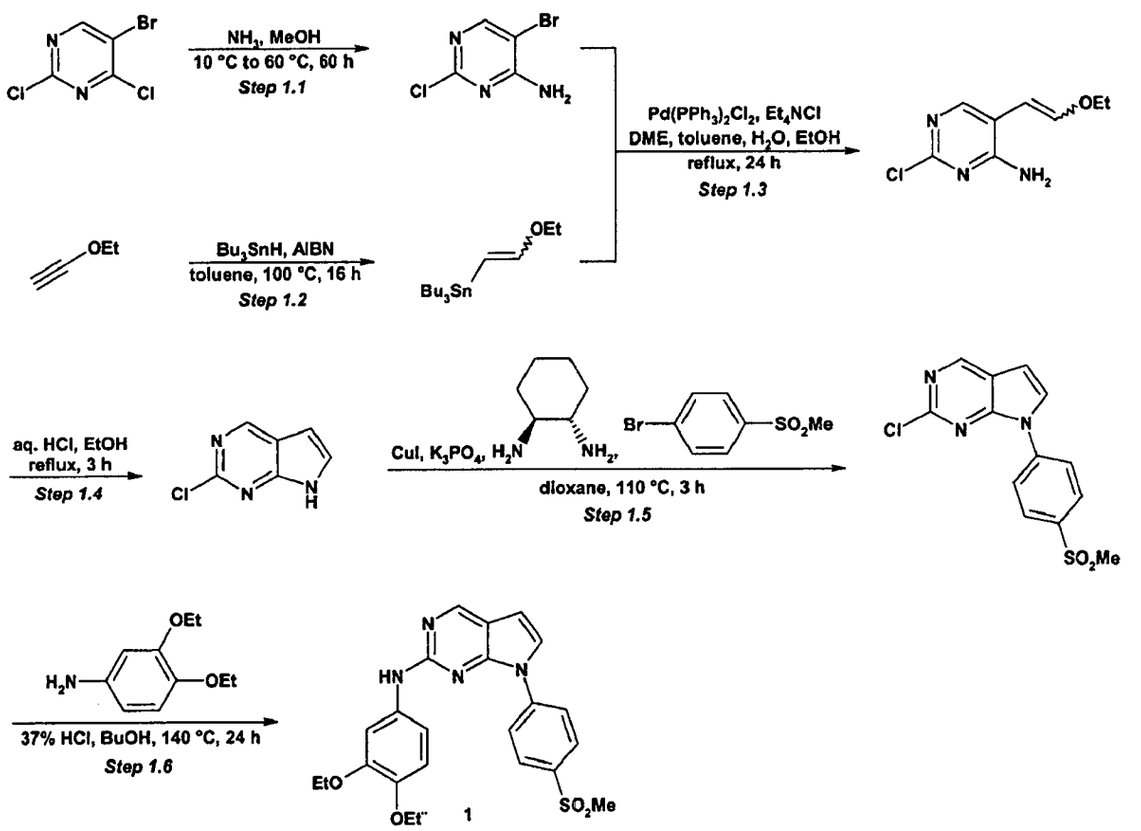
2-(4-Amino-phenyl)-morpholine-4-carboxylic acid tert-butyl ester (racemic)

(S)-3-(3-Amino-phenyl)-morpholine-4-carboxylic acid tert-butyl ester

Example 1: (3,4-Diethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (1)

The compound is prepared according to Scheme 1.

**Scheme 1**




Step 1.1: 5-Bromo-2-chloro-pyrimidin-4-ylamine

2,4-Dichloro-5-bromopyrimidine (200 g, 0.88 mol) is added slowly to $NH_3$ (1000 ml, 7 M in MeOH) while the reaction mixture is kept below 10 °C. The reaction mixture is stirred at rt for 2 h, heated to 60 °C for 2 h, and then cooled again to rt and stirred for 55 h. It is concentrated under reduced pressure, and the residue is suspended in $H_2O$ (500 ml). The aqueous layer is extracted with EtOAc (3x) and the combined organic layers are dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound as a white solid.

Step 1.2: 1-Ethoxy-propene

To a solution of ethoxyethyne (120 g, 0.69 mol, 40% in hexane) in toluene (1500 mL) is added slowly tributyltin hydride (190 g, 0.65 mol) and AIBN (4.6 g, 0.028 mol). The reaction mixture is heated to 100 °C for 16 h. The reaction mixture is concentrated under reduced pressure and dried under HV. The brown residual oil (80% purity of title compound) is used for next step without purification.

Step 1.3: 2-Chloro-5-(2-ethoxy-vinyl)-pyrimidin-4-ylamine

5-Bromo-2-chloro-pyrimidin-4-ylamine (88.0 g, 0.43 mol), 1-ethoxy-propene (220 g, 0.49 mol), $Pd(PPh_3)_2Cl_2$ (35.0 g, 0.05 mol) and $Et_4NCl$ (67.0 g, 0.40 mol) are suspended in solvent (750 mL, DME/toluene/$H_2O$/EtOH 10:1:3:6) under nitrogen. The reaction mixture is heated to reflux for 24 h, cooled to rt, and then diluted with water. The aqueous layer is extracted with EtOAc (3x). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography ($SiO_2$, gradient elution, EtOAc / petroleum ether 1:10 → 1:4) to yield the title compound as a yellow solid.

Step 1.4: 2-Chloro-7H-pyrrolo[2,3-d]pyrimidine

To a solution of 2-Chloro-5-(2-ethoxy-vinyl)-pyrimidin-4-ylamine (38.0 g, 0.19 mol) in EtOH (1000 ml) is added concentrated aqueous HCl (37%, 100 g, 1.00 mol) at rt. The reaction mixture is heated to reflux for 3 h and then evaporated to dryness under reduced pressure. Aqueous sodium carbonate solution (5%, 500 mL) is added to the residue, and the mixture is extracted with EtOAc (3x). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is recrystallized from hexane/ether (4/1, 250 ml) to give the title compound as an off-white solid.

Step 1.5: 2-Chloro-7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

In a seal tube, 2-chloro-7H-pyrrolo[2,3-d]pyrimidine (600 mg, 3.56 mmol), 4-bromophenylmethylsulfone (700 mg, 4.10 mmol), CuI (239 mg, 1.23 mmol), and $K_3PO_4$ (2.67 g, 12.3 mmol) are suspended in 1,4-dioxane (30 mL). Then, *trans*-1,2-diaminocyclohexane (149 µL, 1.23 mmol) is added at rt. The reaction vial is flushed with Ar and the mixture is heated to 110 °C for 3 h. After cooling to rt, the reaction mixture is concentrated under reduce pressure. The residue is suspended in EtOAc and washed with saturated aqueous NaCl solution (3x). The organic layer is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The solid residue is triturated with small amounts of EtOAc to yield the title compound as a brown solid.

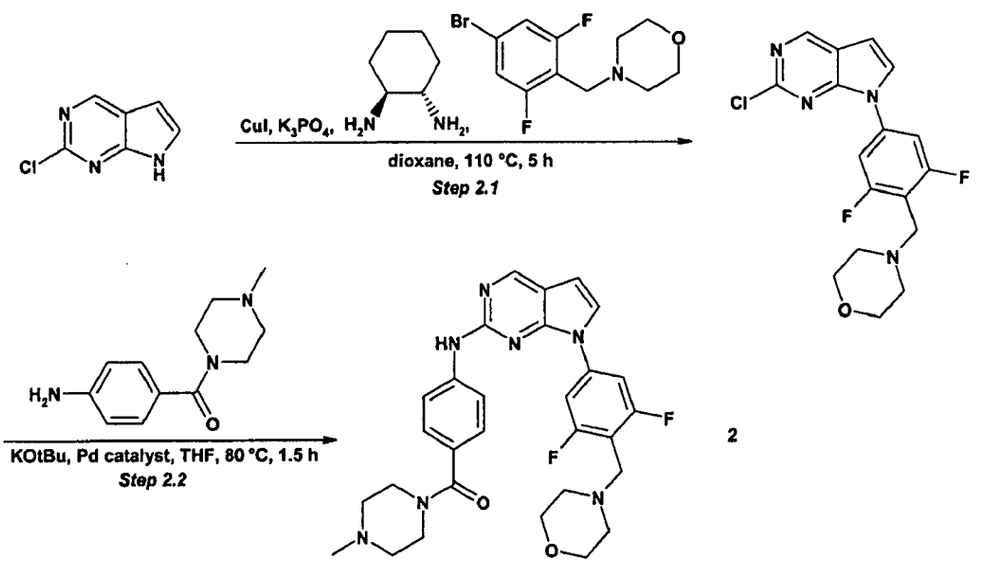
Step 1.6: (3,4-Diethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (**1**)

To a suspension of 2-chloro-7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (30.0 mg, 0.093 mmol) in BuOH (1.5 mL) is added 3,4-diethoxyaniline (41.0 mg, 0.220 mmol) and concentrated aqueous HCl (37%, 23.0 µL, 0.232 mmol). The reaction mixture is heated to 140 °C for 24 h, cooled to rt, and concentrated under reduce pressure. The residue is purified by reverse phase prep-HPLC (Waters) to afford the title compound (**1**) as a yellow solid. HPLC: $t_R$ = 1.61 min (Method A); MS-ES: $(M+H)^+$ = 453.

Example 2: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone (2)

The compound is prepared according to Scheme 2.

**Scheme 2**




Step 2.1: 2-Chloro-7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

In a sealed tube, 2-chloro-7H-pyrrolo[2,3-d]pyrimidine (200 mg, 1.24 mmol), 4-(4-bromo-2,6-difluoro-benzyl)-morpholine (418 mg, 1.36 mmol), CuI (72.1 mg, 0.371 mmol), and $K_3PO_4$ (804 mg, 3.71 mmol) are suspended in 1,4-dioxane (8 mL). Then, *trans*-1,2-diaminocyclohexane (45.0 µL, 0.371 mmol) is added at rt. The reaction vial is flushed with Ar and the mixture is heated to 110 °C for 5 h. After cooling to rt, the reaction mixture is diluted with EtOAc and the organic layer is washed with saturated aqueous $Na_2CO_3$ solution (2x). The organic layer is dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue is purified by column chromatography ($SiO_2$, gradient elution, hexane / EtOAc 100:0 → 30:70) to yield the title compound as a white solid.

Step 2.2: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone (2)

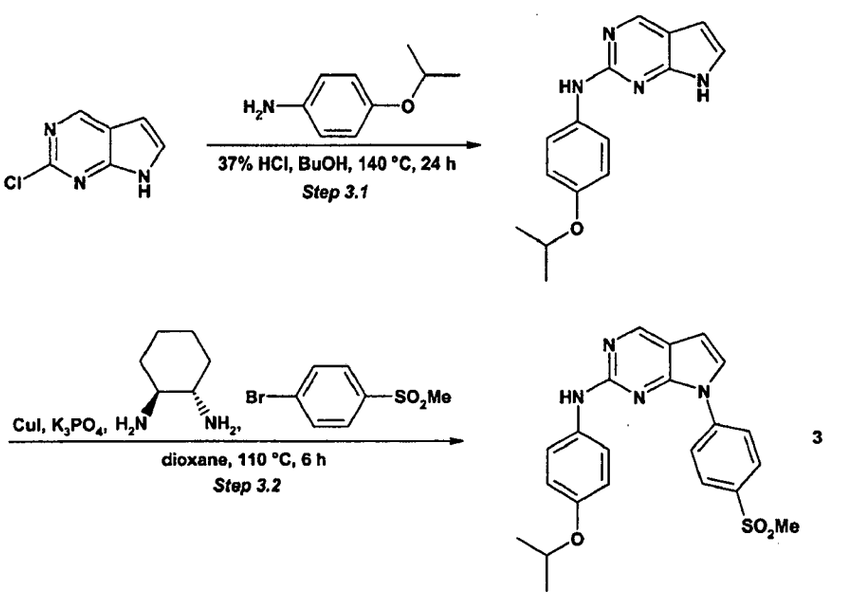
In a sealed tube, 2-chloro-7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (50.0 mg, 0.130 mmol), (4-Amino-phenyl)-(4-methyl-piperazin-1-yl)-methanone (42.1 mg, 0.182 mmol), KOtBu (21.1 mg, 0.182 mmol) and SK-CC02-A (12.5 mg, 0.020 mmol, Pd catalyst 2-(Dimethylaminomethyl)-ferrocen-1-yl-palladium(II)-chlorid Dinorbornylphosphin Complex, Fluka No. 44696) are suspended in THF (2 ml) under Ar. The reaction mixture is stirred at 80 °C for 1.5 h, cooled to rt, and then filtered through a Celite

plug. The filtrate is concentrated under reduce pressure. The residue is purified by reverse phase prep-HPLC (Waters) to afford the title compound (**2**) as a white solid. HPLC: $t_R$ = 0.89 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 3: (4-Isopropoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (3)

The compound is prepared according to Scheme 3.

**Scheme 3**




Step 3.1: (4-Isopropoxy-phenyl)-(7H-pyrrolo[2,3-d]pyrimidin-2-yl)-amine

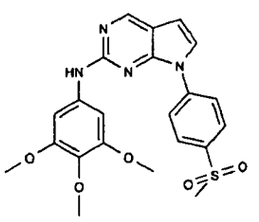
To a suspension of 2-chloro-7H-pyrrolo[2,3-d]pyrimidine (700 mg, 4.33 mmol) in BuOH (10 mL) is added 4-isopropoxyaniline (1.31 g, 8.66 mmol) and concentrated aqueous HCl (37%, 1.28 mL, 13.0 mmol). The reaction mixture is heated to 140 °C for 24 h, cooled to rt, and concentrated under reduce pressure. The residue is dissolved in EtOAc and the organic layer is washed with saturated aqueous $Na_2CO_3$ solution (2x). The organic layer is dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue solid residue is triturated with hexane to yield the title compound as an off-white solid.

Step 3.2: (4-Isopropoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (**3**)

In a sealed tube, (4-Isopropoxy-phenyl)-(7H-pyrrolo[2,3-d]pyrimidin-2-yl)-amine (350 mg, 1.17 mmol), 4-bromophenylmethylsulfone (552 mg, 2.35 mmol), CuI (68.4 mg, 0.352 mmol), and $K_3PO_4$ (763 mg, 3.52 mmol) are suspended in 1,4-dioxane (10 mL). Then, *trans*-1,2-diaminocyclohexane (42.7 μL, 0.352 mmol) is added at rt. The reaction vial is flushed with Ar

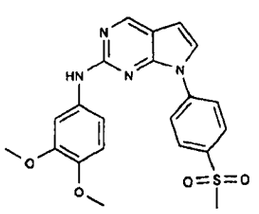
and the mixture is heated to 110 °C for 6 h. After cooling to rt, the reaction mixture is diluted with EtOAc and the organic layer is washed with saturated aqueous NaCl solution (3x). The organic layer is dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue is purified by reverse phase prep-HPLC (Waters) to afford the title compound (**3**) as an off-white solid. HPLC: $t_R$ = 1.67 min (Method A); MS-ES: $(M+H)^+$ = 423.

Example 4: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4,5-trimethoxy-phenyl)-amine



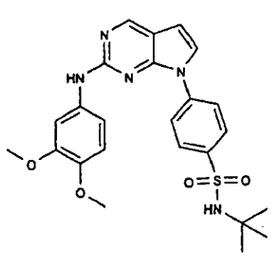
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.48 min (Method A); MS-ES: $(M+H)^+$ = 455.

Example 5: (3,4-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



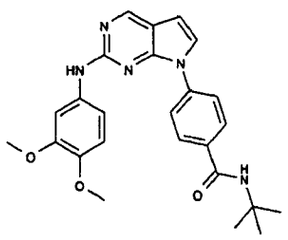
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.37 min (Method A); MS-ES: $(M+H)^+$ = 425.

Example 6: N-tert-Butyl-4-[2-(3,4-dimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide



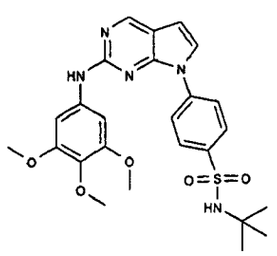
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.73 min (Method A); MS-ES: $(M+H)^+$ = 482.

Example 7: N-tert-Butyl-4-[2-(3,4-dimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide



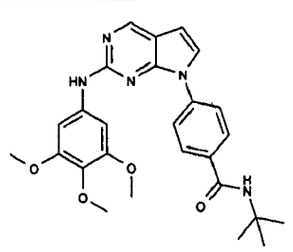
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.71 min (Method A); MS-ES: $(M+H)^+$ = 446.

Example 8: N-tert-Butyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide



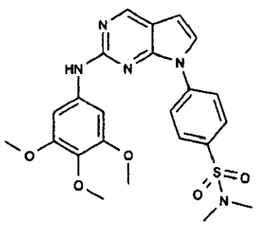
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.83 min (Method A); MS-ES: $(M+H)^+$ = 512.

Example 9: N-tert-Butyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide



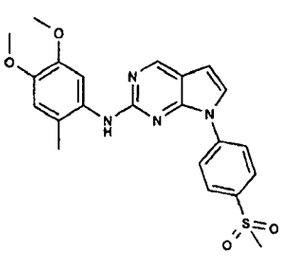
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.81 min (Method A); MS-ES: $(M+H)^+$ = 476.

Example 10: N,N-Dimethyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide



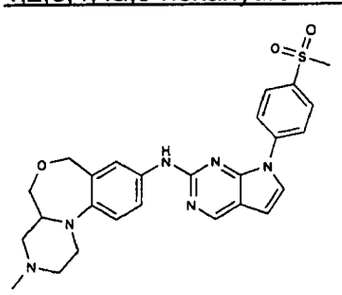
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.69 min (Method A); MS-ES: $(M+H)^+$ = 484.

Example 11: (4,5-Dimethoxy-2-methyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



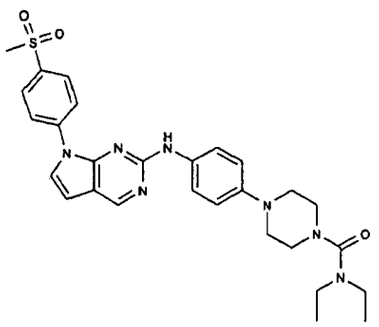
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.32 min (Method A); MS-ES: $(M+H)^+$ = 439.

Example 12: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methyl-1,2,3,4,4a,5-hexahydro-7H-6-oxa-3,11b-diaza-dibenzo[a,c]cyclohepten-9-yl)-amine



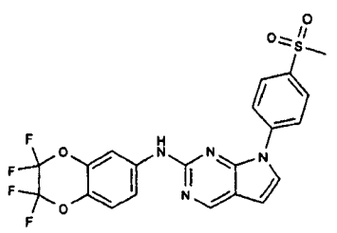
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.06 min (Method A); MS-ES: $(M+H)^+$ = 505.

Example 13: 4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic acid diethylamide



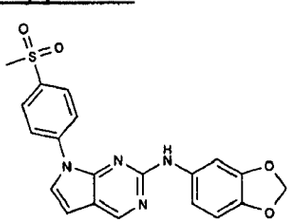
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.44 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 14: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-amine



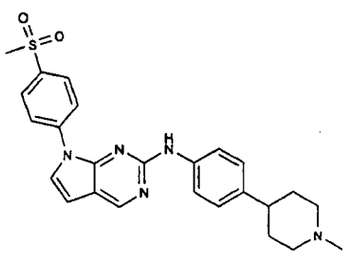
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 2.30 min (Method A); MS-ES: $(M+H)^+$ = 495.

Example 15: Benzo[1,3]dioxol-5-yl-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



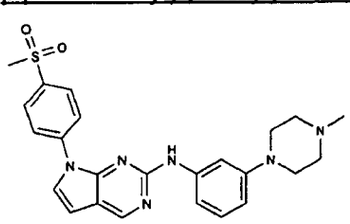
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.42 min (Method A); MS-ES: $(M+H)^+$ = 409.

Example 16: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(1-methyl-piperidin-4-yl)-phenyl]-amine



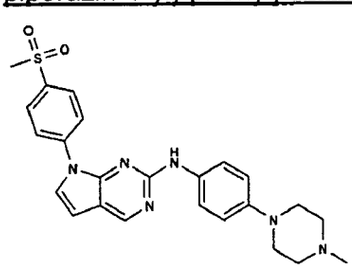
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 462.

Example 17: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-yl)-phenyl]-amine



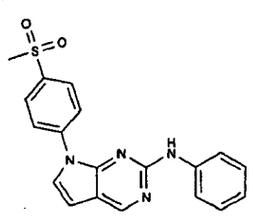
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 463.

Example 18: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-yl)-phenyl]-amine



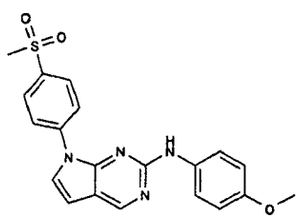
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 0.98 min (Method A); MS-ES: $(M+H)^+$ = 463.

Example 19: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-phenyl-amine



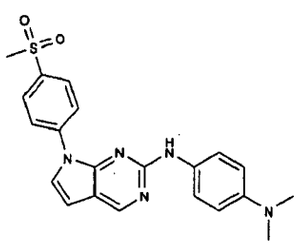
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.46 min (Method A); MS-ES: $(M+H)^+$ = 365.

Example 20: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxy-phenyl)-amine



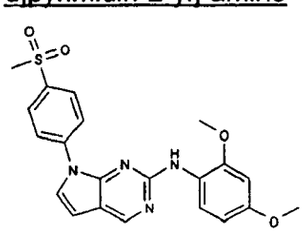
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.41 min (Method A); MS-ES: $(M+H)^+$ = 395.

Example 21: N-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-N',N'-dimethyl-benzene-1,4-diamine



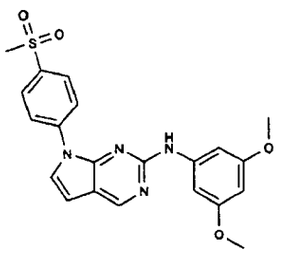
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.07 min (Method A); MS-ES: $(M+H)^+$ = 408.

Example 22: (2,4-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



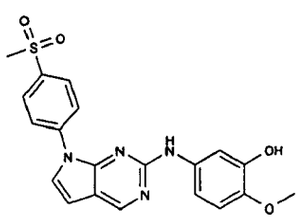
The compound is prepared analogous to Example 1. MS-ES: $(M+H)^+$ = 425.

Example 23: (3,5-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



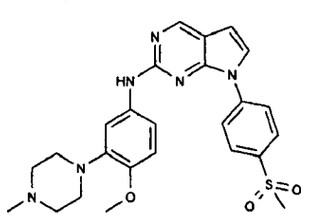
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.62 min (Method A); MS-ES: $(M+H)^+$ = 425.

Example 24: 5-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methoxy-phenol



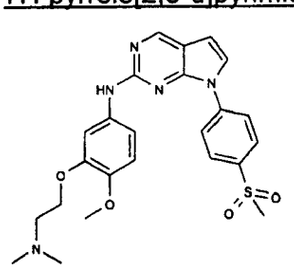
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.22 min (Method A); MS-ES: $(M+H)^+$ = 411.

Example 25: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amine



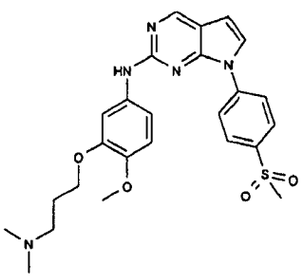
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.07 min (Method A); MS-ES: $(M+H)^+$ = 493.

Example 26: [3-(2-Dimethylamino-ethoxy)-4-methoxy-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



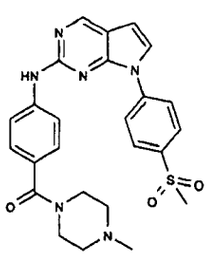
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 482.

Example 27: [3-(3-Dimethylamino-propoxy)-4-methoxy-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



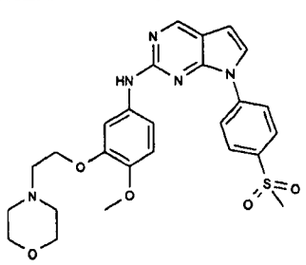
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.10 min (Method A); MS-ES: $(M+H)^+$ = 496.

Example 28: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



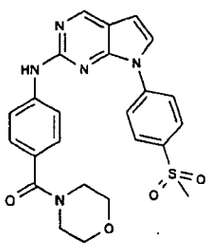
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.02 min (Method A); MS-ES: $(M+H)^+$ = 491.

Example 29: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine



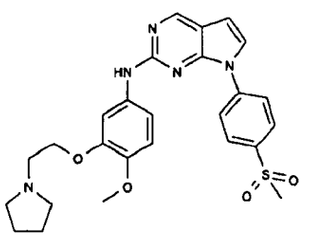
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.11 min (Method A); MS-ES: $(M+H)^+$ = 524.

Example 30: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



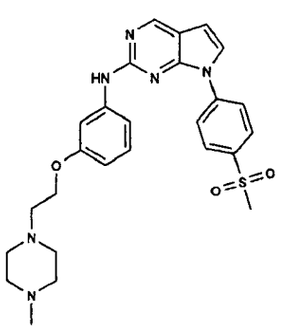
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.33 min (Method A); MS-ES: $(M+H)^+$ = 478.

Example 31: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine



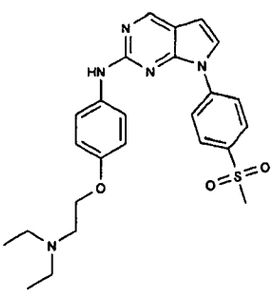
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 508.

Example 32: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{3-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl}-amine



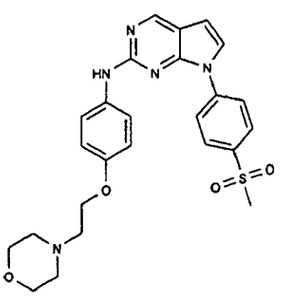
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.05 min (Method A); MS-ES: $(M+H)^+$ = 507.

Example 33: [4-(2-Diethylamino-ethoxy)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



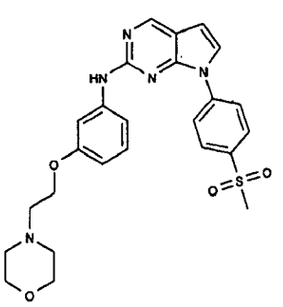
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 480.

Example 34: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-amine



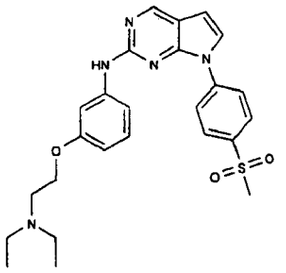
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.01 min (Method A); MS-ES: $(M+H)^+$ = 494.

Example 35: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine



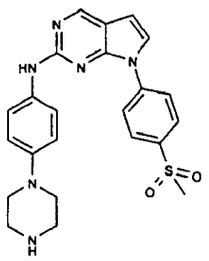
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 494.

Example 36: [3-(2-Diethylamino-ethoxy)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



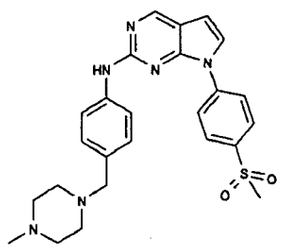
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.20 min (Method A); MS-ES: $(M+H)^+$ = 480.

Example 37: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-yl-phenyl)-amine



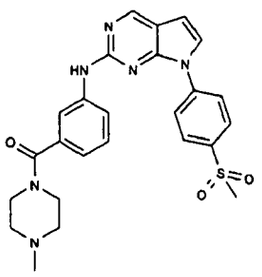
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 0.98 min (Method A); MS-ES: $(M+H)^+$ = 449.

Example 38: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



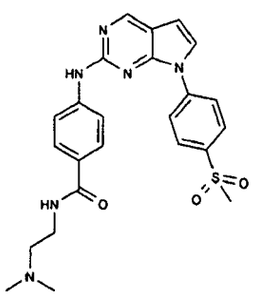
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.98 min (Method A); MS-ES: $(M+H)^+$ = 477.

Example 39: {3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



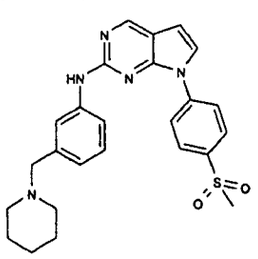
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.02 min (Method A); MS-ES: $(M+H)^+$ = 491.

Example 40: N-(2-Dimethylamino-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide



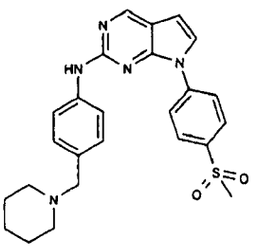
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.10 min (Method A); MS-ES: $(M+H)^+$ = 479.

Example 41: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-piperidin-1-ylmethyl-phenyl)-amine



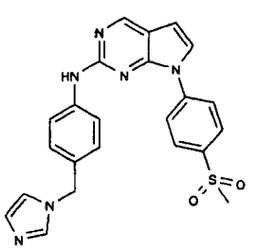
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.16 min (Method A); MS-ES: $(M+H)^+$ = 462.

Example 42: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperidin-1-ylmethyl-phenyl)-amine



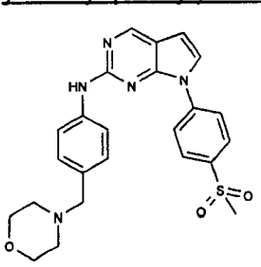
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 462.

Example 43: (4-Imidazol-1-ylmethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



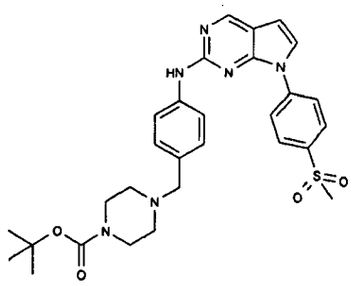
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.06 min (Method A); MS-ES: $(M+H)^+$ = 445.

Example 44: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine



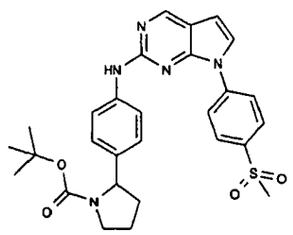
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 464.

Example 45: 4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester



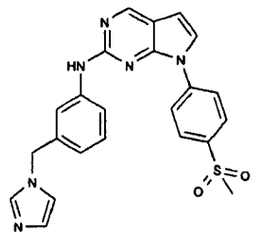
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.41 min (Method A); MS-ES: $(M+H)^+$ = 563.

Example 46: 2-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-pyrrolidine-1-carboxylic acid tert-butyl ester



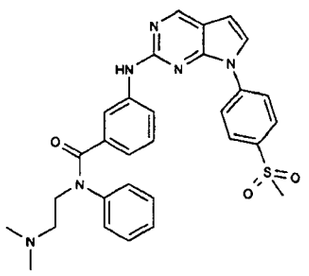
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.92 min (Method A); MS-ES: $(M+H)^+$ = 534.

Example 47: (3-Imidazol-1-ylmethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



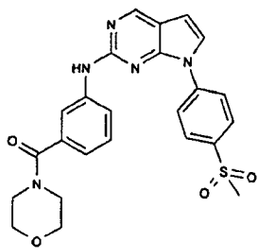
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 445.

Example 48: N-(2-Dimethylamino-ethyl)-3-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-phenyl-benzamide



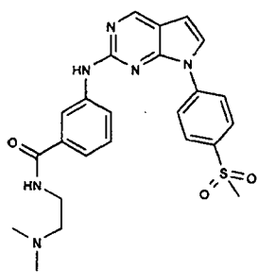
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.28 min (Method A); MS-ES: $(M+H)^+$ = 555.

Example 49: {3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



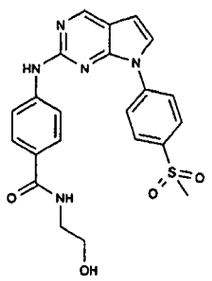
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.32 min (Method A); MS-ES: $(M+H)^+$ = 478.

Example 50: N-(2-Dimethylamino-ethyl)-3-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide



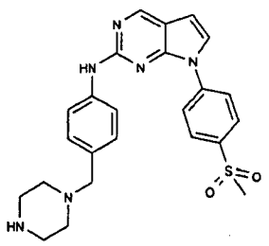
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.04 min (Method A); MS-ES: $(M+H)^+$ = 479.

Example 51: N-(2-Hydroxy-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide



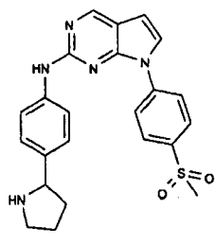
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.17 min (Method A); MS-ES: $(M+H)^+$ = 452.

Example 52: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-ylmethyl-phenyl)-amine



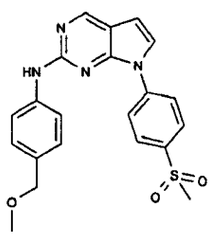
The compound is prepared by treatment of Example 45 with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 464.

Example 53: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-pyrrolidin-2-yl-phenyl)-amine



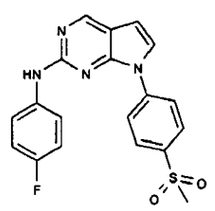
The compound is prepared by treatment of Example 46 with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 434.

Example 54: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine



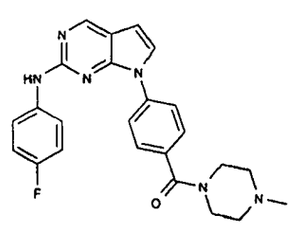
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.46 min (Method A); MS-ES: $(M+H)^+$ = 409.

Example 55: (4-Fluoro-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



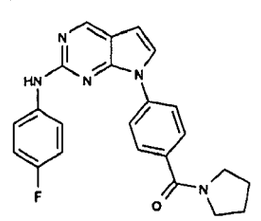
The compound is prepared analogous to Example 1. HPLC: $t_R$ = 1.52 min (Method A); MS-ES: $(M+H)^+$ = 383.

Example 56: {4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



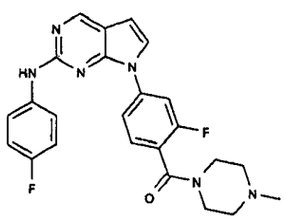
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.06 min (Method A); MS-ES: $(M+H)^+$ = 431.

Example 57: {4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-pyrrolidin-1-yl-methanone



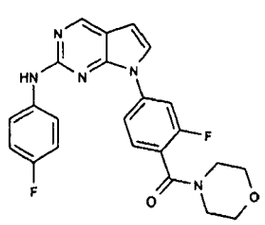
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.56 min (Method A); MS-ES: $(M+H)^+$ = 402.

Example 58: {2-Fluoro-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



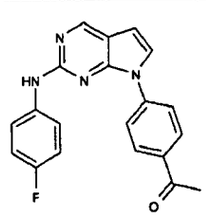
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.11 min (Method A); MS-ES: $(M+H)^+$ = 449.

Example 59: {2-Fluoro-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



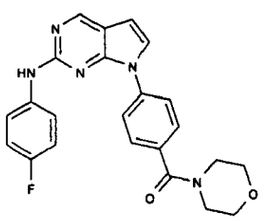
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.54 min (Method A); MS-ES: $(M+H)^+$ = 436.

Example 60: 1-{4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone



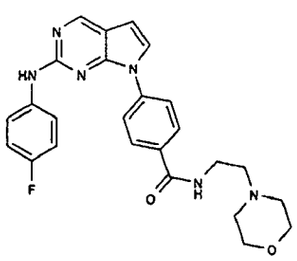
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.71 min (Method A); MS-ES: $(M+H)^+$ = 347.

Example 61: {4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



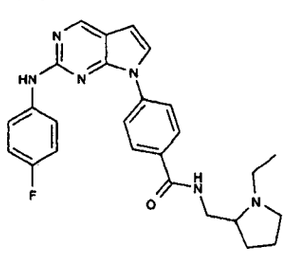
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.42 min (Method A); MS-ES: $(M+H)^+$ = 418.

Example 62: 4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide



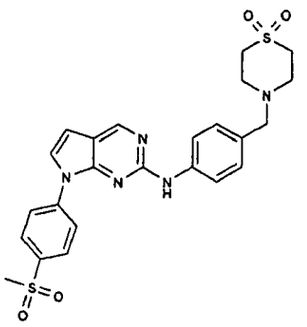
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 461.

Example 63: N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide



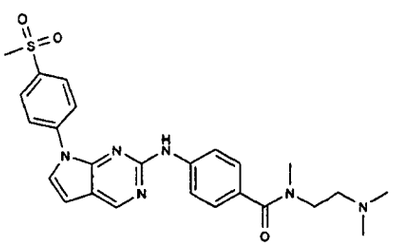
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.23 min (Method A); MS-ES: $(M+H)^+$ = 459.

Example 64: [4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



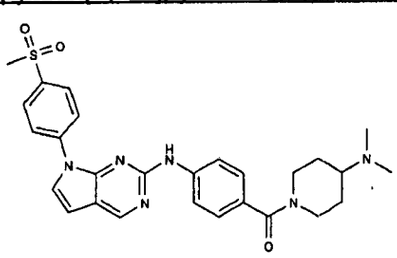
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.11 min (Method A); MS-ES: $(M+H)^+$ = 512.

Example 65: N-(2-Dimethylamino-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-methyl-benzamide



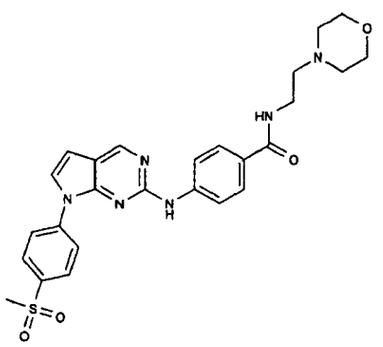
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.04 min (Method A); MS-ES: $(M+H)^+$ = 493.

Example 66: (4-Dimethylamino-piperidin-1-yl)-{4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-methanone



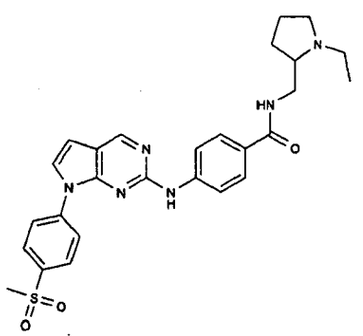
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.02 min (Method A); MS-ES: $(M+H)^+$ = 519.

Example 67: 4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-(2-morpholin-4-yl-ethyl)-benzamide



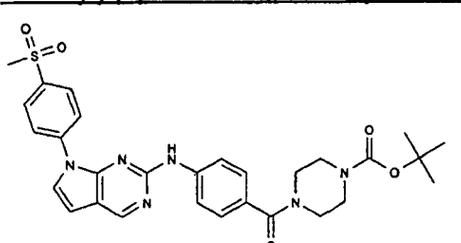
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.10 min (Method A); MS-ES: $(M+H)^+$ = 521.

Example 68: N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide



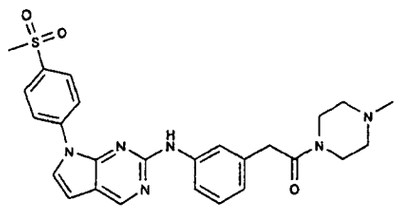
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.18 min (Method A); MS-ES: $(M+H)^+$ = 519.

Example 69: 4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester



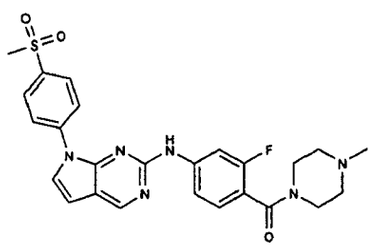
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.80 min (Method A); MS-ES: $(M+H)^+$ = 577.

Example 70: 2-{3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



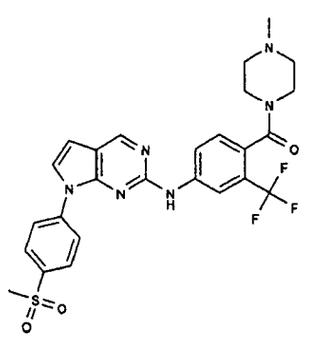
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.03 min (Method A); MS-ES: $(M+H)^+$ = 505.

Example 71: {2-Fluoro-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



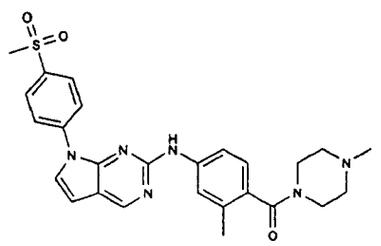
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 509.

Example 72: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-trifluoromethyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone



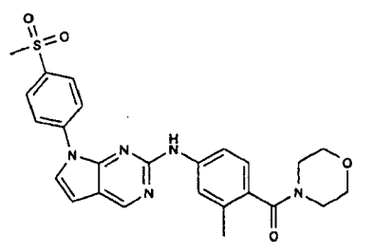
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.23 min (Method A); MS-ES: $(M+H)^+$ = 559.

Example 73: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone



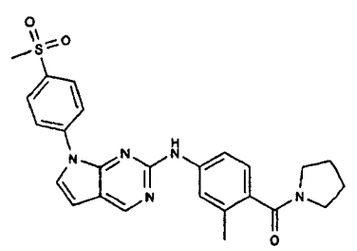
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.02 min (Method A); MS-ES: $(M+H)^+$ = 505.

Example 74: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-morpholin-4-yl-methanone



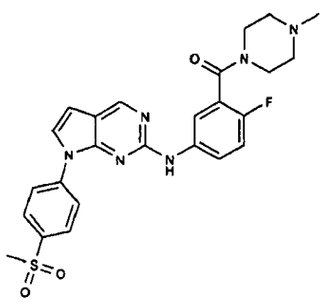
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.31 min (Method A); MS-ES: $(M+H)^+$ = 492.

Example 75: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-pyrrolidin-1-yl-methanone



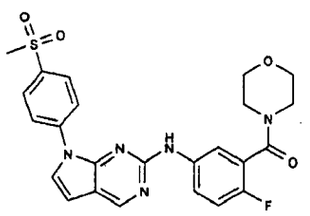
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.42 min (Method A); MS-ES: $(M+H)^+$ = 476.

Example 76: {2-Fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



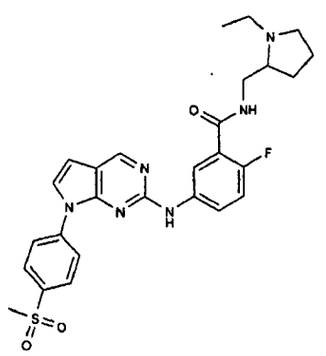
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.06 min (Method A); MS-ES: $(M+H)^+$ = 509.

Example 77: {2-Fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



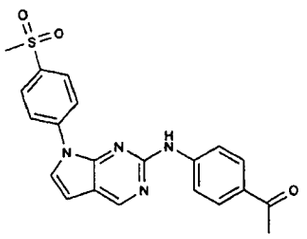
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.38 min (Method A); MS-ES: $(M+H)^+$ = 496.

Example 78: N-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide



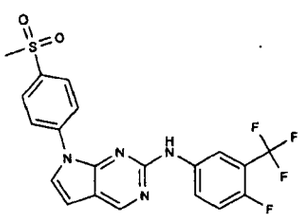
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.14 min (Method A); MS-ES: $(M+H)^+$ = 537.

Example 79: 1-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-ethanone



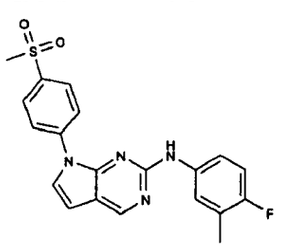
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.61 min (Method A); MS-ES: $(M+H)^+$ = 407.

Example 80: (4-Fluoro-3-trifluoromethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



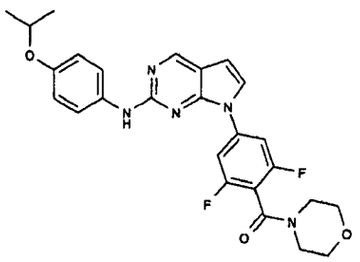
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 2.01 min (Method A); MS-ES: $(M+H)^+$ = 451.

Example 81: (4-Fluoro-3-methyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



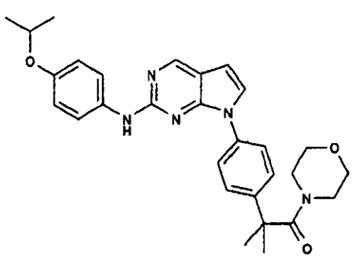
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.67 min (Method A); MS-ES: $(M+H)^+$ = 397.

Example 82: {2,6-Difluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



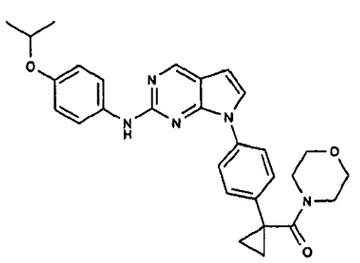
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.76 min (Method A); MS-ES: $(M+H)^+$ = 494.

Example 83: 2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-2-methyl-1-morpholin-4-yl-propan-1-one



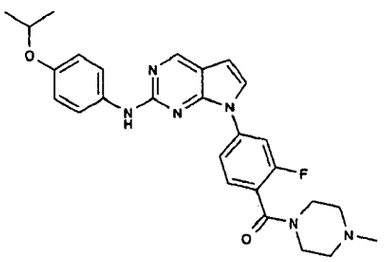
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.79 min (Method A); MS-ES: $(M+H)^+$ = 500.

Example 84: (1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-morpholin-4-yl-methanone



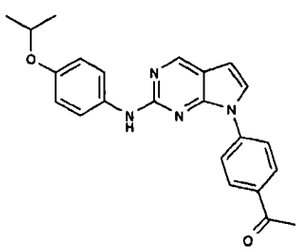
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.69 min (Method A); MS-ES: $(M+H)^+$ = 498.

Example 85: {2-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



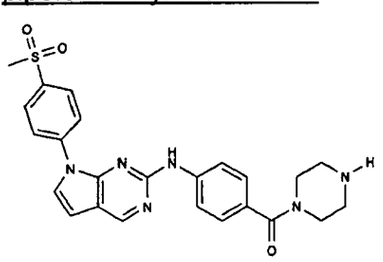
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.23 min (Method A); MS-ES: $(M+H)^+$ = 489.

Example 86: 1 1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone



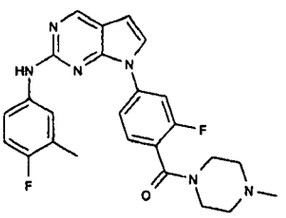
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.83 min (Method A); MS-ES: $(M+H)^+$ = 387.

Example 87: {4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-piperazin-1-yl-methanone



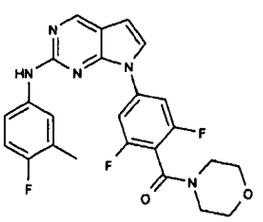
The compound is prepared by treatment of Example 69 with TFA in $CH_2Cl_2$ at rt. MS-ES: $(M+H)^+$ = 477.

Example 88: {2-Fluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



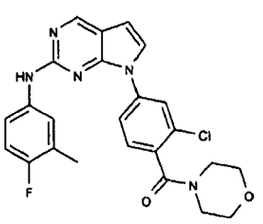
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.24 min (Method A); MS-ES: $(M+H)^+$ = 463.

Example 89: {2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



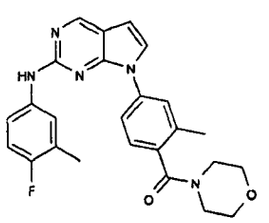
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.78 min (Method A); MS-ES: $(M+H)^+$ = 468.

Example 90: {2-Chloro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



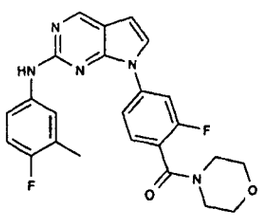
The compound is prepared analogous to Example 3. MS-ES: $(M+H)^+$ = 466.

Example 91: {4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



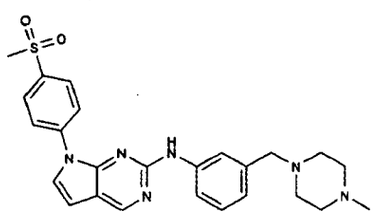
The compound is prepared analogous to Example 3. MS-ES: $(M+H)^+$ = 446.

Example 92: {2-Fluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



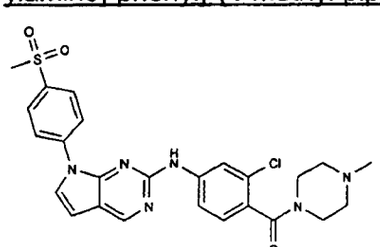
The compound is prepared analogous to Example 3. MS-ES: $(M+H)^+$ = 450.

Example 93: 7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



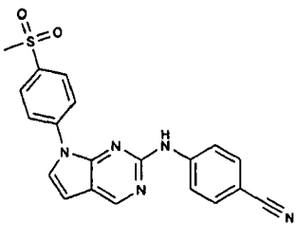
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.02 min (Method A); MS-ES: $(M+H)^+$ = 477.

Example 94: {2-Chloro-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



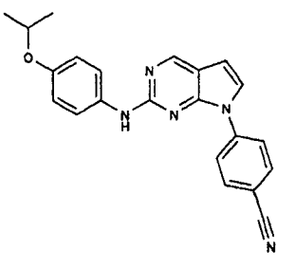
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 525.

Example 95: 4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzonitrile



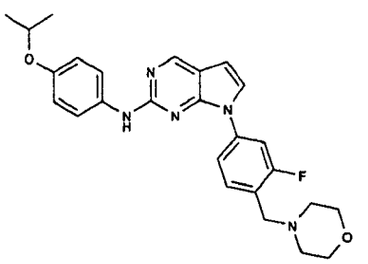
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.77 min (Method A); MS-ES: $(M+H)^+$ = 390.

Example 96: 4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzonitrile



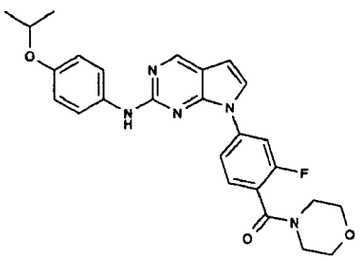
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.90 min (Method A); MS-ES: $(M+H)^+$ = 370.

Example 97: [7-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine



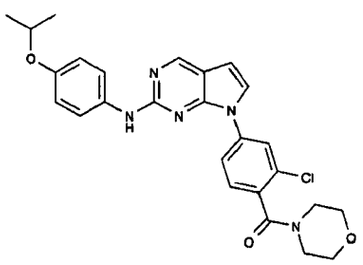
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.27 min (Method A); MS-ES: $(M+H)^+$ = 462.

Example 98: {2-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



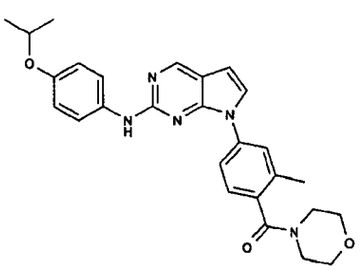
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.64 min (Method A); MS-ES: $(M+H)^+$ = 476.

Example 99: {2-Chloro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



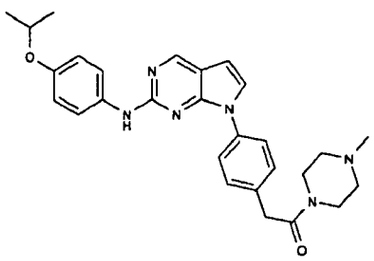
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.69 min (Method A); MS-ES: $(M+H)^+$ = 492.

Example 100: {4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



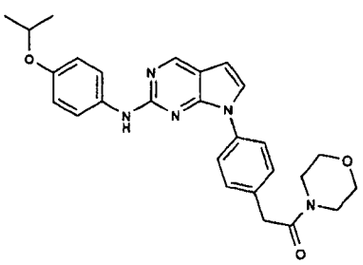
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.61 min (Method A); MS-ES: $(M+H)^+$ = 472.

Example 101: 2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



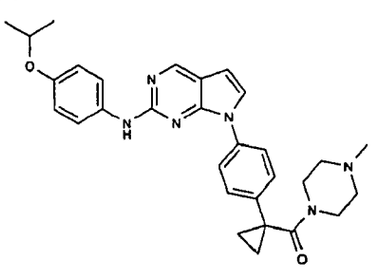
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.27 min (Method A); MS-ES: $(M+H)^+$ = 485.

Example 102: 2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone



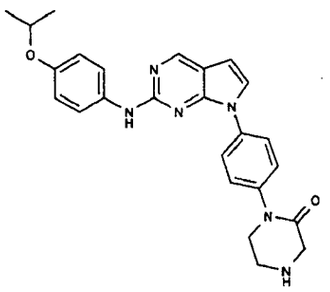
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.60 min (Method A); MS-ES: $(M+H)^+$ = 472.

Example 103: (1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone



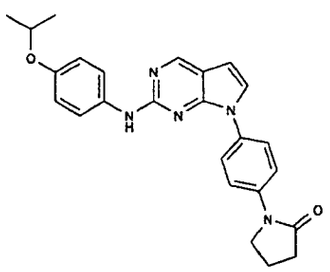
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.36 min (Method A); MS-ES: $(M+H)^+$ = 511.

Example 104: 1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-piperazin-2-one



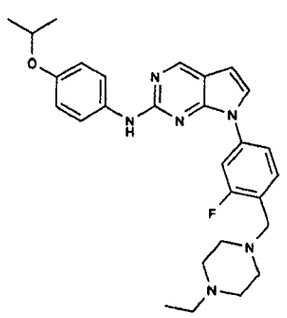
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 443.

Example 105: 1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-pyrrolidin-2-one



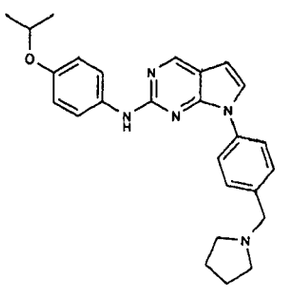
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.72 min (Method A); MS-ES: $(M+H)^+$ = 428.

Example 106: {7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine



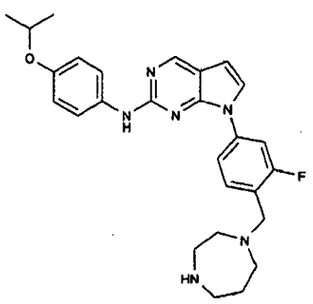
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.25 min (Method A); MS-ES: $(M+H)^+$ = 489.

Example 107: (4-Isopropoxy-phenyl)-[7-(4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



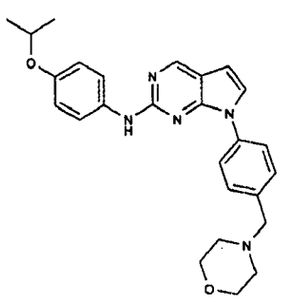
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.27 min (Method A); MS-ES: $(M+H)^+$ = 428.

Example 108: 7-(4-[1,4]Diazepan-1-ylmethyl-3-fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine



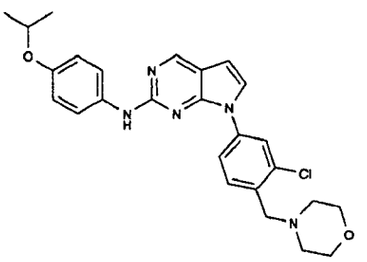
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.14 min (Method A); MS-ES: $(M+H)^+$ = 475.

Example 109: (4-Isopropoxy-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



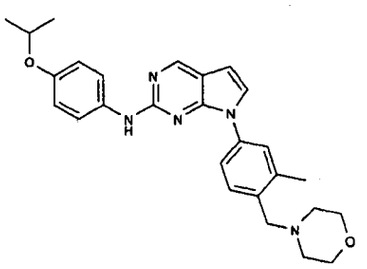
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.23 min (Method A); MS-ES: $(M+H)^+$ = 444.

Example 110: [7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine



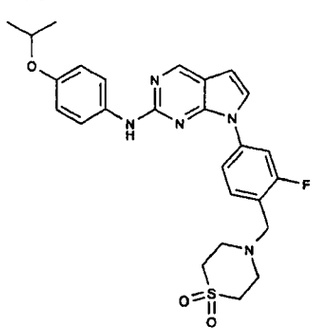
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.33 min (Method A); MS-ES: $(M+H)^+$ = 478.

Example 111: (4-Isopropoxy-phenyl)-[7-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



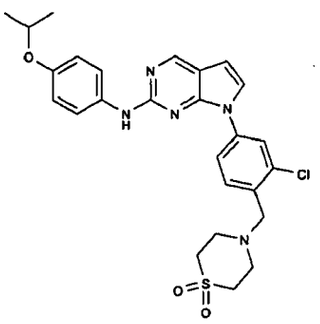
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.28 min (Method A); MS-ES: $(M+H)^+$ = 458.

Example 112: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine



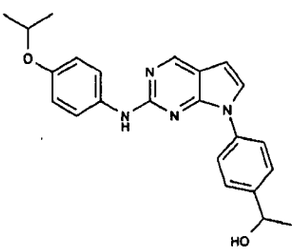
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.55 min (Method A); MS-ES: $(M+H)^+$ = 510.

Example 113: {7-[3-Chloro-4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine



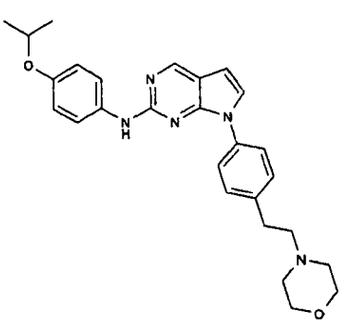
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.73 min (Method A); MS-ES: $(M+H)^+$ = 526.

Example 114: 1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanol



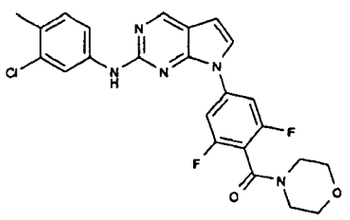
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.63 min (Method A); MS-ES: $(M+H)^+$ = 389.

Example 115: (4-Isopropoxy-phenyl)-{7-[4-(2-morpholin-4-yl-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



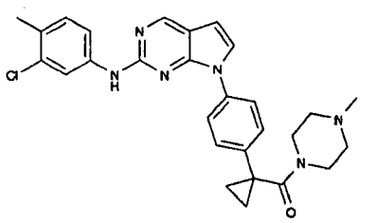
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.27 min (Method A); MS-ES: $(M+H)^+$ = 458.

Example 116: {4-[2-(3-Chloro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-phenyl}-morpholin-4-yl-methanone



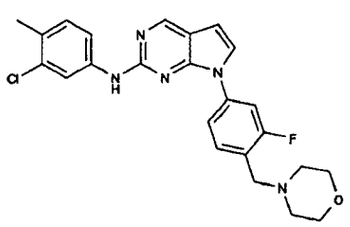
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 2.03 min (Method A); MS-ES: $(M+H)^+$ = 484.

Example 117: (1-{4-[2-(3-Chloro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone



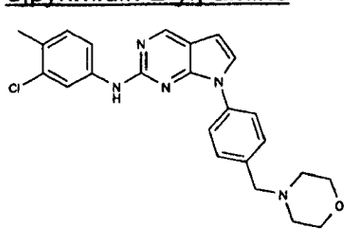
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.47 min (Method A); MS-ES: $(M+H)^+$ = 501.

Example 118: (3-Chloro-4-methyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



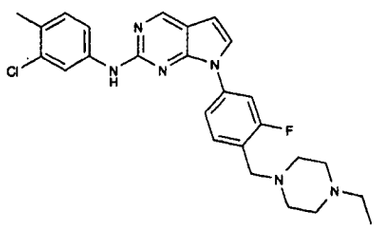
The compound is prepared analogous to Example 3. MS-ES: $(M+H)^+$ = 452.

Example 119: (3-Chloro-4-methyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



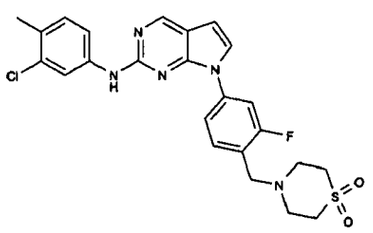
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.33 min (Method A); MS-ES: $(M+H)^+$ = 434.

Example 120: (3-Chloro-4-methyl-phenyl)-{7-[4-(4-ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



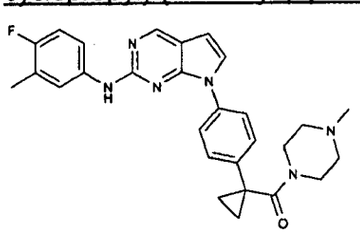
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.38 min (Method A); MS-ES: $(M+H)^+$ = 479.

Example 121: (3-Chloro-4-methyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



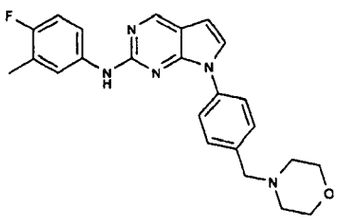
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.73 min (Method A); MS-ES: $(M+H)^+$ = 500.

Example 122: (1-{4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone



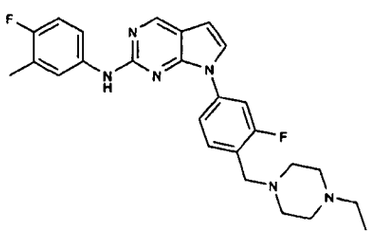
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.33 min (Method A); MS-ES: $(M+H)^+$ = 485.

Example 123: (4-Fluoro-3-methyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



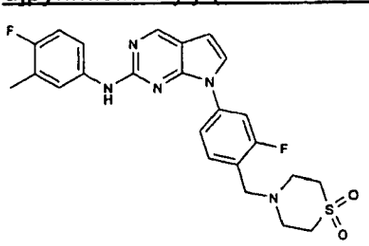
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.18 min (Method A); MS-ES: $(M+H)^+$ = 418.

Example 124: {7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine



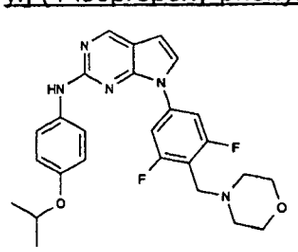
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.24 min (Method A); MS-ES: $(M+H)^+$ = 463.

Example 125: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine



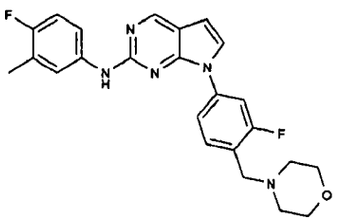
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.53 min (Method A); MS-ES: $(M+H)^+$ = 484.

Example 126: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine



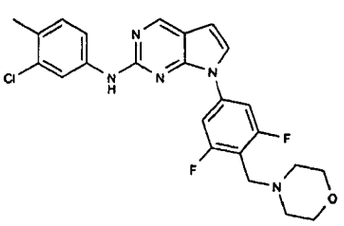
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.32 min (Method A); MS-ES: $(M+H)^+$ = 480.

Example 127: (4-Fluoro-3-methyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



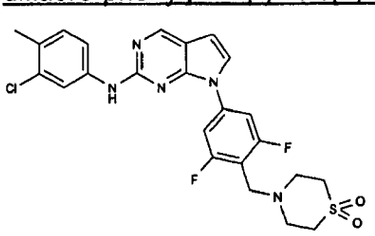
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.26 min (Method A); MS-ES: $(M+H)^+$ = 436.

Example 128: (3-Chloro-4-methyl-phenyl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



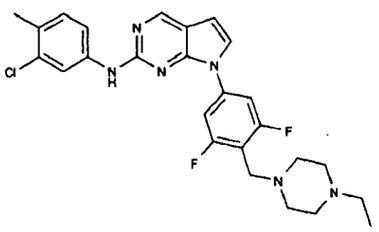
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.48 min (Method A); MS-ES: $(M+H)^+$ = 470.

Example 129: (3-Chloro-4-methyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



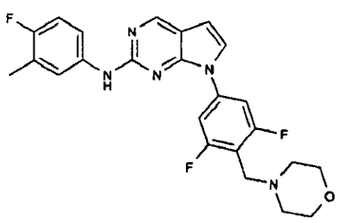
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.96 min (Method A); MS-ES: $(M+H)^+$ = 518.

Example 130: (3-Chloro-4-methyl-phenyl)-{7-[4-(4-ethyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



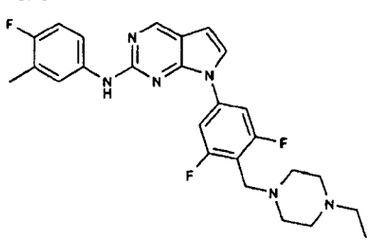
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.51 min (Method A); MS-ES: $(M+H)^+$ = 497.

Example 131: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-fluoro-3-methyl-phenyl)-amine



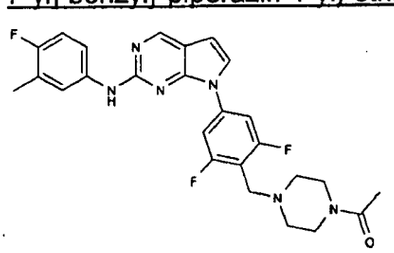
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.39 min (Method A); MS-ES: $(M+H)^+$ = 454.

Example 132: {7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine



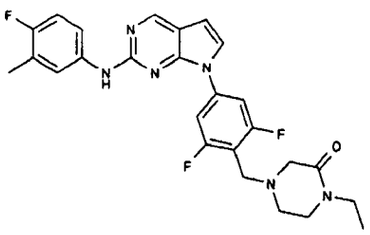
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.35 min (Method A); MS-ES: $(M+H)^+$ = 481.

Example 133: 1-(4-{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-1-yl)-ethanone



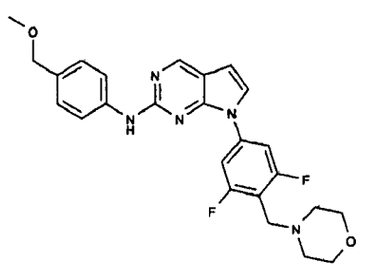
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.26 min (Method A); MS-ES: $(M+H)^+$ = 495.

Example 134: 4-{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-1-ethyl-piperazin-2-one



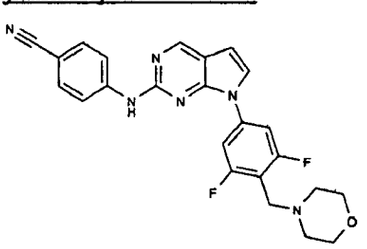
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.43 min (Method A); MS-ES: $(M+H)^+$ = 495.

Example 135: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine



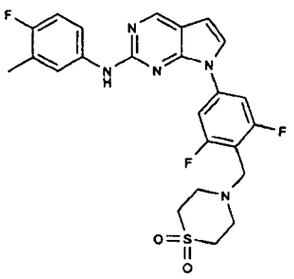
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 466.

Example 136: 4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzonitrile



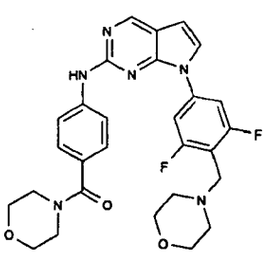
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.38 min (Method A); MS-ES: $(M+H)^+$ = 447.

Example 137: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amin



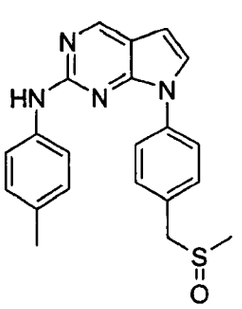
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.71 min (Method A); MS-ES: $(M+H)^+$ = 502.

Example 138: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



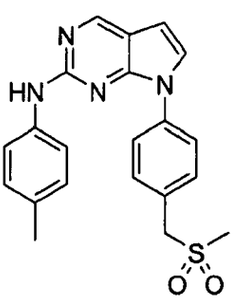
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 535.

Example 139: [7-(4-Methanesulfinylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine



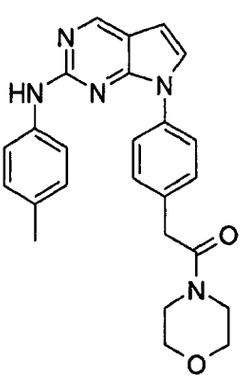
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.96 min. (Method B); MS-ES: $(M+H)^+$ = 377; TLC***: $R_f$ = 0.22

Example 140: [7-(4-Methanesulfonylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine



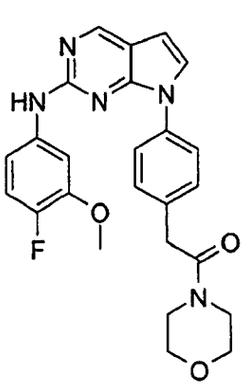
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.23 min. (Method B); MS-ES: $(M+H)^+$ = 393; TLC***: $R_f$ = 0.42

Example 141: 1-Morpholin-4-yl-2-[4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone



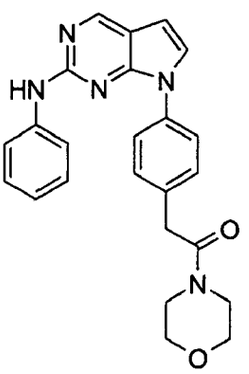
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.36 min. (Method B); MS-ES: $(M+H)^+$ = 428; TLC‡: $R_f$ = 0.14

Example 142: 2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone



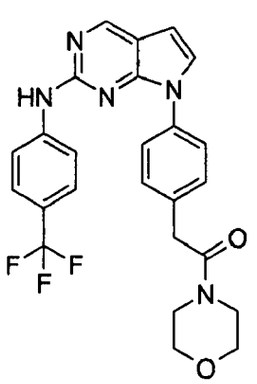
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.27 min. (Method B); MS-ES: $(M+H)^+$ = 462; TLC‡: $R_f$ = 0.23

Example 143: 1-Morpholin-4-yl-2-[4-(2-phenylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone



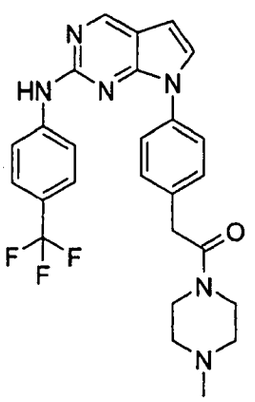
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.04 min. (Method B); MS-ES: $(M+H)^+$ = 414; TLC‡: $R_f$ = 0.11

Example 144: 1-Morpholin-4-yl-2-{4-[2-(4-trifluoromethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone



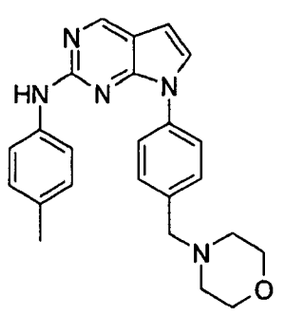
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 9.22 min. (Method B); MS-ES: $(M+H)^+$ = 482; TLC‡: $R_f$ = 0.12

Example 145: 1-(4-Methyl-piperazin-1-yl)-2-{4-[2-(4-trifluoromethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone



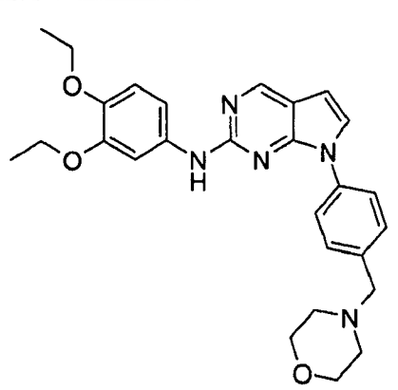
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.15 min. (Method B); MS-ES: $(M+H)^+$ = 495; TLC*: $R_f$ = 0.29

Example 146: [7-(4-Morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine



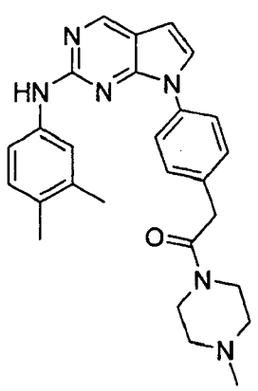
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.28 min. (Method B); MS-ES: $(M+H)^+$ = 400; TLC‡: $R_f$ = 0.17

Example 147: (3,4-Diethoxy-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



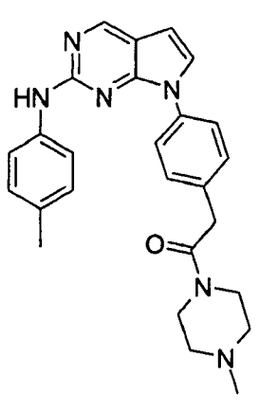
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.47 min. (Method B); MS-ES: $(M+H)^+$ = 474

Example 148: 2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



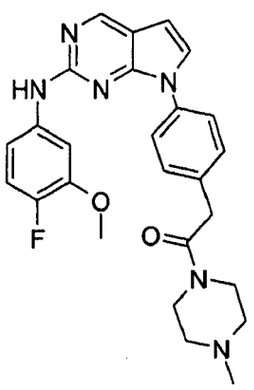
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.50 min. (Method B); MS-ES: $(M+H)^+$ = 455; TLC*: $R_f$ = 0.36

Example 149: 1-(4-Methyl-piperazin-1-yl)-2-[4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone



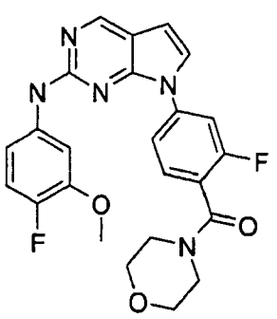
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.25 min. (Method B); MS-ES: $(M+H)^+$ = 441; TLC*: $R_f$ = 0.37

Example 150: 2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



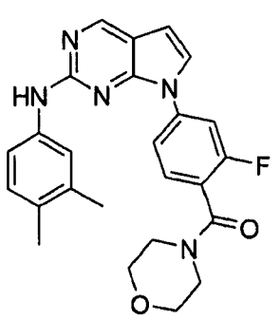
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.21 min. (Method B); MS-ES: $(M+H)^+$ = 475; TLC*: $R_f$ = 0.36

Example 151: {2-Fluoro-4-[2-(4-fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



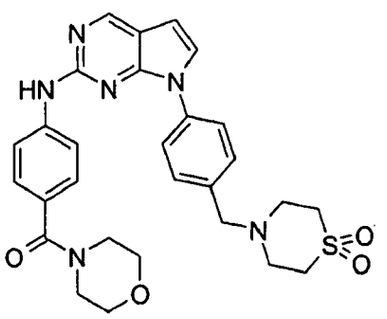
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.40 min. (Method B); MS-ES: $(M+H)^+$ = 466; TLC‡: $R_f$ = 0.16

Example 152: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



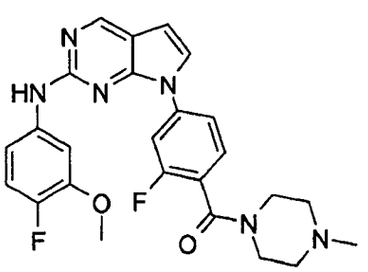
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.76 min. (Method B); MS-ES: $(M+H)^+$ = 446; TLC‡: $R_f$ = 0.26

Example 153: (4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-phenyl)-morpholin-4-yl-methanone



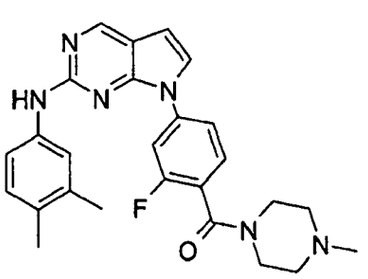
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.03 min. (Method B); MS-ES: $(M+H)^+$ = 547; TLC**: $R_f$ = 0.29

Example 154: {2-Fluoro-4-[2-(4-fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



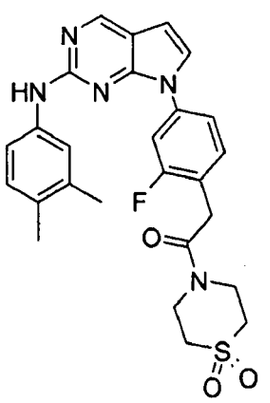
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.26 min. (Method B); MS-ES: $(M+H)^+$ = 479; TLC**: $R_f$ = 0.23

Example 155: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-(4-methyl-piperazin-1-yl)-methanone



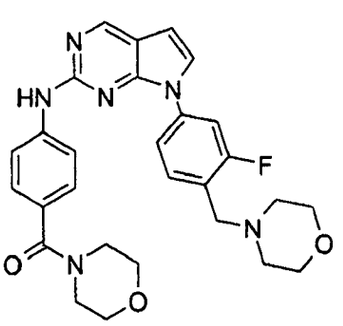
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.45 min. (Method B); MS-ES: $(M+H)^+$ = 459; TLC**: $R_f$ = 0.31

Example 156: 2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-1-(1,1-dioxido-1-thiomorpholin-4-yl)-ethanone



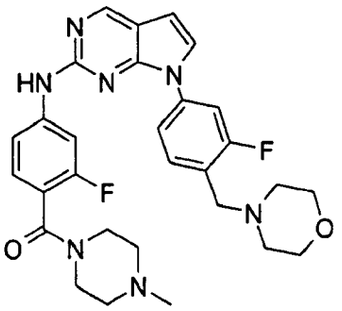
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.51 min. (Method B); MS-ES: $(M+H)^+$ = 508; TLC**: $R_f$ = 0.67

Example 157: {4-[7-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



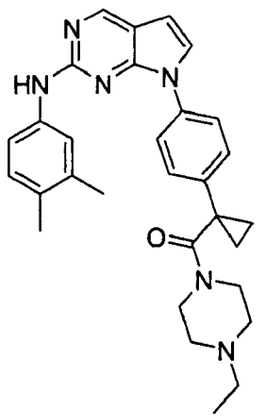
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.03 min. (Method B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$ = 0.29

Example 158: {2-Fluoro-4-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



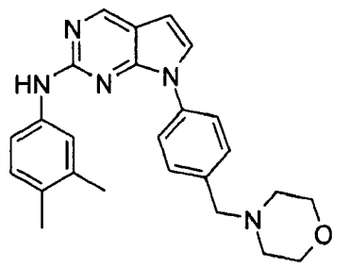
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 6.71 min. (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.57

Example 159: (1-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-ethyl-piperazin-1-yl)-methanone



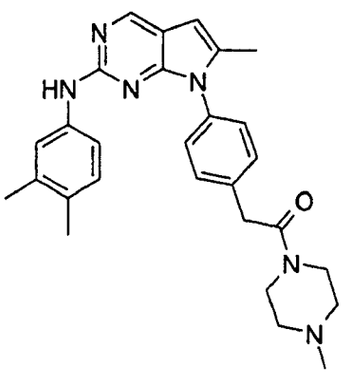
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.20 min. (Method B); MS-ES: $(M+H)^+$ = 495; TLC**: $R_f$ = 0.11

Example 160: (3,4-Dimethyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



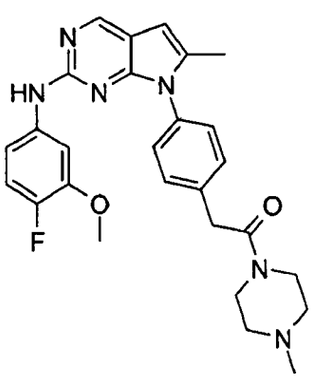
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.80 min. (Method B); MS-ES: $(M+H)^+$ = 414; TLC**: $R_f$ = 0.21

Example 161: 2-{4-[2-(3,4-Dimethyl-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



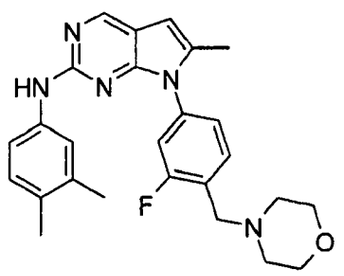
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.76 min. (Method B); MS-ES: $(M+H)^+$ = 469; TLC**: $R_f$ = 0.31

Example 162: 2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



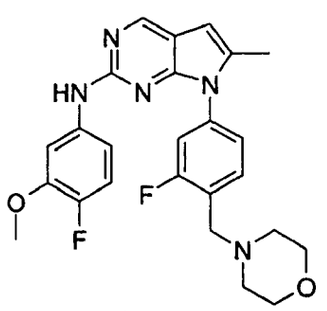
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.31 min. (Method B); MS-ES: $(M+H)^+$ = 489; TLC***: $R_f$ = 0.20

Example 163: (3,4-Dimethyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



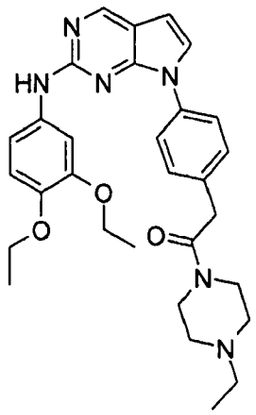
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.58 min. (Method B); MS-ES: $(M+H)^+$ = 446; TLC***: $R_f$ = 0.40

Example 164: (4-Fluoro-3-methoxy-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



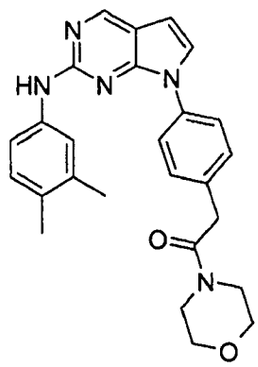
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.23 min. (Method B); MS-ES: $(M+H)^+$ = 466; TLC***: $R_f$ = 0.32

Example 165: 2-{4-[2-(3,4-Diethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-ethyl-piperazin-1-yl)-ethanone



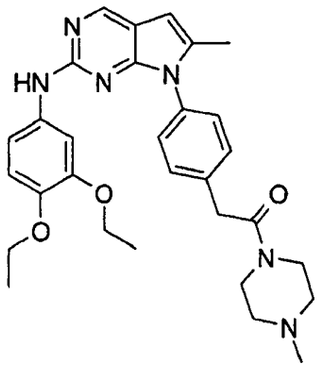
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.53 min. (Method B); MS-ES: $(M+H)^+$ = 529; TLC*: $R_f$ = 0.43

Example 166: 2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone



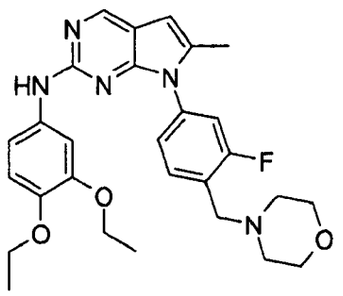
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.63 min. (Method B); MS-ES: $(M+H)^+$ = 442; TLC**: $R_f$ = 0.30

Example 167: 2-{4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone



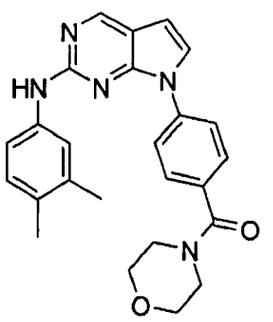
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.52 min. (Method B); MS-ES: (M+H)+ = 529; TLC*: $R_f$ = 0.50

Example 168: (3,4-Diethoxy-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



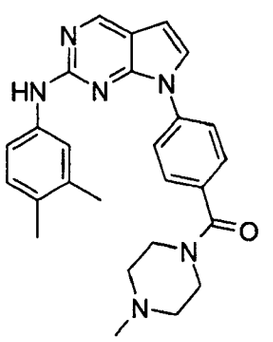
The compound is prepared analogous to Example 3. But during the synthesis of the pyrrolopyrimidine core, tributyl-(1-propynyl)-tin was used instead of tributyl-(2-ethoxy-vinyl)-stannane as described in Example 1 to obtain 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine. HPLC: $t_R$ = 7.49 min. (Method B); MS-ES: $(M+H)^+$ = 506; TLC***: $R_f$ = 0.24

Example 169: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



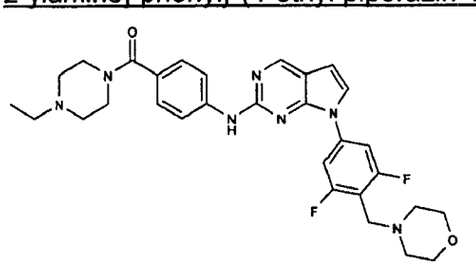
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.54 min. (Method B); MS-ES: $(M+H)^+$ = 428; TLC*: $R_f$ = 0.66

Example 170: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



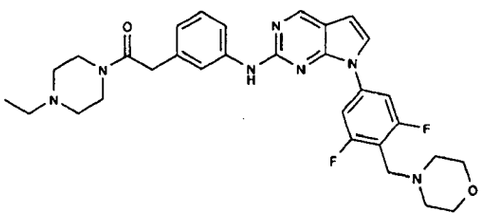
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.36 min. (Method B); MS-ES: $(M+H)^+$ = 441; TLC**: $R_f$ = 0.18

Example 171: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-ethyl-piperazin-1-yl)-methanone



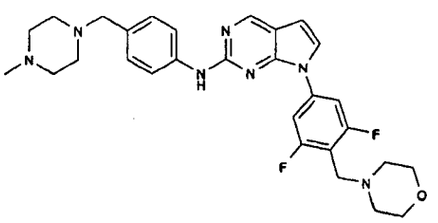
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 562.

Example 172: 2-{3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-1-(4-ethyl-piperazin-1-yl)-ethanone



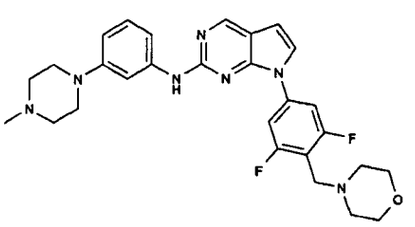
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 576.

Example 173: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



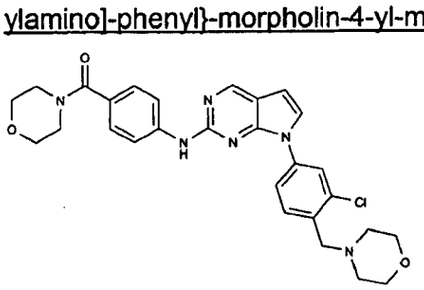
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 534.

Example 174: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-yl)-phenyl]-amine



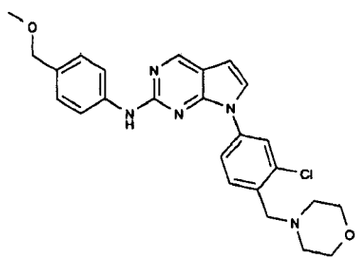
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 520.

Example 175: {4-[7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



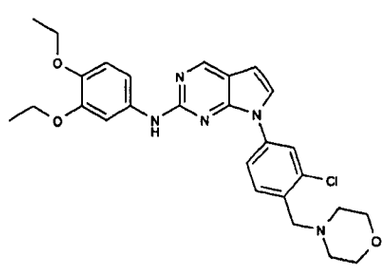
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 533.

Example 176: [7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine



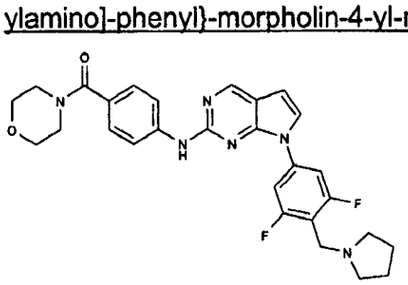
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.19 min (Method A); MS-ES: $(M+H)^+$ = 464.

Example 177: [7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4-diethoxy-phenyl)-amine



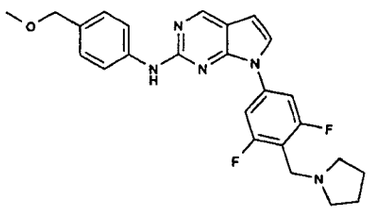
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.28 min (Method A); MS-ES: $(M+H)^+$ = 508.

Example 178: {4-[7-(3,5-Difluoro-4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



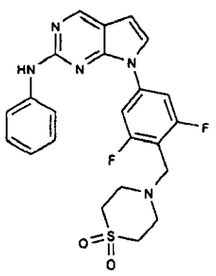
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 519.

Example 179: [7-(3,5-Difluoro-4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine



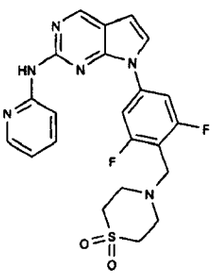
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.21 min (Method A); MS-ES: $(M+H)^+$ = 450.

Example 180: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-phenyl-amine



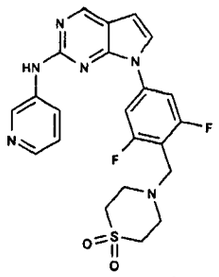
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.53 min (Method A); MS-ES: $(M+H)^+$ = 470.

Example 181: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-2-yl-amine



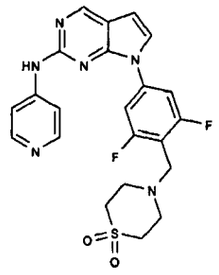
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.20 min (Method A); MS-ES: $(M+H)^+$ = 471.

Example 182: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-3-yl-amine



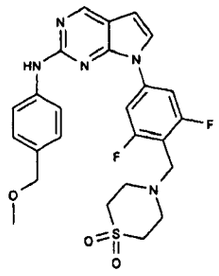
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.17 min (Method A); MS-ES: $(M+H)^+$ = 471.

Example 183: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-4-yl-amine



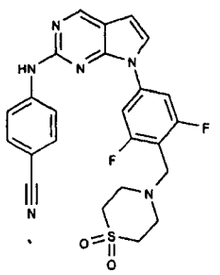
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.21 min (Method A); MS-ES: $(M+H)^+$ = 471.

Example 184: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methoxymethyl-phenyl)-amine



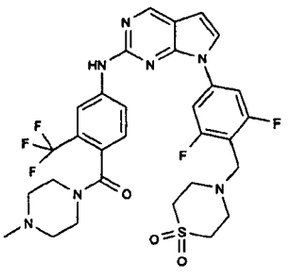
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.52 min (Method A); MS-ES: $(M+H)^+$ = 514.

Example 185: 4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzonitrile



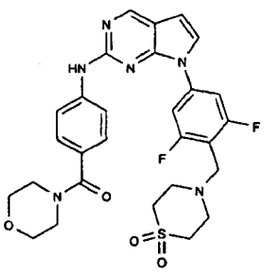
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.78 min (Method A); MS-ES: $(M+H)^+$ = 495.

Example 186: (4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-trifluoromethyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone



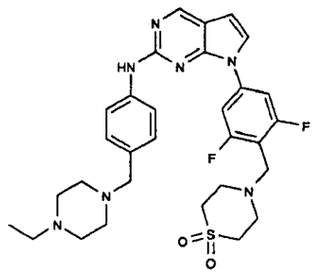
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.35 min (Method A); MS-ES: $(M+H)^+$ = 664.

Example 187: (4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-phenyl)-morpholin-4-yl-methanone



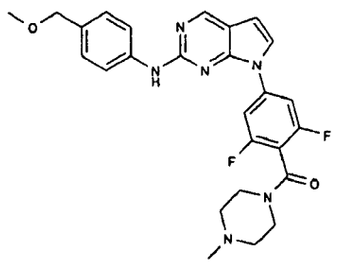
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.36 min (Method A); MS-ES: $(M+H)^+$ = 583.

Example 188: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amine



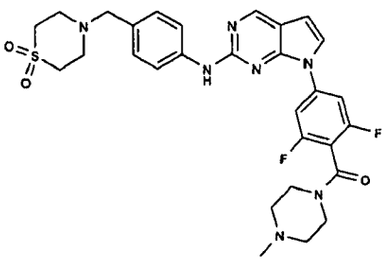
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.14 min (Method A); MS-ES: $(M+H)^+$ = 596.

Example 189: {2,6-Difluoro-4-[2-(4-methoxymethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



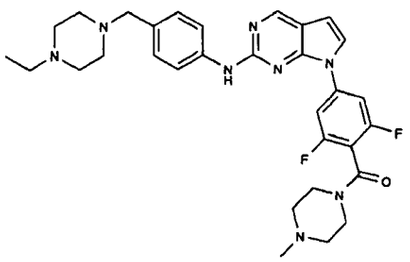
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.18 min (Method A); MS-ES: $(M+H)^+$ = 493.

Example 190: (4-{2-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone



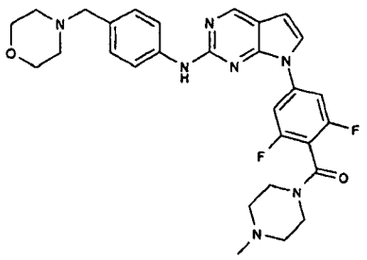
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.98 min (Method A); MS-ES: $(M+H)^+$ = 596.

Example 191: (4-{2-[4-(4-Ethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone



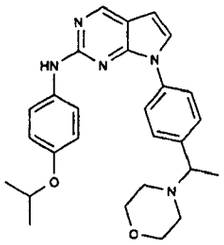
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 575.

Example 192: {2,6-Difluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



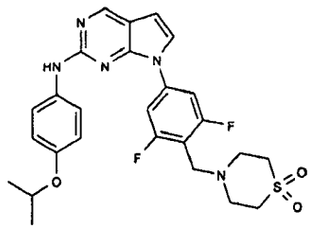
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.96 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 193: (4-Isopropoxy-phenyl)-{7-[4-(1-morpholin-4-yl-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine (racemic)



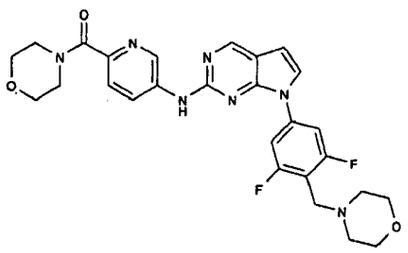
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.28 min (Method A); MS-ES: $(M+H)^+$ = 458.

Example 194: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine



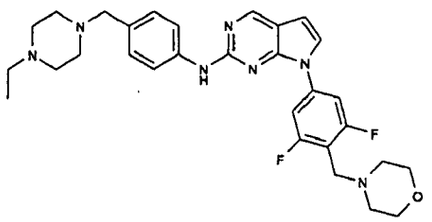
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.73 min (Method A); MS-ES: $(M+H)^+$ = 528.

Example 195: {5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-morpholin-4-yl-methanone



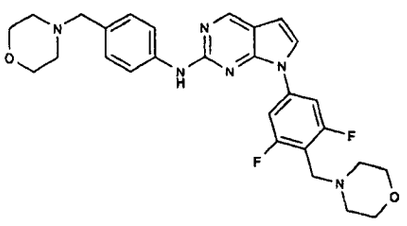
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.07 min (Method A); MS-ES: $(M+H)^+$ = 536.

Example 196: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amine



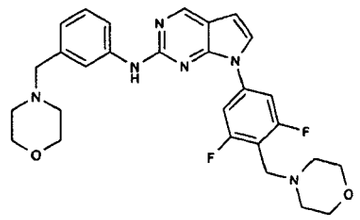
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.92 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 197: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine



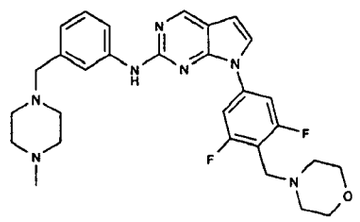
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.94 min (Method A); MS-ES: $(M+H)^+$ = 521.

Example 198: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-morpholin-4-ylmethyl-phenyl)-amine



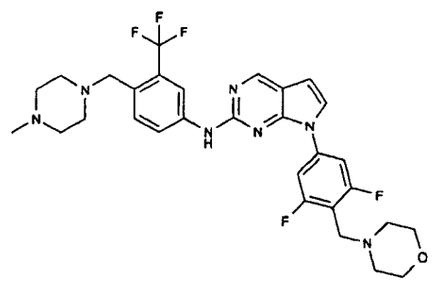
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.94 min (Method A); MS-ES: $(M+H)^+$ = 521.

Example 199: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



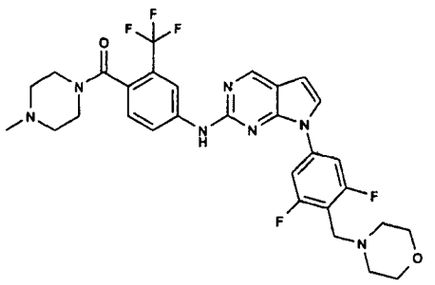
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 534.

Example 200: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amine



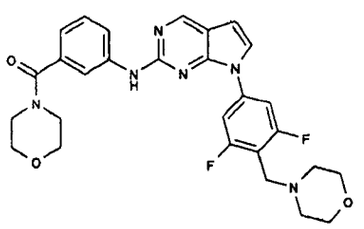
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.17 min (Method A); MS-ES: $(M+H)^+$ = 602.

Example 201: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-trifluoromethyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone



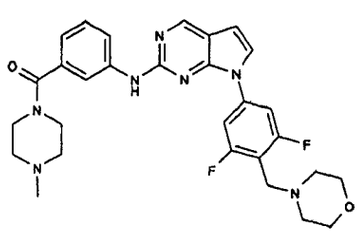
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 616.

Example 202: {3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone



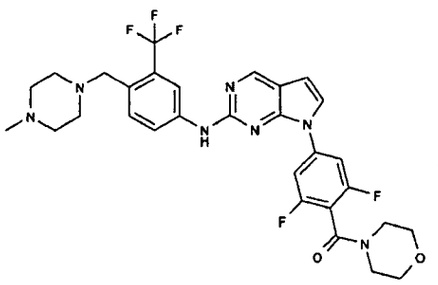
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 535.

Example 203: {3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone



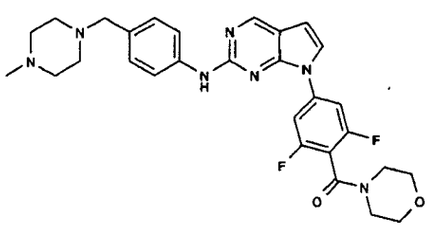
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.89 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 204: (2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



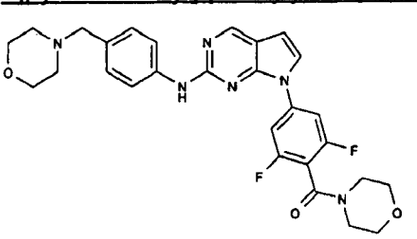
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.43 min (Method A); MS-ES: $(M+H)^+$ = 616.

Example 205: (2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



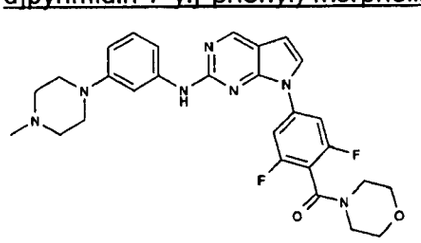
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.10 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 206: {2,6-Difluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



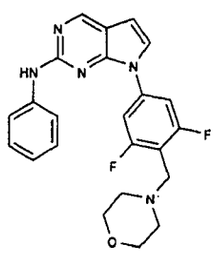
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.17 min (Method A); MS-ES: $(M+H)^+$ = 535.

Example 207: (2,6-Difluoro-4-{2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



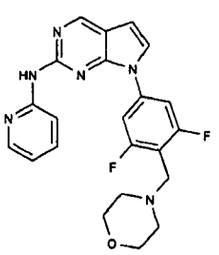
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.20 min (Method A); MS-ES: $(M+H)^+$ = 534.

Example 208: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-phenyl-amine



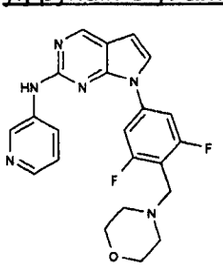
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.16 min (Method A); MS-ES: $(M+H)^+$ = 422.

Example 209: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-2-yl-amine



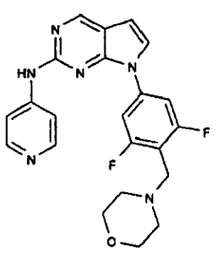
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.95 min (Method A); MS-ES: $(M+H)^+$ = 423.

Example 210: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-3-yl-amine



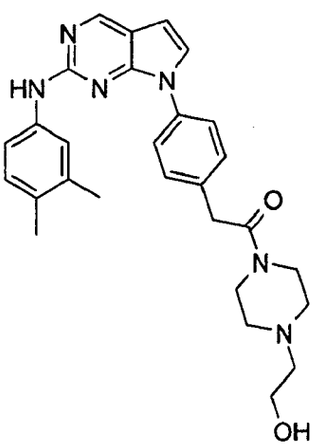
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 423.

Example 211: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-4-yl-amine



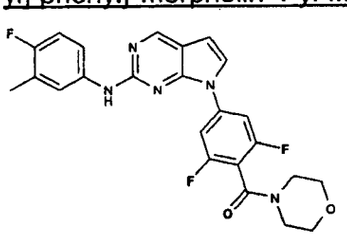
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.96 min (Method A); MS-ES: $(M+H)^+$ = 423.

Example 212: 2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethanone



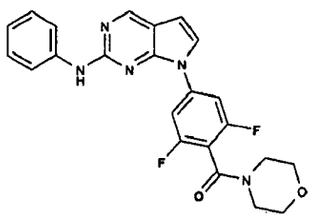
The compound is prepared analogous to Example 3 (scheme 3). HPLC: $t_R$ = 7.59 min. (Method B); MS-ES: $(M+H)^+$ = 485; TLC**: $R_f$ = 0.17

Example 213: {2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



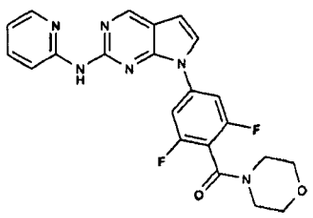
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.78 min (Method A); MS-ES: $(M+H)^+$ = 468.

Example 214: [2,6-Difluoro-4-(2-phenylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone



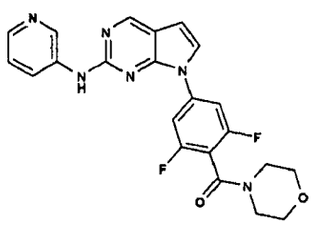
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.60 min (Method A); MS-ES: $(M+H)^+$ = 436.

Example 215: {2,6-Difluoro-4-[2-(pyridin-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



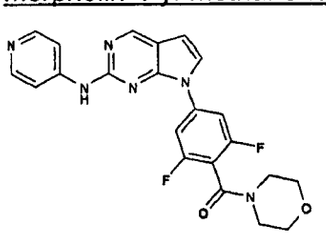
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.24 min (Method A); MS-ES: $(M+H)^+$ = 437.

Example 216: {2,6-Difluoro-4-[2-(pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



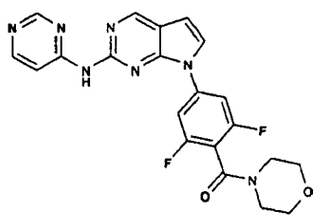
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.22 min (Method A); MS-ES: $(M+H)^+$ = 437.

Example 217: {2,6-Difluoro-4-[2-(pyridin-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



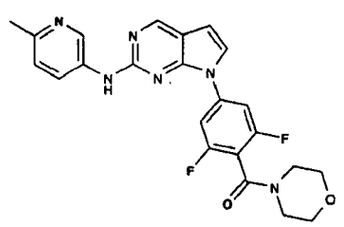
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.24 min (Method A); MS-ES: $(M+H)^+$ = 437.

Example 218: {2,6-Difluoro-4-[2-(pyrimidin-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



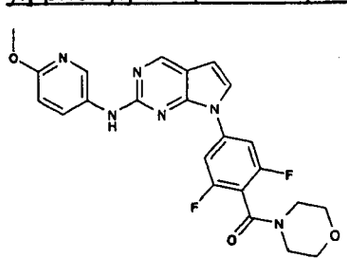
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 438.

Example 219: {2,6-Difluoro-4-[2-(6-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



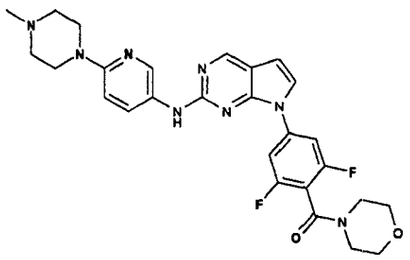
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.26 min (Method A); MS-ES: $(M+H)^+$ = 451.

Example 220: {2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



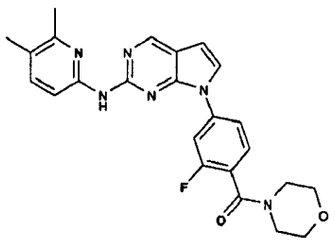
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.39 min (Method A); MS-ES: $(M+H)^+$ = 467.

Example 221: {2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



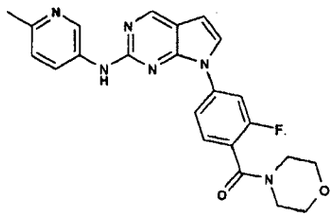
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.05 min (Method A); MS-ES: $(M+H)^+$ = 535.

Example 222: {4-[2-(5,6-Dimethyl-pyridin-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



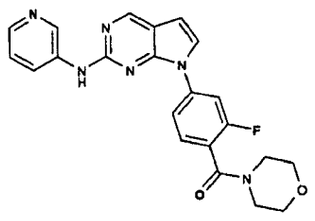
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.33 min (Method A); MS-ES: $(M+H)^+$ = 447.

Example 223: {2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



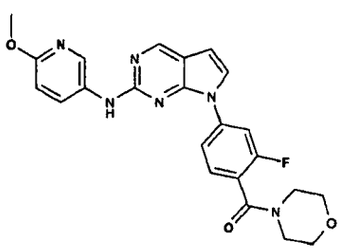
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.21 min (Method A); MS-ES: $(M+H)^+$ = 433.

Example 224: {2-Fluoro-4-[2-(pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



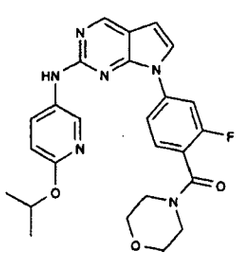
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.17 min (Method A); MS-ES: $(M+H)^+$ = 419.

Example 225: {2-Fluoro-4-[2-(6-methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



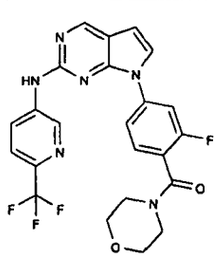
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.29 min (Method A); MS-ES: $(M+H)^+$ = 449.

Example 226: {2-Fluoro-4-[2-(6-isopropoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



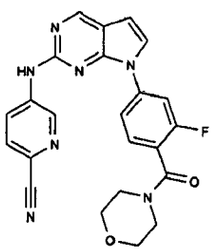
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.52 min (Method A); MS-ES: $(M+H)^+$ = 477.

Example 227: {2-Fluoro-4-[2-(6-trifluoromethyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



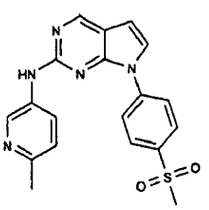
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.91 min (Method A); MS-ES: $(M+H)^+$ = 487.

Example 228: 5-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-pyridine-2-carbonitrile



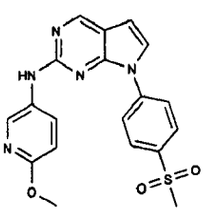
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.71 min (Method A); MS-ES: $(M+H)^+$ = 444.

Example 229: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-methyl-pyridin-3-yl)-amine



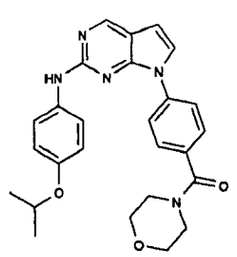
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 380.

Example 230: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-methoxy-pyridin-3-yl)-amine



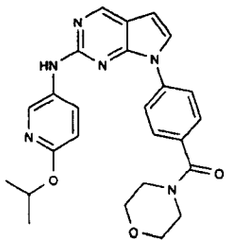
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.26 min (Method A); MS-ES: $(M+H)^+$ = 396.

Example 231: {4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



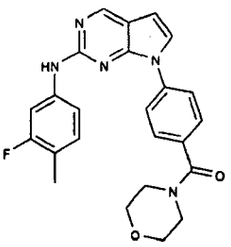
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.57 min (Method A); MS-ES: $(M+H)^+$ = 458.

Example 232: {4-[2-(6-Isopropoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



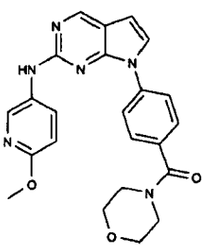
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.42 min (Method A); MS-ES: $(M+H)^+$ = 459.

Example 233: {4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



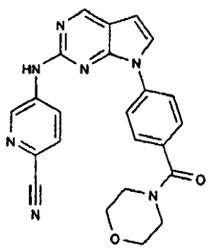
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.64 min (Method A); MS-ES: $(M+H)^+$ = 432.

Example 234: {4-[2-(6-Methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



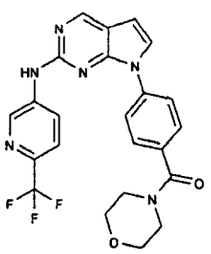
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.20 min (Method A); MS-ES: $(M+H)^+$ = 431.

Example 235: 5-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-pyridine-2-carbonitrile



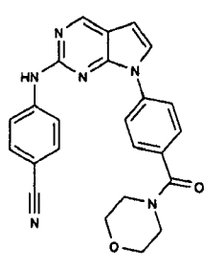
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.55 min (Method A); MS-ES: $(M+H)^+$ = 426.

Example 236: Morpholin-4-yl-{4-[2-(6-trifluoromethyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone



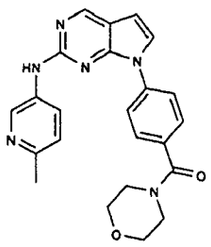
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.76 min (Method A); MS-ES: $(M+H)^+$ = 469.

Example 237: 4-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzonitrile



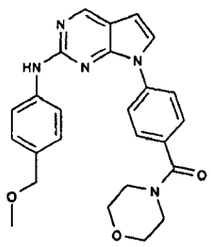
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.58 min (Method A); MS-ES: $(M+H)^+$ = 425.

Example 238: {4-[2-(6-Methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



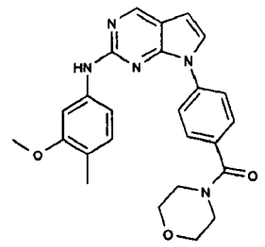
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 415.

Example 239: {4-[2-(4-Methoxymethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



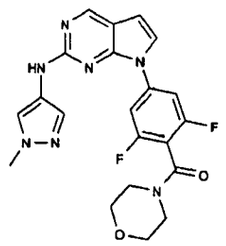
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.36 min (Method A); MS-ES: $(M+H)^+$ = 444.

Example 240: {4-[2-(3-Methoxy-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



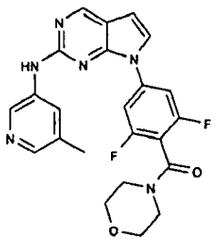
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.57 min (Method A); MS-ES: $(M+H)^+$ = 444.

Example 241: {2,6-Difluoro-4-[2-(1-methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



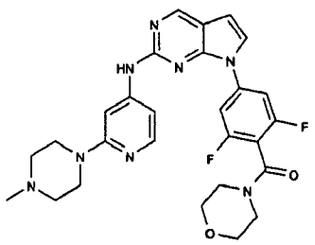
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.18 min (Method A); MS-ES: $(M+H)^+$ = 440.

Example 242: {2,6-Difluoro-4-[2-(5-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



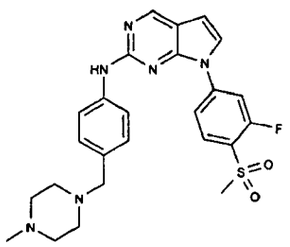
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.27 min (Method A); MS-ES: $(M+H)^+$ = 451.

Example 243: (2,6-Difluoro-4-{2-[2-(4-methyl-piperazin-1-yl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



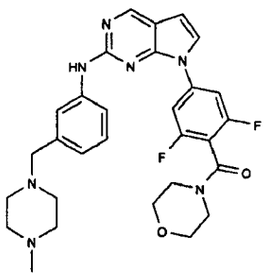
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 535.

Example 244: [7-(3-Fluoro-4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



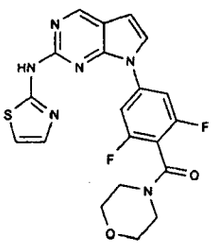
The compound is prepared analogous to Example 2. MS-ES: $(M+H)^+$ = 495.

Example 245: (2,6-Difluoro-4-{2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



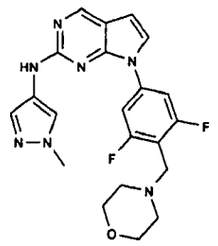
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.13 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 246: {2,6-Difluoro-4-[2-(thiazol-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



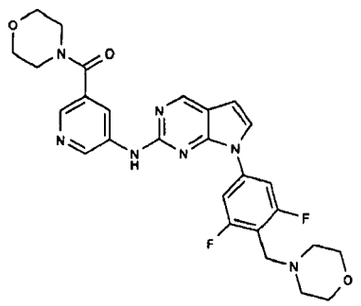
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.26 min (Method A); MS-ES: $(M+H)^+$ = 443.

Example 247: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1-methyl-1H-pyrazol-4-yl)-amine



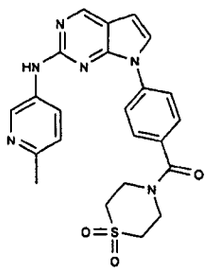
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.85 min (Method A); MS-ES: $(M+H)^+$ = 426.

Example 248: {5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-morpholin-4-yl-methanone



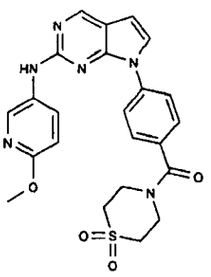
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.97 min (Method A); MS-ES: $(M+H)^+$ = 536.

Example 249: (1,1-Dioxido-thiomorpholin-4-yl)-{4-[2-(6-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone



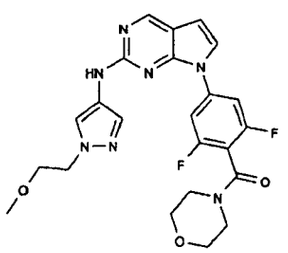
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.09 min (Method A); MS-ES: $(M+H)^+$ = 463.

Example 250: (1,1-Dioxido-thiomorpholin-4-yl)-{4-[2-(6-methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone



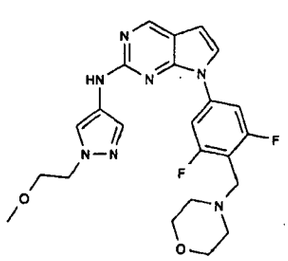
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.15 min (Method A); MS-ES: $(M+H)^+$ = 479.

Example 251: (2,6-Difluoro-4-{2-[1-(2-methoxy-ethyl)-1H-pyrazol-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



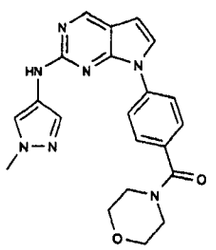
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.23 min (Method A); MS-ES: $(M+H)^+$ = 484.

Example 252: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-amine



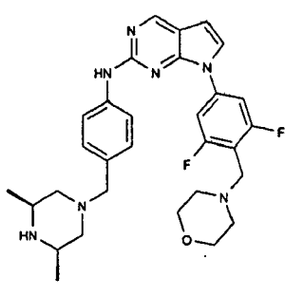
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.90 min (Method A); MS-ES: $(M+H)^+$ = 470.

Example 253: {4-[2-(1-Methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



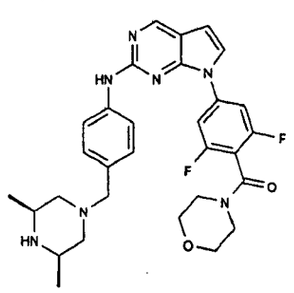
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.05 min (Method A); MS-ES: $(M+H)^+$ = 404.

Example 254: 7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine



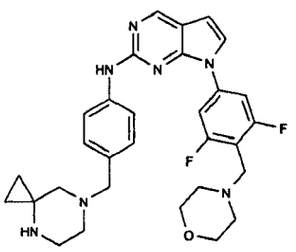
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.92 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 255: (4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone



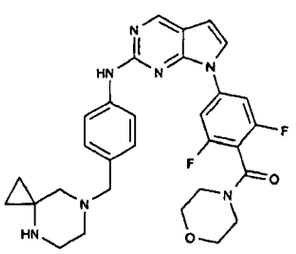
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.11 min (Method A); MS-ES: $(M+H)^+$ = 562.

Example 256: 4-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



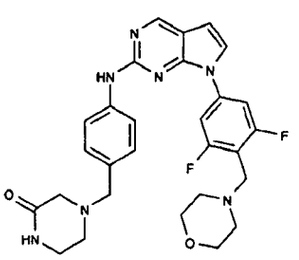
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.90 min (Method A); MS-ES: $(M+H)^+$ = 546.

Example 257: 4-{2-[4-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone



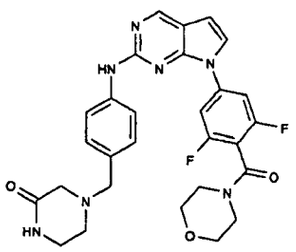
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.08 min (Method A); MS-ES: $(M+H)^+$ = 560.

Example 258: 4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-2-one



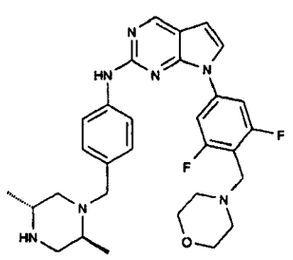
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.87 min (Method A); MS-ES: $(M+H)^+$ = 534.

Example 259: 4-(4-{7-[3,5-Difluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-2-one



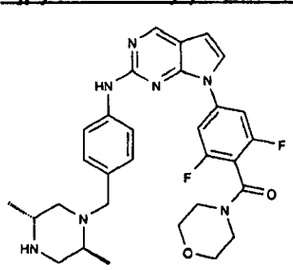
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.11 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 260: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((2S,5R)-2,5-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic)



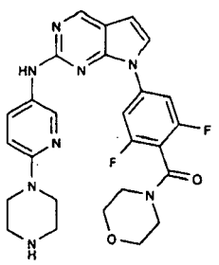
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.93 min (Method A); MS-ES: $(M+H)^+$ = 548.

Example 261: (4-{2-[4-((2S,5R)-2,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone (racemic)



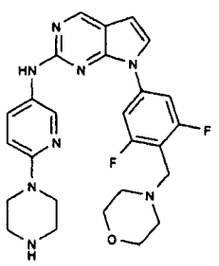
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.12 min (Method A); MS-ES: $(M+H)^+$ = 562.

Example 262: {2,6-Difluoro-4-[2-(6-piperazin-1-yl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



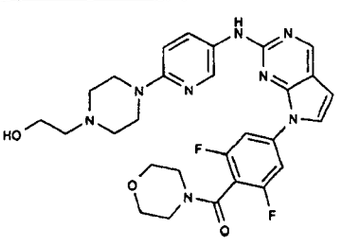
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. MS-ES: $(M+H)^+$ = 521.

Example 263: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-yl-pyridin-3-yl)-amine



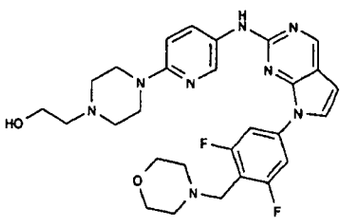
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. MS-ES: $(M+H)^+$ = 507.

Example 264: [2,6-Difluoro-4-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridin-3-ylamino}-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone



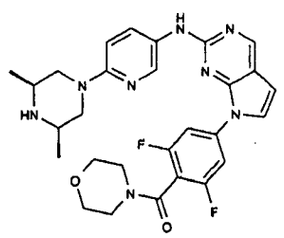
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.37 min (Method C); MS-ES: $(M+H)^+$ = 565.

Example 265: 2-(4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-1-yl)-ethanol



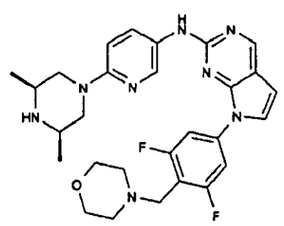
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.91 min (Method C); MS-ES: $(M+H)^+$ = 551.

Example 266: (4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone



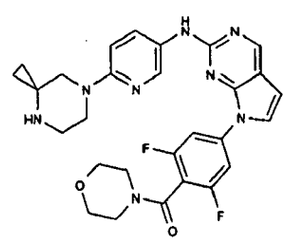
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.37 min (Method C); MS-ES: $(M+H)^+$ = 549.

Example 267: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine



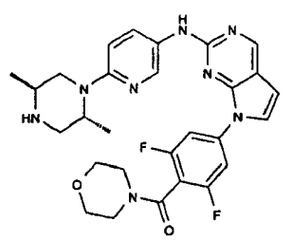
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.99 min (Method C); MS-ES: $(M+H)^+$ = 535.

Example 268: (4-{2-[6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone



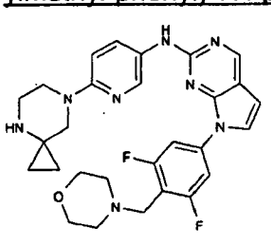
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.43 min (Method C); MS-ES: $(M+H)^+$ = 547.

Example 269: (4-{2-[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone (racemic)



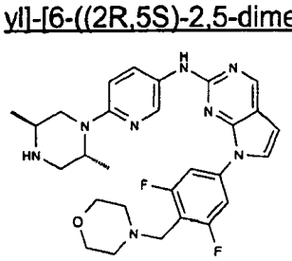
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.46 min (Method C); MS-ES: $(M+H)^+$ = 549.

Example 270: [6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



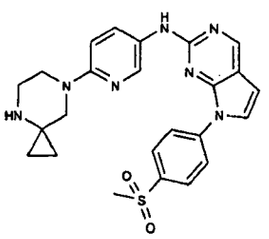
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.99 min (Method C); MS-ES: $(M+H)^+$ = 533.

Example 271: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-((2R,5S)-2,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic)



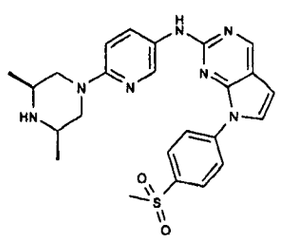
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.02 min (Method C); MS-ES: $(M+H)^+$ = 535.

Example 272: [6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



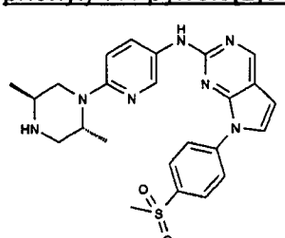
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.23 min (Method C); MS-ES: $(M+H)^+$ = 476.

Example 273: [6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



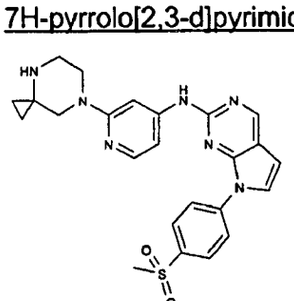
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.29 min (Method C); MS-ES: $(M+H)^+$ = 478.

Example 274: [6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (racemic)



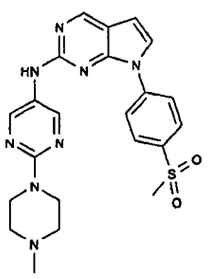
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.30 min (Method C); MS-ES: $(M+H)^+$ = 478.

Example 275: [2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



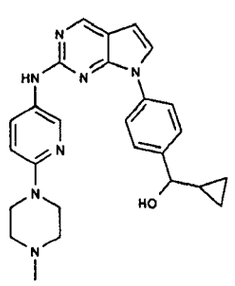
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.43 min (Method C); MS-ES: $(M+H)^+$ = 476.

Example 276: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-amine



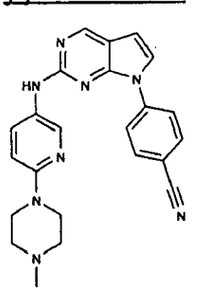
The compound is prepared analogous to Example 2. MS-ES: $(M+H)^+$ = 465.

Example 277: Cyclopropyl-(4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanol



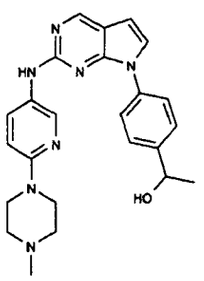
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 3.20 min (Method D); MS-ES: $(M+H)^+$ = 456.

Example 278: 4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile



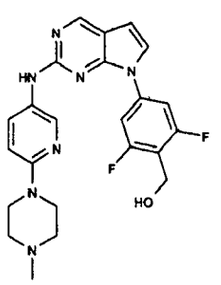
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 3.21 min (Method D); MS-ES: $(M+H)^+$ = 411.

Example 279: 1-(4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-ethanol



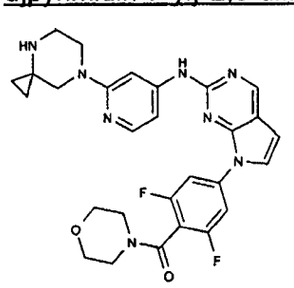
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 2.80 min (Method D); MS-ES: $(M+H)^+$ = 430.

Example 280: (2,6-Difluoro-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanol



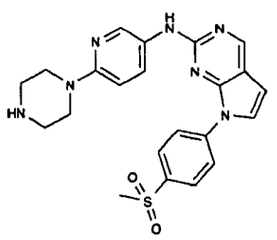
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 2.83 min (Method D); MS-ES: $(M+H)^+$ = 452.

Example 281: (4-{2-[2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone



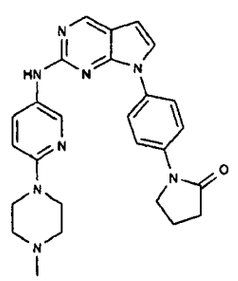
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.61 min (Method C); MS-ES: $(M+H)^+$ = 547.

Example 282: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-yl-pyridin-3-yl)-amine



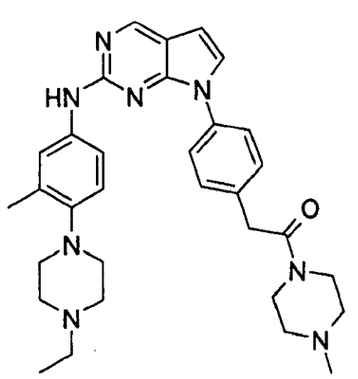
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4N HCl in dioxan at rt. HPLC: $t_R$ = 4.19 min (Method C); MS-ES: $(M+H)^+$ = 450.

Example 283: 1-(4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-pyrrolidin-2-one



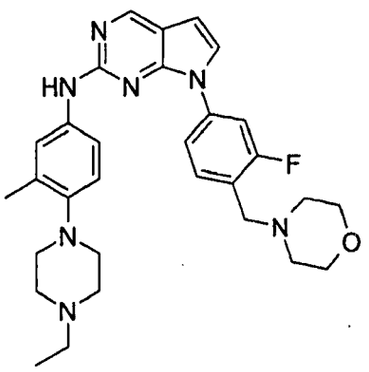
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 3.03 min (Method D); MS-ES: $(M+H)^+$ = 469.

Example 284: 2-(4-{2-[4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-1-(4-methyl-piperazin-1-yl)-ethanone



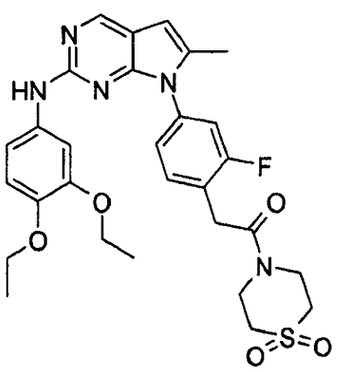
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 6.74 min (Method B); MS-ES: $(M+H)^+$ = 553; TLC**: $R_f$ = 0.10

Example 285: [4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenyl]-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



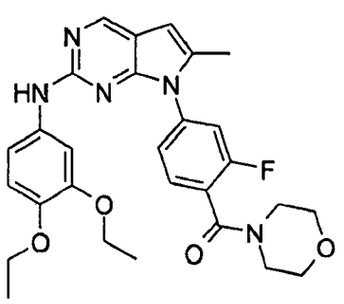
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 6.75 min. (Method B); MS-ES: $(M+H)^+$ = 530; TLC**: $R_f$ = 0.21

Example 286: 2-{4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone



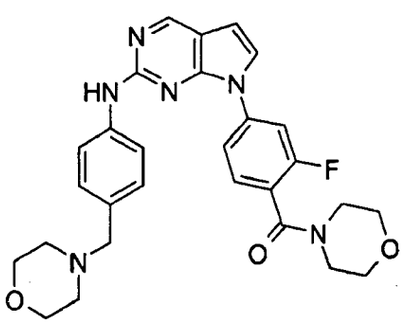
The compound is prepared analogous to Example 3. But instead of using 2-cloro-7H-pyrrolo[2,3-d]pyrimidine, 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine is used in the first step. This starting material is obtained by using tributyl-(1-propynyl)tin in the Stille coupling in the synthesis for the pyrrolopyrimidine as exemplified in the reaction scheme of Example 1. HPLC: $t_R$ = 8.46 min. (Method B); MS-ES: $(M+H)^+$ = 582; TLC**: $R_f$ = 0.51

Example 287: {4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



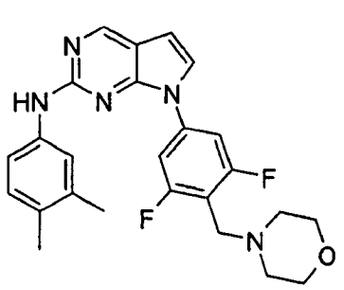
The compound is prepared analogous to Example 3. But instead of using 2-cloro-7H-pyrrolo[2,3-d]pyrimidine, 2-chloro-6-methyl-7H-pyrrolo[2,3-d]pyrimidine is used in the first step. This starting material is obtained by using tributyl-(1-propynyl)tin in the Stille coupling in the synthesis for the pyrrolopyrimidine as exemplified in the reaction scheme of Example 1. HPLC: $t_R$ = 8.59 min. (Method B); MS-ES: $(M+H)^+$ = 520; TLC‡: $R_f$ = 0.22

Example 288: {2-Fluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



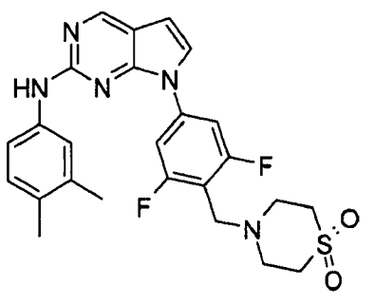
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.22 min. (Method B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$ = 0.37

Example 289: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4-dimethyl-phenyl)-amine



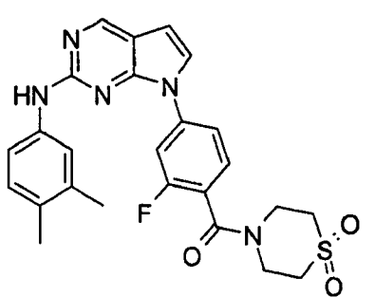
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.85 min. (Method B); MS-ES: $(M+H)^+$ = 450; TLC‡: $R_f$ = 0.41

Example 290: (3,4-Dimethyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



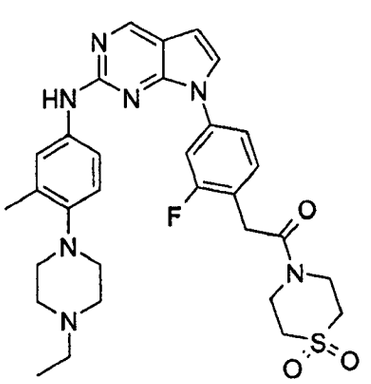
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.88 min. (Method B); MS-ES: $(M+H)^+$ = 498; TLC‡: $R_f$ = 0.32

Example 291: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-(1,1-dioxido-thiomorpholin-4-yl)-methanone



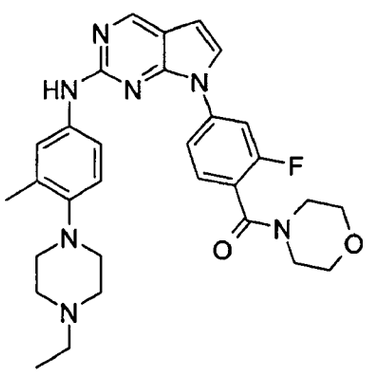
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.49 min. (Method B); MS-ES: $(M+H)^+$ = 494; TLC‡: $R_f$ = 0.28

Example 292: 1-(1,1-Dioxido-thiomorpholin-4-yl)-2-(4-{2-[4-(4-ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-ethanone



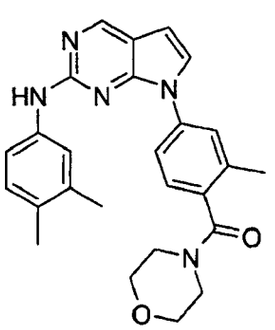
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.37 min. (Method B); MS-ES: $(M+H)^+$ = 606; TLC**: $R_f$ = 0.34

Example 293: (4-{2-[4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



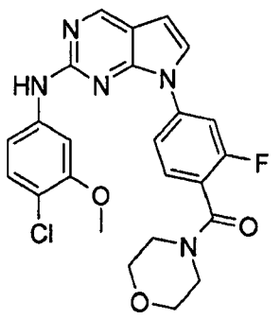
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.47 min. (Method B); MS-ES: $(M+H)^+$ = 544; TLC**: $R_f$ = 0.35

Example 294: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



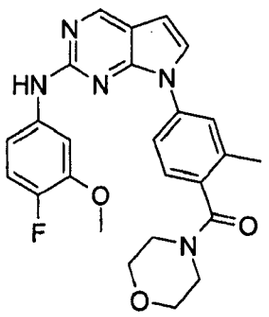
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.66 min. (Method B); MS-ES: $(M+H)^+$ = 442; TLC**: $R_f$ = 0.48

Example 295: {4-[2-(4-Chloro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



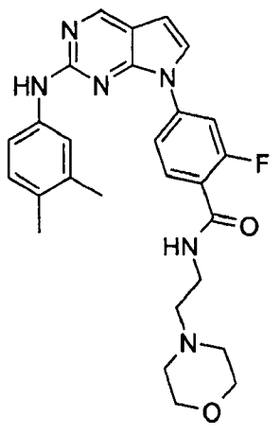
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.95 min. (Method B); MS-ES: $(M+H)^+$ = 482; TLC**: $R_f$ = 0.46

Example 296: {4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone



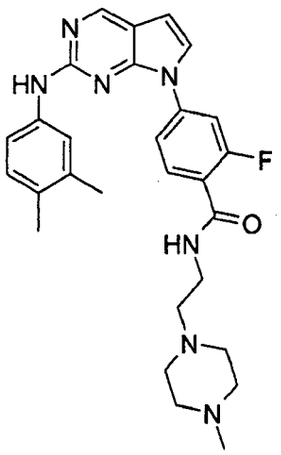
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.29 min. (Method B); MS-ES: $(M+H)^+$ = 462; TLC**: $R_f$ = 0.25

Example 297: 4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-N-(2-morpholin-4-yl-ethyl)-benzamide



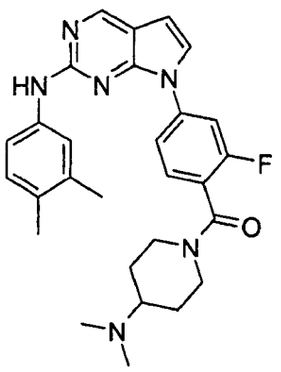
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.71 min. (Method B); MS-ES: $(M+H)^+$ = 489; TLC**: $R_f$ = 0.33

Example 298: 4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-N-[2-(4-methyl-piperazin-1-yl)-ethyl]-benzamide



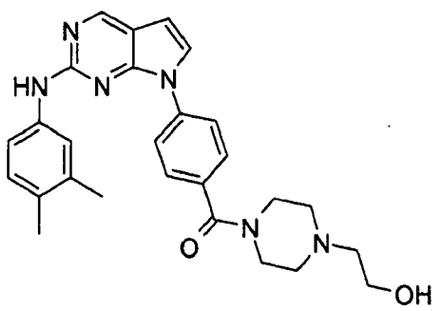
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.37 min. (Method B); MS-ES: $(M+H)^+$ = 502; TLC*: $R_f$ = 0.24

Example 299: (4-Dimethylamino-piperidin-1-yl)-{4-[2-(3,4-dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-methanone



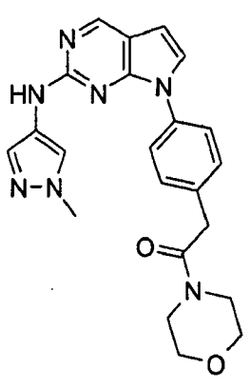
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.67 min. (Method B); MS-ES: $(M+H)^+$ = 487; TLC*: $R_f$ = 0.30

Example 300: {4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone



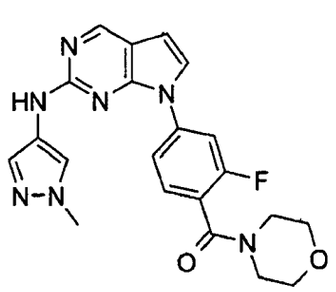
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.27 min. (Method B); MS-ES: $(M+H)^+$ = 471; TLC*: $R_f$ = 0.50

Example 301: 2-{4-[2-(1-Methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone



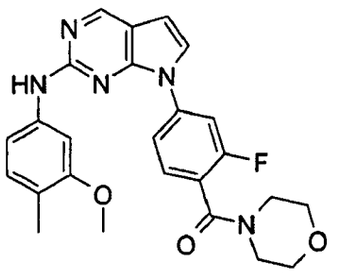
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.25 min. (Method B); MS-ES: $(M+H)^+$ = 418; TLC*: $R_f$ = 0.55

Example 302: {2-Fluoro-4-[2-(1-methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



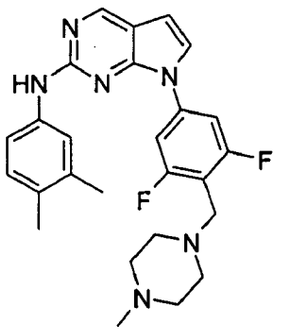
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.23 min. (Method B); MS-ES: $(M+H)^+$ = 422; TLC*: $R_f$ = 0.50

Example 303: {2-Fluoro-4-[2-(3-methoxy-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



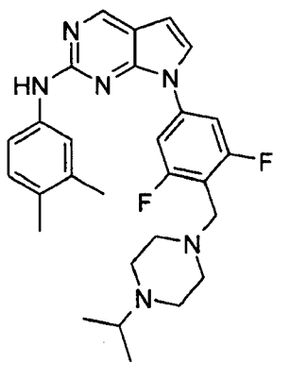
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.67 min. (Method B); MS-ES: $(M+H)^+$ = 462; TLC*: $R_f$ = 0.59

Example 304: {7-[3,5-Difluoro-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine



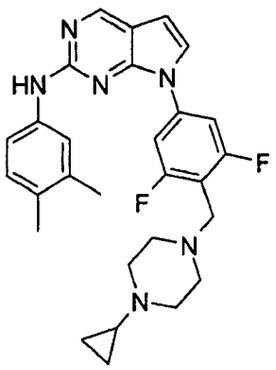
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.97 min. (Method B); MS-ES: $(M+H)^+$ = 463; TLC**: $R_f$ = 0.17

Example 305: {7-[3,5-Difluoro-4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine



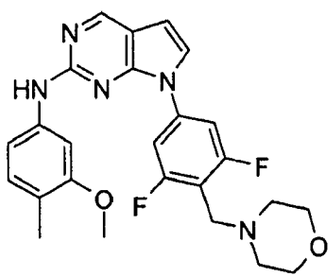
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.15 min. (Method B); MS-ES: $(M+H)^+$ = 491; TLC**: $R_f$ = 0.32

Example 306: {7-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine



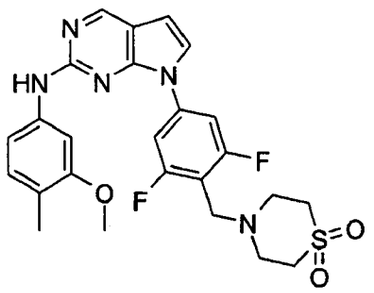
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.50 min. (Method B); MS-ES: $(M+H)^+$ = 489; TLC**: $R_f$ = 0.50

Example 307: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methoxy-4-methyl-phenyl)-amine



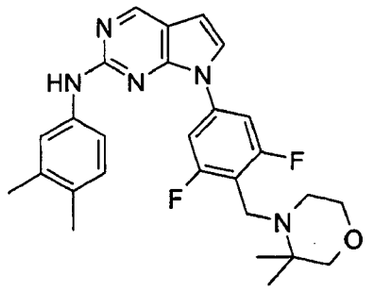
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.80 min. (Method B); MS-ES: $(M+H)^+$ = 466; TLC*: $R_f$ = 0.77

Example 308: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3-methoxy-4-methyl-phenyl)-amine



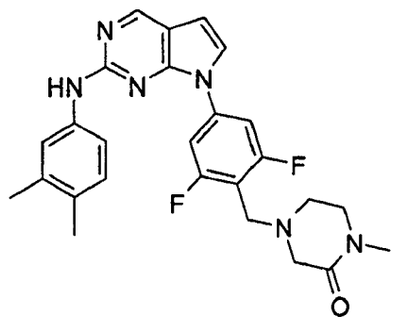
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.81 min. (Method B); MS-ES: $(M+H)^+$ = 514; TLC*: $R_f$ = 0.67

Example 309: {7-[4-(3,3-Dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine



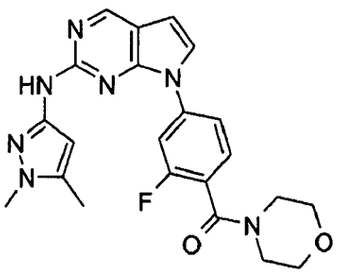
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.23 min. (Method B); MS-ES: $(M+H)^+$ = 478; TLC*: $R_f$ = 0.80

Example 310: 4-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-benzyl}-1-methyl-piperazin-2-one



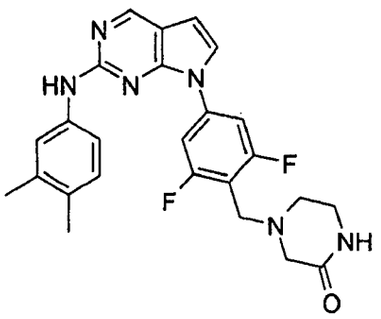
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.05 min. (Method B); MS-ES: $(M+H)^+$ = 477; TLC*: $R_f$ = 0.67

Example 311: {4-[2-(1,5-Dimethyl-1H-pyrazol-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone



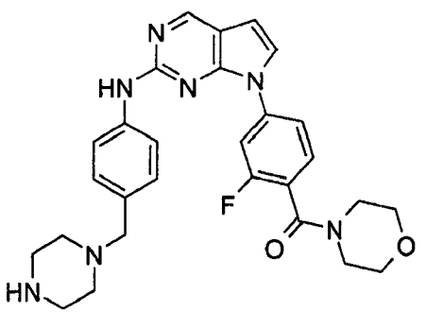
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.94 min. (Method B); MS-ES: $(M+H)^+$ = 436; TLC*: $R_f$ = 0.37

Example 312: 4-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-benzyl}-piperazin-2-one



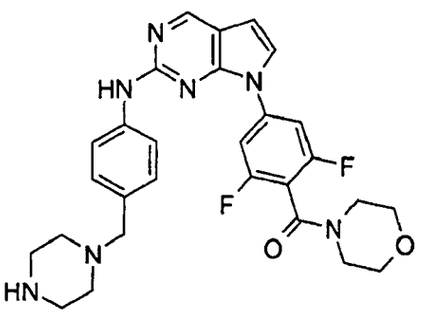
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.81 min. (Method B); MS-ES: $(M+H)^+$ = 463; TLC*: $R_f$ = 0.61

Example 313: {2-Fluoro-4-[2-(4-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



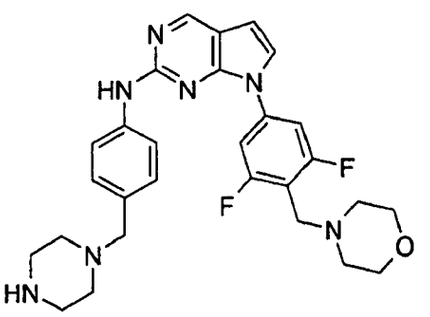
The compound is prepared analogous to Example 2. The final product is obtained by cleaving the Boc-protecting group under acidic conditions (4 M HCl in dioxane). HPLC: $t_R$ = 6.83 min. (Method B); MS-ES: $(M+H)^+$ = 516

Example 314: {2,6-Difluoro-4-[2-(4-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



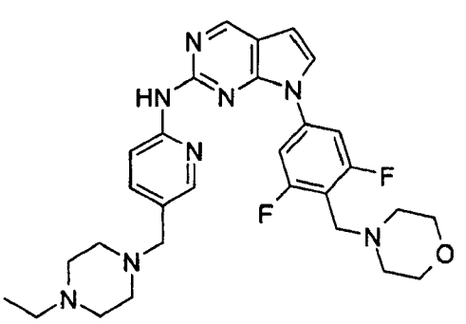
The compound is prepared analogous to Example 2. The final product is obtained by cleaving the Boc-protecting group under acidic conditions (4 M HCl in dioxane). HPLC: $t_R$ = 7.00 min. (Method B); MS-ES: $(M+H)^+$ = 534

Example 315: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-ylmethyl-phenyl)-amine



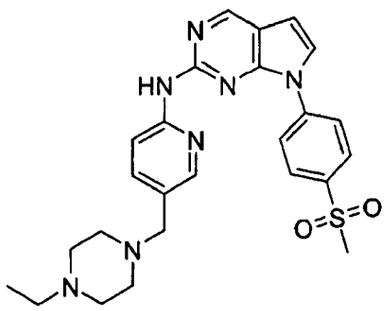
The compound is prepared analogous to Example 2. The final product is obtained by cleaving the Boc-protecting group under acidic conditions (4 M HCl in dioxane). HPLC: $t_R$ = 6.60 min. (Method B); MS-ES: $(M+H)^+$ = 520

Example 316: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine



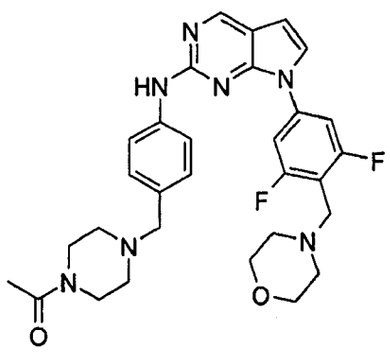
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.42 min. (Method B); MS-ES: $(M+H)^+$ = 549; TLC*: $R_f$ = 0.11

Example 317: [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



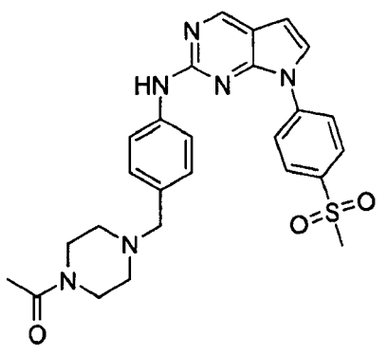
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.91 min. (Method B); MS-ES: $(M+H)^+$ = 492

Example 318: 1-(4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-1-yl)-ethanone



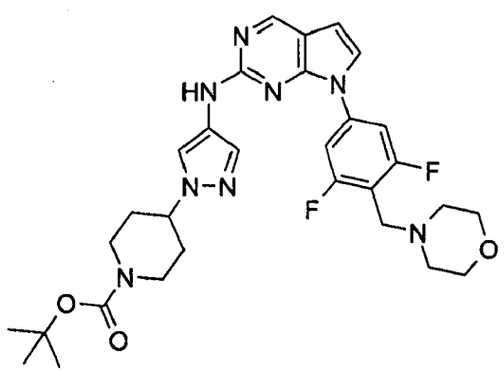
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.61 min. (Method B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.25

Example 319: 1-(4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-1-yl)-ethanone



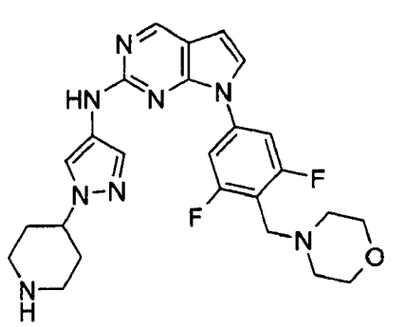
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.01 min. (Method B); MS-ES: $(M+H)^+$ = 505; TLC*: $R_f$ = 0.21

Example 320: 4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester



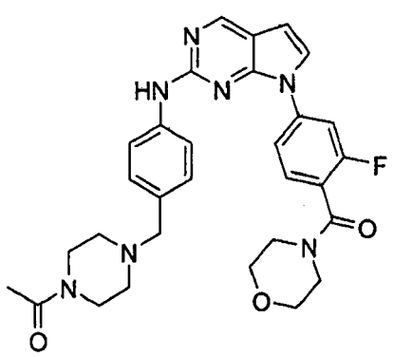
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.04 min. (Method B); MS-ES: $(M+H)^+$ = 595; TLC*: $R_f$ = 0.43

Example 321: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1-piperidin-4-yl-1H-pyrazol-4-yl)-amine



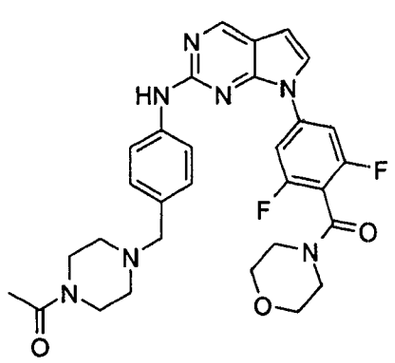
The compound is prepared from Example 320 by cleaving the Boc-protecting group under acidic conditions (4 M HCl in dioxane). HPLC: $t_R$ = 6.13 min. (Method B); MS-ES: $(M+H)^+$ = 495

Example 322: 1-[4-(4-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone



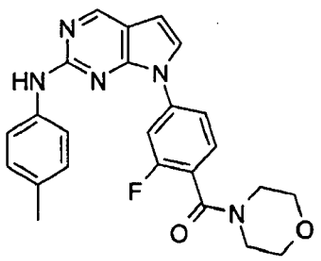
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.23 min. (Method B); MS-ES: $(M+H)^+$ = 558; TLC*: $R_f$ = 0.25

Example 323: 1-[4-(4-{7-[3,5-Difluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone



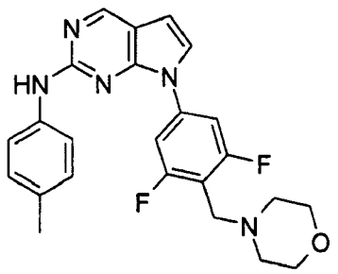
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.46 min. (Method B); MS-ES: $(M+H)^+$ = 576; TLC*: $R_f$ = 0.18

Example 324: [2-Fluoro-4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone



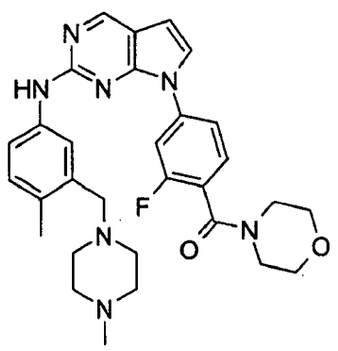
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 8.47 min. (Method B); MS-ES: $(M+H)^+$ = 432

Example 325: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine



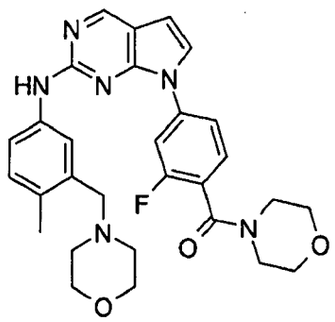
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 7.60 min. (Method B); MS-ES: $(M+H)^+$ = 436; TLC*: $R_f$ = 0.77

Example 326: (2-Fluoro-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



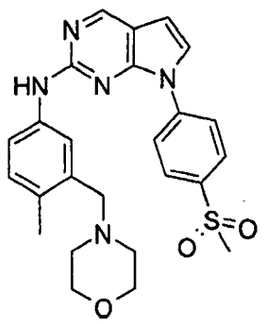
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.30 min. (Method B); MS-ES: $(M+H)^+$ = 544; TLC*: $R_f$ = 0.35

Example 327: {2-Fluoro-4-[2-(4-methyl-3-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



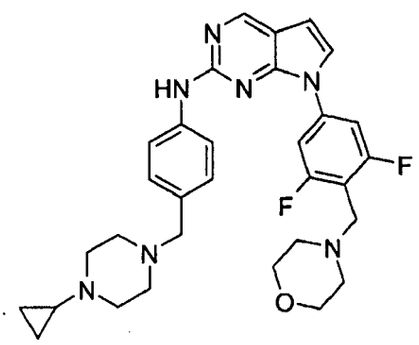
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.44 min. (Method B); MS-ES: $(M+H)^+$ = 531; TLC*: $R_f$ = 0.48

Example 328: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-morpholin-4-ylmethyl-phenyl)-amine



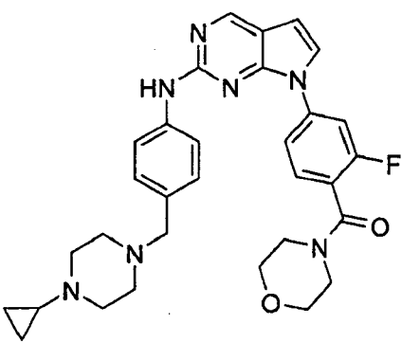
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.32 min. (Method B); MS-ES: $(M+H)^+$ = 478; TLC*: $R_f$ = 0.56

Example 329: [4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



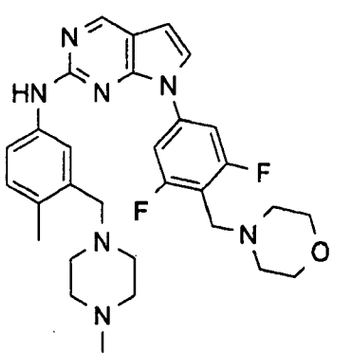
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.75 min. (Method B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.23

Example 330: (4-{2-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



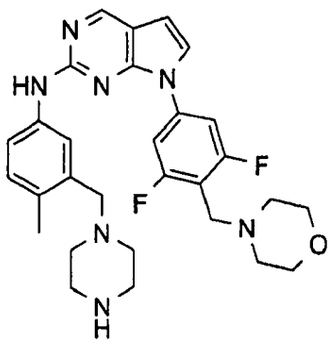
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.16 min. (Method B); MS-ES: $(M+H)^+$ = 556; TLC*: $R_f$ = 0.30

Example 331: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



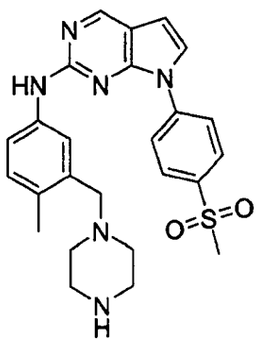
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.72 min. (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.35

Example 332: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine



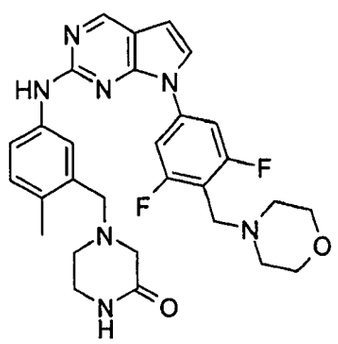
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.45 min. (Method B); MS-ES: $(M+H)^+$ = 534

Example 333: [7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine



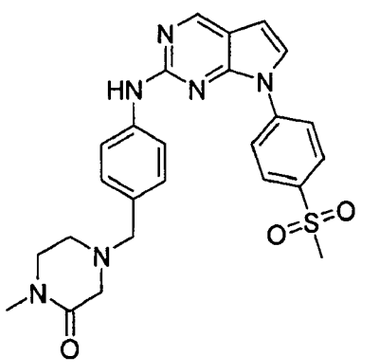
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.90 min. (Method B); MS-ES: $(M+H)^+$ = 477

Example 334: 4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d] pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazin-2-one



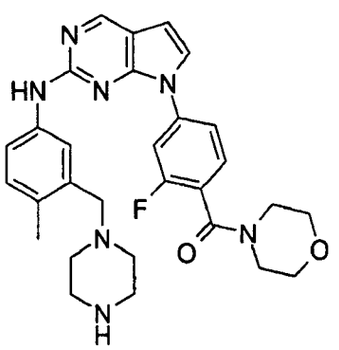
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.55 min. (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.39

Example 335: 4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-1-methyl-piperazin-2-one



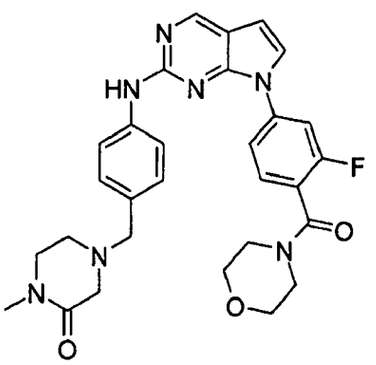
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.04 min. (Method B); MS-ES: $(M+H)^+$ = 491; TLC**: $R_f$ = 0.10

Example 336: {2-Fluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



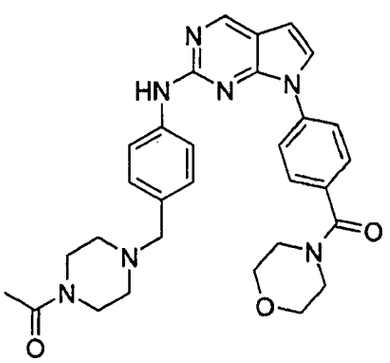
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 7.10 min. (Method B); MS-ES: $(M+H)^+$ = 530

Example 337: 4-(4-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-1-methyl-piperazin-2-one



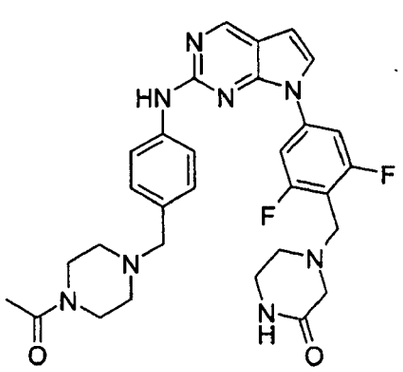
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.19 min. (Method B); MS-ES: $(M+H)^+$ = 544; TLC*: $R_f$ = 0.27

Example 338: 1-[4-(4-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone



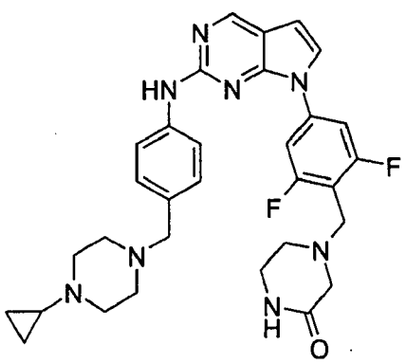
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.02 min. (Method B); MS-ES: $(M+H)^+$ = 540; TLC*: $R_f$ = 0.24

Example 339: 4-(4-{2-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one



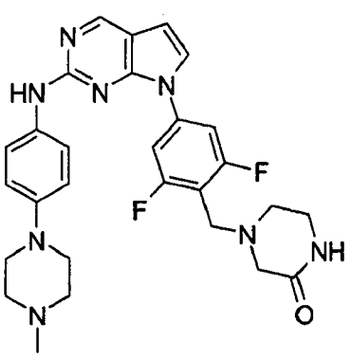
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.70 min. (Method B); MS-ES: $(M+H)^+$ = 575; TLC*: $R_f$ = 0.15

Example 340: 4-(4-{2-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one



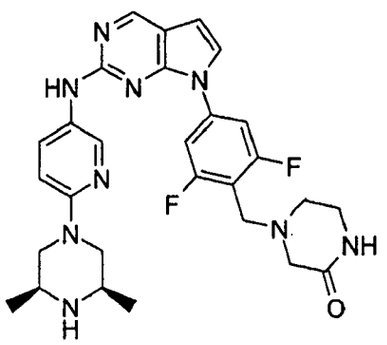
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.76 min. (Method B); MS-ES: $(M+H)^+$ = 573; TLC*: $R_f$ = 0.15

Example 341: 4-(2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzyl)-piperazin-2-one



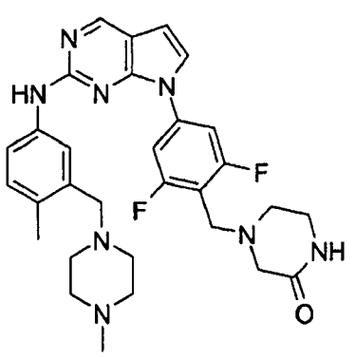
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.47 min. (Method B); MS-ES: $(M+H)^+$ = 533

Example 342: 4-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one



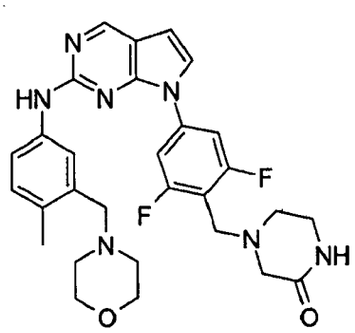
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.42 min. (Method B); MS-ES: $(M+H)^+$ = 548

Example 343: 4-(2,6-Difluoro-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzyl)-piperazin-2-one



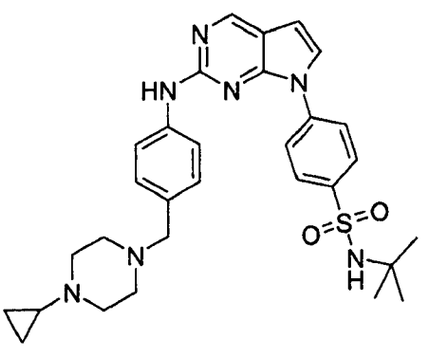
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.77 min. (Method B); MS-ES: $(M+H)^+$ = 561; TLC*: $R_f$ = 0.18

Example 344: 4-{2,6-Difluoro-4-[2-(4-methyl-3-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-2-one



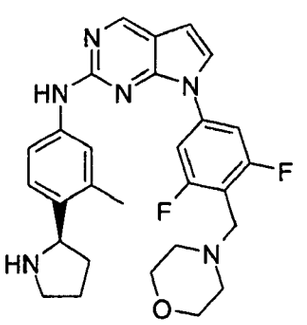
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.88 min. (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.35

Example 345: N-tert-Butyl-4-{2-[4-(4-cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



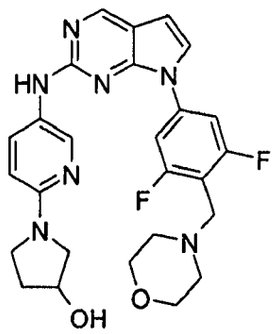
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.02 min. (Method B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.18

Example 346: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((R)-3-methyl-4-pyrrolidin-2-yl-phenyl)-amine



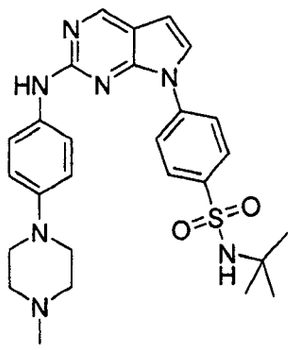
The compound is prepared analogous to Example 2. The corresponding Boc-protected aniline is obtained from the procedure described in the *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539 starting from 4-bromo-3-methyl-phenylamine. HPLC: $t_R$ = 0.58 min (Method G); MS-ES: $(M+H)^+$ = 505

Example 347: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-pyrrolidin-3-ol (racemic)



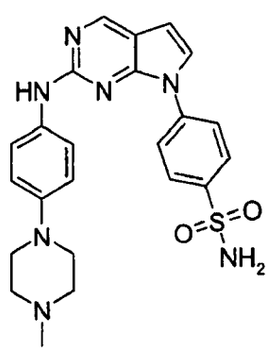
The compound is prepared analogous to Example 2, using a TBDPS-protected alcohol derivative in Step 2.2. Final deprotection is achieved with 1 M TBAF in THF at rt. HPLC: $t_R$ = 0.57 min (Method G); MS-ES: $(M+H)^+$ = 508

Example 348: N-tert-Butyl-4-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



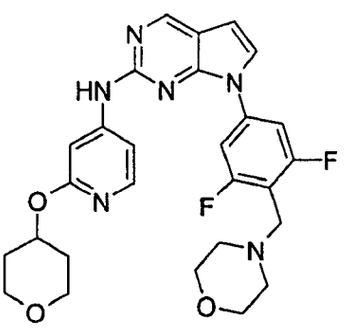
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.82 min. (Method B); MS-ES: $(M+H)^+$ = 520; TLC*: $R_f$ = 0.12

Example 349: 4-{2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



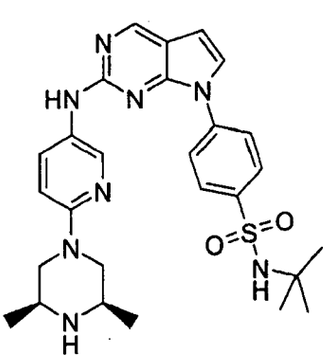
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.71 min. (Method B); MS-ES: $(M+H)^+$ = 464; TLC*: $R_f$ = 0.03

Example 350: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(tetrahydro-pyran-4-yloxy)-pyridin-4-yl]-amine



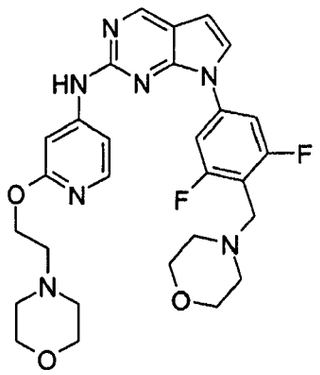
The compound is prepared analogous to 2. HPLC: $t_R$ = 0.67 min (Method G); MS-ES: $(M+H)^+$ = 523

Example 351: N-tert-Butyl-4-{2-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



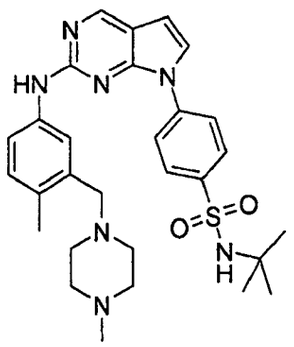
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.77 min. (Method B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.05

Example 352: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-yl]-amine



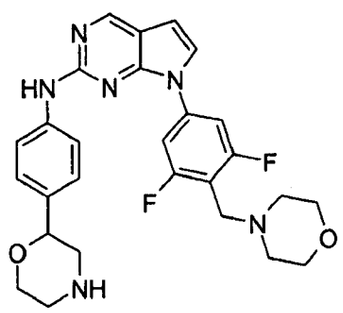
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.58 min (Method G); MS-ES: $(M+H)^+$ = 552

Example 353: N-tert-Butyl-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



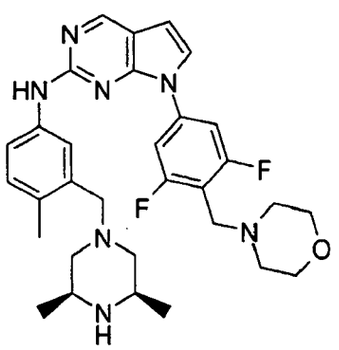
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.07 min. (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.22

Example 354: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-2-yl-phenyl)-amine (racemic)



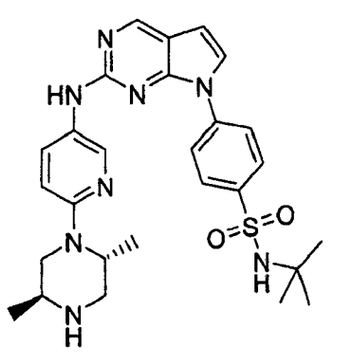
The compound is prepared analogous to Example 2, using a Boc-protected morpholine derivative in Step 2.2. Final deprotection is achieved with 1 M HCl in EtOH at 60 °C. HPLC: $t_R$ = 0.59 min (Method G); MS-ES: $(M+H)^+$ = 507

Example 355: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine



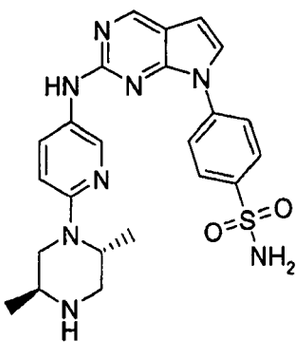
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.73 min. (Method B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.22

Example 356: N-tert-Butyl-4-{2-[6-((2R,5S)-2,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide (racemic)



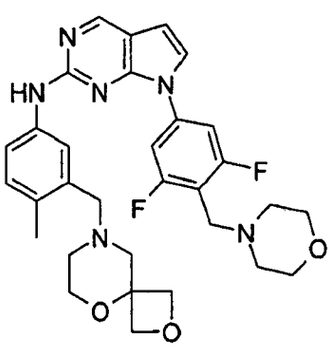
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.77 min. (Method B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.04

Example 357: 4-{2-[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide (racemic)



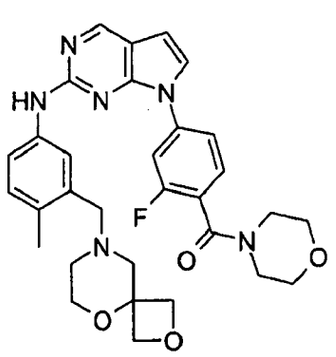
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.64 min. (Method B); MS-ES: $(M+H)^+$ = 479; TLC*: $R_f$ = 0.14

Example 358: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(2,5-dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-4-methyl-phenyl]-amine



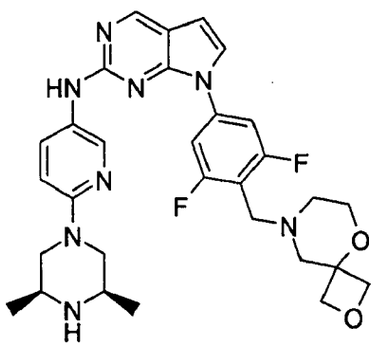
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.93 min. (Method B); MS-ES: $(M+H)^+$ = 577; TLC*: $R_f$ = 0.58

Example 359: (4-{2-[3-(2,5-Dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



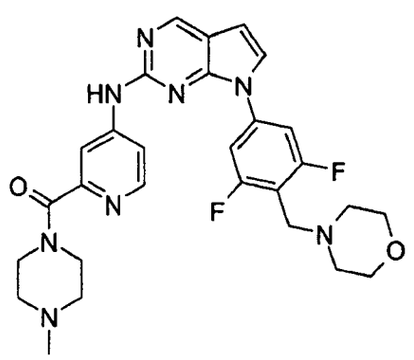
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.60 min. (Method B); MS-ES: $(M+H)^+$ = 573; TLC*: $R_f$ = 0.51

Example 360: [6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(2,5-dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



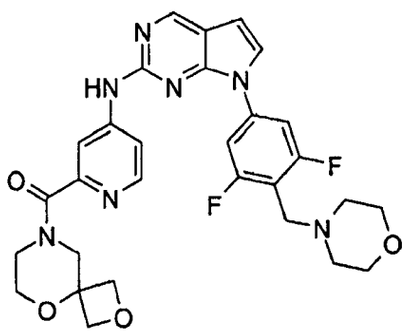
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.65 min. (Method B); MS-ES: $(M+H)^+$ = 577; TLC (15% methanol / 85% methylene chloride): $R_f$ = 0.16

Example 361: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(4-methyl-piperazin-1-yl)-methanone



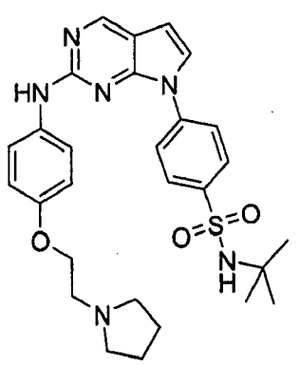
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.47 min. (Method B); MS-ES: $(M+H)^+$ = 549; TLC (15% methanol / 85% methylene chloride): $R_f$ = 0.15

Example 362: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(2,5-dioxa-8-aza-spiro[3.5]non-8-yl)-methanone



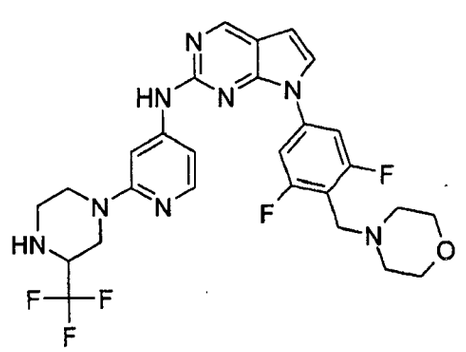
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.95 min. (Method B); MS-ES: $(M+H)^+$ = 578; TLC (15% methanol / 85% methylene chloride): $R_f$ = 0.47

Example 363: N-tert-Butyl-4-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



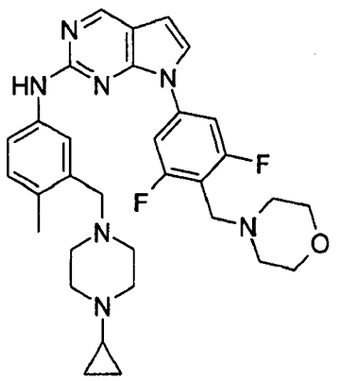
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.03 min. (Method B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.10

Example 364: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-trifluoromethyl-piperazin-1-yl)-pyridin-4-yl]-amine (racemic)



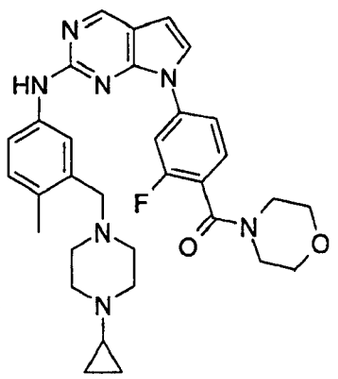
The compound is prepared analogous to Example 2. HPLC (racemic mixture): $t_R$ = 3.62 min and 4.37 min (Method C); MS-ES: $(M+H)^+$ = 575

Example 365: [3-(4-Cyclopropyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



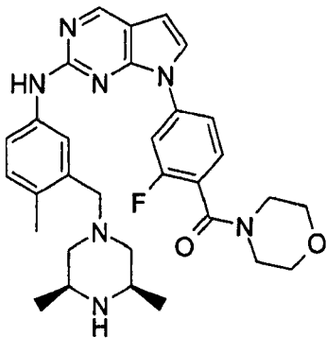
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.94 min. (Method B); MS-ES: $(M+H)^+$ = 574; TLC*: $R_f$ = 0.38

Example 366: (4-{2-[3-(4-Cyclopropyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



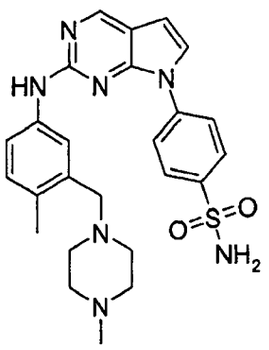
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.62 min. (Method B); MS-ES: $(M+H)^+$ = 570; TLC*: $R_f$ = 0.55

Example 367: (4-{2-[3-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



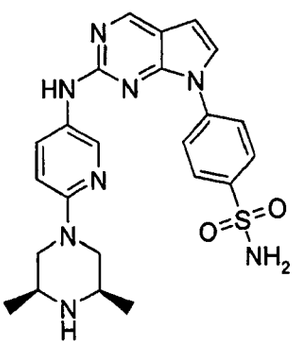
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.41 min (Method B); MS-ES: $(M+H)^+$ = 558

Example 368: 4-{2-[4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



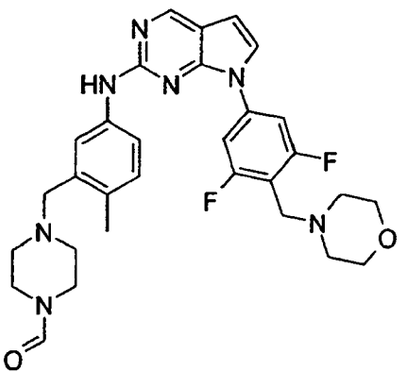
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.84 min (Method B); MS-ES: $(M+H)^+$ = 492; TLC*: $R_f$ = 0.03

Example 369: 4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



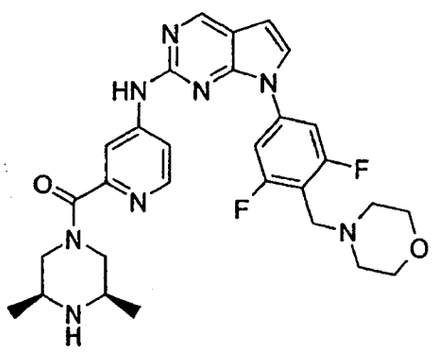
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.67 min (Method B); MS-ES: $(M+H)^+$ = 479; TLC (50% methanol / 50% methylene chloride): $R_f$ = 0.26

Example 370: 4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d] pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazine-1-carbaldehyde



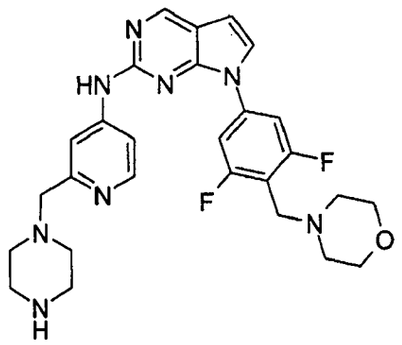
The compound is obtained by treating [7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine (Example 332) with formic acid 4-nitro-phenyl ester in presence of triethylamine in THF. HPLC: $t_R$ = 6.84 min (Method B); MS-ES: $(M+H)^+$ = 562

Example 371: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone



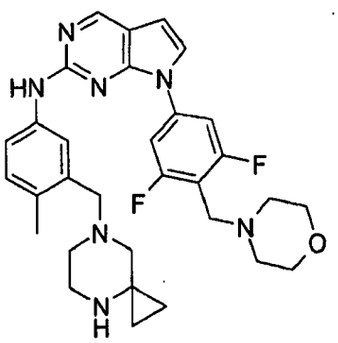
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.53 min (Method B); MS-ES: $(M+H)^+$ = 563; TLC (15% methanol / 85% methylene chloride): $R_f$ = 0.28

Example 372: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2-piperazin-1-ylmethyl-pyridin-4-yl)-amine



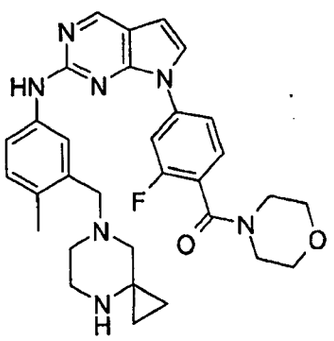
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.52 min (Method B); MS-ES: $(M+H)^+$ = 521; TLC (64% methanol / 32% methylene chloride / 4% aq. ammonia 24% ): $R_f$ = 0.49

Example 373: [3-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



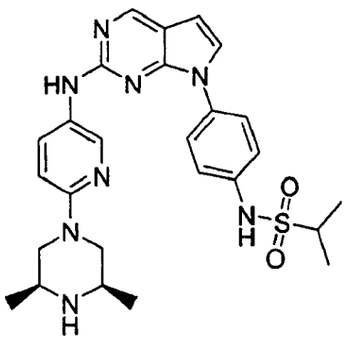
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.62 min (Method B); MS-ES: $(M+H)^+$ = 560

Example 374: (4-{2-[3-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



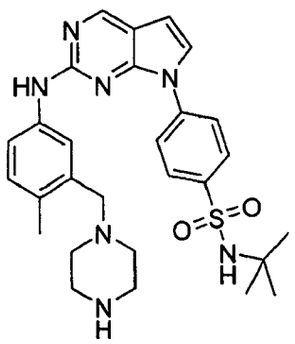
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.33 min (Method B); MS-ES: $(M+H)^+$ = 556

Example 375: Propane-2-sulfonic acid (4-{2-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-amide



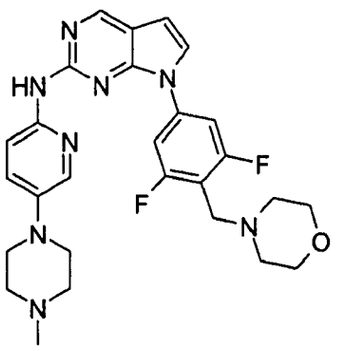
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.26 min (Method B); MS-ES: $(M+H)^+$ = 521; TLC (50% methanol / 50% methylene chloride): $R_f$ = 0.30

Example 376: N-tert-Butyl-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide



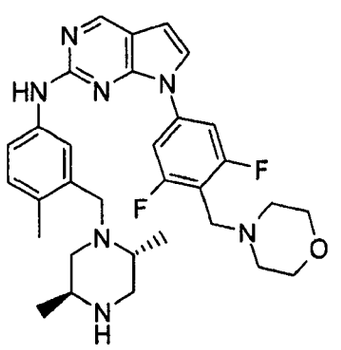
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 7.86 min (Method B); MS-ES: $(M+H)^+$ = 534; TLC (50% methanol / 50% methylene chloride): $R_f$ = 0.09

Example 377: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine



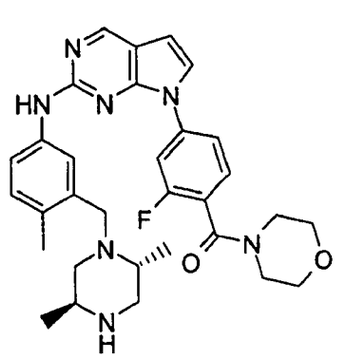
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.90 min (Method C); MS-ES: $(M+H)^+$ = 521

Example 378: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-((2R,5S)-2,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic)



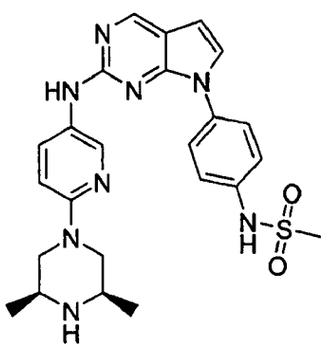
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.73 min (Method B); MS-ES: $(M+H)^+$ = 562; TLC (100% methanol): $R_f$ = 0.11

Example 379: (4-{2-[3-((2R,5S)-2,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone (racemic)



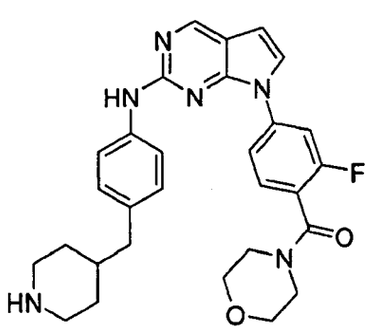
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.38 min (Method B); MS-ES: $(M+H)^+$ = 558; TLC (100% methanol): $R_f$ = 0.12

Example 380: N-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanesulfonamide



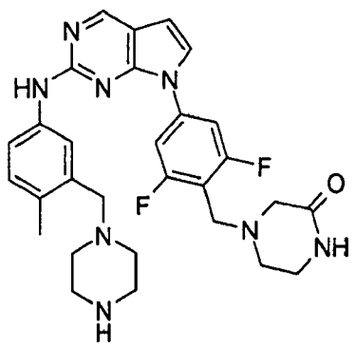
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.89 min (Method B); MS-ES: $(M+H)^+$ = 493; TLC (50% methanol / 50% methylene chloride): $R_f$ = 0.25

Example 381: {2-Fluoro-4-[2-(4-piperidin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



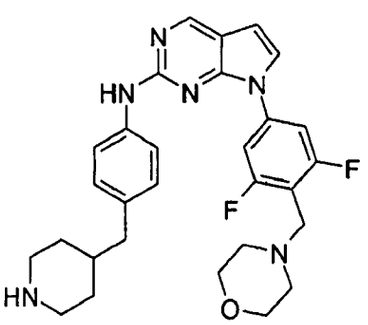
The compound is prepared analogous to Example 2, using a trifluoroacetyl-protected piperidine derivative in Step 2.2. Final deprotection is achieved with $K_2CO_3$ in methanol / water at rt. The corresponding aniline is obtained by the procedure described in patent WO98/05292 p.104-105 compound (111), followed by nitro reduction. HPLC: $t_R$ = 7.52 min (Method B); MS-ES: $(M+H)^+$ = 515; TLC (50% methanol / 50% methylene chloride): $R_f$ = 0.06

Example 382: 4-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-2-one



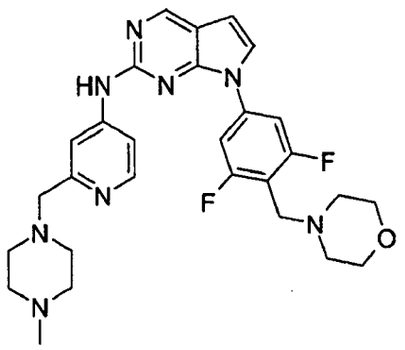
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.64 min (Method B); MS-ES: $(M+H)^+$ = 547

Example 383: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperidin-4-ylmethyl-phenyl)-amine



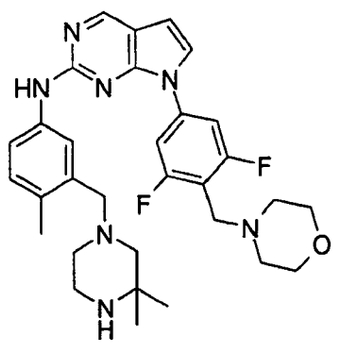
The compound is prepared analogous to Example 2, using a trifluoroacetyl-protected piperidine derivative in Step 2.2. Final deprotection is achieved with $K_2CO_3$ in methanol / water at rt. The corresponding aniline is obtained by the procedure described in patent WO98/05292 p.104-105 compound (111), followed by nitro reduction. HPLC: $t_R$ = 6.93 min (Method B); MS-ES: $(M+H)^+$ = 519; TLC (49% methanol / 49% methylene chloride / 2% 7N ammonia in methanol): $R_f$ = 0.06

Example 384: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine



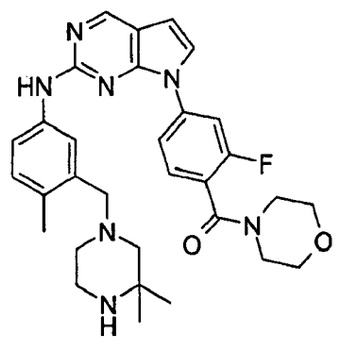
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.57 min (Method B); MS-ES: $(M+H)^+$ = 535

Example 385: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3,3-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine



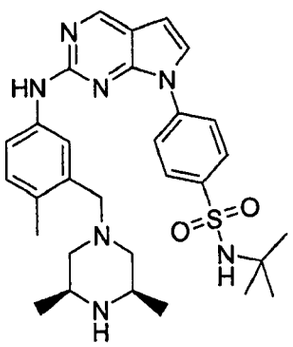
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.03 min (Method B); MS-ES: $(M+H)^+$ = 562

Example 386: (4-{2-[3-(3,3-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



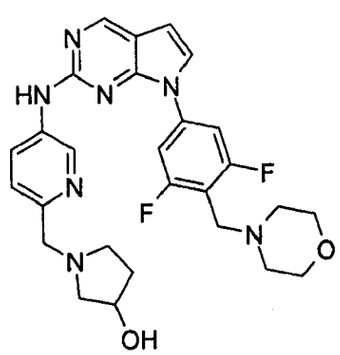
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.82 min (Method B); MS-ES: $(M+H)^+$ = 558

Example 387: N-tert-Butyl-4-{2-[3-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



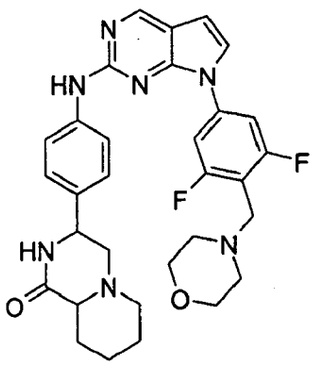
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.06 min (Method B); MS-ES: $(M+H)^+$ = 562; TLC (33% methanol / 67% methylene chloride): $R_f$ = 0.23

Example 388: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d] pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-pyrrolidin-3-ol (racemic)



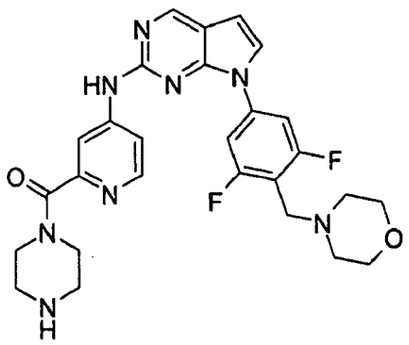
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.00 min (Method C); MS-ES: $(M)^+$ = 521

Example 389: 3-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d] pyrimidin-2-ylamino]-phenyl}-hexahydro-pyrido[1,2-a]pyrazin-1-one



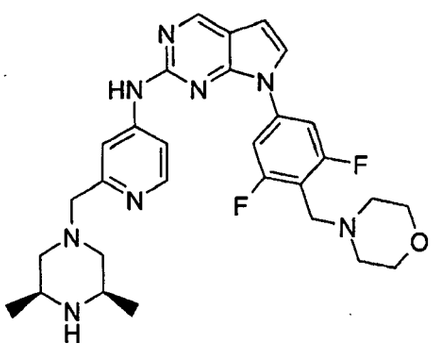
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.60 min (Method G); MS-ES: $(M+H)^+$ = 574

Example 390: {4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-1-yl-methanone



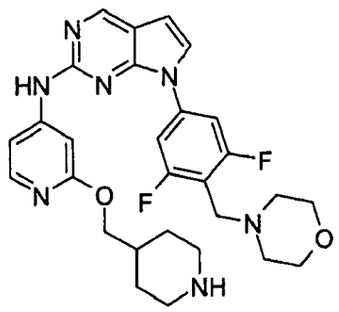
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.37 min (Method B); MS-ES: $(M+H)^+$ = 535

Example 391: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine



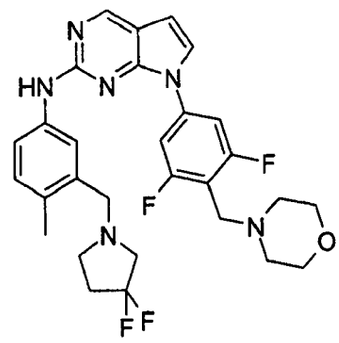
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.75 min (Method B); MS-ES: $(M+H)^+$ = 549

Example 392: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(piperidin-4-ylmethoxy)-pyridin-4-yl]-amine



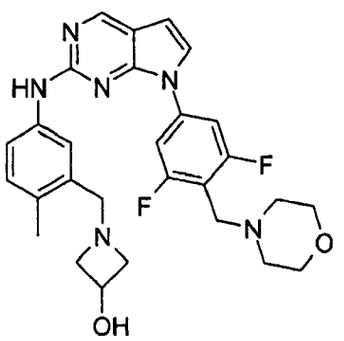
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.67 min (Method B); MS-ES: $(M+H)^+$ = 536; TLC (33% methanol / 66% methylene chloride / 1% aq. ammonia 24%): $R_f$ = 0.28

Example 393: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3,3-difluoro-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine



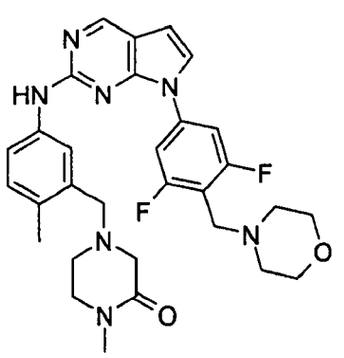
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.08 min (Method B); MS-ES: $(M+H)^+$ = 555; TLC*: $R_f$ = 0.63

Example 394: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-azetidin-3-ol



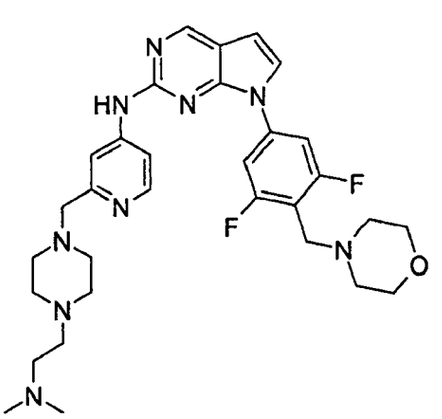
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.67 min (Method B); MS-ES: $(M+H)^+$ = 521; TLC (20% methanol / 80% methylene chloride): $R_f$ = 0.36

Example 395: 4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1-methyl-piperazin-2-one



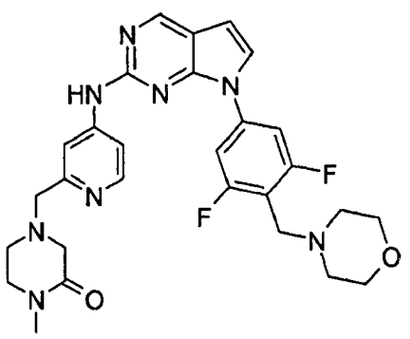
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.83 min (Method B); MS-ES: $(M+H)^+$ = 562

Example 396: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{2-[4-(2-dimethylamino-ethyl)-piperazin-1-ylmethyl]-pyridin-4-yl}-amine



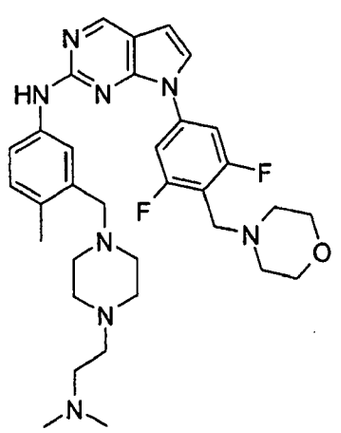
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.51 min (Method B); MS-ES: $(M+H)^+$ = 592

Example 397: 4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-1-methyl-piperazin-2-one



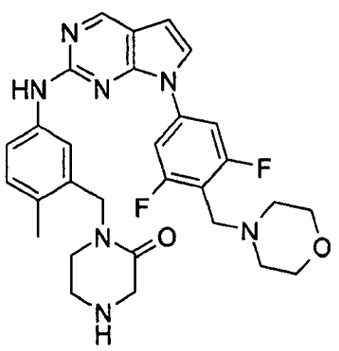
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.00 min (Method B); MS-ES: $(M+H)^+$ = 579

Example 398: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{3-[4-(2-dimethylamino-ethyl)-piperazin-1-ylmethyl]-4-methyl-phenyl}-amine



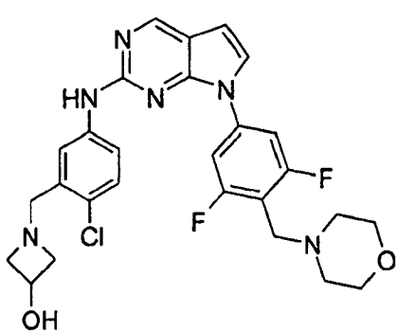
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.81 min (Method B); MS-ES: $(M+H)^+$ = 605

Example 399: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazin-2-one



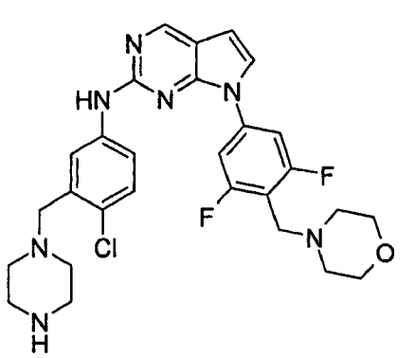
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.76 min (Method B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.27

Example 400: 1-{2-Chloro-5-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-azetidin-3-ol



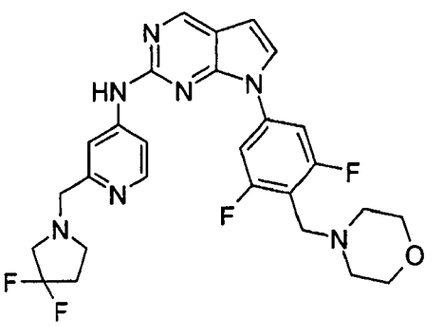
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.04 min (Method B); MS-ES: $(M+H)^+$ = 541

Example 401: (4-Chloro-3-piperazin-1-ylmethyl-phenyl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



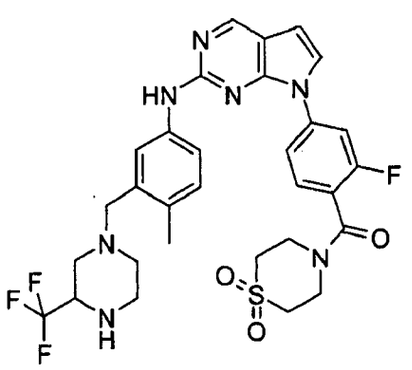
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.93 min (Method B); MS-ES: $(M+H)^+$ = 554

Example 402: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3,3-difluoro-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine



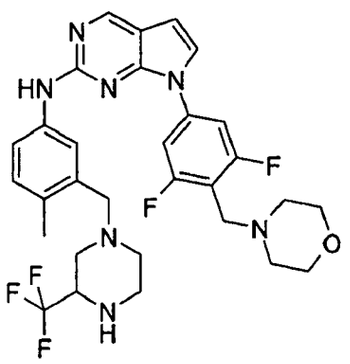
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.71 min (Method B); MS-ES: $(M+H)^+$ = 542

Example 403: (1,1-Dioxido-thiomorpholin-4-yl)-(2-fluoro-4-{2-[4-methyl-3-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanone (racemic)



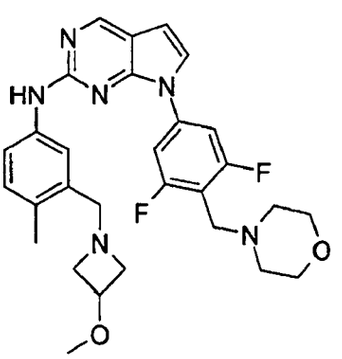
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.74 min (Method B); MS-ES: $(M+H)^+$ = 646; TLC*: $R_f$ = 0.41

Example 404: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic)



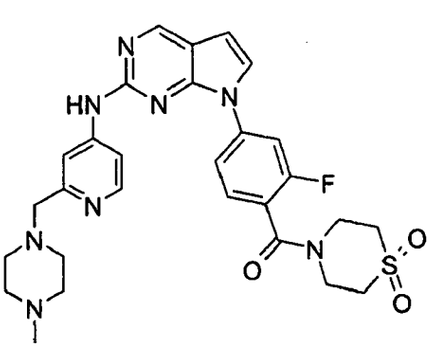
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.25 min (Method B); MS-ES: $(M+H)^+$ = 602; TLC*: $R_f$ = 0.31

Example 405: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3-methoxy-azetidin-1-ylmethyl)-4-methyl-phenyl]-amine



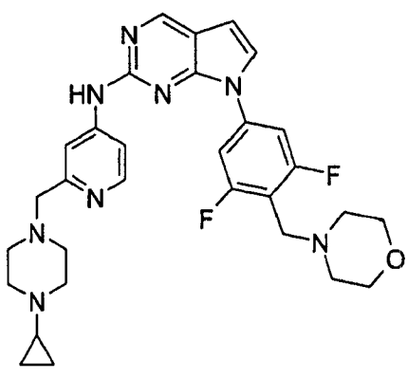
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.02 min (Method B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.19

Example 406: (1,1-Dioxido-thiomorpholin-4-yl)-(2-fluoro-4-{2-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanone



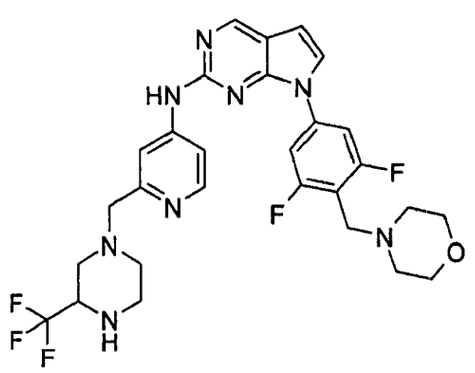
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.18 min (Method B); MS-ES: $(M+H)^+$ = 579

Example 407: [2-(4-Cyclopropyl-piperazin-1-ylmethyl)-pyridin-4-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



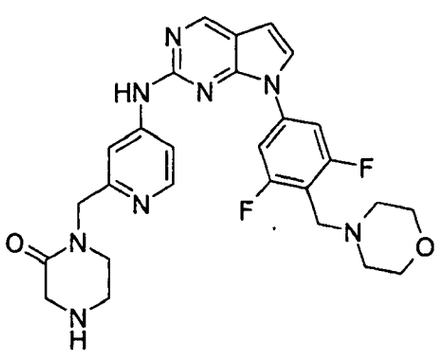
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.81 min (Method B); MS-ES: $(M+H)^+$ = 561

Example 408: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-trifluoromethyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine (racemic)



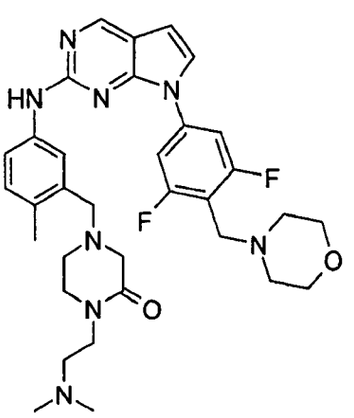
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.85 min (Method B); MS-ES: $(M+H)^+$ = 589

Example 409: 1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-piperazin-2-one



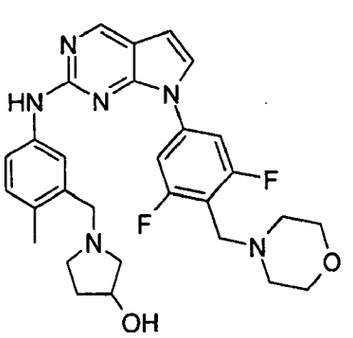
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.38 min (Method B); MS-ES: $(M+H)^+$ = 535

Example 410: 4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1-(2-dimethylamino-ethyl)-piperazin-2-one



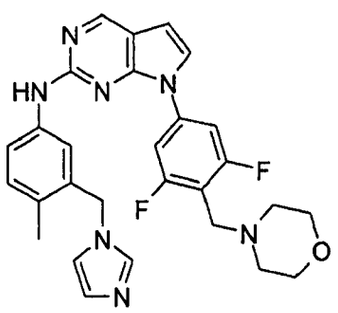
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.86 min (Method B); MS-ES: $(M+H)^+$ = 619; TLC*: $R_f$ = 0.14

Example 411: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-pyrrolidin-3-ol (racemic)



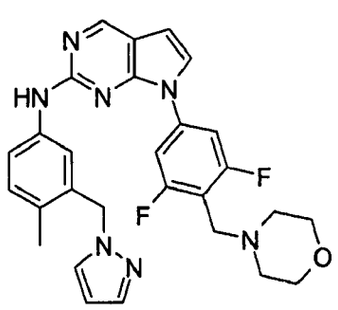
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.81 min (Method B); MS-ES: $(M+H)^+$ = 535; TLC* with 1% aq. ammonia 24%: $R_f$ = 0.66

Example 412: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-imidazol-1-ylmethyl-4-methyl-phenyl)-amine



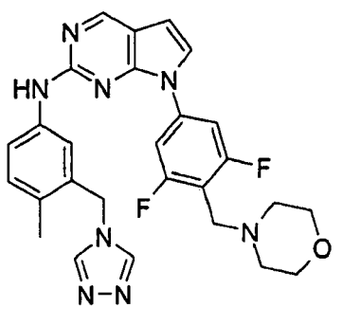
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.90 min (Method B); MS-ES: $(M+H)^+$ = 516; TLC*: $R_f$ = 0.52

Example 413: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-pyrazol-1-ylmethyl-phenyl)-amine



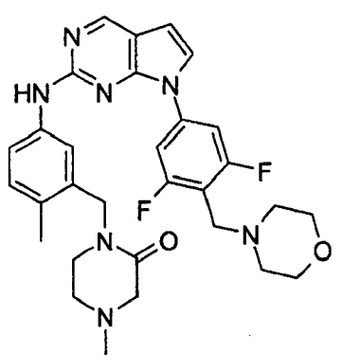
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.81 min (Method B); MS-ES: $(M+H)^+$ = 516; TLC*: $R_f$ = 0.77

Example 414: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-[1,2,4]triazol-4-ylmethyl-phenyl)-amine



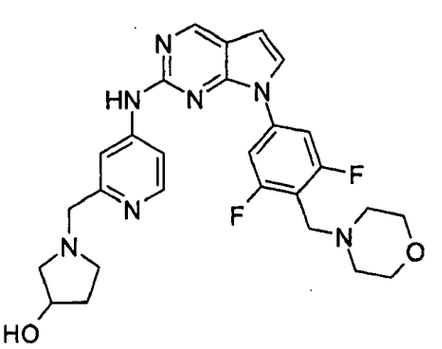
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.30 min (Method B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$ = 0.40

Example 415: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-4-methyl-piperazin-2-one



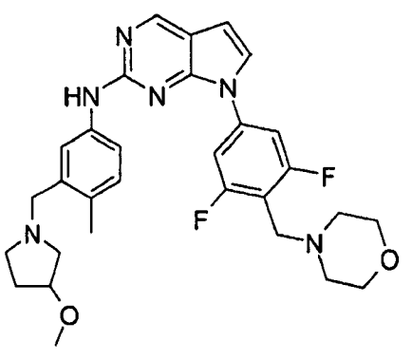
The compound is obtained from the reaction of 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazin-2-one (Example 399) with formaldehyde and sodium cyanoborohydride in methanol and DCM 2:1 at rt. HPLC: $t_R$ = 6.91 min (Method B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.28

Example 416: 1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-pyrrolidin-3-ol (racemic)



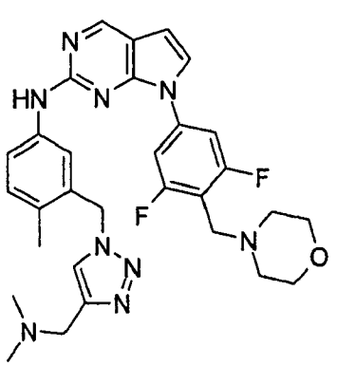
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.45 min (Method B); MS-ES: $(M+H)^+$ = 522

Example 417: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-l]-[3-(3-methoxy-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic)



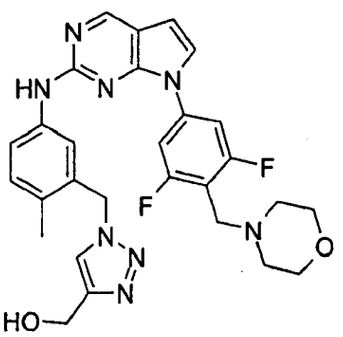
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.22 min (Method B); MS-ES: $(M+H)^+$ = 549

Example 418: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-dimethylaminomethyl-[1,2,3]triazol-1-ylmethyl)-4-methyl-phenyl]-amine



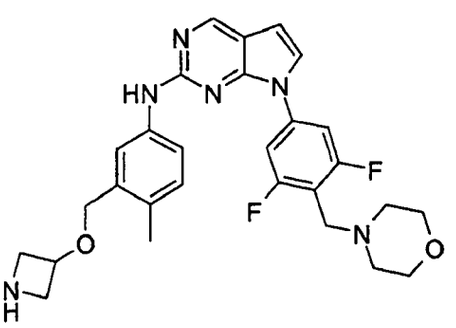
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.11 min (Method B); MS-ES: $(M+H)^+$ = 574; TLC*: $R_f$ = 0.19

Example 419: (1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1H-[1,2,3]triazol-4-yl)-methanol



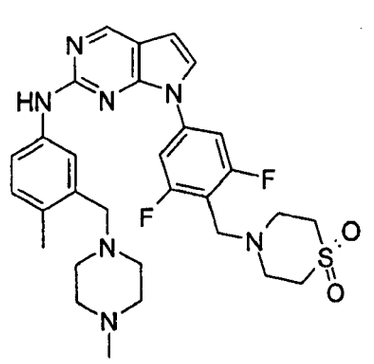
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.19 min (Method B); MS-ES: $(M+H)^+$ = 547; TLC*: $R_f$ = 0.31

Example 420: [3-(Azetidin-3-yloxymethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



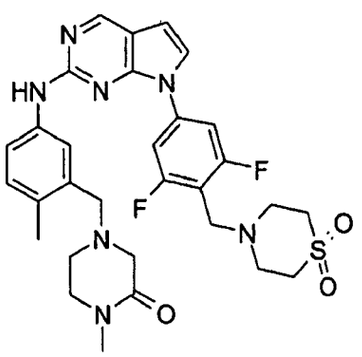
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 6.98 min (Method B); MS-ES: $(M+H)^+$ = 521

Example 421: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine



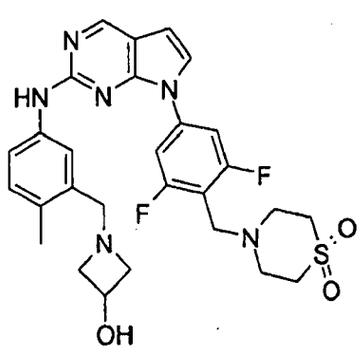
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.63 min (Method B); MS-ES: $(M+H)^+$ = 596; TLC*: $R_f$ = 0.17

Example 422: 4-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-1-methyl-piperazin-2-one



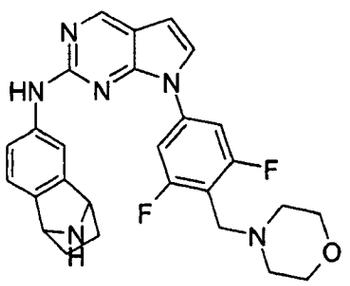
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.71 min (Method B); MS-ES: $(M+H)^+$ = 610; TLC*: $R_f$ = 0.23

Example 423: 1-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-azetidin-3-ol



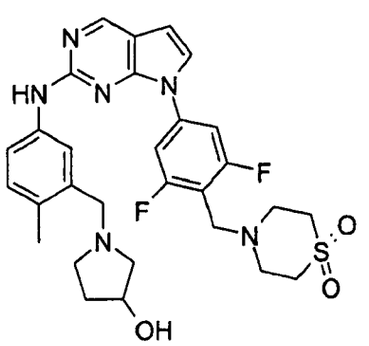
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.55 min (Method B); MS-ES: $(M+H)^+$ = 569; TLC*: $R_f$ = 0.14

Example 424: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl)-amine



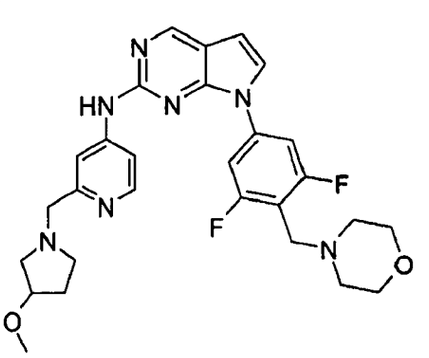
The compound is prepared analogous to Example 2, using a Boc-protected derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane and then TFA at rt. The aniline building block is obtained from patent WO 2007/072158 p.45 Scheme 4. HPLC: $t_R$ = 6.78 min (Method B); MS-ES: $(M+H)^+$ = 489; TLC (33% methanol / 67% methylene chloride): $R_f$ = 0.52

Example 425: 1-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-pyrrolidin-3-ol (racemic)



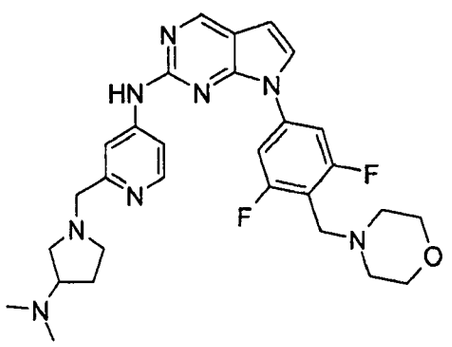
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.68 min (Method B); MS-ES: $(M+H)^+$ = 583; TLC*: $R_f$ = 0.10

Example 426: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-methoxy-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine (racemic)



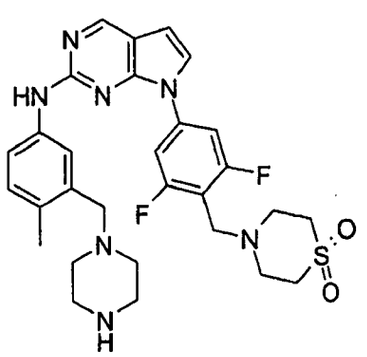
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.77 min (Method B); MS-ES: $(M+H)^+$ = 536

Example 427: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-dimethylamino-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine (racemic)



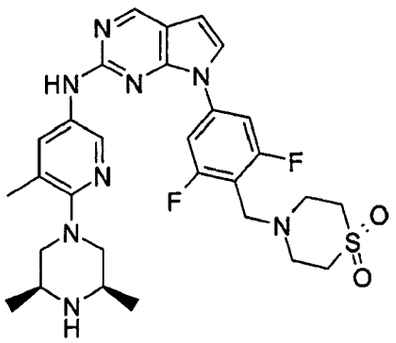
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.79 min (Method B); MS-ES: $(M+H)^+$ = 549

Example 428: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine



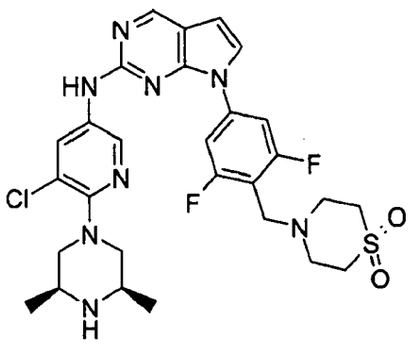
The compound is prepared analogous to Example 2, using a Boc-protected derivative in Step 2.2. Final deprotection is achieved with 4 M HCl in dioxane at rt. HPLC: $t_R$ = 7.43 min (Method B); MS-ES: $(M+H)^+$ = 582; TLC*: $R_f$ = 0.15

Example 429: [6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



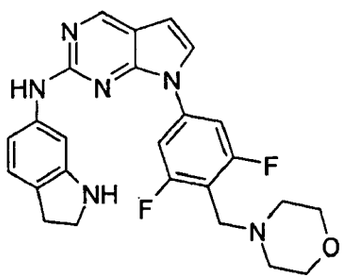
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.74 min (Method B); MS-ES: $(M+H)^+$ = 597; TLC*: $R_f$ = 0.06

Example 430: [5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



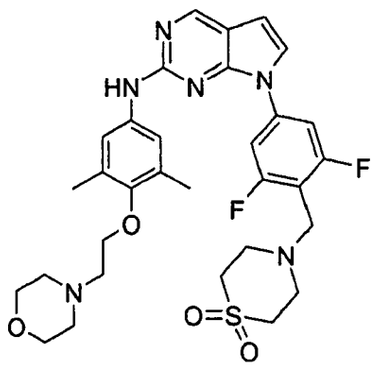
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.33 min (Method B); MS-ES: $(M+H)^+$ = 617; TLC*: $R_f$ = 0.15

Example 431: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,3-dihydro-1H-indol-6-yl)-amine



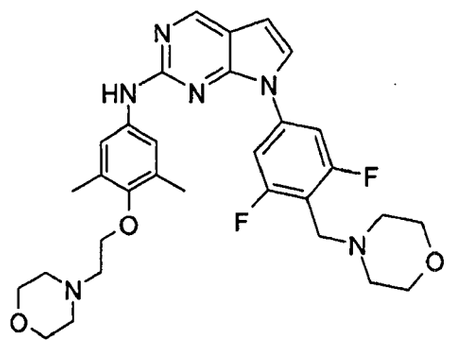
The compound is prepared analogous to Example 2 with the aniline derivative obtained from the hydrogenation of 6-nitro-2,3-dihydro-1H-indole. HPLC: $t_R$ = 6.71 min (Method B); MS-ES: $(M+H)^+$ = 463; TLC**: $R_f$ = 0.24

Example 432: [3,5-Dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenyl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



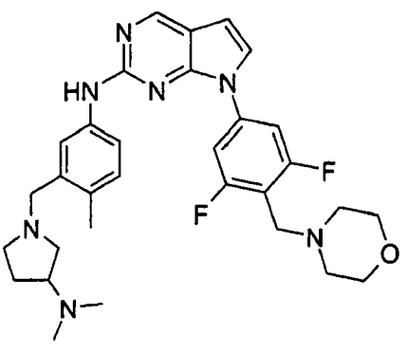
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.86 min (Method B); MS-ES: $(M+H)^+$ = 627

Example 433: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3,5-dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amine



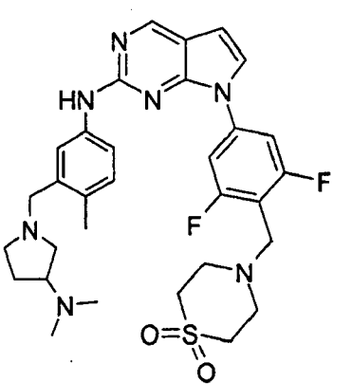
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.04 min (Method B); MS-ES: $(M+H)^+$ = 579

Example 434: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3-dimethylamino-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic)



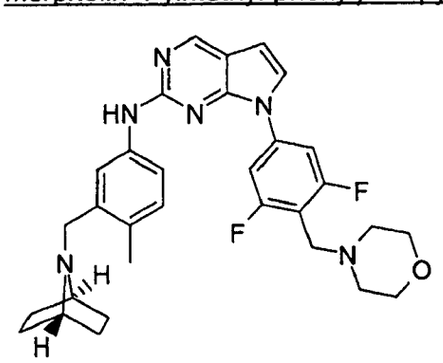
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.78 min (Method B); MS-ES: $(M+H)^+$ = 562

Example 435: [3-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine (racemic)



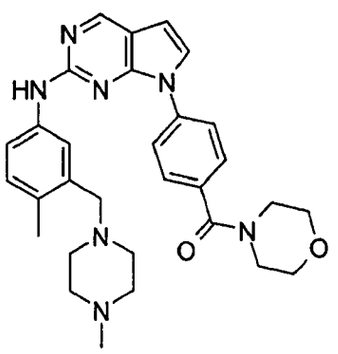
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.57 min (Method B); MS-ES: $(M+H)^+$ = 610

Example 436: [3-(7-Aza-bicyclo[2.2.1]hept-7-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



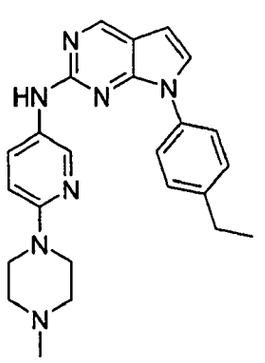
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.37 min (Method B); MS-ES: $(M+H)^+$ = 545

Example 437: (4-{2-[4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone



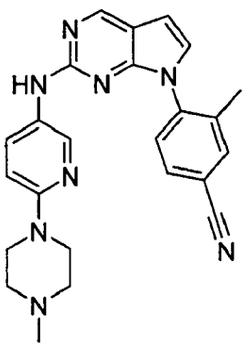
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.10 min (Method B); MS-ES: $(M+H)^+$ = 526; TLC*: $R_f$ = 0.23

Example 438: [7-(4-Ethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine



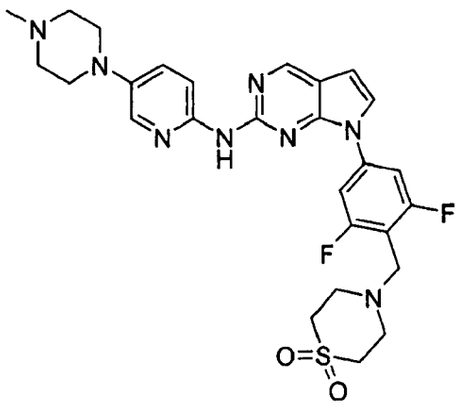
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 4.79 min (Method F); MS-ES: $(M+H)^+$ = 414

Example 439: 3-Methyl-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile



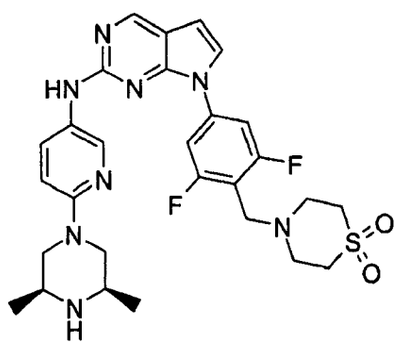
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 4.45 min (Method F); MS-ES: $(M+H)^+$ = 425

Example 440: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine



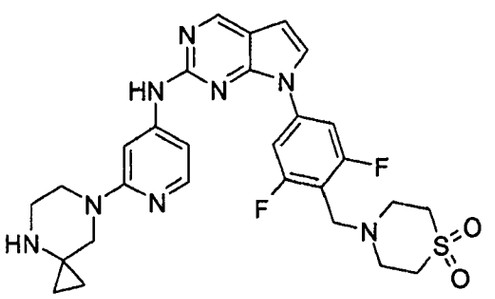
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.29 min (Method F); MS-ES: $(M+H)^+$ = 569

Example 441: [6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



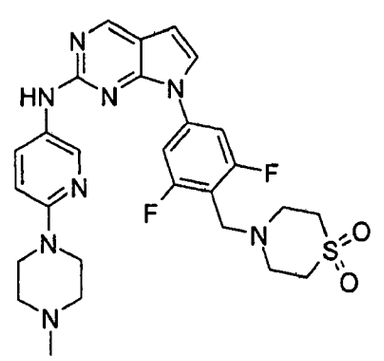
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.40 min (Method F); MS-ES: $(M+H)^+$ = 583; TLC (20% methanol / 80% methylene chloride): $R_f$ = 0.32

Example 442: [2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine



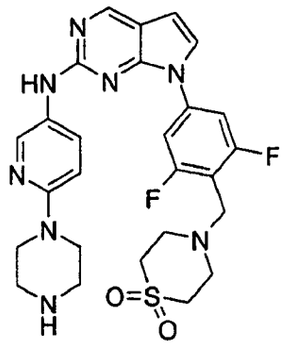
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.48 min (Method F); MS-ES: $(M+H)^+$ = 581; TLC (20% methanol / 80% methylene chloride): $R_f$ = 0.38

Example 443: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine



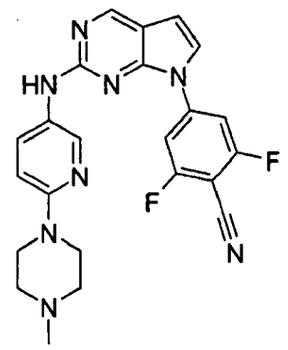
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.36 min (Method F); MS-ES: $(M+H)^+$ = 569

Example 444: {7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(6-piperazin-1-yl-pyridin-3-yl)-amine



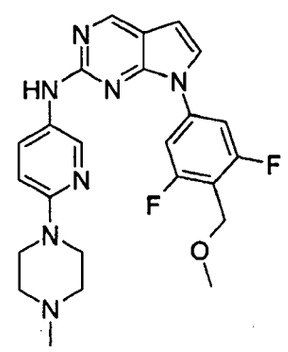
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 4.29 min (Method F); MS-ES: $(M+H)^+$ = 555

Example 445: 2,6-Difluoro-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile



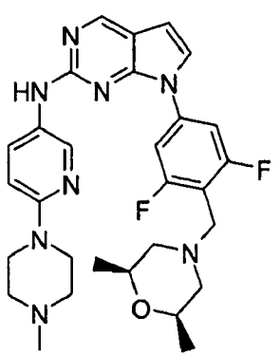
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 4.74 min (Method F); MS-ES: $(M+H)^+$ = 447

Example 446: [7-(3,5-Difluoro-4-methoxymethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine



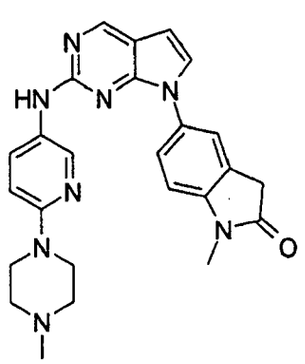
The compound is prepared analogous to Example 3. The corresponding aryle bromide is obtained from the reaction of (4-bromo-2,6-difluoro-phenyl)-methanol with iodomethane in presence of sodium hydride in THF. HPLC: $t_R$ = 4.69 min (Method F); MS-ES: $(M+H)^+$ = 466

Example 447: {7-[4-(cis-2,6-dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine



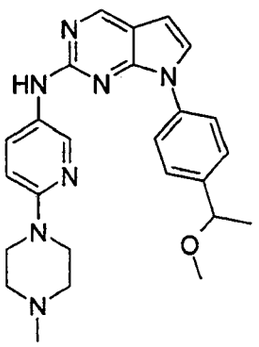
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.14 min (Method F); MS-ES: $(M+H)^+$ = 549

Example 448: 1-Methyl-5-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-1,3-dihydro-indol-2-one



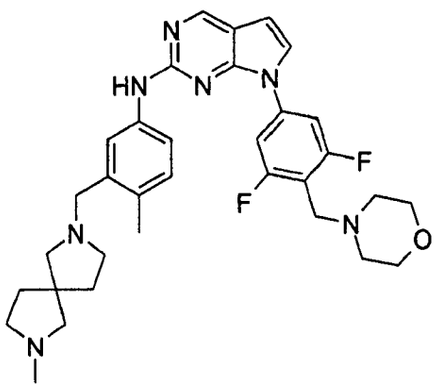
The compound is prepared analogous to Example 3. HPLC: $t_R$ = 4.25 min (Method F); MS-ES: $(M+H)^+$ = 455

Example 449: {7-[4-(1-Methoxy-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic)



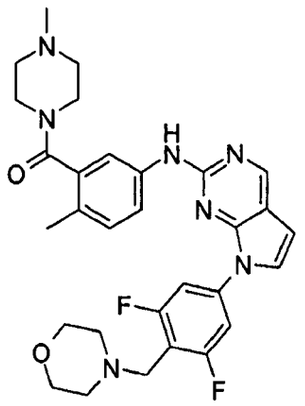
The compound is prepared analogous to Example 3. The corresponding aryle bromide is obtained from the reaction of 1-(4-bromo-phenyl)-ethanol on iodomethane under Ar in presence of sodium hydride in THF. HPLC: $t_R$ = 4.54 min (Method F); MS-ES: $(M+H)^+$ = 444

Example 450: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(7-methyl-2,7-diaza-spiro[4.4]non-2-ylmethyl)-phenyl]-amine



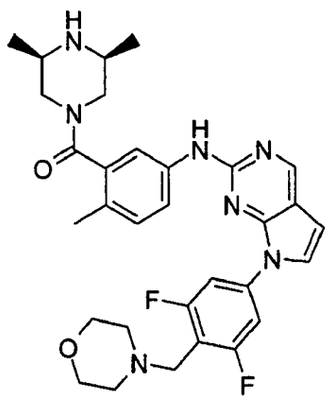
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 6.71 min (Method B); MS-ES: $(M+H)^+$ = 588; TLC (53% chloroform, 36% methanol, 10% water, 0.5% acetic acid): $R_f$ = 0.25

Example 451: {5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone



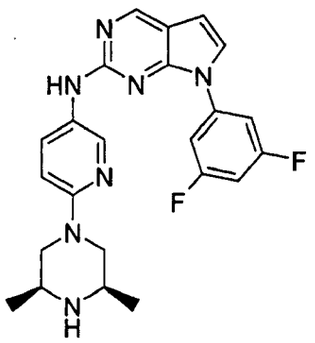
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.94 min (Method C); MS-ES: $(M+H)^+$ = 562

Example 452: {5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone



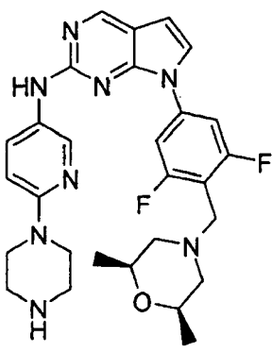
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.00 min (Method C); MS-ES: $(M+H)^+$ = 576

Example 453: [7-(3,5-Difluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine



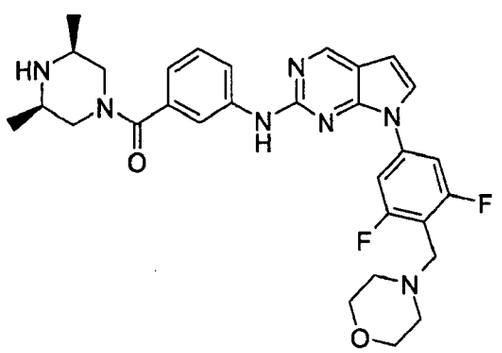
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.74 min (Method E1); MS-ES: $(M+H)^+$ = 436

Example 454: {7-[4-(cis-2,6-dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(6-piperazin-1-yl-pyridin-3-yl)-amine



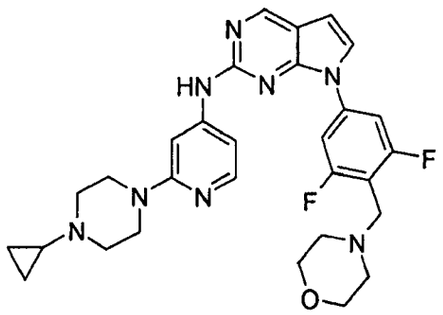
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 1.14 min (Method E2); MS-ES: $(M+H)^+$ = 535

Example 455: {3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone



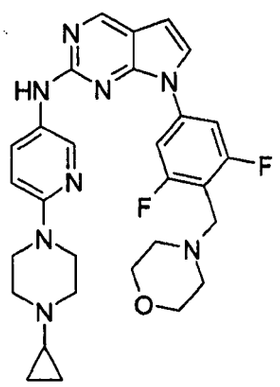
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.97 min (Method C); MS-ES: $(M+H)^+$ = 562

Example 456: [2-(4-Cyclopropyl-piperazin-1-yl)-pyridin-4-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



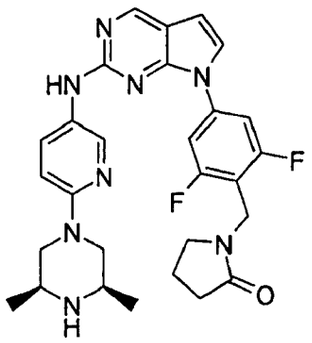
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.96 min (Method C); MS-ES: $(M+H)^+$ = 547

Example 457: [6-(4-Cyclopropyl-piperazin-1-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



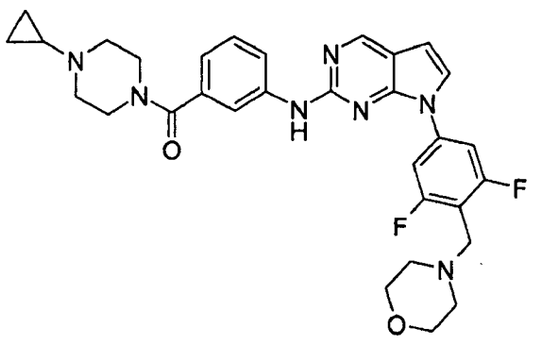
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.89 min (Method C); MS-ES: $(M+H)^+$ = 547

Example 458: 1-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-pyrrolidin-2-one



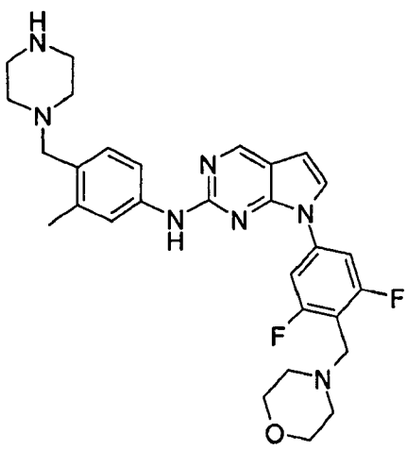
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.81 min (Method E1); MS-ES: $(M+H)^+$ = 533

Example 459: (4-Cyclopropyl-piperazin-1-yl)-{3-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-methanone



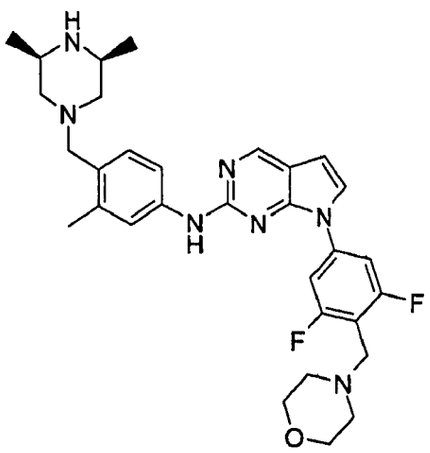
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.02 min (Method C); MS-ES: $(M+H)^+$ = 574

Example 460: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methyl-4-piperazin-1-ylmethyl-phenyl)-amine



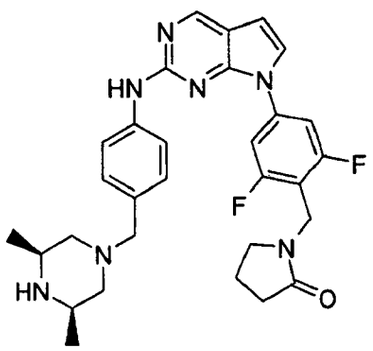
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.96 min (Method C); MS-ES: $(M+H)^+$ = 534

Example 461: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-3-methyl-phenyl]-amine



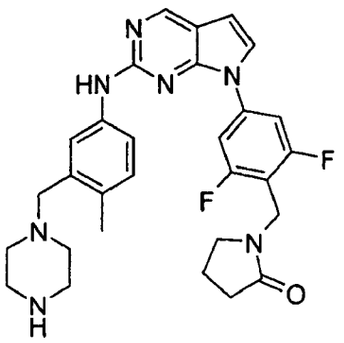
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.01 min (Method C); MS-ES: $(M+H)^+$ = 562

Example 462: 1-{4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-pyrrolidin-2-one



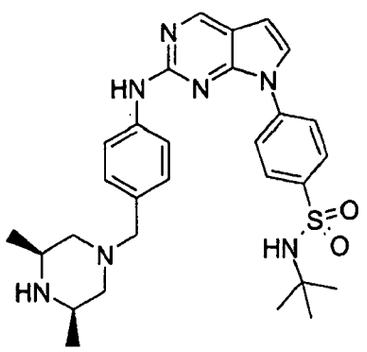
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.70 min (Method E1); MS-ES: $(M+H)^+$ = 546

Example 463: 1-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-pyrrolidin-2-one



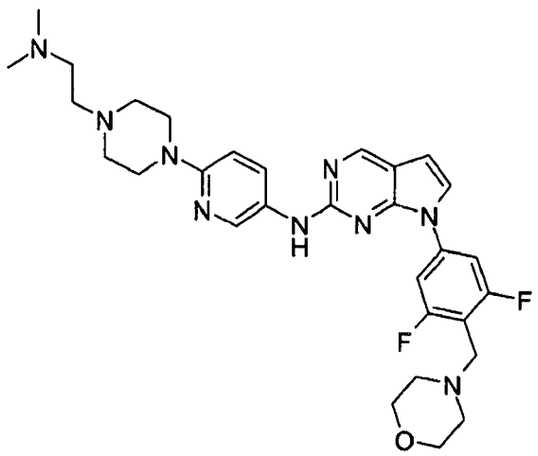
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 0.72 min (Method E1); MS-ES: $(M+H)^+$ = 532

Example 464: N-tert-Butyl-4-{2-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide



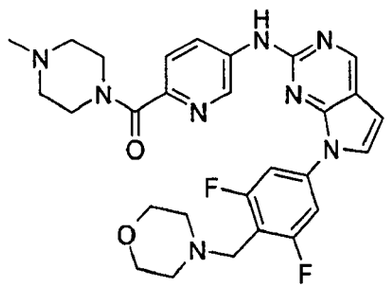
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.76 min (Method E1); MS-ES: $(M+H)^+$ = 548

Example 465: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{6-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-pyridin-3-yl}-amine



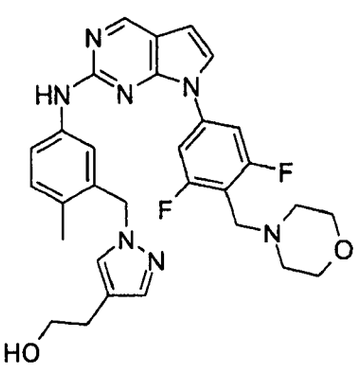
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.84 min (Method C); MS-ES: $(M+H)^+$ = 578

Example 466: {5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(4-methyl-piperazin-1-yl)-methanone



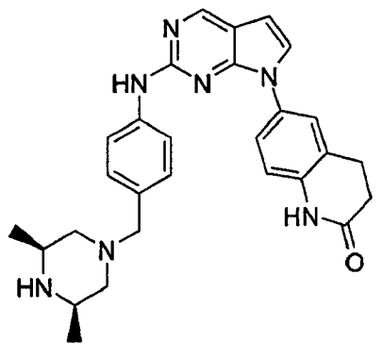
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.99 min (Method F); MS-ES: $(M+H)^+$ = 549

Example 467: 2-(1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1H-pyrazol-4-yl)-ethanol



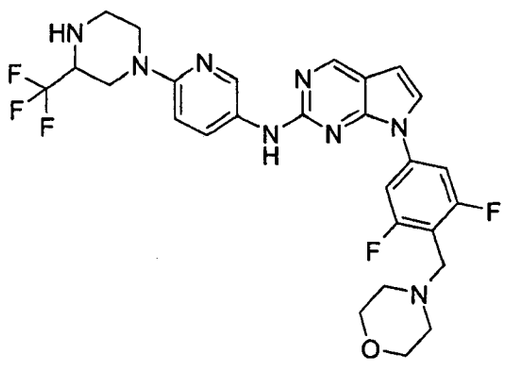
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.34 min (Method B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.36

Example 468: 6-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-3,4-dihydro-1H-quinolin-2-one



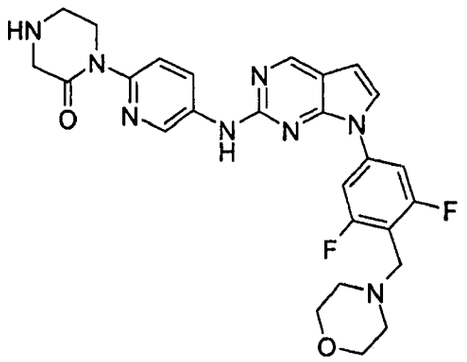
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.49 min (Method E1); MS-ES: $(M+H)^+$ = 482

Example 469: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(3-trifluoromethyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic)



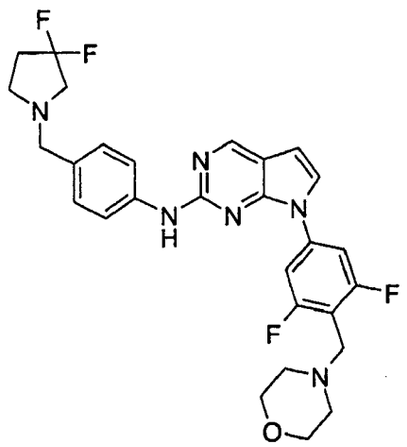
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.06 min (Method C); MS-ES: $(M+H)^+$ = 575

Example 470: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one



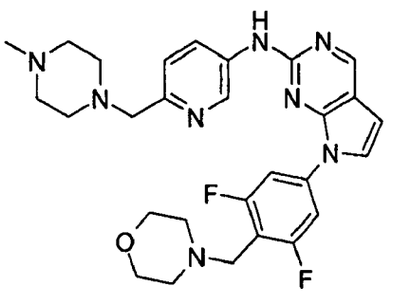
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.91 min (Method C); MS-ES: $(M+H)^+$ = 521

Example 471: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3,3-difluoro-pyrrolidin-1-ylmethyl)-phenyl]-amine



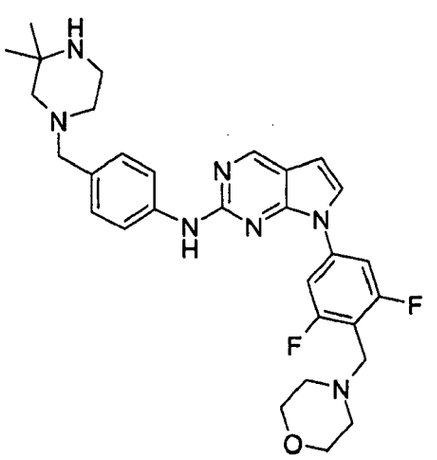
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.19 min (Method F); MS-ES: $(M+H)^+$ = 541

Example 472: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-amine



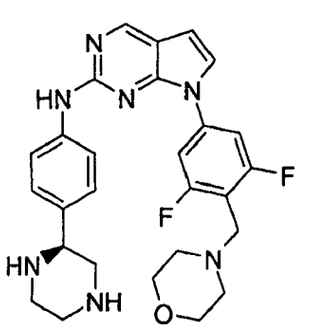
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.12 min (Method E2); MS-ES: $(M+H)^+$ = 535

Example 473: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3,3-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine



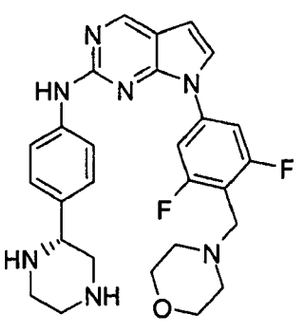
The compound is prepared analogous to Example 2. HPLC: $t_R$ = .01 min (Method C); MS-ES: $(M+H)^+$ = 548

Example 474: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-piperazin-2-yl-phenyl)-amine



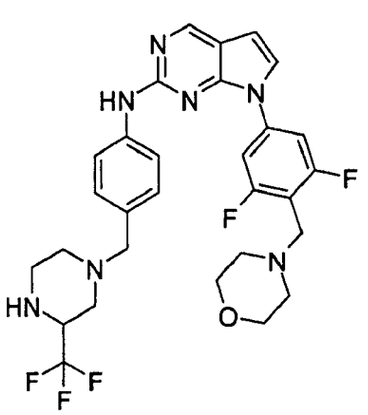
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. The aniline used for this synthesis is prepared from 2-(4-nitro-phenyl)-piperazine (racemic) via Boc-protection, nitro reduction and chiral separation (other enantiomer used for Example 475). HPLC: $t_R$ = 0.68 min (Method E2); MS-ES: $(M+H)^+$ = 506

Example 475: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((R)-4-piperazin-2-yl-phenyl)-amine



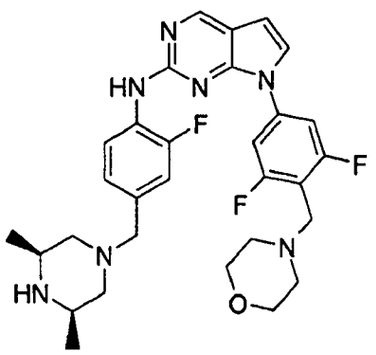
The compound is prepared analogous to Example 2 and represents the enantiomer of Example 474. HPLC: $t_R$ = 0.68 min (Method E2); MS-ES: $(M+H)^+$ = 506

Example 476: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic)



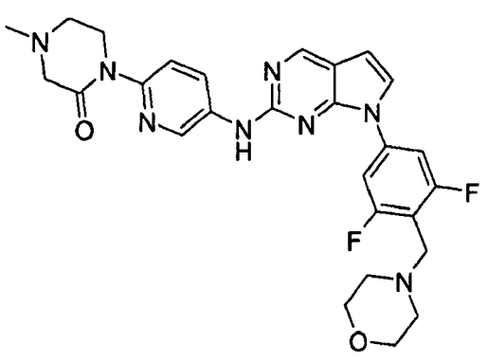
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.24 min (Method C); MS-ES: $(M+H)^+$ = 588

Example 477: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-2-fluoro-phenyl]-amine



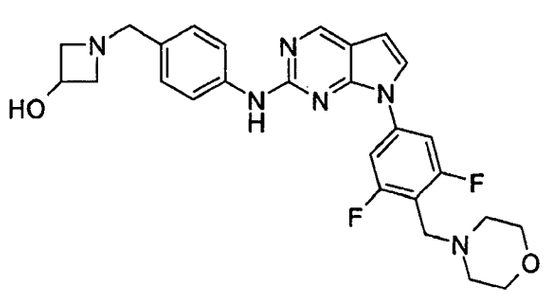
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.06 min (Method C); MS-ES: $(M+H)^+$ = 566

Example 478: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-4-methyl-piperazin-2-one



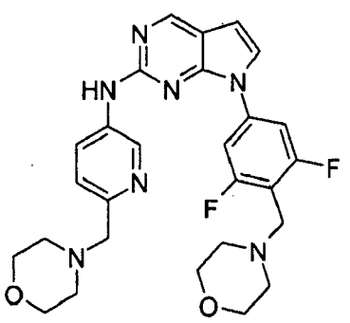
The compound is obtained from the reaction of 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one (Example 470) with formaldehyde and sodium cyanoborohydride in methanol and DCM 2:1 at rt. HPLC: $t_R$ = 3.94 min (Method C); MS-ES: $(M+H)^+$ = 535

Example 479: 1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-azetidin-3-ol



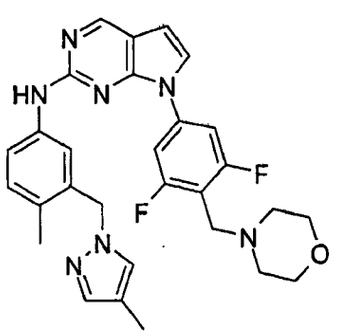
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.97 min (Method C); MS-ES: $(M+H)^+$ = 507

Example 480: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-morpholin-4-ylmethyl-pyridin-3-yl)-amine



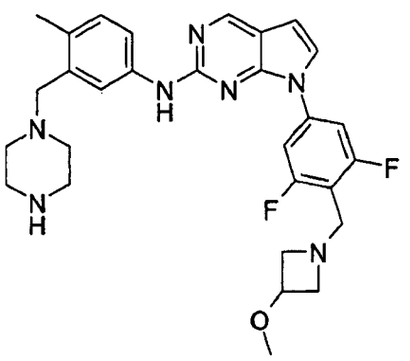
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.20 min (Method E2); MS-ES: $(M+H)^+$ = 522

Example 481: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(4-methyl-pyrazol-1-ylmethyl)-phenyl]-amine



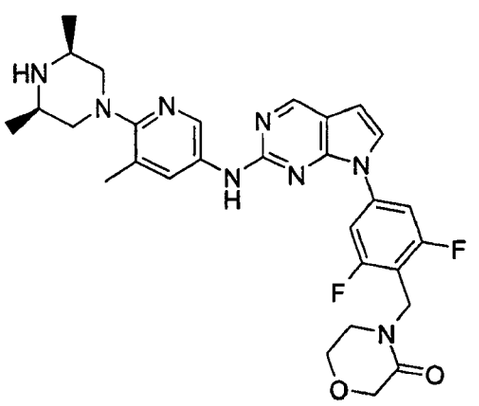
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 8.11 min (Method B); MS-ES: $(M+H)^+$ = 530; TLC*: $R_f$ = 0.67

Example 482: {7-[3,5-Difluoro-4-(3-methoxy-azetidin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine



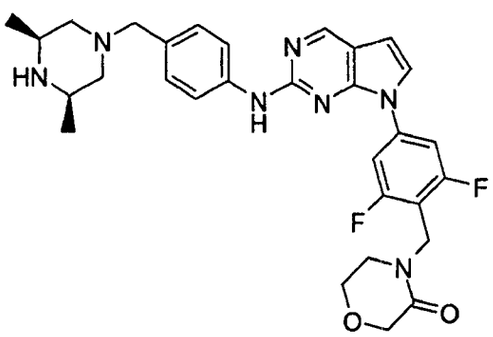
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 4.05 min (Method F); MS-ES: $(M+H)^+$ = 534

Example 483: 4-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-morpholin-3-one



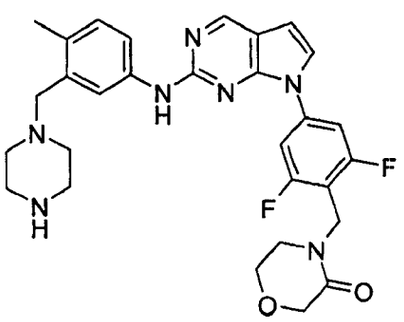
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.58 min (Method F); MS-ES: $(M+H)^+$ = 563

Example 484: 4-(4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-morpholin-3-one



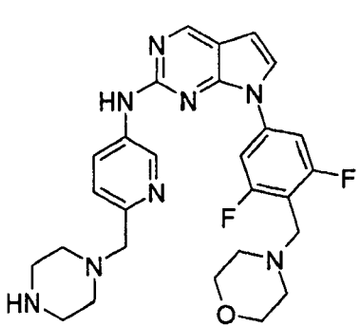
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.40 min (Method F); MS-ES: $(M+H)^+$ = 562

Example 485: 4-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-morpholin-3-one



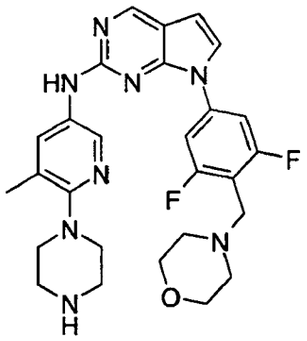
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 4.44 min (Method F); MS-ES: $(M+H)^+$ = 548

Example 486: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-ylmethyl-pyridin-3-yl)-amine



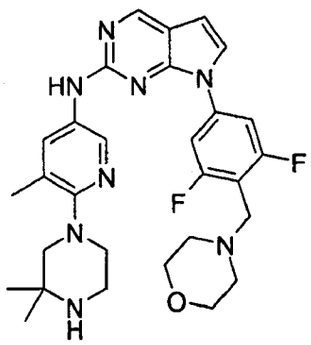
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 1.12 min (Method E); MS-ES: $(M+H)^+$ = 521

Example 487: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(5-methyl-6-piperazin-1-yl-pyridin-3-yl)-amine



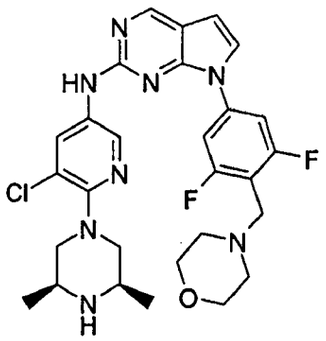
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.99 min (Method C); MS-ES: $(M+H)^+$ = 521

Example 488: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-amine



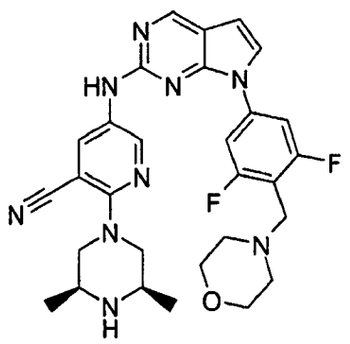
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.16 min (Method C); MS-ES: $(M+H)^+$ = 549

Example 489: [5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



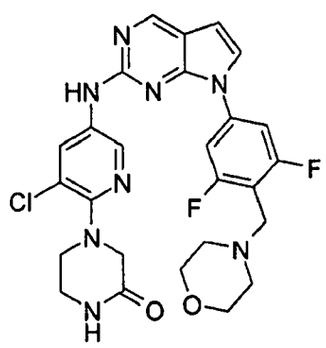
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.42 min (Method F); MS-ES: $(M+H)^+$ = 569

Example 490: 5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-(cis-3,5-dimethyl-piperazin-1-yl)-nicotinonitrile



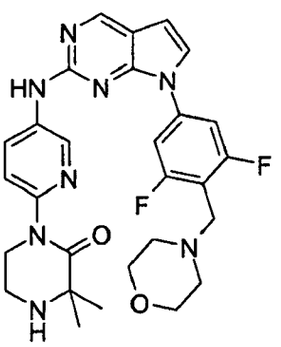
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.34 min (Method C); MS-ES: $(M+H)^+$ = 560

Example 491: 4-{3-Chloro-5-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one



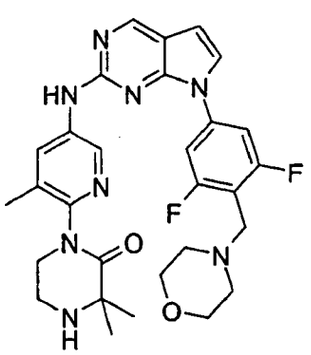
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.56 min (Method C); MS-ES: $(M+H)^+$ = 555

Example 492: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d] pyrimidin-2-ylamino]-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one



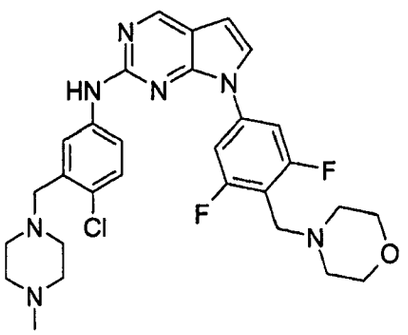
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.04 min (Method C); MS-ES: $(M+H)^+$ = 549

Example 493: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-3-methyl-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one



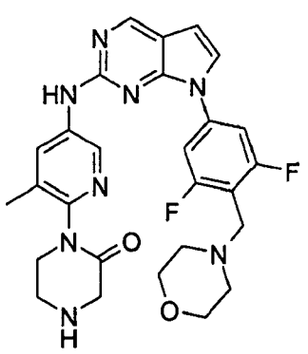
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 3.54 min (Method C); MS-ES: $(M+H)^+$ = 563

Example 494: [4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



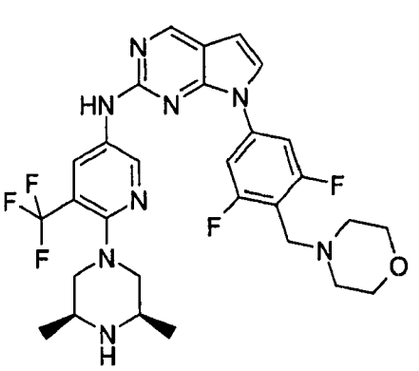
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 7.25 min (Method B); MS-ES: $(M+H)^+$ = 568

Example 495: 1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-3-methyl-pyridin-2-yl}-piperazin-2-one



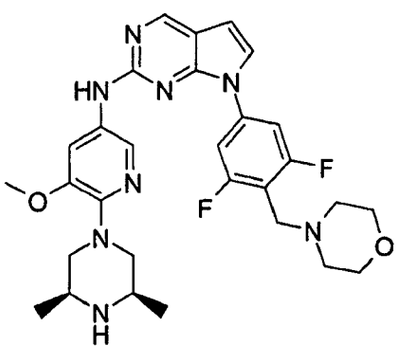
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.98 min (Method C); MS-ES: $(M+H)^+$ = 535

Example 496: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-trifluoromethyl-pyridin-3-yl]-amine



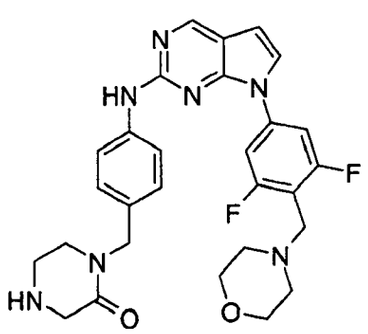
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.67 min (Method C); MS-ES: $(M+H)^+$ = 603

Example 497: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-methoxy-pyridin-3-yl]-amine



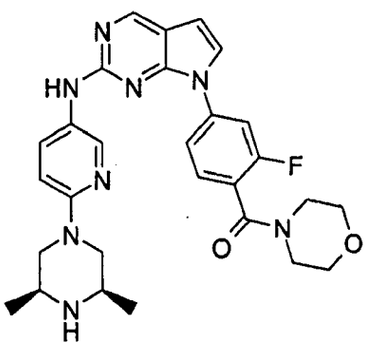
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.07 min (Method C); MS-ES: $(M+H)^+$ = 565

Example 498: 1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-2-one



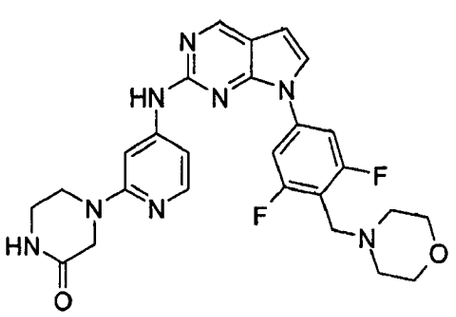
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.96 min (Method C); MS-ES: $(M+H)^+$ = 534

Example 499: (4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone



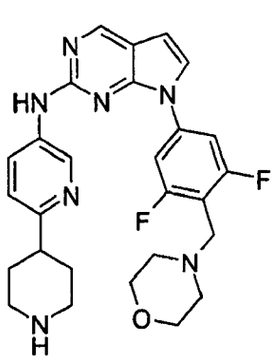
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.27 min (Method C); MS-ES: $(M+H)^+$ = 531

Example 500: 4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one



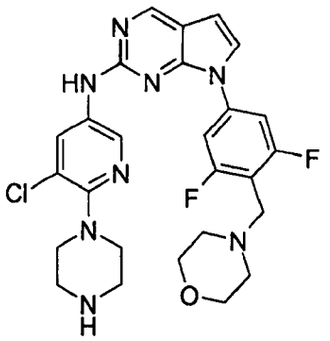
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.20 min (Method C); MS-ES: $(M+H)^+$ = 521

Example 501: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl)-amine



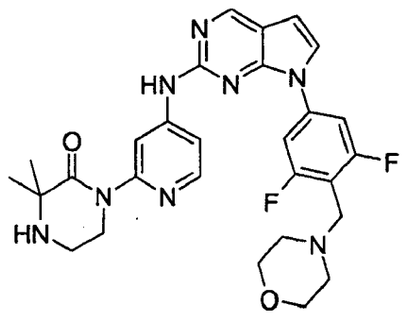
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 3.92 min (Method C); MS-ES: $(M+H)^+$ = 506

Example 502: (5-Chloro-6-piperazin-1-yl-pyridin-3-yl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



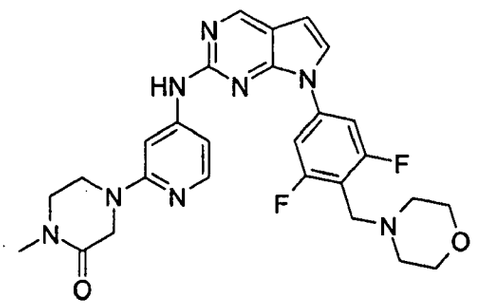
The compound is prepared analogous to Example 2, using a Boc-protected piperazine derivative in Step 2.2. Final deprotection is achieved with TFA in $CH_2Cl_2$ at rt. HPLC: $t_R$ = 4.27 min (Method C); MS-ES: $(M+H)^+$ = 541

Example 503: 1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one



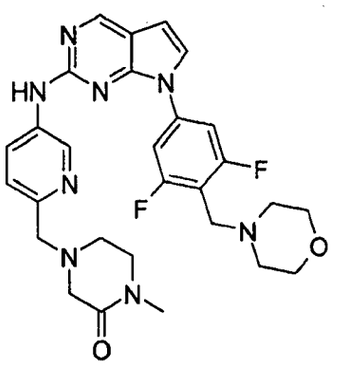
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.00 min (Method C); MS-ES: $(M+H)^+$ = 549

Example 504: 4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-1-methyl-piperazin-2-one



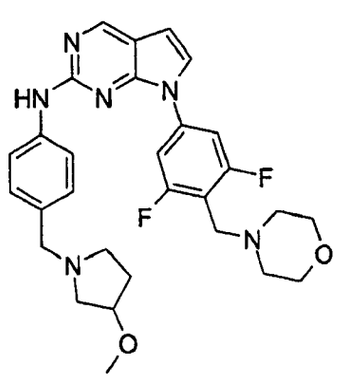
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.23 min (Method C); MS-ES: $(M+H)^+$ = 535

Example 505: 4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-1-methyl-piperazin-2-one



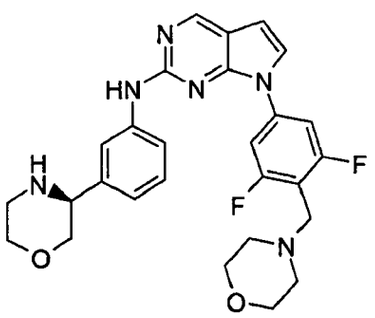
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.06 min (Method C); MS-ES: $(M+H)^+$ = 549

Example 506: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl]-amine (racemic)



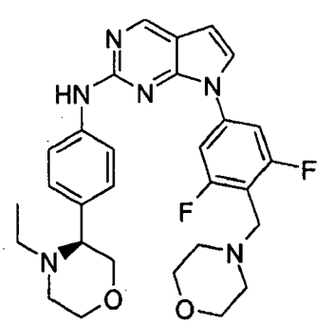
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 4.17 min (Method C); MS-ES: $(M+H)^+$ = 535

Example 507: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-3-morpholin-3-yl-phenyl)-amine



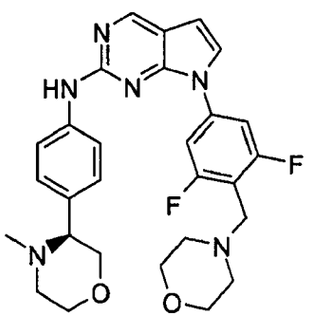
The compound is prepared analogous to Example 2, using a Boc-protected morpholine derivative in Step 2.2. Final deprotection is achieved with HCl in EtOH at 60 °C. HPLC: $t_R$ = 0.60 min (Method G); MS-ES: $(M+H)^+$ = 507

Example 508: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((S)-4-ethyl-morpholin-3-yl)-phenyl]-amine



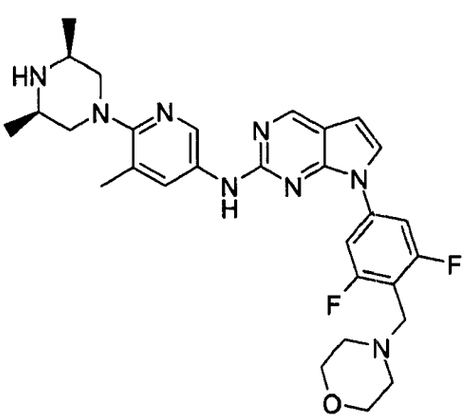
The compound is obtained by treating [7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-3-morpholin-3-yl-phenyl)-amine (Example 507) with acetaldehyde in methanol and sodium cyanoborohydride at rt to 60°C. HPLC: $t_R$ = 0.63 min (Method G); MS-ES: $(M+H)^+$ = 535

Example 509: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((S)-4-methyl-morpholin-3-yl)-phenyl]-amine



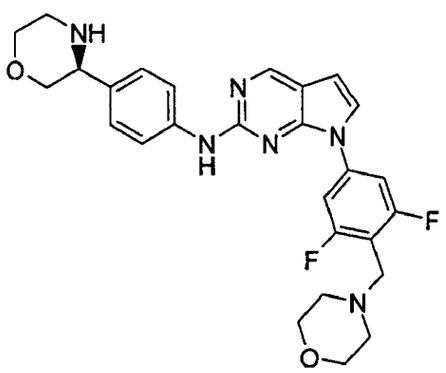
The compound is obtained by treating [7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-3-morpholin-3-yl-phenyl)-amine (Example 507) with formaldehyde in methanol and sodium cyanoborohydride at rt to 60°C. HPLC: $t_R$ = 0.61 min (Method G); MS-ES: $(M+H)^+$ = 521

Example 510: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-amine



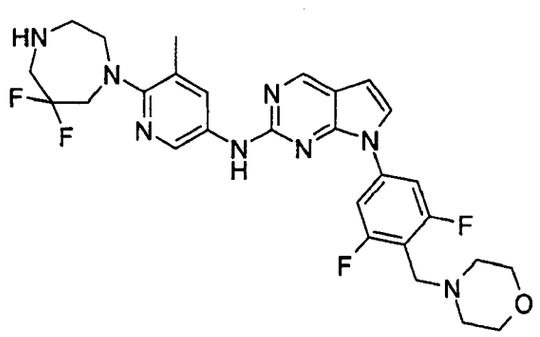
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.61 min (Method G); MS-ES: $(M+H)^+$ = 549; TLC (10% methanol / 90% methylene chloride / 1% ammonia): $R_f$ = 0.18

Example 511: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-morpholin-3-yl-phenyl)-amine



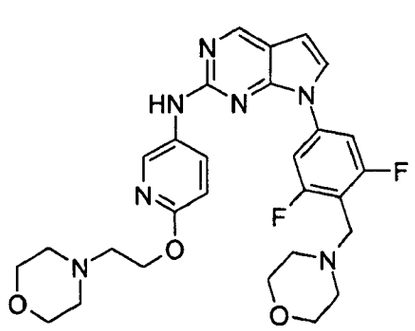
The compound is prepared analogous to Example 2, using a Boc-protected morpholine derivative in Step 2.2. Final deprotection is achieved with 1.25 M HCl in EtOH at 60 °C. HPLC: $t_R$ = 0.61 min (Method G); MS-ES: $(M+H)^+$ = 507; TLC (10% methanol / 90% methylene chloride / 1% ammonia): $R_f$ = 0.50

Example 512: [6-(6,6-Difluoro-[1,4]diazepan-1-yl)-5-methyl-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



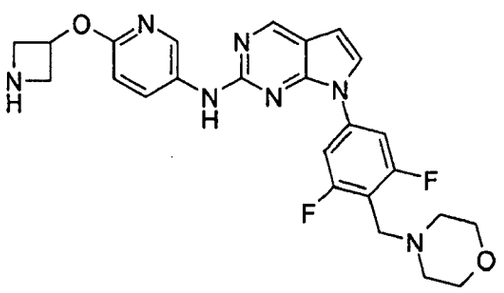
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.65 min (Method G); MS-ES: $(M+H)^+$ = 571

Example 513: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(2-morpholin-4-yl-ethoxy)-pyridin-3-yl]-amine



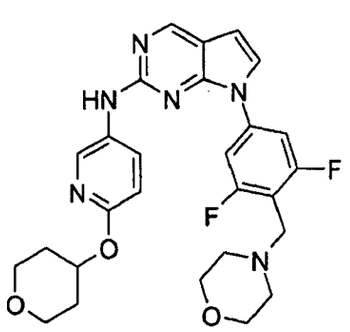
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.59 min (Method G); MS-ES: $(M+H)^+$ = 552

Example 514: [6-(Azetidin-3-yloxy)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



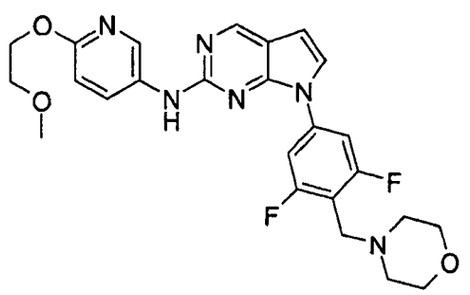
The compound is prepared analogous to Example 2, using a Boc-protected azetidine derivative in Step 2.2. Final deprotection is achieved with 1.25 M HCl in EtOH at 60 °C. HPLC: $t_R$ = 0.55 min (Method G); MS-ES: $(M+H)^+$ = 538

Example 515: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-amine



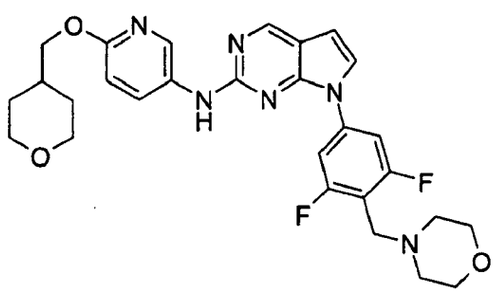
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.71 min (Method G); MS-ES: $(M+H)^+$ = 523

Example 516: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-amine



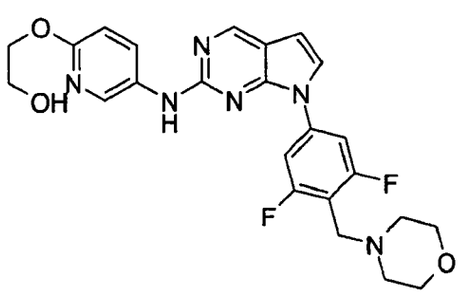
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.67 min (Method G); MS-ES: $(M+H)^+$ = 497

Example 517: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(tetrahydro-pyran-4-ylmethoxy)-pyridin-3-yl]-amine



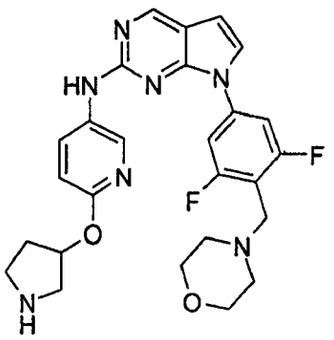
The compound is prepared analogous to Example 2. HPLC: $t_R$ = 0.74 min (Method G); MS-ES: $(M+H)^+$ = 537

Example 518: 2-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yloxy}-ethanol



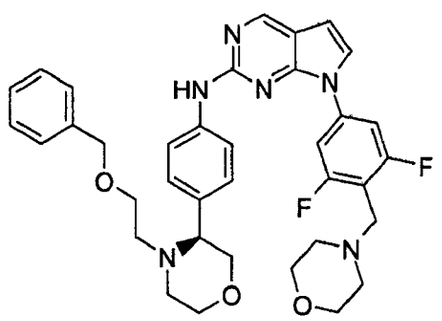
The compound is prepared analogous to Example 2, using a TBDPS-protected alcohol derivative in Step 2.2. Final deprotection is achieved with 1 M TBAF in THF at rt. HPLC: $t_R$ = 0.60 min (Method G) and MS-ES: $(M+H)^+$ = 483.

Example 519: [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(pyrrolidin-3-yloxy)-pyridin-3-yl]-amine (racemic)



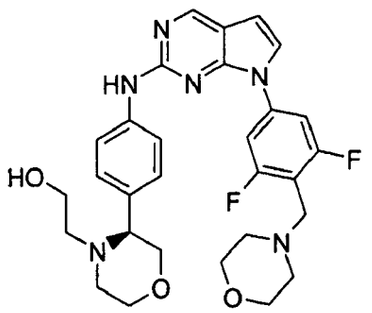
The compound is prepared analogous to Example 2, using a Boc-protected pyrrolidine derivative in Step 2.2. Final deprotection is achieved with 1.25 M HCl in EtOH at 50 °C. HPLC: $t_R$ = 0.58 min (Method G); MS-ES: $(M+H)^+$ = 508

Example 520: {4-[(S)-4-(2-Benzyloxy-ethyl)-morpholin-3-yl]-phenyl}-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine



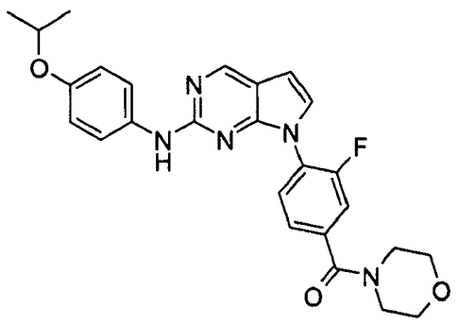
The compound is obtained by treating [7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-morpholin-3-yl-phenyl)-amine (Example 511) with benzyloxyacetaldehyde in methanol and sodium cyanoborohydride at 60 °C. HPLC: $t_R$ = 0.78 min (Method G); MS-ES: $(M+H)^+$ = 641

Example 521: 2-((S)-3-{4-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl)-ethanol



The compound is obtained by treating [7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-morpholin-3-yl-phenyl)-amine (Example 511) with (tert-butyldimethylsilyloxy)-acetaldehyde in methanol and sodium cyanoborohydride at 60°C, followed by a deprotection with TBAF in THF. HPLC: $t_R$ = 0.60 min (Method G); MS-ES: $(M+H)^+$ = 551

Example 522: {3-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone



The compound is prepared analogous to Example 3. HPLC: $t_R$ = 1.60 min (Method A); MS-ES: $(M+H)^+$ = 476.

Example 523: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in the preceding Examples, are prepared as follows:
250 g pulverized active ingredient is suspended in 2L Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Assays

Compounds of the present invention are assayed to measure their capacity to inhibit JAK2 and either STAT1 or STAT5 translocation pathway as described above. Results are provided in the Table 2:

Table 2: Inhibition of JAK2 and the STAT1 / STAT5 translocation pathway

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 1 | <0.003 | 0.0435 | n.d. |
| 2 | 0.0032 | 0.19 | n.d. |
| 3 | 0.0094 | 0.0985 | n.d. |
| 4 | 0.0022 | 0.0367 | n.d. |
| 5 | < 0.003 | n.d. | n.d. |
| 6 | < 0.003 | n.d. | n.d. |
| 7 | 0.0062 | 0.2545 | n.d. |
| 8 | < 0.003 | 0.032 | n.d. |
| 9 | < 0.003 | n.d. | n.d. |
| 10 | < 0.003 | n.d. | n.d. |
| 11 | 0.19 | n.d. | n.d. |
| 12 | < 0.003 | n.d. | n.d. |
| 13 | 0.0038 | 0.032 | n.d. |
| 14 | 2.1 | n.d. | n.d. |
| 15 | 0.0085 | n.d. | n.d. |
| 16 | < 0.003 | 0.025 | n.d. |
| 17 | < 0.003 | 0.0205 | n.d. |
| 18 | < 0.003 | n.d. | n.d. |
| 19 | 0.0069 | n.d. | n.d. |
| 20 | 0.0039 | n.d. | n.d. |
| 21 | 0.023 | n.d. | n.d. |
| 22 | 0.17 | n.d. | n.d. |
| 23 | 0.0036 | n.d. | n.d. |
| 24 | 0.0035 | n.d. | n.d. |
| 25 | < 0.003 | n.d. | n.d. |
| 26 | < 0.003 | n.d. | n.d. |
| 27 | < 0.003 | 0.085 | n.d. |
| 28 | 0.004 | n.d. | n.d. |
| 29 | < 0.003 | 0.091 | n.d. |
| 30 | < 0.003 | 0.2045 | n.d. |
| 31 | < 0.003 | 0.046 | n.d. |
| 32 | 0.0054 | n.d. | n.d. |
| 33 | < 0.003 | n.d. | n.d. |
| 34 | < 0.003 | 0.0695 | n.d. |
| 35 | 0.0049 | n.d. | n.d. |
| 36 | < 0.003 | 0.0109 | n.d. |
| 37 | < 0.003 | n.d. | n.d. |
| 38 | 0.0045 | n.d. | n.d. |
| 39 | 0.014 | 1.3695 | n.d. |
| 40 | < 0.003 | 0.155 | n.d. |
| 41 | < 0.003 | 0.075 | n.d. |
| 42 | 0.0031 | 0.17 | n.d. |
| 43 | < 0.003 | 0.35 | n.d. |
| 44 | < 0.003 | 0.1425 | n.d. |
| 45 | 0.0061 | n.d. | n.d. |
| 46 | 0.038 | n.d. | n.d. |
| 47 | < 0.003 | 0.073 | n.d. |
| 48 | 0.027 | 4.213 | n.d. |
| 49 | 0.014 | 0.878 | n.d. |
| 50 | < 0.003 | 0.184 | n.d. |
| 51 | < 0.003 | n.d. | n.d. |
| 52 | < 0.003 | n.d. | n.d. |
| 53 | < 0.003 | 0.0905 | n.d. |
| 54 | 0.0044 | 3.1085 | n.d. |
| 55 | 0.02 | n.d. | n.d. |
| 56 | 0.032 | 4.675 | n.d. |
| 57 | < 0.003 | 0.7725 | n.d. |
| 58 | 0.012 | 5.295 | n.d. |
| 59 | 0.0065 | 0.92 | n.d. |
| 60 | 0.0081 | 4.0785 | n.d. |
| 61 | 0.0071 | 0.835 | n.d. |
| 62 | 0.18 | 5.39 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 63 | 0.073 | n.d. | n.d. |
| 64 | < 0.003 | 0.04 | n.d. |
| 65 | 0.0054 | 0.0995 | n.d. |
| 66 | 0.0035 | 0.0755 | n.d. |
| 67 | < 0.003 | 0.039 | n.d. |
| 68 | < 0.003 | 0.105 | n.d. |
| 69 | 0.0048 | n.d. | n.d. |
| 70 | 0.0056 | 0.275 | n.d. |
| 71 | 0.0068 | 0.362 | n.d. |
| 72 | 0.0037 | 0.75 | n.d. |
| 73 | < 0.003 | 0.0805 | n.d. |
| 74 | < 0.003 | 0.0755 | n.d. |
| 75 | < 0.003 | 0.0825 | n.d. |
| 76 | 0.038 | 0.9345 | n.d. |
| 77 | 0.038 | 2.62 | n.d. |
| 78 | 0.029 | 0.545 | n.d. |
| 79 | 0.0048 | 0.257 | n.d. |
| 80 | 0.43 | 10 | n.d. |
| 81 | 0.018 | 2.7 | n.d. |
| 82 | 0.0041 | 0.86 | n.d. |
| 83 | < 0.003 | 0.46 | n.d. |
| 84 | < 0.003 | 0.275 | n.d. |
| 85 | 0.0038 | 3.505 | n.d. |
| 86 | 0.008 | 12.975 | n.d. |
| 87 | 0.0038 | 18.3 | n.d. |
| 88 | 0.0089 | 3.27 | n.d. |
| 89 | < 0.003 | 0.41 | n.d. |
| 90 | 0.0034 | 0.715 | n.d. |
| 91 | < 0.003 | 0.435 | n.d. |
| 92 | 0.0042 | 0.26 | n.d. |
| 93 | < 0.003 | 0.191 | n.d. |
| 94 | 0.0038 | 0.259 | n.d. |
| 95 | 0.0165 | 2.365 | n.d. |
| 96 | 0.0485 | 26.2 | n.d. |
| 97 | 0.0094 | 1.455 | n.d. |
| 98 | 0.0056 | 0.575 | n.d. |
| 99 | 0.0039 | 0.555 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 100 | < 0.003 | 0.51 | n.d. |
| 101 | < 0.003 | 0.18 | n.d. |
| 102 | < 0.003 | 0.275 | n.d. |
| 103 | < 0.003 | 0.22 | n.d. |
| 104 | 0.0036 | 0.865 | n.d. |
| 105 | 0.0115 | 5.845 | n.d. |
| 106 | 0.033 | 8.385 | n.d. |
| 107 | 0.0081 | 1.835 | n.d. |
| 108 | 0.0066 | 1.685 | n.d. |
| 109 | 0.0083 | 0.3105 | n.d. |
| 110 | 0.0135 | 1.1125 | n.d. |
| 111 | 0.0145 | 0.8465 | n.d. |
| 112 | < 0.003 | 0.073 | n.d. |
| 113 | 0.0042 | 0.108 | n.d. |
| 114 | 0.0059 | 0.2015 | n.d. |
| 115 | 0.016 | 0.7145 | n.d. |
| 116 | 0.0125 | 0.563 | n.d. |
| 117 | 0.0094 | 0.384 | n.d. |
| 118 | 0.075 | 1.515 | n.d. |
| 119 | 0.088 | 1.757 | n.d. |
| 120 | 0.155 | 7.851 | n.d. |
| 121 | 0.0155 | 0.152 | n.d. |
| 122 | 0.0033 | 0.1645 | n.d. |
| 123 | 0.028 | 0.8025 | n.d. |
| 124 | 0.085 | 2.155 | n.d. |
| 125 | < 0.003 | 0.12 | n.d. |
| 126 | 0.011 | 1.6225 | n.d. |
| 127 | 0.0105 | 0.7205 | n.d. |
| 128 | 0.12 | 3.6775 | n.d. |
| 129 | 0.009 | 0.471 | n.d. |
| 130 | 0.115 | 8.412 | n.d. |
| 131 | 0.016 | 1.502 | n.d. |
| 132 | 0.0405 | 6.2805 | n.d. |
| 133 | 0.0071 | 0.573 | n.d. |
| 134 | 0.0205 | 1.875 | n.d. |
| 135 | 0.0049 | 0.42 | n.d. |
| 136 | 0.011 | 0.775 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 137 | 0.0033 | 0.15 | n.d. |
| 138 | < 0.003 | 0.165 | n.d. |
| 139 | 0.011 | 0.63 | n.d. |
| 140 | 0.0045 | 0.31 | n.d. |
| 141 | < 0.003 | 0.13 | n.d. |
| 142 | < 0.003 | 0.101 | n.d. |
| 143 | < 0.003 | 0.195 | n.d. |
| 144 | 0.0047 | 0.475 | n.d. |
| 145 | 0.007 | 0.365 | n.d. |
| 146 | 0.03 | 2.51 | n.d. |
| 147 | < 0.003 | 0.033 | n.d. |
| 148 | 0.0079 | 0.047 | n.d. |
| 149 | 0.13 | 1.509 | n.d. |
| 150 | 0.0045 | 0.0645 | n.d. |
| 151 | 0.0057 | 0.2285 | n.d. |
| 152 | 0.0035 | 0.168 | n.d. |
| 153 | < 0.003 | 0.0175 | n.d. |
| 154 | 0.25 | 6.435 | n.d. |
| 155 | 0.2 | 3.275 | n.d. |
| 156 | 0.013 | 0.06 | n.d. |
| 157 | 0.0061 | 0.13 | n.d. |
| 158 | 0.0094 | 0.265 | n.d. |
| 159 | 0.0465 | 1.123 | n.d. |
| 160 | 0.0418 | 0.973 | n.d. |
| 161 | 0.87 | 9.348 | n.d. |
| 162 | 0.305 | 9.695 | n.d. |
| 163 | 0.295 | 23.495 | n.d. |
| 164 | 0.23 | 10.725 | n.d. |
| 165 | < 0.003 | 0.125 | n.d. |
| 166 | 0.0034 | 0.145 | n.d. |
| 167 | 0.039 | 2.07 | n.d. |
| 168 | 0.0305 | 3.905 | n.d. |
| 169 | 0.0043 | 0.093 | n.d. |
| 170 | 0.017 | 0.3745 | n.d. |
| 171 | < 0.003 | 0.26 | n.d. |
| 172 | < 0.003 | 0.22 | n.d. |
| 173 | 0.0055 | 0.235 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 174 | < 0.003 | 0.15 | n.d. |
| 175 | < 0.003 | 0.275 | n.d. |
| 176 | 0.0073 | 1.55 | n.d. |
| 177 | 0.0053 | 1.035 | n.d. |
| 178 | 0.0091 | 0.79 | n.d. |
| 179 | 0.0104 | 1.515 | n.d. |
| 180 | < 0.003 | 0.12 | n.d. |
| 181 | 0.0155 | 16.6 | n.d. |
| 182 | < 0.003 | 0.125 | n.d. |
| 183 | 0.0033 | 0.095 | n.d. |
| 184 | < 0.003 | 0.035 | n.d. |
| 185 | < 0.003 | 0.29 | n.d. |
| 186 | < 0.003 | 0.095 | n.d. |
| 187 | < 0.003 | 0.055 | n.d. |
| 188 | < 0.003 | 0.06 | n.d. |
| 189 | 0.0095 | 0.846 | n.d. |
| 190 | 0.0052 | 0.439 | n.d. |
| 191 | 0.0285 | 3.9175 | n.d. |
| 192 | 0.0115 | 1.488 | n.d. |
| 193 | 0.0084 | 0.351 | n.d. |
| 194 | < 0.003 | 0.2015 | n.d. |
| 195 | 0.0053 | 0.3525 | n.d. |
| 196 | < 0.003 | 0.176 | n.d. |
| 197 | < 0.003 | 0.09 | n.d. |
| 198 | < 0.003 | n.d. | n.d. |
| 199 | < 0.003 | 0.222 | n.d. |
| 200 | 0.0037 | n.d. | n.d. |
| 201 | < 0.003 | 0.199 | n.d. |
| 202 | 0.0045 | 0.198 | n.d. |
| 203 | 0.0074 | 0.4125 | n.d. |
| 204 | < 0.003 | n.d. | n.d. |
| 205 | 0.005 | n.d. | n.d. |
| 206 | < 0.003 | n.d. | n.d. |
| 207 | < 0.003 | n.d. | n.d. |
| 208 | 0.0048 | 0.442 | n.d. |
| 209 | 0.125 | n.d. | n.d. |
| 210 | 0.0058 | 0.634 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 211 | 0.0059 | n.d. | n.d. |
| 212 | < 0.003 | 0.1055 | n.d. |
| 213 | 0.0059 | 0.7275 | n.d. |
| 214 | 0.0051 | 0.643 | n.d. |
| 215 | 0.42 | 10 | n.d. |
| 216 | 0.0033 | 0.579 | n.d. |
| 217 | 0.0073 | 0.993 | n.d. |
| 218 | 1.05 | 10 | n.d. |
| 219 | 0.0077 | 0.518 | n.d. |
| 220 | 0.011 | 0.88 | n.d. |
| 221 | 0.0047 | 0.36 | n.d. |
| 222 | 0.29 | n.d. | n.d. |
| 223 | 0.0092 | 0.455 | n.d. |
| 224 | 0.0085 | 1.075 | n.d. |
| 225 | 0.0074 | 0.4335 | n.d. |
| 226 | 0.0105 | 0.666 | n.d. |
| 227 | 0.0415 | n.d. | n.d. |
| 228 | 0.0565 | n.d. | n.d. |
| 229 | 0.021 | 1.5765 | n.d. |
| 230 | 0.0205 | 2.475 | n.d. |
| 231 | 0.0032 | 0.2575 | n.d. |
| 232 | 0.019 | 1.16 | n.d. |
| 233 | 0.0064 | 1.182 | n.d. |
| 234 | 0.0081 | 0.91 | n.d. |
| 235 | 0.056 | n.d. | n.d. |
| 236 | 0.046 | n.d. | n.d. |
| 237 | 0.007 | 2.555 | n.d. |
| 238 | 0.0111 | 0.785 | n.d. |
| 239 | 0.0039 | 0.66 | n.d. |
| 240 | 0.0052 | 0.73 | n.d. |
| 241 | 0.0054 | 0.37 | n.d. |
| 242 | 0.0043 | 0.355 | n.d. |
| 243 | < 0.003 | 0.225 | n.d. |
| 244 | < 0.003 | 0.43 | n.d. |
| 245 | < 0.003 | 0.43 | n.d. |
| 246 | 0.028 | 3.995 | n.d. |
| 247 | 0.0037 | 0.255 | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 248 | 0.024 | 4.27 | n.d. |
| 249 | 0.0043 | 0.815 | n.d. |
| 250 | 0.0091 | 0.94 | n.d. |
| 251 | 0.0061 | 0.45 | n.d. |
| 252 | 0.0033 | 0.34 | n.d. |
| 253 | 0.0071 | 0.13 | n.d. |
| 254 | < 0.003 | n.d. | n.d. |
| 255 | 0.0069 | 0.115 | n.d. |
| 256 | < 0.003 | 0.115 | n.d. |
| 257 | 0.01 | 0.15 | n.d. |
| 258 | < 0.003 | 0.08 | n.d. |
| 259 | < 0.003 | 0.08 | n.d. |
| 260 | 0.005 | 0.28 | n.d. |
| 261 | 0.012 | 0.18 | n.d. |
| 262 | 0.0042 | 0.285 | n.d. |
| 263 | < 0.003 | 0.055 | n.d. |
| 264 | < 0.003 | 0.165 | n.d. |
| 265 | < 0.003 | 0.04 | n.d. |
| 266 | 0.0084 | 0.15 | n.d. |
| 267 | < 0.003 | 0.05 | n.d. |
| 268 | 0.0078 | 0.21 | n.d. |
| 269 | 0.01 | 0.465 | n.d. |
| 270 | 0.0043 | 0.035 | n.d. |
| 271 | 0.0031 | 0.065 | n.d. |
| 272 | 0.011 | 0.175 | n.d. |
| 273 | 0.006 | 0.19 | n.d. |
| 274 | 0.0072 | 0.52 | n.d. |
| 275 | 0.007 | n.d. | n.d. |
| 276 | 0.12 | n.d. | n.d. |
| 277 | 0.0083 | n.d. | n.d. |
| 278 | 0.011 | n.d. | n.d. |
| 279 | 0.004 | n.d. | n.d. |
| 280 | 0.0035 | n.d. | n.d. |
| 281 | 0.024 | n.d. | n.d. |
| 282 | 0.082 | n.d. | n.d. |
| 283 | 0.023 | n.d. | n.d. |
| 284 | 0.0037 | n.d. | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 285 | < 0.003 | n.d. | n.d. |
| 286 | 0.0106 | 0.285 | n.d. |
| 287 | 0.0465 | 0.441 | n.d. |
| 288 | < 0.003 | 0.0675 | n.d. |
| 289 | < 0.017 | 0.2315 | n.d. |
| 290 | < 0.003 | 0.037 | n.d. |
| 291 | < 0.003 | 0.054 | n.d. |
| 292 | < 0.003 | 0.0125 | n.d. |
| 293 | < 0.003 | 0.008 | n.d. |
| 294 | < 0.003 | 0.415 | n.d. |
| 295 | 0.0145 | 0.795 | n.d. |
| 296 | < 0.003 | 1.105 | n.d. |
| 297 | 0.03 | 2.145 | n.d. |
| 298 | 0.023 | 2.21 | n.d. |
| 299 | 0.0185 | 0.145 | n.d. |
| 300 | 0.0175 | 2.03 | n.d. |
| 301 | < 0.003 | 0.05 | n.d. |
| 302 | 0.0061 | 0.085 | n.d. |
| 303 | 0.0049 | 0.295 | n.d. |
| 304 | 0.0135 | 1.485 | n.d. |
| 305 | 0.026 | 2.675 | n.d. |
| 306 | 0.0395 | 0.55 | n.d. |
| 307 | 0.014 | 0.12 | n.d. |
| 308 | < 0.003 | 0.015 | n.d. |
| 309 | 0.78 | 4.155 | n.d. |
| 310 | 0.0064 | 0.57 | n.d. |
| 311 | 0.031 | 1.4 | n.d. |
| 312 | 0.013 | 0.565 | n.d. |
| 313 | 0.0037 | n.d. | n.d. |
| 314 | < 0.003 | n.d. | n.d. |
| 315 | < 0.003 | n.d. | n.d. |
| 316 | 0.073 | n.d. | n.d. |
| 317 | 0.94 | n.d. | n.d. |
| 318 | < 0.003 | n.d. | n.d. |
| 319 | < 0.003 | n.d. | n.d. |
| 320 | 0.0095 | n.d. | n.d. |
| 321 | < 0.003 | n.d. | n.d. |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 322 | < 0.003 | n.d. | n.d. |
| 323 | 0.0032 | n.d. | n.d. |
| 324 | 0.026 | n.d. | n.d. |
| 325 | 0.025 | n.d. | n.d. |
| 326 | < 0.003 | n.d. | n.d. |
| 327 | < 0.003 | n.d. | n.d. |
| 328 | 0.016 | n.d. | n.d. |
| 329 | 0.004 | n.d. | n.d. |
| 330 | 0.014 | n.d. | n.d. |
| 331 | 0.003 | n.d. | 0.0028 |
| 332 | 0.003 | 0.375 | 0.073 |
| 333 | 0.0039 | 0.53 | n.d. |
| 334 | 0.003 | 0.26 | n.d. |
| 335 | 0.0093 | 0.36 | n.d. |
| 336 | 0.0036 | 0.205 | n.d. |
| 337 | 0.0061 | 0.185 | n.d. |
| 338 | 0.0039 | 0.135 | n.d. |
| 339 | 0.0037 | 0.285 | n.d. |
| 340 | 0.0072 | 0.27 | n.d. |
| 341 | 0.003 | n.d. | n.d. |
| 342 | 0.003 | 0.4788 | n.d. |
| 343 | 0.003 | 0.1512 | n.d. |
| 344 | 0.003 | n.d. | n.d. |
| 345 | 0.0033 | n.d. | n.d. |
| 346 | 0.003 | n.d. | 0.0028 |
| 347 | 0.003 | n.d. | 0.0133 |
| 348 | 0.0062 | n.d. | n.d. |
| 349 | 0.016 | n.d. | n.d. |
| 350 | 0.003 | n.d. | 0.0218 |
| 351 | 0.0043 | n.d. | 0.0013 |
| 352 | 0.003 | n.d. | 0.0221 |
| 353 | 0.0049 | n.d. | 0.017 |
| 354 | 0.003 | n.d. | 0.0013 |
| 355 | 0.0037 | n.d. | 0.0053 |
| 356 | 0.0032 | n.d. | 0.0059 |
| 357 | 0.0069 | n.d. | n.d. |
| 358 | 0.0072 | n.d. | 0.059 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 359 | 0.0074 | n.d. | 0.135 |
| 360 | 0.0033 | n.d. | 0.0072 |
| 361 | 0.023 | n.d. | 0.2595 |
| 362 | 0.024 | n.d. | 0.152 |
| 363 | 0.0032 | n.d. | 0.011 |
| 364 | 0.003 | n.d. | 0.0028 |
| 365 | 0.0046 | n.d. | 0.043 |
| 366 | 0.0086 | n.d. | 0.065 |
| 367 | 0.0084 | n.d. | 0.144 |
| 368 | 0.0032 | n.d. | n.d. |
| 369 | 0.003 | n.d. | 0.057 |
| 370 | 0.003 | n.d. | 0.0313 |
| 371 | 0.013 | n.d. | 0.135 |
| 372 | 0.0047 | n.d. | 0.057 |
| 373 | 0.0043 | n.d. | n.d. |
| 374 | 0.0099 | n.d. | n.d. |
| 375 | 0.0065 | n.d. | 0.0077 |
| 376 | 0.003 | n.d. | 0.067 |
| 377 | 0.049 | n.d. | >2.6 |
| 378 | 0.013 | n.d. | 0.045 |
| 379 | 0.011 | n.d. | n.d. |
| 380 | 0.0032 | n.d. | 0.046 |
| 381 | 0.003 | n.d. | 0.043 |
| 382 | 0.0035 | n.d. | 0.121 |
| 383 | 0.0051 | n.d. | 0.0061 |
| 384 | 0.003 | n.d. | 0.012 |
| 385 | 0.003 | n.d. | 0.0655 |
| 386 | 0.11 | n.d. | 0.101 |
| 387 | 0.0096 | n.d. | 0.0455 |
| 388 | 0.003 | n.d. | n.d. |
| 389 | 0.003 | n.d. | n.d. |
| 390 | 0.015 | n.d. | 0.104 |
| 391 | 0.0049 | n.d. | 0.15 |
| 392 | 0.003 | n.d. | 0.068 |
| 393 | 0.013 | n.d. | 0.052 |
| 394 | 0.003 | n.d. | 0.0016 |
| 395 | 0.003 | n.d. | 0.017 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 396 | 0.003 | n.d. | 0.147 |
| 397 | 0.003 | n.d. | 0.013 |
| 398 | 0.003 | n.d. | 0.245 |
| 399 | 0.003 | n.d. | 0.0066 |
| 400 | 0.007 | n.d. | 0.0017 |
| 401 | 0.007 | n.d. | 0.1385 |
| 402 | 0.003 | n.d. | 1.372 |
| 403 | 0.003 | n.d. | 0.0225 |
| 404 | 0.0056 | n.d. | 0.141 |
| 405 | 0.003 | n.d. | 0.0032 |
| 406 | 0.004 | n.d. | >4 |
| 407 | 0.003 | n.d. | 0.305 |
| 408 | 0.003 | n.d. | 0.0092 |
| 409 | 0.003 | n.d. | 0.0816 |
| 410 | 0.003 | n.d. | 0.0083 |
| 411 | 0.003 | n.d. | 0.0026 |
| 412 | 0.003 | n.d. | 0.0265 |
| 413 | 0.003 | n.d. | 0.0285 |
| 414 | 0.003 | n.d. | 0.0042 |
| 415 | 0.003 | n.d. | 0.0069 |
| 416 | 0.003 | n.d. | n.d. |
| 417 | 0.003 | n.d. | 0.005 |
| 418 | 0.0046 | n.d. | 0.016 |
| 419 | 0.0043 | n.d. | 0.0385 |
| 420 | 0.003 | n.d. | n.d. |
| 421 | 0.003 | n.d. | 0.0027 |
| 422 | 0.003 | n.d. | 0.0057 |
| 423 | 0.003 | n.d. | 0.0059 |
| 424 | 0.003 | n.d. | 0.009 |
| 425 | 0.003 | n.d. | 0.0036 |
| 426 | 0.003 | n.d. | 0.0183 |
| 427 | 0.003 | n.d. | 0.0332 |
| 428 | 0.003 | n.d. | 0.0107 |
| 429 | 0.003 | n.d. | 0.041 |
| 430 | 0.003 | n.d. | 0.0036 |
| 431 | 0.0032 | n.d. | 0.0235 |
| 432 | 0.003 | n.d. | 0.0004 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 433 | 0.003 | n.d. | 0.0063 |
| 434 | 0.003 | n.d. | 0.0315 |
| 435 | 0.003 | n.d. | 0.0034 |
| 436 | 0.003 | n.d. | 0.0061 |
| 437 | 0.0033 | n.d. | n.d. |
| 438 | 0.003 | n.d. | n.d. |
| 439 | 0.019 | n.d. | n.d. |
| 440 | 0.0032 | n.d. | 0.061 |
| 441 | 0.003 | 0.045 | n.d. |
| 442 | 0.003 | n.d. | n.d. |
| 443 | 0.003 | 0.0095 | n.d. |
| 444 | 0.003 | 0.09 | n.d. |
| 445 | 0.043 | n.d. | n.d. |
| 446 | 0.0043 | 0.05 | 0.0013 |
| 447 | 0.0096 | 0.105 | 0.0118 |
| 448 | 0.005 | n.d. | 0.0074 |
| 449 | 0.003 | n.d. | n.d. |
| 450 | 0.003 | n.d. | n.d. |
| 451 | 0.0038 | n.d. | 0.024 |
| 452 | 0.0062 | n.d. | 0.0795 |
| 453 | 0.0041 | n.d. | 0.036 |
| 454 | 0.0045 | n.d. | 0.0535 |
| 455 | 0.0043 | n.d. | 0.038 |
| 456 | 0.003 | n.d. | 0.0019 |
| 457 | 0.003 | n.d. | 0.021 |
| 458 | 0.003 | n.d. | 0.0014 |
| 459 | 0.0051 | n.d. | 0.1045 |
| 460 | 0.003 | n.d. | n.d. |
| 461 | 0.003 | n.d. | n.d. |
| 462 | 0.003 | n.d. | 0.051 |
| 463 | 0.003 | n.d. | 0.048 |
| 464 | 0.003 | n.d. | 0.059 |
| 465 | 0.003 | n.d. | 0.0032 |
| 466 | 0.0079 | n.d. | 0.056 |
| 467 | 0.0046 | n.d. | n.d. |
| 468 | 0.003 | n.d. | 0.014 |
| 469 | 0.003 | n.d. | 0.025 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 470 | 0.061 | n.d. | 0.017 |
| 471 | 0.0035 | n.d. | 0.0315 |
| 472 | 0.0036 | n.d. | 0.092 |
| 473 | 0.003 | n.d. | 0.0123 |
| 474 | 0.003 | n.d. | 0.0086 |
| 475 | 0.003 | n.d. | 0.0053 |
| 476 | 0.003 | n.d. | 0.0345 |
| 477 | 0.017 | n.d. | 0.718 |
| 478 | 0.0055 | n.d. | 0.051 |
| 479 | 0.0035 | n.d. | 0.015 |
| 480 | 0.003 | n.d. | 0.071 |
| 481 | 0.0051 | n.d. | n.d. |
| 482 | 0.003 | n.d. | 0.15 |
| 483 | 0.003 | n.d. | 0.0123 |
| 484 | 0.003 | n.d. | 0.067 |
| 485 | 0.003 | n.d. | 0.11 |
| 486 | 0.003 | n.d. | 0.487 |
| 487 | 0.003 | n.d. | 0.0058 |
| 488 | 0.003 | n.d. | 0.0405 |
| 489 | 0.0007 | n.d. | 0.012 |
| 490 | 0.0034 | n.d. | 0.014 |
| 491 | 0.003 | n.d. | 0.015 |
| 492 | 0.0022 | n.d. | 0.0555 |
| 493 | 0.003 | n.d. | 0.1045 |
| 494 | 0.003 | n.d. | 0.394 |
| 495 | 0.003 | n.d. | 0.051 |
| 496 | 0.003 | n.d. | 0.0972 |
| 497 | 0.003 | n.d. | 0.0077 |
| 498 | 0.003 | n.d. | 0.083 |
| 499 | 0.0048 | n.d. | 0.22 |
| 500 | 0.003 | n.d. | 0.016 |
| 501 | 0.003 | n.d. | 0.038 |
| 502 | 0.003 | n.d. | 0.017 |
| 503 | 0.003 | n.d. | 0.0275 |
| 504 | 0.003 | n.d. | 0.0815 |
| 505 | 0.0041 | n.d. | 0.06 |
| 506 | 0.003 | n.d. | 0.038 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 507 | <0.003 | n.d. | 0.0002 |
| 508 | 0.0041 | n.d. | 0.0148 |
| 509 | <0.003 | n.d. | 0.0431 |
| 510 | 0.003 | n.d. | 0.001 |
| 511 | 0.003 | n.d. | 0.0039 |
| 512 | 0.003 | n.d. | 0.014 |
| 513 | 0.0046 | n.d. | 0.116 |
| 514 | 0.025 | n.d. | 1.323 |
| 515 | 0.003 | n.d. | 0.054 |
| 516 | 0.0064 | n.d. | 0.119 |

| ex.# | JAK2/IC50 [µmol l-1] | STAT1/IC50 [µmol l-1] | STAT5/IC50 [µmol l-1] |
|---|---|---|---|
| 517 | 0.003 | n.d. | 0.0695 |
| 518 | 0.003 | n.d. | 0.0395 |
| 519 | 0.0036 | n.d. | 0.0605 |
| 520 | 0.057 | n.d. | 0.543 |
| 521 | 0.003 | n.d. | n.d. |
| 522 | 0.008 | 2.89 | n.d. |

n.d. = not determined

As shown in Table 2, the compounds of ex. 1 – 522 show JAK2 inhibition IC50-values in the range < 0.003 – 2.1 µmol l-1, in particular in the range < 0.003 – 0.05 µmol l-1.

Compounds of the invention selectively inhibit JAK2 when compared to other kinases, for example cMet, cKit, ALK and PDGFRa as shown by the results of Table 3.

The compounds are assayed in an antibody based kinase phosphorylation assay using the recombinant domains of cMet, cKit, ALK and PDGFRalpha kinases and a generic phospho-tyrosine peptide substrate. LanthaScreen™ is the detection of Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) using lanthanide chelates to measure interactions between various binding partners. In a TR-FRET kinase assay, a long-lifetime lanthanide donor species is conjugated to an antibody that specifically binds to a phosphorylated product of a kinase reaction that is labeled with a suitable acceptor fluorophore. This antibody-mediated interaction brings the lanthanide donor and the acceptor into proximity such that resonance energy transfer can take place, resulting in a detectible increase in FRET. The LanthaScreen is run at ambient temperature and terminated by the addition of stop solution, followed by Tb-labeled P-20 antibody. After incubating in the dark, the plates are transferred to a fluorescence reader for counting. The effect of compound on the enzymatic activity is in all assays obtained from the linear progress curves and determined from one reading (end point measurement).

Table 3:

| ex.# | JAK2/IC50 [µmol l-1] | cMet/IC50 [µmol l-1] | cKit/IC50 [µmol l-1] | ALK/IC50 [µmol l-1] | PDGFRa/IC50 [µmol l-1] |
|---|---|---|---|---|---|
| 96 | 0.0485 | > 10 | > 10 | > 10 | > 10 |
| 151 | 0.0057 | > 10 | > 10 | > 10 | > 10 |
| 184 | < 0.003 | > 10 | > 10 | > 10 | > 10 |
| 203 | 0.0064 | 6.9 | 4.7 | > 10 | > 10 |
| 235 | 0.056 | > 10 | > 10 | > 10 | > 10 |
| 238 | 0.0111 | 8.2 | > 10 | > 10 | 6.6 |
| 278 | 0.011 | 1.4 | 1.35 | > 10 | 2.65 |
| 300 | 0.0175 | > 10 | 3.4 | > 10 | 7.7 |
| 301 | < 0.003 | 3.6 | 4.75 | > 10 | 5.6 |
| 311 | 0.031 | > 10 | > 10 | > 10 | > 10 |
| 332 | 0.001 | 7.567 | 1.552 | 9.05 | 6.7 |
| 372 | 0.0047 | > 10 | 5.7 | > 10 | > 10 |
| 380 | 0.0032 | 5.4 | 1.7 | > 10 | 5.3 |
| 382 | 0.0035 | 2.4 | 1.1 | > 10 | 7.7 |
| 440 | 0.0032 | > 10 | > 10 | > 10 | > 10 |
| 446 | 0.0043 | 6 | 2.65 | > 10 | 7.45 |
| 503 | < 0.003 | 6.1 | 9.5 | > 10 | > 10 |
| 521 | < 0.003 | 3.5 | 2.9 | > 10 | 2.8 |

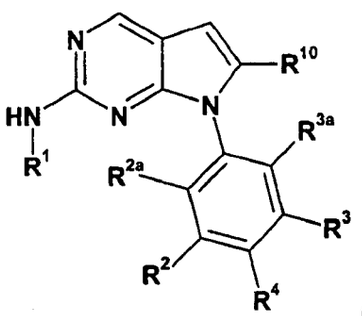
Compounds of the present invention are further assayed to measure their capacity to inhibit JAK1, as described above. Compounds of ex. 1 – 522 show in this assay IC50-values in the range of < 0.003 – > 10 µmol l-1.

Compounds of the present invention are further assayed to measure their capacity to inhibit JAK3 as described above. Compounds of ex. 1 – 522 show in this assay IC50-values in the range of < 0.003 – > 10 µmol l-1.

Compounds of the present invention are further assayed to measure their capacity to inhibit TYK2 as described above. Compounds of ex. 1 – 522 show in this assay IC50-values in the range of < 0.003 – > 10 µmol l-1.

## CLAIMS

1. A compound of the formula I,



(I)

wherein

$R^1$ represents unsubstituted or substituted heterocyclyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl;

$R^2$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

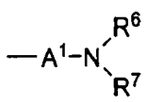
$R^3$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

or $R^2$ and/or $R^3$ are connected to $R^5$ or $R^7$ to form a cyclic moiety fused to the phenyl ring to which $R^2/R^3$ are attached;

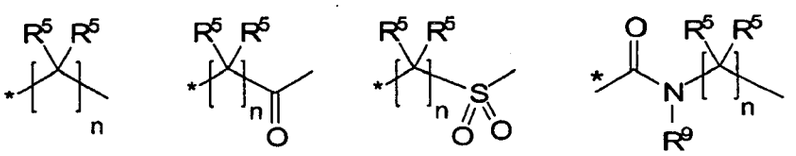
$R^{2a}$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^{3a}$ represents hydrogen, halogen, lower alkyl, lower alkyloxy, lower haloalkyl, cycloalkyl, cycloalkyloxy, halocycloalkyl, cycloalkyloxy, halocycloalkyloxy;

$R^4$ represents a group:



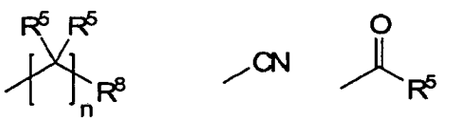
wherein $A^1$ represents one of the following groups:



in which the atom marked * is bond to the phenyl ring;

or

$R^4$ represents one of the following groups:



$R^5$ represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle

or

$R^6$ represents hydrogen or optionally substituted alkyl and

$R^7$ represents optionally substituted alkyl;

$R^8$ represents alkyl, hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;

$R^9$ represents H or lower alkyl;

$R^{10}$ represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;

n represens 0, 1 or 2;

or salts thereof.

2. A compound of the formula I according to claim 1, wherein

$R^1$ represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl

wherein said heterocyclyl is selected from unsaturated, saturated or partially saturated heterocycles which are monocyclic bicyclic, tricyclic or spirocyclic and have 4 to 16, ring atoms wherein one to four heteroatoms are present;

wherein said aryl is selected from aromatic moieties with 6 to 14 ring carbon atoms;

wherein said substiutents are independently selected from one or more, preferably one to four of the following moieties: $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-

alkyl]-piperazin-1-yl-$C_1$-$C_7$-alkyl, morpholino-$C_1$-$C_7$-alkyl, thiomorpholino-$C_1$-$C_7$-alkyl, S-mono- or S,S-dioxo-thiomorpholino-$C_1$-$C_7$-alkyl, carbamoyl-$C_1$-$C_7$-alkyl, [N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-carbamoyl]-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfinyl-$C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkanesulfonyl-$C_1$-$C_7$-alkyl, halo, hydroxyl, $C_1$-$C_7$-alkoxy, amino, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-amino, $C_1$-$C_7$-alkanoylamino, pyrrolidino, oxo-pyrrolidino, piperidino, piperazin-1-yl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-alkyl]-piperazin-1-yl, morpholino, thiomorpholino, S-oxo- or S,S-dioxothiomorpholino, $C_1$-$C_7$-alkanesulfonylamino, carbamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl and/or (N'-mono- or N',N'-di-($C_1$-$C_7$-alkyl)-amino-$C_1$-$C_7$-alkyl)-carbamoyl, pyrrolidin-1-carbonyl, piperidin-1-carbonyl, piperazin-1-carbonyl, 4-($C_1$-$C_7$-alkyl)piperazin-1-carbonyl, morpholin-1-carbonyl, thiomorpholin-1-carbonyl, S-oxo- or S,S-dioxothiomorpholin-1-carbonyl, sulfo, $C_1$-$C_7$-alkanesulfonyl, $C_1$-$C_7$-alkanesulfinyl, sulfamoyl, N-mono- or N,N-di-($C_1$-$C_7$-alkyl)-sulfamoyl, morpholinosulfonyl, thiomorpholinosulfonyl, cyano and nitro;

$R^2$ represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy;

$R^{2a}$ represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy;

$R^3$ represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy;

$R^{3a}$ represents hydrogen, halogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy

$R^5$ represents hydrogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-haloalkyl, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-halocycloalkyl, or form, together with the carbon to which they are attached, a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle substituted by one or more substituents,

wherein said heterocycle is saturated, contains 5 or 6 ring atoms and 1, 2 or 3 heteroatoms selected from the group of N, O and S, and
wherein said substituents are selected from the group consisting of oxo(e.g. in C=O or SO2), hydroxy, halo, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyl, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyl, $C_3$-$C_6$-halocycloalkyloxy hydroxy- $C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkylamino, di- $C_1$-$C_7$-alkylamino;

$R^8$ represents hydroxy, $C_1$-$C_7$-alkyloxy, $C_1$-$C_7$-haloalkyloxy, $C_3$-$C_6$-cycloalkyloxy, $C_3$-$C_6$-halocycloalkyloxy, $C_1$-$C_7$-alkyl- sulfonyl, $C_1$-$C_7$-haloalkyl- sulfonyl, $C_3$-$C_6$-cycloalkyl- sulfonyl, $C_3$-$C_6$-halocycloalkyl- sulfonyl, $C_1$-$C_7$-alkyl- sulfinyl, $C_1$-$C_7$-haloalkyl-sulfinyl, $C_3$-$C_6$-cycloalkyl- sulfinyl, $C_3$-$C_6$-halocycloalkyl- sulfinyl;

$R^{10}$ represents hydrogen, $C_1$-$C_7$-alkyl, $C_1$-$C_7$-haloalkyl, $C_3$-$C_6$-cycloalkyl, $C_3$-$C_6$-halocycloalkyl

or a salt thereof.

3. A compound of the formula I according to claim 1 or 2, wherein,

$R^2$ represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro;

$R^{2a}$ represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro

$R^3$ represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro;

$R^{3a}$ represents hydrogen, fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopentyl, cyclopropyloxy or cyclopentyloxy in each case optionally substituted by one or more substituents selected from the group consisting of fluoro and chloro;

$R^5$ represents hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_2$-haloalkyl, or form, together with the carbon to which they are attached, a cyclopropyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle optionally substituted by one to three substituents,
wherein said heterocycle is selected from the group of morpholinyl, piperazinyl, thiazidinyl, pyrrolidinyl and
wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopropyloxy, hydroxy- $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkylamino, di-$C_1$-$C_4$-alkylamino;

$R^8$ represents hydroxy, methoxy, ethoxy, iso-propoxy, halomethoxy, methylsulfonyl, cyclopropylsulfonyl, methylsulfinyl;

$R^{10}$ represents hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_2$-haloalkyl, cyclopropyl.

or a salt thereof.

4. A compound of the formula I according to any of claims 1 to 3, wherein

$R^2$ represents hydrogen, fluoro, chloro, methyl;

$R^{2a}$ represents hydrogen;

$R^3$ represents hydrogen, fluoro, chloro, methyl;

$R^{3a}$ represents hydrogen;

$R^5$ represents hydrogen, methyl or form, together with the carbon to which they are attached, a cyclopropyl;

$R^8$ represents hydroxy or methylsulfonyl;

$R^{10}$ represents hydrogen or methyl;

or a salt thereof.

5. A compound of the formula I according to any of claims 1 to 3, wherein

$R^2$ represents hydrogen, fluoro, chloro, methyl;

$R^{2a}$ represents hydrogen;

$R^3$ represents hydrogen, fluoro, chloro, methyl;

$R^{3a}$ represents hydrogen;

$R^5$ represents hydrogen, methyl or form, together with the carbon to which they are attached, a cyclopropyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle optionally substituted by one to three substituents,

wherein said heterocycle is selected from the group of morpholinyl, piperazinyl, thiazidinyl, pyrrolidinyl and

wherein said substituents are selected from the group consisting of oxo (e.g. in C=O or $SO_2$), fluoro, chloro, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkyloxy, cyclopropyl, cyclopropyloxy, hydroxy- $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkylamino, di-$C_1$-$C_4$-alkylamino;

$R^8$ represents hydroxy or methylsulfonyl;

$R^{10}$ represents hydrogen or methyl;

or a salt thereof.

6. A compound of the formula I according to claim 1, wherein at least one of $R^2$ and $R^3$ does not represent hydrogen.

7. A compound selected from the group consisting of:

(3,4-Diethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

(4-Isopropoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4,5-trimethoxy-phenyl)-amine;

(3,4-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

N-tert-Butyl-4-[2-(3,4-dimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide;

N-tert-Butyl-4-[2-(3,4-dimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide;

N-tert-Butyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide;

N-tert-Butyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide;

N,N-Dimethyl-4-[2-(3,4,5-trimethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide;

(4,5-Dimethoxy-2-methyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methyl-1,2,3,4,4a,5-hexahydro-7H-6-oxa-3,11b-diaza-dibenzo[a,c]cyclohepten-9-yl)-amine;

4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-piperazine-1-carboxylic acid diethylamide;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-amine;
Benzo[1,3]dioxol-5-yl-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(1-methyl-piperidin-4-yl)-phenyl]-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-yl)-phenyl]-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-yl)-phenyl]-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-phenyl-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxy-phenyl)-amine;
N-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-N',N'-dimethyl-benzene-1,4-diamine;
(2,4-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
(3,5-Dimethoxy-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
5-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methoxy-phenol;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amine;
[3-(2-Dimethylamino-ethoxy)-4-methoxy-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
[3-(3-Dimethylamino-propoxy)-4-methoxy-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine;
{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{3-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl}-amine;

[4-(2-Diethylamino-ethoxy)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine;

[3-(2-Diethylamino-ethoxy)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-yl-phenyl)-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;

{3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

N-(2-Dimethylamino-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-piperidin-1-ylmethyl-phenyl)-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperidin-1-ylmethyl-phenyl)-amine;

(4-Imidazol-1-ylmethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine;

4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester;

2-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-pyrrolidine-1-carboxylic acid tert-butyl ester;

(3-Imidazol-1-ylmethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

N-(2-Dimethylamino-ethyl)-3-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-phenyl-benzamide;

{3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

N-(2-Dimethylamino-ethyl)-3-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide;
N-(2-Hydroxy-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-ylmethyl-phenyl)-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-pyrrolidin-2-yl-phenyl)-amine;
[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine;
(4-Fluoro-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
{4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
{4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-pyrrolidin-1-yl-methanone;
{2-Fluoro-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
{2-Fluoro-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
1-{4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone;
{4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone
4-[2-(4-Fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-N-(2-morpholin-4-yl-ethyl)-benzamide;
N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[2-(4-fluoro-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzamide;
[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
N-(2-Dimethylamino-ethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-methyl-benzamide;
(4-Dimethylamino-piperidin-1-yl)-{4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-methanone;
4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-N-(2-morpholin-4-yl-ethyl)-benzamide;
N-(1-Ethyl-pyrrolidin-2-ylmethyl)-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide;

4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzoyl}-piperazine-1-carboxylic acid tert-butyl ester;

2-{3-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;

{2-Fluoro-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-trifluoromethyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-morpholin-4-yl-methanone;

{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-pyrrolidin-1-yl-methanone;

{2-Fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{2-Fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

N-(1-Ethyl-pyrrolidin-2-ylmethyl)-2-fluoro-5-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzamide;

1-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-ethanone;

(4-Fluoro-3-trifluoromethyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-Fluoro-3-methyl-phenyl)-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{2,6-Difluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-2-methyl-1-morpholin-4-yl-propan-1-one;

(1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

1 1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone;

{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-piperazin-1-yl-methanone;
{2-Fluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{2-Chloro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone;
{2-Fluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;
{2-Chloro-4-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzonitrile;
4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzonitrile;
[7-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine;
{2-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{2-Chloro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone;
2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;
2-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone;
(1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone;
1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-piperazin-2-one;
1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-pyrrolidin-2-one;

{7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine;

(4-Isopropoxy-phenyl)-[7-(4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

7-(4-[1,4]Diazepan-1-ylmethyl-3-fluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine;

(4-Isopropoxy-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine;

(4-Isopropoxy-phenyl)-[7-(3-methyl-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine;

{7-[3-Chloro-4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine;

1-{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanol;

(4-Isopropoxy-phenyl)-{7-[4-(2-morpholin-4-yl-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

{4-[2-(3-Chloro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-phenyl}-morpholin-4-yl-methanone;

(1-{4-[2-(3-Chloro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone;

(3-Chloro-4-methyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(3-Chloro-4-methyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(3-Chloro-4-methyl-phenyl)-{7-[4-(4-ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

(3-Chloro-4-methyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

(1-{4-[2-(4-Fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-methyl-piperazin-1-yl)-methanone;

(4-Fluoro-3-methyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3-fluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-isopropoxy-phenyl)-amine;

(4-Fluoro-3-methyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(3-Chloro-4-methyl-phenyl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(3-Chloro-4-methyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

(3-Chloro-4-methyl-phenyl)-{7-[4-(4-ethyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-fluoro-3-methyl-phenyl)-amine;

{7-[4-(4-Ethyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amine;

1-(4-{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-1-yl)-ethanone;

4-{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-1-ethyl-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine;

4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzonitrile;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-fluoro-3-methyl-phenyl)-amin;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

[7-(4-Methanesulfinylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine;

[7-(4-Methanesulfonylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine;

1-Morpholin-4-yl-2-[4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone;

2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone;

1-Morpholin-4-yl-2-[4-(2-phenylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone;
1-Morpholin-4-yl-2-{4-[2-(4-trifluoromethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone;
1-(4-Methyl-piperazin-1-yl)-2-{4-[2-(4-trifluoromethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-ethanone;
[7-(4-Morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine;
(3,4-Diethoxy-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;
1-(4-Methyl-piperazin-1-yl)-2-[4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-ethanone;
2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;
{2-Fluoro-4-[2-(4-fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone;
(4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-phenyl)-morpholin-4-yl-methanone;
{2-Fluoro-4-[2-(4-fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-1-(1,1-dioxido-1-thiomorpholin-4-yl)-ethanone;
{4-[7-(3-Fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;
{2-Fluoro-4-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;
(1-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-cyclopropyl)-(4-ethyl-piperazin-1-yl)-methanone;
(3,4-Dimethyl-phenyl)-[7-(4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

2-{4-[2-(3,4-Dimethyl-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;

2-{4-[2-(4-Fluoro-3-methoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;

(3,4-Dimethyl-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-Fluoro-3-methoxy-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

2-{4-[2-(3,4-Diethoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-ethyl-piperazin-1-yl)-ethanone;

2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone;

2-{4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-(4-methyl-piperazin-1-yl)-ethanone;

(3,4-Diethoxy-phenyl)-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-6-methyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-ethyl-piperazin-1-yl)-methanone;

2-{3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-1-(4-ethyl-piperazin-1-yl)-ethanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-yl)-phenyl]-amine;

{4-[7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

[7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine;

[7-(3-Chloro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4-diethoxy-phenyl)-amine;

{4-[7-(3,5-Difluoro-4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-pyrrolidin-1-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methoxymethyl-phenyl)-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-phenyl-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-2-yl-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-3-yl-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-pyridin-4-yl-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methoxymethyl-phenyl)-amine;

4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzonitrile;

(4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-trifluoromethyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

(4-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-phenyl)-morpholin-4-yl-methanone;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amine;

{2,6-Difluoro-4-[2-(4-methoxymethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

(4-{2-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

(4-{2-[4-(4-Ethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-(4-methyl-piperazin-1-yl)-methanone;

{2,6-Difluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

(4-Isopropoxy-phenyl)-{7-[4-(1-morpholin-4-yl-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine (racemic);

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-isopropoxy-phenyl)-amine;

{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-ethyl-piperazin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-4-ylmethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-morpholin-4-ylmethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-amine;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-trifluoromethyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl-methanone;

{3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

(2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

(2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

(2,6-Difluoro-4-{2-[3-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-phenyl-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-2-yl-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-3-yl-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-pyridin-4-yl-amine;

2-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-ethanone;

{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

[2,6-Difluoro-4-(2-phenylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(pyridin-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(pyridin-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(pyrimidin-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(6-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{4-[2-(5,6-Dimethyl-pyridin-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(4-fluoro-3-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(6-methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(6-isopropoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(6-trifluoromethyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

5-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-pyridine-2-carbonitrile;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-methyl-pyridin-3-yl)-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-methoxy-pyridin-3-yl)-amine;
{4-[2-(4-Isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(6-Isopropoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(3-Fluoro-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(6-Methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
5-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-pyridine-2-carbonitrile;
Morpholin-4-yl-{4-[2-(6-trifluoromethyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone;
4-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzonitrile;
{4-[2-(6-Methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(4-Methoxymethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{4-[2-(3-Methoxy-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{2,6-Difluoro-4-[2-(1-methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
{2,6-Difluoro-4-[2-(5-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
(2,6-Difluoro-4-{2-[2-(4-methyl-piperazin-1-yl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;
[7-(3-Fluoro-4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;
(2,6-Difluoro-4-{2-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;
{2,6-Difluoro-4-[2-(thiazol-2-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1-methyl-1H-pyrazol-4-yl)-amine;

{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-3-yl}-morpholin-4-yl-methanone;

(1,1-Dioxido-thiomorpholin-4-yl)-{4-[2-(6-methyl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone;

(1,1-Dioxido-thiomorpholin-4-yl)-{4-[2-(6-methoxy-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-methanone;

(2,6-Difluoro-4-{2-[1-(2-methoxy-ethyl)-1H-pyrazol-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-amine;

{4-[2-(1-Methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine;

(4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone;

4-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

4-{2-[4-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone;

4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-2-one;

4-(4-{7-[3,5-Difluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((2S,5R)-2,5-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic);

(4-{2-[4-((2S,5R)-2,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone (racemic);

{2,6-Difluoro-4-[2-(6-piperazin-1-yl-pyridin-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-yl-pyridin-3-yl)-amine;

[2,6-Difluoro-4-(2-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridin-3-ylamino}-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone;

2-(4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-1-yl)-ethanol;

(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine;

(4-{2-[6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone;

(4-{2-[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone (racemic);

Example 270: [6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-((2R,5S)-2,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic);

[6-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine (racemic);

[2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-amine;

Cyclopropyl-(4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanol;

4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile;

1-(4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-ethanol;

(2,6-Difluoro-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanol;

(4-{2-[2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-phenyl)-morpholin-4-yl-methanone;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-yl-pyridin-3-yl)-amine;

1-(4-{2-[6-(4-Methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-pyrrolidin-2-one;

2-(4-{2-[4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-1-(4-methyl-piperazin-1-yl)-ethanone;

[4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenyl]-[7-(3-fluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

2-{4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-1-(1,1-dioxido-thiomorpholin-4-yl)-ethanone;

{4-[2-(3,4-Diethoxy-phenylamino)-6-methyl-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(4-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3,4-dimethyl-phenyl)-amine;

(3,4-Dimethyl-phenyl)-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-(1,1-dioxido-thiomorpholin-4-yl)-methanone;

1-(1,1-Dioxido-thiomorpholin-4-yl)-2-(4-{2-[4-(4-ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-ethanone;

(4-{2-[4-(4-Ethyl-piperazin-1-yl)-3-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone;

{4-[2-(4-Chloro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone;

{4-[2-(4-Fluoro-3-methoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-methyl-phenyl}-morpholin-4-yl-methanone;

4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-N-[2-(4-methyl-piperazin-1-yl)-ethyl]-benzamide;

(4-Dimethylamino-piperidin-1-yl)-{4-[2-(3,4-dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-methanone;

{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

2-{4-[2-(1-Methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-1-morpholin-4-yl-ethanone;

{2-Fluoro-4-[2-(1-methyl-1H-pyrazol-4-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(3-methoxy-4-methyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{7-[3,5-Difluoro-4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine;

{7-[3,5-Difluoro-4-(4-isopropyl-piperazin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine;

{7-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methoxy-4-methyl-phenyl)-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3-methoxy-4-methyl-phenyl)-amine;

{7-[4-(3,3-Dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(3,4-dimethyl-phenyl)-amine;

4-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-benzyl}-1-methyl-piperazin-2-one;

{4-[2-(1,5-Dimethyl-1H-pyrazol-3-ylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2-fluoro-phenyl}-morpholin-4-yl-methanone;

4-{4-[2-(3,4-Dimethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-2,6-difluoro-benzyl}-piperazin-2-one;

{2-Fluoro-4-[2-(4-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

{2,6-Difluoro-4-[2-(4-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperazin-1-ylmethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-amine;

[5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[7-(4-methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

1-(4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-1-yl)-ethanone;

1-(4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-1-yl)-ethanone;

4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyrazol-1-yl}-piperidine-1-carboxylic acid tert-butyl ester;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1-piperidin-4-yl-1H-pyrazol-4-yl)-amine;

1-[4-(4-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone;

1-[4-(4-{7-[3,5-Difluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone;

[2-Fluoro-4-(2-p-tolylamino-pyrrolo[2,3-d]pyrimidin-7-yl)-phenyl]-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-p-tolyl-amine;

(2-Fluoro-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

{2-Fluoro-4-[2-(4-methyl-3-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-morpholin-4-ylmethyl-phenyl)-amine;

[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-{2-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine;

[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine;

4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazin-2-one;

4-{4-[7-(4-Methanesulfonyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-1-methyl-piperazin-2-one;

{2-Fluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

4-(4-{7-[3-Fluoro-4-(morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-1-methyl-piperazin-2-one;

1-[4-(4-{7-[4-(Morpholine-4-carbonyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-benzyl)-piperazin-1-yl]-ethanone;

4-(4-{2-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one;

4-(4-{2-[4-(4-Cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one;

4-(2,6-Difluoro-4-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzyl)-piperazin-2-one;

4-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-piperazin-2-one;

4-(2,6-Difluoro-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzyl)-piperazin-2-one;

4-{2,6-Difluoro-4-[2-(4-methyl-3-morpholin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-2-one;

N-tert-Butyl-4-{2-[4-(4-cyclopropyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((R)-3-methyl-4-pyrrolidin-2-yl-phenyl)-amine;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-pyrrolidin-3-ol (racemic);

N-tert-Butyl-4-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

4-{2-[4-(4-Methyl-piperazin-1-yl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(tetrahydro-pyran-4-yloxy)-pyridin-4-yl]-amine;

N-tert-Butyl-4-{2-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(2-morpholin-4-yl-ethoxy)-pyridin-4-yl]-amine;

N-tert-Butyl-4-{2-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-morpholin-2-yl-phenyl)-amine (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine;

N-tert-Butyl-4-{2-[6-((2R,5S)-2,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide (racemic);

4-{2-[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(2,5-dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-4-methyl-phenyl]-amine;

(4-{2-[3-(2,5-Dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(2,5-dioxa-8-aza-spiro[3.5]non-8-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(4-methyl-piperazin-1-yl)-methanone;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(2,5-dioxa-8-aza-spiro[3.5]non-8-yl)-methanone;

N-tert-Butyl-4-{2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-trifluoromethyl-piperazin-1-yl)-pyridin-4-yl]-amine (racemic);

[3-(4-Cyclopropyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-{2-[3-(4-Cyclopropyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

(4-{2-[3-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

4-{2-[4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazine-1-carbaldehyde;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2-piperazin-1-ylmethyl-pyridin-4-yl)-amine;

[3-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-{2-[3-(4,7-Diaza-spiro[2.5]oct-7-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

Propane-2-sulfonic acid (4-{2-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-amide;

N-tert-Butyl-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-((2R,5S)-2,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic);

(4-{2-[3-((2R,5S)-2,5-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone (racemic);

N-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanesulfonamide;

{2-Fluoro-4-[2-(4-piperidin-4-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone;

4-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-piperidin-4-ylmethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3,3-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenyl]-amine;

(4-{2-[3-(3,3-Dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

N-tert-Butyl-4-{2-[3-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-4-methyl-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-pyrrolidin-3-ol (racemic);

3-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-hexahydro-pyrido[1,2-a]pyrazin-1-one;

{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-1-yl-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(piperidin-4-ylmethoxy)-pyridin-4-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3,3-difluoro-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-azetidin-3-ol;

4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1-methyl-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{2-[4-(2-dimethylamino-ethyl)-piperazin-1-ylmethyl]-pyridin-4-yl}-amine;

4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-1-methyl-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{3-[4-(2-dimethylamino-ethyl)-piperazin-1-ylmethyl]-4-methyl-phenyl}-amine;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-piperazin-2-one;

1-{2-Chloro-5-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-azetidin-3-ol;

(4-Chloro-3-piperazin-1-ylmethyl-phenyl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3,3-difluoro-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine;

(1,1-Dioxido-thiomorpholin-4-yl)-(2-fluoro-4-{2-[4-methyl-3-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanone (racemic);
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic);
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3-methoxy-azetidin-1-ylmethyl)-4-methyl-phenyl]-amine;
(1,1-Dioxido-thiomorpholin-4-yl)-(2-fluoro-4-{2-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-methanone;
[2-(4-Cyclopropyl-piperazin-1-ylmethyl)-pyridin-4-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-trifluoromethyl-piperazin-1-ylmethyl)-pyridin-4-yl]-amine (racemic);
1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-piperazin-2-one;
4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1-(2-dimethylamino-ethyl)-piperazin-2-one;
1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-pyrrolidin-3-ol (racemic);
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-imidazol-1-ylmethyl-4-methyl-phenyl)-amine;
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-pyrazol-1-ylmethyl-phenyl)-amine;
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(4-methyl-3-[1,2,4]triazol-4-ylmethyl-phenyl)-amine;
1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-4-methyl-piperazin-2-one;
1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-pyrrolidin-3-ol (racemic);
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-l]-[3-(3-methoxy-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic);
[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(4-dimethylaminomethyl-[1,2,3]triazol-1-ylmethyl)-4-methyl-phenyl]-amine;
(1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1H-[1,2,3]triazol-4-yl)-methanol;

[3-(Azetidin-3-yloxymethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[4-methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amine;

4-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-1-methyl-piperazin-2-one;

1-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-azetidin-3-ol;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-6-yl)-amine;

1-(5-{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino}-2-methyl-benzyl)-pyrrolidin-3-ol (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-methoxy-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[2-(3-dimethylamino-pyrrolidin-1-ylmethyl)-pyridin-4-yl]-amine (racemic);

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine;

[6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

[5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(2,3-dihydro-1H-indol-6-yl)-amine;

[3,5-Dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenyl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3,5-dimethyl-4-(2-morpholin-4-yl-ethoxy)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[3-(3-dimethylamino-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-amine (racemic);

[3-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-4-methyl-phenyl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine (racemic);

[3-(7-Aza-bicyclo[2.2.1]hept-7-ylmethyl)-4-methyl-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

(4-{2-[4-Methyl-3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-phenyl)-morpholin-4-yl-methanone;

[7-(4-Ethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine;

3-Methyl-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[5-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-amine;

[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

[2-(4,7-Diaza-spiro[2.5]oct-7-yl)-pyridin-4-yl]-{7-[4-(1,1-dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine;

{7-[4-(1,1-Dioxido-thiomorpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(6-piperazin-1-yl-pyridin-3-yl)-amine;

2,6-Difluoro-4-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzonitrile;

[7-(3,5-Difluoro-4-methoxymethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine;

{7-[4-(cis-2,6-dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine;

1-Methyl-5-{2-[6-(4-methyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-1,3-dihydro-indol-2-one;

{7-[4-(1-Methoxy-ethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(7-methyl-2,7-diaza-spiro[4.4]non-2-ylmethyl)-phenyl]-amine;

{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(4-methyl-piperazin-1-yl)-methanone;

{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-phenyl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone;

[7-(3,5-Difluoro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-amine;

{7-[4-(cis-2,6-dimethyl-morpholin-4-ylmethyl)-3,5-difluoro-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(6-piperazin-1-yl-pyridin-3-yl)-amine;

{3-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-(cis-3,5-dimethyl-piperazin-1-yl)-methanone;

[2-(4-Cyclopropyl-piperazin-1-yl)-pyridin-4-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[6-(4-Cyclopropyl-piperazin-1-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

1-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-pyrrolidin-2-one;

(4-Cyclopropyl-piperazin-1-yl)-{3-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-methanone;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(3-methyl-4-piperazin-1-ylmethyl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-3-methyl-phenyl]-amine;

1-(4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-pyrrolidin-2-one;

1-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-pyrrolidin-2-one;

N-tert-Butyl-4-{2-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-benzenesulfonamide;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-{6-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-pyridin-3-yl}-amine;

{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-(4-methyl-piperazin-1-yl)-methanone;

2-(1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-methyl-benzyl}-1H-pyrazol-4-yl)-ethanol;

6-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-3,4-dihydro-1H-quinolin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(3-trifluoromethyl-piperazin-1-yl)-pyridin-3-yl]-amine (racemic);

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3,3-difluoro-pyrrolidin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3,3-dimethyl-piperazin-1-ylmethyl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-piperazin-2-yl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((R)-4-piperazin-2-yl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3-trifluoromethyl-piperazin-1-ylmethyl)-phenyl]-amine (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(cis-3,5-dimethyl-piperazin-1-ylmethyl)-2-fluoro-phenyl]-amine;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-4-methyl-piperazin-2-one;

1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-azetidin-3-ol;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-morpholin-4-ylmethyl-pyridin-3-yl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-methyl-3-(4-methyl-pyrazol-1-ylmethyl)-phenyl]-amine;

{7-[3,5-Difluoro-4-(3-methoxy-azetidin-1-ylmethyl)-phenyl]-7H-pyrrolo[2,3-d]pyrimidin-2-yl}-(4-methyl-3-piperazin-1-ylmethyl-phenyl)-amine;

4-(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-morpholin-3-one;

4-(4-{2-[4-(cis-3,5-Dimethyl-piperazin-1-ylmethyl)-phenylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2,6-difluoro-benzyl)-morpholin-3-one;

4-{2,6-Difluoro-4-[2-(4-methyl-3-piperazin-1-ylmethyl-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-benzyl}-morpholin-3-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(6-piperazin-1-ylmethyl-pyridin-3-yl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(5-methyl-6-piperazin-1-yl-pyridin-3-yl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-amine;

[5-Chloro-6-(cis-3,5-dimethyl-piperazin-1-yl)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-2-(cis-3,5-dimethyl-piperazin-1-yl)-nicotinonitrile;

4-{3-Chloro-5-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-3-methyl-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one;

[4-Chloro-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

1-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-3-methyl-pyridin-2-yl}-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-trifluoromethyl-pyridin-3-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-methoxy-pyridin-3-yl]-amine;

1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-benzyl}-piperazin-2-one;

(4-{2-[6-(cis-3,5-Dimethyl-piperazin-1-yl)-pyridin-3-ylamino]-pyrrolo[2,3-d]pyrimidin-7-yl}-2-fluoro-phenyl)-morpholin-4-yl-methanone;

4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-5-yl)-amine;

(5-Chloro-6-piperazin-1-yl-pyridin-3-yl)-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

1-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-3,3-dimethyl-piperazin-2-one;

4-{4-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yl}-1-methyl-piperazin-2-one;

4-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-ylmethyl}-1-methyl-piperazin-2-one;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-(3-methoxy-pyrrolidin-1-ylmethyl)-phenyl]-amine (racemic);

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-3-morpholin-3-yl-phenyl)-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((S)-4-ethyl-morpholin-3-yl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[4-((S)-4-methyl-morpholin-3-yl)-phenyl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(cis-3,5-dimethyl-piperazin-1-yl)-5-methyl-pyridin-3-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-((S)-4-morpholin-3-yl-phenyl)-amine;

[6-(6,6-Difluoro-[1,4]diazepan-1-yl)-5-methyl-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(2-morpholin-4-yl-ethoxy)-pyridin-3-yl]-amine;

[6-(Azetidin-3-yloxy)-pyridin-3-yl]-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(2-methoxy-ethoxy)-pyridin-3-yl]-amine;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(tetrahydro-pyran-4-ylmethoxy)-pyridin-3-yl]-amine;

2-{5-[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-pyridin-2-yloxy}-ethanol;

[7-(3,5-Difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-[6-(pyrrolidin-3-yloxy)-pyridin-3-yl]-amine (racemic);

{4-[(S)-4-(2-Benzyloxy-ethyl)-morpholin-3-yl]-phenyl}-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl]-amine;

2-((S)-3-{4-[7-(3,5-difluoro-4-morpholin-4-ylmethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylamino]-phenyl}-morpholin-4-yl)-ethanol

{3-Fluoro-4-[2-(4-isopropoxy-phenylamino)-pyrrolo[2,3-d]pyrimidin-7-yl]-phenyl}-morpholin-4-yl-methanone.

8. A compound of the formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form as pharmaceutical.

9. A compound of the formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form for use as pharmaceutical, in particular for the use in one or more Protein tyrosine kinase mediated diseases.

10. Use of a compound of formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form for the treatment of one or more Protein tyrosine kinase mediated diseases.

11. Use of a compound of formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form for the manufacture of a medicament for the treatment of one or more Protein tyrosine kinase mediated diseases.

12. A method for the treatment of a Protein tyrosine kinase mediated disease comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form.

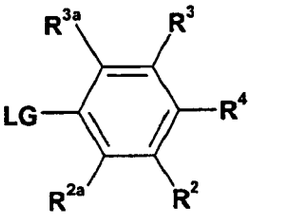
13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form as active ingredient; one or more pharmaceutically acceptable carrier material(s) and / or diluents.

14. A combined pharmaceutical composition, adapted for simultaneous or sequential administration, comprising a therapeutically effective amount of a compound of formula I according to any one of claims 1 to 7 in free form or in pharmaceutically acceptable salt form; therapeutically effective amount(s) of one or more combination partners; one or more pharmaceutically acceptable carrier material(s) and / or diluents.

15. A pharmaceutical composition according to claim 13 or a combined pharmaceutical composition according to claim 14 for use in the treatment of a Protein tyrosine kinase mediated disease, in particular a JAK2 and/or JAK 3 kinase mediated disease.

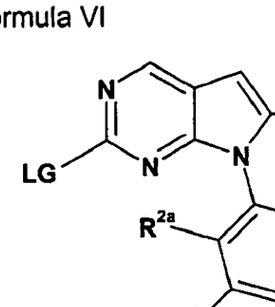
16. A process for the manufacture of a compound of the formula I according to any one of caims 1 to 7 comprising either

Method a) reacting in a first step a compound of the formula II,



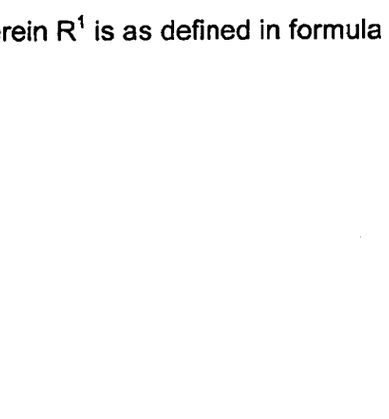
(II)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group with a compound of the formula IV,



(IV)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group in a Cu-catalyzed Buchwald reaction to obtain a compound of formula VI



(VI)

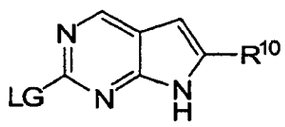
wherein the substituents are as defined above and reacting in a second step the obtained compound of formula VI with a compound of formula (III)

$NH_2-R^1$ (III)

wherein $R^1$ is as defined in formula I to obtain a compound of formula I;

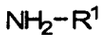
or

method B) reacting in a first step a compound of the formula II,



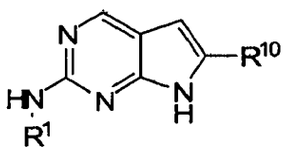
(II)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group with a compound of the formula III,



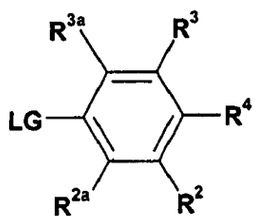
(III)

wherein $R^1$ is as defined in formula I either in a Pd-catalyzed Buchwald reaction or under acidic conditions to obtain a compound of formula (V)



(V)

wherein the substituents are as defined above and reacting in a second step the obtained compound of formula (V) with a compound of formula IV



(IV)

wherein the substituents are as defined for a compound of the formula I and LG represents a leaving group to obtain a compound of formula I;

and, optionally converting a compound of the formula I obtainable according to method A) or method B) into a different compound of the formula I, and/or converting an obtainable salt of a compound of the formula I into a different salt thereof, and/or converting an obtainable free compound of the formula I into a salt thereof, and/or separating an obtainable isomer of a compound of the formula I from one or more different obtainable isomers of the formula I.

SEQUENCE LISTING

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<120> HETEROCYCLIC COMPOUNDS

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<151> 2008-02-06

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**(71) Solicitante** *(para todos los Estados designados excepto US)*: **NOVARTIS AG** [CH/CH]; Lichstrasse 35, CH-4056 Basel (CH).

**(72) Inventores: y**
**(75) Inventores/Solicitantes** *(solo para US)*: **GAUL, Christoph** [DE/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **GERSPACHER, Marc** [CH/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **HOLZER, Philipp** [CH/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **PISSOT SOLDERMANN, Carole** [FR/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 BAsel (CH).

**(74) Agente: DYER, James**; Novartis Pharma Ag Patent Department CH-4002 Basel (CH).

**(81) Estados Designados** *(a menos que se indique otra cosa, para cada tipo de protección nacional disponible)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

**(84) Estados Designados** *(a menos que se indique otra cosa, para cada tipo de protección regional disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR),. OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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*- en cuanto al derecho del solicitante para solicitar y ser otorgada una patente (Regla 4.17(ii))*

**Publicada:**
*- con informe de búsqueda internacional (Art. 21(3))*
*-antes del término del límite de tiempo para enmendar las reivindicaciones y para volver a publicar en caso de recibir las enmiendas (Regla 48.2(h))*
*-con lista de secuencias por separado de la descripción (Regla 5.2(a))*

**(54) Título:** PIRROLO[2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA

**(57) Resumen:**

La invención se refiere a los compuestos de la fórmula I, y sales de los mismos, en donde los sustituyentes son como se definen en la memoria descriptiva, a procesos para la preparación de los mismos; a productos farmacéuticos que contienen tales compuestos, en particular para el uso en una o más enfermedades mediadas por la cinasa de proteína tirosina.

# PIRROLO[2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA

La invención se refiere a derivados de 7-fenil-7H-pirrolo-[2,3d]-pirimidin-2-il-amino de la fórmula I que se da más adelante, así como a sales de los mismos; a procesos para la preparación de los mismos; composiciones farmacéuticas que comprenden un compuesto de la fórmula (I), opcionalmente en la presencia de un componente de combinación; a la aplicación de un compuesto de la fórmula (I) en un proceso para el tratamiento del cuerpo humano o animal (en particular con respecto a una enfermedad proliferativa); y al uso de un compuesto de la fórmula (I) para la fabricación de un medicamento para el tratamiento de estas enfermedades.

Las cinasas Janus (JAKs) forman una familia de cinasas de proteína tirosina intracelulares con cuatro miembros, JAK1, JAK2, JAK3 y TYK2. Estas cinasas son importantes en la mediación de la señalización del receptor de citoquina que induce diferentes respuestas biológicas, incluyendo proliferación, diferenciación y apoptosis celular. Los experimentos de eliminación genética en ratones han demostrado que las JAKs son, entre otras cosas, importantes en la hematopoiesis. En adición, se demostró que JAK2 está implicada en las enfermedades mieloproliferativas y en los cánceres. Se ha observado la activación de JAK2 por las reconfiguraciones de cromosomas y/o por la pérdida de los reguladores de senda negativos JAK/STAT (STAT = factor(es) de

transducción y activación de señales) en las malignidades hematológicas, así como en ciertos tumores sólidos.

La Publicación Internacional Número WO 2005/080393 da a conocer, entre otras cosas, derivados de 7H-pirrolo-[2,3d]-pirimidin-2-il-amino que son útiles en el tratamiento de los trastornos asociados con una actividad de cinasa anormal o mal regulada.

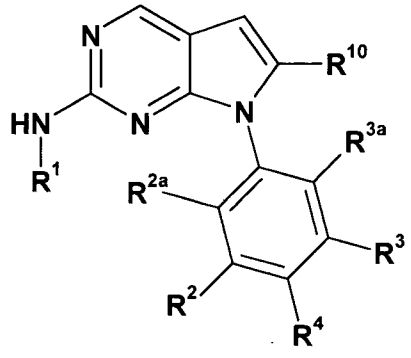
Bioorganic & Medical Chemistry Letters 16 (2006), 2689 da a conocer y diseño y la síntesis de ciertas 7H-pirrolo-[2,3d]-pirimidinas como inhibidores de cinasa de adhesión focal.

Ahora se ha encontrado que los derivados de 7-fenil-7H-pirrolo-[2,3d]-pirimidin-2-il-amino de la fórmula I que se da más adelante, tienen propiedades farmacológicas convenientes e inhiben, por ejemplo, la actividad de cinasa de tirosina de las cinasas Janus, tales como la cinasa JAK2 y/o la cinasa JAK3 (pero también JAK-1). Por consiguiente, los compuestos de la fórmula I son adecuados, por ejemplo, para utilizarse en el tratamiento de enfermedades dependientes de la actividad de cinasa de tirosina de la cinasa JAK2 (y/o JAK3), en especial enfermedades proliferativas, tales como enfermedades tumorales, leucemias, policitemia vera, trombocitemia esencial, y mielofibrosis con metaplasia mieloide. A través de la inhibición de la cinasa JAK-3, los compuestos de la invención también tienen utilidad como agentes inmunosupresores, por ejemplo para el tratamiento de enfermedades, tales como rechazo de trasplante de órgano, lupus eritematoso, esclerosis múltiple, artritis reumatoide, soriasis, dermatitis, enfermedad de Crohn, diabetes tipo-

1760

1 y complicaciones de diabetes tipo-1.

En un primer aspecto, la invención se refiere a los compuestos de la fórmula I:



(I)

en donde:

$R^1$ representa heterociclilo insustituido o sustituido, arilo insustituido o sustituido, cicloalquilo insustituido o sustituido;

$R^2$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^3$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

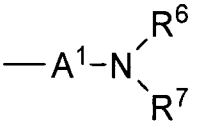
o $R^2$ y/o $R^3$ se conectan con $R^5$ o $R^7$ para formar una fracción cíclica fusionada con el anillo de fenilo con el que $R^2/R^3$ están unidos;

$R^{2a}$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

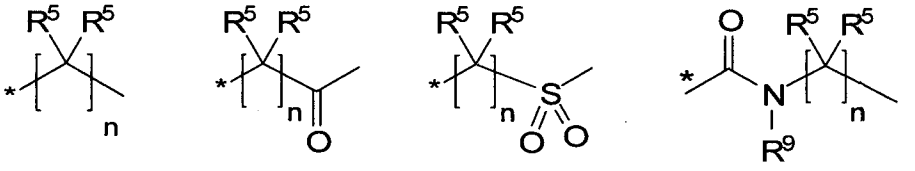
$R^{3a}$ representa hidrógeno, halógeno, alquilo inferior,

alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^4$ representa un grupo:



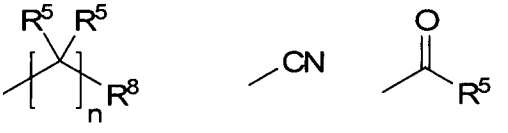
en donde $A^1$ representa uno de los siguientes grupos:



en donde el átomo marcado con * es un enlace con el anillo de fenilo;

o

$R^4$ representa uno de los siguientes grupos:



$R^5$ representa, independientemente de cada otro hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo o forma, junto con el átomo de carbono con el que está unido, un cicloalquilo;

$R^6$ y $R^7$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido;

o

$R^6$ representa hidrógeno o alquilo opcionalmente sustituido; y

$R^7$ representa alquilo opcionalmente sustituido;

$R^8$ representa alquilo, hidroxilo, alquiloxilo inferior, halo-alquiloxilo inferior, cicloalquiloxilo, halo-cicloalquiloxilo, alquilo inferior-sulfonilo, halo-alquilo inferior-sulfonilo, cicloalquil-sulfonilo, halo-cicloalquil-sulfonilo, alquilo inferior-sulfinilo, halo-alquilo inferior-sulfinilo, cicloalquil-sulfinilo, halo-cicloalquil-sulfinilo;

$R^9$ representa H o alquilo inferior;

$R^{10}$ representa hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo;

n representa 0, 1 ó 2;

o sales de los mismos.

La invención se puede apreciar más completamente haciendo referencia a la siguiente descripción, incluyendo el siguiente glosario de términos y los ejemplos concluyentes. Para mayor brevedad, las divulgaciones de las publicaciones citadas en esta memoria descriptiva se incorporan a la presente como referencia. Como se utilizan en la presente, los términos "incluyen", "contienen" y "comprenden" se utilizan en la presente en su sentido abierto no limitante.

Cualquier fórmula dada en la presente pretende representar los compuestos que tienen las estructuras ilustradas por la fórmula estructural así como ciertas variaciones o formas. En particular, los compuestos de cualquier fórmula dada en la presente, pueden tener centros asimétricos, y por consiguiente, pueden existir en diferentes formas enantioméricas. Si está presente cuando menos un átomo de

carbono asimétrico en un compuesto de la fórmula I, este compuesto puede existir en una forma ópticamente activa o en la forma de una mezcla de isómeros ópticos, por ejemplo, en la forma de una mezcla racémica. Todos los isómeros ópticos y sus mezclas, incluyendo las mezclas racémicas, son parte de la presente invención. Por consiguiente, cualquier fórmula dada en la presente pretende representar un racemato, una o más formas enantioméricas, una o más formas diaestereoméricas, una o más formas atropisoméricas, y mezclas de las mismas. Adicionalmente, ciertas estructuras pueden existir como isómeros geométricos (es decir, isómeros *cis* y *trans*), como tautómeros, o como atropisómeros. Adicionalmente, cualquier fórmula dada en la presente pretende representar hidratos, solvatos, y polimorfos de estos compuestos, y mezclas de los mismos.

Cualquier fórmula dada en la presente también pretende representar las formas no marcadas, así como las formas isotópicamente marcadas de los compuestos. los compuestos isotópicamente marcados tienen las estructuras ilustradas por las fórmulas dadas en la presente, excepto que uno o más átomos son reemplazados por un átomo que tenga una masa atómica o número de masa seleccionados. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}F$ $^{31}P$, $^{32}P$, $^{35}S$, $^{36}Cl$, $^{125}I$, respectivamente. Se incluyen diferentes compuestos isotópicamente marcados de la presente invención, por ejemplo aquéllos en los que

se incorporan isótopos radioactivos, tales como $^{3}H$, $^{13}C$, y $^{14}C$. Estos compuestos isotópicamente marcados son útiles en los estudios metabólicos (de preferencia con $^{14}C$), en los estudios cinéticos de reacción (con, por ejemplo $^{2}H$ ó $^{3}H$), en las técnicas de detección o o toma de imágenes [tales como tomografía por emisión de positrones (PET) o tomografía computarizada con emisión de un solo fotón (SPECT), incluyendo ensayos de distribución de fármaco o sustrato en el tejido, o en el tratamiento radioactivo de los pacientes. En particular, se puede preferir un compuesto $^{18}F$ o marcado para los estudios de PET o SPECT. Además, la sustitución con isótopos más pesados, tales como deuterio (es decir, $^{2}H$) puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo mayor vida media *in vivo* o requerimientos de dosificación reducida. Los compuestos isotópicamente marcados de esta invención y los pro-fármacos de los mismos, en términos generales, se pueden preparar llevando a cabo los procedimientos que se dan a conocer en los esquemas o en los Ejemplos, y en las preparaciones descritas más adelante, mediante la sustitución de un reactivo no isotópicamente marcado, por un reactivo isotópicamente marcado fácilmente disponible.

Cuando se hace referencia a cualquier fórmula dada en la presente, la selección de una fracción particular a partir de una lista de posibles especies para una variable especificada, no pretende definir la fracción para la variable que aparezca en cualquier otra parte. En otras palabras, cuando una variable aparezca más de una

vez, la elección de la especie a partir de una lista especificada es independiente de la elección de la especie para la misma variable en cualquier otra parte de la fórmula (en donde una o más y hasta todas las expresiones más generales en las modalidades caracterizadas como preferidas anteriormente o más adelante, pueden ser reemplazadas con una definición más específica, conduciendo de esta manera a una modalidad más preferida de la invención, respectivamente).

Cuando se utiliza la forma plural (por ejemplo, los compuestos, sales), ésta incluye al singular (por ejemplo, un solo compuesto, una sola sal). "Un compuesto" no excluye que esté presente (por ejemplo, en una formulación farmacéutica) más de un compuesto de la fórmula I (o una sal del mismo).

La sal de adición de ácido de los compuestos de la fórmula I son de preferencia las sales farmacéuticamente aceptables. Estas sales se conocen en el campo.

Las siguientes definiciones generales se aplicarán en esta memoria descriptiva, a menos que se especifique de otra manera:

**Halógeno** (o halo) denota flúor, bromo, cloro o yodo, en particular flúor, cloro. Los grupos y fracciones sustituidos por halógeno, tales como alquilo sustituido por halógeno (halo-alquilo), pueden estar mono-, poli- o per-halogenados.

**Atomos heterogéneos** son átomos diferentes de Carbono e Hidrógeno, de preferencia nitrógeno (N), oxígeno (O) o azufre (S).

**Los grupos, fracciones o moléculas que contienen carbono**,

contienen de 1 a 8, de preferencia de 1 a 6, más preferiblemente de 1 a 4, y de una manera muy preferible 1 ó 2 átomos de carbono. Cualquier grupo o fracción que contenga carbono no cíclico, con más de 1 átomo de carbono, es de cadena recta o ramificada.

El sufijo "inferior" o "de 1 a 7 átomos de carbono" denota un radical que tiene hasta e incluyendo un máximo de 7, en especial hasta e incluyendo un máximo de 4 átomos de carbono, siendo los radicales en cuestión lineales o ramificados con ramificación individual o múltiple.

"**Alquilo**" se refiere a un grupo alquilo de cadena recta o de cadena ramificada, de preferencia representa un alquilo de 1 a 12 átomos de carbono de cadena recta o de cadena ramificada, y representa de una manera particularmente preferible, un alquilo de 1 a 7 átomos de carbono de cadena recta o de cadena ramificada; por ejemplo, metilo, etilo, propilo normal o isopropilo, butilo normal, isobutilo, butilo secundario o butilo terciario, pentilo normal, hexilo normal, heptilo normal, octilo normal, nonilo normal, decilo normal, undecilo normal, dodecilo normal, dándose una preferencia particular a metilo, etilo, propilo normal, isopropilo y butilo normal, e isobutilo. Alquilo puede estar insustituido o sustituido. Los sustituyentes ilustrativos incluyen, pero no se limitan a, hidroxilo, alcoxilo, oxo (es decir, =O), halógeno y amino. Un ejemplo de un alquilo sustituido es trifluoro-metilo. Cicloalquilo también puede ser un sustituyente para alquilo. Un ejemplo de este caso es la fracción de (alquil)-ciclopropilo o alcandiil-ciclopropilo, por ejemplo, $-CH_2$-ciclopropilo.

Alquilo de 1 a 7 átomos de carbono es de preferencia alquilo con desde e incluyendo 1 hasta e incluyendo 7, de preferencia desde e incluyendo 1 hasta e incluyendo 4, y es lineal o ramificado; de preferencia, alquilo inferior es butilo, tal como butilo normal, butilo secundario, isobutilo, butilo terciario, propilo, tal como propilo normal o isopropilo, etilo, o de preferencia metilo.

Cada parte de alquilo de otros grupos como "alcoxilo", "alcoxi-alquilo", "alcoxi-carbonilo", "alcoxi-carbonil-alquilo", "alquil-sulfonilo", "alquil-sulfinilo", "alquil-amino", y "halo-alquilo", tendrán el mismo significado que se describe en la definición de "alquilo" anteriormente mencionada.

"**Alcandiilo**" se refiere a un grupo alcandiilo de cadena recta o de cadena ramificada enlazado por dos átomos de carbono diferentes a la fracción, de preferencia representa un alcandiilo de 1 a 12 átomos de carbono de cadena recta o de cadena ramificada, y representa de una manera particularmente preferible, un alcandiilo de 1 a 6 átomos de carbono de cadena recta o de cadena ramificada; por ejemplo, metandiilo ($-CH_2-$), 1,2-etandiilo ($-CH_2-CH_2-$), 1,1-etandiilo (($-CH(CH_3)-$), 1,1-, 1,2-, 1,3-propandiilo, y 1,1-, 1,2-, 1,3-, 1,4-butandiilo, dándose una preferencia particular a metandiilo, 1,1-etandiilo, 1,2-etandiilo, 1,3-propandiilo, y 1,4-butandiilo.

"**Alquendiilo**" se refiere a un grupo alquendiilo de cadena recta o de cadena ramificada enlazado por dos átomos de carbono diferentes a la molécula, de preferencia representa un alquendiilo de 2 a 6 átomos de carbono de cadena recta o de cadena ramificada;

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por ejemplo, -CH=CH-, -CH=C($CH_3$)-, -CH=CH-$CH_2$-, -C($CH_3$)=CH-$CH_2$-, -CH=C($CH_3$)-$CH_2$-, -CH=CH-C($CH_3$)H-, -CH=CH-CH=CH-, -C($CH_3$)=CH-CH=CH-, -CH=C($CH_3$)-CH=CH-, dándose una preferencia particular a -CH=CH-$CH_2$-, -CH=CH-CH=CH-. Alquendiilo puede estar sustituido o insustituido

"**Cicloalquilo**" se refiere a un carbociclo monocíclico, policíclico fusionado, o policíclico espiro, saturado o parcialmente saturado, que tiene de 3 a 12 átomos del anillo por carbociclo. Los ejemplos ilustrativos de los grupos cicloalquilo incluyen las siguientes fracciones: ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Cicloalquilo puede estar insustituido o sustituido; los sustituyentes de ejemplo se proporcionan en la definición para alquilo.

**"Arilo"** se refiere a un sistema de anillo homocíclico aromático con 6 o más átomos de carbono; arilo es de preferencia una fracción aromática con 6 a 14 átomos de carbono del anillo, más preferiblemente con 6 a 10 átomos de carbono del anillo, tal como fenilo o naftilo, de preferencia fenilo. Arilo puede estar insustituido o sustituido por uno o más, de preferencia hasta tres, más preferiblemente hasta dos sustituyentes seleccionados independientemente a partir del grupo que consiste en heterociclilo insustituido o sustituido como se describe más adelante, en especial pirrolidinilo, tal como pirrolidino, oxo-pirrolidinilo, tal como oxo-pirrolidino, alquilo de 1 a 7 átomos de carbono-pirrolidinilo, 2,5-di-(alquilo de 1 a 7 átomos de carbono)-pirrolidinilo, tal como 2,5-di-

(alquilo de 1 a 7 átomos de carbono)-pirrolidino, tetrahidrofuranilo, tiofenilo, alquilo de 1 a 7 átomos de carbono-pirazolidinilo, piridinilo, alquilo de 1 a 7 átomos de carbono-piperidinilo, piperidino, piperidino sustituido por amino o N-mono- o N,N-di-[alquilo inferior, fenilo, alcanoílo de 1 a 7 átomos de carbono y/o fenil-alquilo inferior)-amino, piperidinilo insustituido o sustituido por N-alquilo inferior enlazado por medio de un átomo de carbono del anillo, piperazino, alquilo inferior-piperazino, morfolino, tiomorfolino, S-oxo-tiomorfolino o S,S-dioxo-tiomorfolino; alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, mono- a tri-[alquilo de 1 a 7 átomos de carbono, halógeno y/o ciano]-fenilo o mono- a tri-[alquilo de 1 a 7 átomos de carbono, halógeno y/o ciano]-naftilo; cicloalquilo de 3 a 8 átomos de carbono, mono- a tri-[alquilo de 1 a 7 átomos de carbono y/o hidroxi]-cicloalquilo de 3 a 8 átomos de carbono; halógeno, hidroxilo, alcoxilo inferior, alcoxilo inferior-alcoxilo inferior, (alcoxilo inferior)-alcoxilo inferior-alcoxilo inferior, halo-alcoxilo de 1 a 7 átomos de carbono, fenoxilo, naftiloxilo, fenil- o naftil-alcoxilo inferior; amino-alcoxilo de

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1 a 7 átomos de carbono, alcanoiloxilo inferior, benzoiloxilo, naftoiloxilo, formilo (CHO), amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carboxilo, alcoxilo inferior-carbonilo, por ejemplo, fenil- o naftil-alcoxilo inferior-carbonilo, tal como benciloxi-carbonilo; alcanoílo de 1 a 7 átomos de carbono, tal como acetilo, benzoílo, naftoílo, carbamoílo, carbamoílo N-mono- o N,N-di-sustituido, tal como carbamoílo N-mono- o N,N-di-sustituido, en donde los sustituyentes se seleccionan a partir de alquilo inferior, (alcoxilo inferior)-alquilo inferior e hidroxi-alquilo inferior; amidino, guanidino, ureido, mercapto, tioalquilo inferior, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo inferior, alquilo inferior-tiofenilo, alquilo inferior-tionaftilo, halo-alquilo inferior-mercapto, sulfo ($-SO_3H$), alcano inferior-sulfonilo, fenil- o naftil-sulfonilo, fenil- o naftil-alquilo inferior-sulfonilo, alquil-fenil-sulfonilo, halo-alquilo inferior-sulfonilo, tal como trifluoro-metan-sulfonilo; sulfonamido, benzo-sulfonamido, azido, azido-alquilo de 1 a 7 átomos de carbono, en especial azido-metilo, alcano de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro; en donde cada fenilo o naftilo (también en fenoxilo o naftoxilo) mencionado anteriormente como sustituyente o parte de un sustituyente de alquilo sustituido (o también de arilo sustituido, heterociclilo etc. mencionados en la presente) está él mismo insustituido o sustituido por uno o más, por

ejemplo, hasta tres, de preferencia 1 ó 2 sustituyentes seleccionados independientemente a partir de halógeno, halo-alquilo inferior, tal como trifluoro-metilo, hidroxilo, alcoxilo inferior, azido, amino, N-mono- o N,N-di-(alquilo inferior y/o alcanoílo de 1 a 7 átomos de carbono)-amino, nitro, carboxilo, alcoxilo inferior-carbonilo, carbamoílo, ciano y/o sulfamoílo.

"**Heterociclilo**" se refiere a un radical heterocíclico que está insaturado (= que lleva el número más alto posible de dobles enlaces conjugados en el(los) anillo(s) es decir, hetero-arilo), saturado o parcialmente saturado, y es de preferencia un anillo monocíclico o, en un aspecto más amplio de la invención, bicíclico, tricíclico o espirocíclico; y tiene de 3 a 24, más preferiblemente de 4 a 16, más preferiblemente de 5 a 10, y de una manera muy preferible 5 ó 6 átomos del anillo; en donde uno o más, de preferencia uno a cuatro, en especial uno o dos átomos de carbono del anillo son reemplazados por un átomo heterogéneo, teniendo el anillo de enlace de preferencia de 4 a 12, en especial de 5 a 7 átomos del anillo. El radical heterocíclico (heterociclilo) puede estar insustituido o sustituido por uno o más, en especial 1 a 3 sustituyentes seleccionados independientemente a partir del grupo que consiste en los sustituyentes definidos anteriormente para alquilo sustituido y/o a partir de uno o más de los siguientes sustituyentes: oxo (=O), tiocarbonilo (=S), imino (=NH), imino-alquilo inferior. Además, heterociclilo es en especial un radical de heterociclilo seleccionado a partir del grupo que consiste en oxiranilo, azirinilo, aziridinilo, 1,2-

oxatiolanilo, tienilo (= tiofenilo), furanilo, tetrahidro-furilo, piranilo, tiopiranilo, tiantrenilo, isobenzo-furanilo, benzo-furanilo, cromenilo, 2H-pirrolilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolidinilo, bencimidazolilo, pirazolilo, pirazinilo, pirazolidinilo, tiazolilo, isotiazolilo, ditiazolilo, oxazolilo, isoxazolilo, piridilo, pirazinilo, pirimidinilo, piperidinilo, piperazinilo, piridazinilo, morfolinilo, tiomorfolinilo, (S-oxo o S,S-dioxo)-tiomorfolinilo, indolizinilo, azepanilo, diazepanilo, en especial 1,4-diazepanilo, isoindolilo, 3H-indolilo, indolilo, bencimidazolilo, cumarilo, indazolilo, triazolilo, tetrazolilo, purinilo, 4H-quinolizinilo, isoquinolilo, quinolilo, tetrahidro-quinolilo, tetrahidro-isoquinolilo, decahidro-quinolilo, octahidro-isoquinolilo, benzo-furanilo, dibenzo-furanilo, benzo-tiofenilo, dibenzo-tiofenilo, ftalazinilo, naftiridinilo, quinoxalilo, quinazolinilo, quinazolinilo, cinolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fenantridinilo, acridinilo, perimidinilo, fenantrolinilo, furazanilo, fenazinilo, fenotiazinilo, fenoxazinilo, cromenilo, isocromanilo, cromanilo, benzo-[1,3]-dioxol-5-ilo y 2,3-dihidro-benzo-[1,4]-dioxin-6-ilo, estando cada uno de estos radicales insustituido o sustituido por uno o más, de preferencia hasta tres sustituyentes seleccionados a partir de aquéllos mencionados anteriormente para arilo sustituido y/o a partir de uno o más de los siguientes sustituyentes: oxo (=O), tiocarbonilo (=S), imino (=NH), imino-alquilo inferior.

**"Aril-alquilo"** se refiere a un grupo arilo enlazado a la molécula por medio de un grupo alquilo, tal como un grupo metilo o

etilo, de preferencia fenetilo o bencilo, en particular bencilo. De una manera similar, cicloalquil-alquilo y heterociclil-alquilo representan un grupo cicloalquilo enlazado a la molécula por medio de un grupo alquilo, o un grupo heterociclilo enlazado a la molécula por medio de un grupo alquilo. En cada instancia, arilo, heterociclilo, cicloalquilo y alquilo pueden estar sustituidos como se definen anteriormente.

"Tratamiento" incluye el tratamiento profiláctico (preventivo) y terapéutico, así como la demora del progreso de una enfermedad o trastorno.

"**Enfermedades mediadas por la cinasa de proteína tirosina**" (en especial las enfermedades mediadas por la cinasa JAK2 y/o JAK3) son en especial los trastornos que responden de una manera benéfica (por ejemplo, disminución de uno o más síntomas, demora del establecimiento de una enfermedad, hasta la cura temporal o completa de una enfermedad) a la inhibición de una cinasa de proteína tirosina, en especial la inhibición de una cinasa JAK (de preferencia JAK2 y/o JAK3) o TYK2, más especialmente la inhibición de la cinasa JAK2 (en donde, entre las enfermedades que se van a tratar, se pueden mencionar en especial las enfermedades proliferativas, tales como las enfermedades tumorales, leucemias, policitemia vera, trombocitemia esencial, y mielofibrosis con metaplasia mieloide) y/o de la cinasa JAK3 (en donde de preferencia se debe mencionar como preferido el tratamiento (por ejemplo, mediante inmunosupresión) de enfermedades, tales como rechazo de trasplante de órgano, lupus eritematoso, esclerosis múltiple, artritis

reumatoide, soriasis, dermatitis, enfermedad de Crohn, diabetes tipo-1 y complicaciones de diabetes tipo-1.

"**Sales**" (las cuales, en el significado de "o sales de los mismos" o de "o una sal del mismo", pueden estar presentes solas o en mezcla con el compuesto libre de la fórmula I) son de preferencia las sales farmacéuticamente aceptables. Estas sales se forman, por ejemplo, como las sales de adición de ácido, de preferencia con ácidos orgánicos o inorgánicos, a partir de los compuestos de la fórmula I con un átomo de nitrógeno básico, en especial las sales farmacéuticamente aceptables. Los ácidos inorgánicos adecuados son, por ejemplo, los ácidos de halógeno, tales como ácido clorhídrico, ácido sulfúrico, o ácido fosfórico. Los ácidos orgánicos adecuados son, por ejemplo, ácidos carboxílicos o ácidos sulfónicos, tales como ácido fumárico o ácido metan-sulfónico. Para propósitos de aislamiento o purificación, también es posible utilizar sales farmacéuticamente inaceptables, por ejemplo picratos o percloratos. Para uso terapéutico, solamente se emplean las sales farmacéuticamente aceptables o los compuestos libres (donde sea aplicable, en la forma de preparaciones farmacéuticas), y por consiguiente, éstas son las preferidas. En vista de la estrecha relación entre los compuestos novedosos en forma libre y aquéllos en la forma de sus sales, incluyendo las sales que se pueden utilizar como intermediarios, por ejemplo en la purificación o identificación de los compuestos novedosos, cualquier referencia a los compuestos libres anteriormente en la presente y posteriormente en la presente

se debe entender para referirse también a las sales correspondientes, como sea apropiado y conveniente.

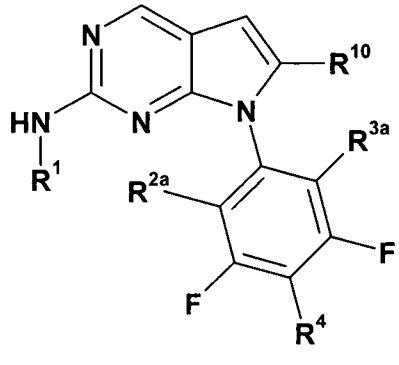
**Combinación** se refiere a cualquiera de una combinación fija en una forma unitaria de dosificación, o un kit de partes para la administración combinada, en donde un compuesto de la fórmula I y un componente de combinación (por ejemplo, otro fármaco, como se explica más adelante, también referido como "agente terapéutico " o "co-agente") se pueden administrar independientemente al mismo tiempo o por separado dentro de intervalos de tiempo, en especial en donde estos intervalos de tiempo permitan que los componentes de la combinación muestren un efecto cooperativo, por ejemplo sinérgico. Los términos "co-administración" o "administración combinada" o similares, como se utilizan en la presente, pretenden abarcar la administración del componente de combinación seleccionado a un solo sujeto que lo necesite (por ejemplo, a un paciente), y se pretende que incluyan los regímenes de tratamiento en donde los agentes no necesariamente se administren por la misma vía de administración o al mismo tiempo. El término "**combinación farmacéutica**", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluye tanto las combinaciones fijas como no fijas de los ingredientes activos. El término "**combinación fija**" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula I, y un componente de combinación, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o

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dosificación. El término "**combinación no fija**" significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula I, y un componente de combinación, se administran ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo específicos, en donde esta administración proporcione niveles terapéuticamente efectivos de los dos compuestos en el cuerpo del paciente. Esto último también se aplica a la terapia de cóctel, por ejemplo, la administración de tres o más ingredientes activos.

En las modalidades preferidas, las cuales se prefieren independientemente, colectivamente, o en cualquier combinación o sub-combinación, la invención se refiere a un compuesto de la fórmula I, en forma de base libre o en forma de sal de adición de ácido, en donde los sustituyentes son como se definen en la presente.

En una modalidad, la invención se refiere a un compuesto de la fórmula IA:

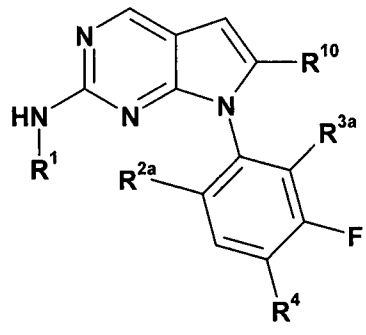



IA

en donde los sustituyentes son como se definen para un compuesto

de la fórmula I.

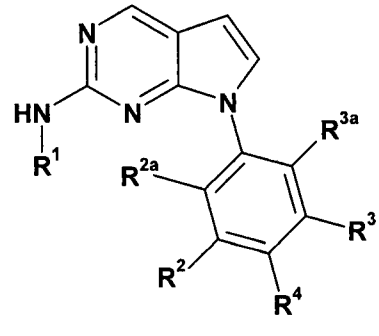
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula IB:



IB

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

En una modalidad adicional, la invención se refiere a un compuesto de la fórmula IC:

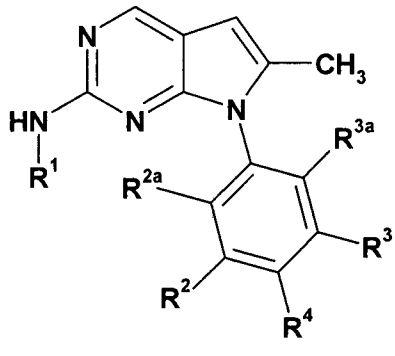


IC

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

En una modalidad adicional, la invención se refiere a un

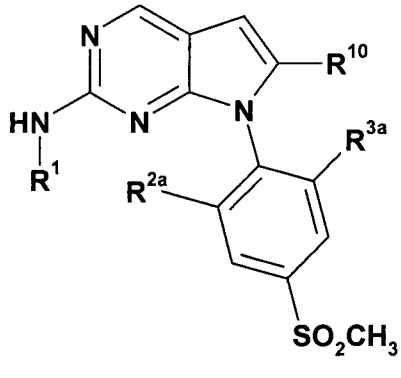
compuesto de la fórmula ID:



ID

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

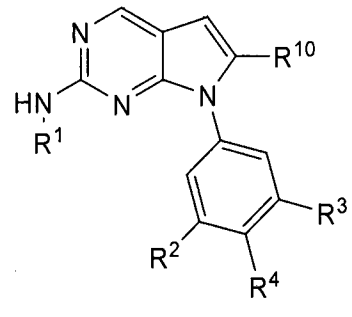
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula IE:



IE

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

En una modalidad adicional, la invención se refiere a los compuestos de la fórmula (I), en donde $R^{2a}$ y $R^{3a}$ son ambos H, es decir, esta modalidad se refiere a los compuestos de la fórmula I':



(I')

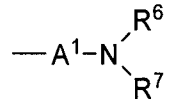
en donde:

$R^1$ representa heterociclilo insustituido o sustituido, arilo insustituido o sustituido, cicloalquilo insustituido o sustituido;

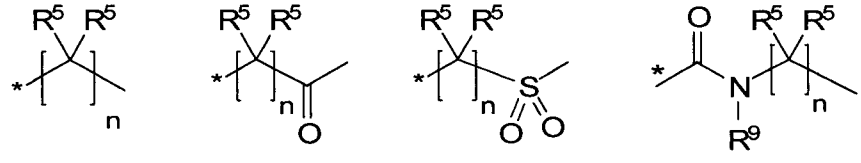
$R^2$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^3$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^4$ representa un grupo:



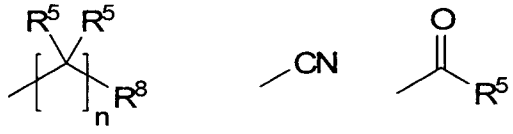
en donde $A^1$ representa uno de los siguientes grupos:



en donde el átomo marcado con * es un enlace con el anillo de fenilo;

o

$R^4$ representa uno de los siguientes grupos:



$R^5$ representa, independientemente de cada otro hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo o forma, junto con el átomo de carbono con el que está unido, un cicloalquilo;

$R^6$ y $R^7$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido;

o

$R^6$ representa hidrógeno o alquilo opcionalmente sustituido; y

$R^7$ representa alquilo opcionalmente sustituido;

$R^8$ representa hidroxilo, alquiloxilo inferior, halo-alquiloxilo inferior, cicloalquiloxilo, halo-cicloalquiloxilo, alquilo inferior-sulfonilo, halo-alquilo inferior-sulfonilo, cicloalquil-sulfonilo, halo-cicloalquil-sulfonilo, alquilo inferior-sulfinilo, halo-alquilo inferior-sulfinilo, cicloalquil-sulfinilo, halo-cicloalquil-sulfinilo;

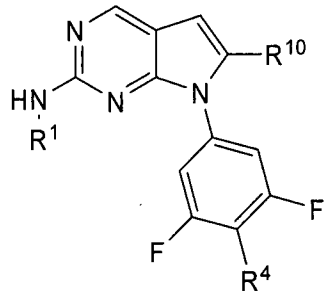
$R^9$ representa H o alquilo inferior;

$R^{10}$ representa hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo;

n representa 0, 1 ó 2;

o sales de los mismos.

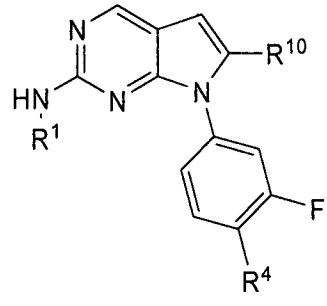
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula I'A:



I'A

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

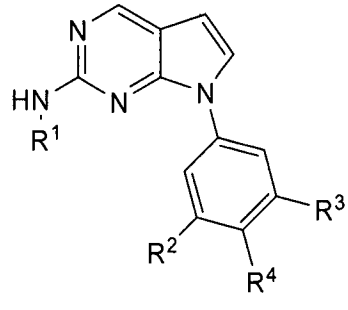
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula I'B:



I'B

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

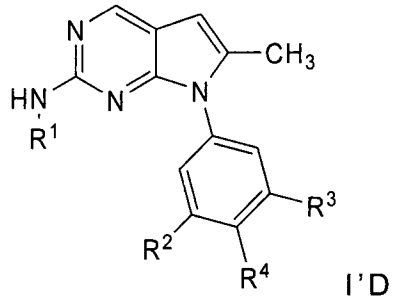
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula I'C:



I'C

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

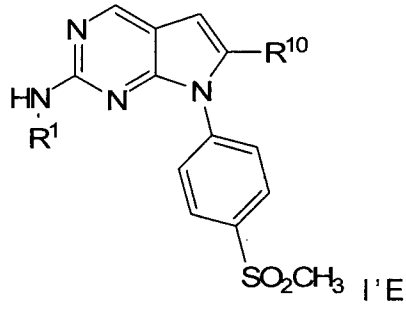
En una modalidad adicional, la invención se refiere a un compuesto de la fórmula I'D:



I'D

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

En una modalidad adicional, la invención se refiere a un compuesto de la fórmula I'E:



I'E

en donde los sustituyentes son como se definen para un compuesto de la fórmula I.

$A^1$ de preferencia representa un enlace directo, carbonilo (-C(=O)-) o metandiilo ($-CH_2-$).

Las siguientes definiciones se aplican a cualquiera de las fórmulas descritas en la presente.

$R^1$ de preferencia representa heterociclilo insustituido o sustituido, o arilo insustituido o sustituido

en donde este heterociclilo se selecciona a partir de

heterociclos insaturados, saturados o parcialmente saturados, los cuales son monocíclicos, bicíclicos, tricíclicos o espirocíclicos, y tienen de 4 a 16 átomos del anillo, en donde están presentes de uno a cuatro átomo heterogéneos;

en donde este arilo se selecciona a partir de fracciones aromáticas con 6 a 14 átomos de carbono del anillo;

en donde los sustituyentes mencionados se seleccionan independientemente a partir de una o más, de preferencia una a cuatro de las siguientes fracciones: alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, pirrolidino-alquilo de 1 a 7 átomos de carbono, oxo-pirrolidino-alquilo de 1 a 7 átomos de carbono, piperidino-alquilo de 1 a 7 átomos de carbono, piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, morfolino-alquilo de 1 a 7 átomos de carbono, tiomorfolino-alquilo de 1 a 7 átomos de carbono, S-mono- o S,S-

dioxo-tiomorfolino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, pirrolidino, oxo-pirrolidino, piperidino, piperazin-1-ilo, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-ilo, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-ilo, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-ilo, morfolino, tiomorfolino, S-oxo- o S,S-dioxo-tiomorfolino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono y/o (N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono)-carbamoílo, pirrolidin-1-carbonilo, piperidin-1-carbonilo, piperazin-1-carbonilo, 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-carbonilo, morfolin-1-carbonilo, tiomorfolin-1-carbonilo, S-oxo- o S,S-dioxo-tiomorfolin-1-carbonilo, sulfo, alcano de 1 a 7 átomos de carbono-sulfonilo,

alcano de 1 a 7 átomos de carbono-sulfinilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro.

$R^1$ de una manera particularmente preferible representa heterociclilo insustituido o sustituido, o arilo insustituido o sustituido

en donde este heterociclilo o arilo se selecciona a partir del grupo que consiste en fenilo, naftilo, indanilo, pirrol, pirrolina, pirrolidina, pirazol, pirazolina, pirazolidina, imidazol, imidazolina, imidazolidina, triazol, triazolina, triazolidina, tetrazol, furano, dihidrofurano, tetrahidrofurano, furazano (oxadiazol), dioxolano, tiofeno, dihidro-tiofeno, tetrahidro-tiofeno, oxazol, oxazolina, oxazolidina, isoxazol, isoxazolina, isoxazolidina, tiazol, tiazolina, tiazolidina, isotiazol, istotiazolina, isotiazolidina, tiadiazol, tiadiazolina, tiadiazolidina, piridina, piperidina, piridazina, pirazina, piperazina, triazina, pirano, tetrahidro-pirano, tiopirano, tetrahidro-tiopirano, oxazina, tiazina, dioxina, morfolina, purina, pterina, y los heterociclos benzo-templados correspondientes, por ejemplo, indol, isoindol, cumarina, cumaron-cinolina, isoquinolina, cinolina, y

en donde este heterociclilo o arilo está sustituido por una o más, de preferencia una a tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, (amino, alquilo de 1 a 7 átomos de carbono-amino, dialquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono, (amino, alquilo de 1 a 7 átomos de carbono-amino, dialquilo de 1 a 7 átomos de carbono-amino)-alquiloxilo de 1

a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, pirrolidino-alquilo de 1 a 7 átomos de carbono, oxo-pirrolidino-alquilo de 1 a 7 átomos de carbono, piperidino-alquilo de 1 a 7 átomos de carbono, piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, morfolino-alquilo de 1 a 7 átomos de carbono, tiomorfolino-alquilo de 1 a 7 átomos de carbono, S-mono- o S,S-dioxo-tiomorfolino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, pirrolidino, oxo-pirrolidino, piperidino, piperazin-1-ilo, 4-(alquilo de 1

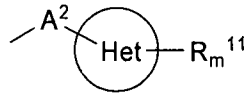
a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-ilo, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-ilo, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-ilo, morfolino, tiomorfolino, S-oxo- o S,S-dioxo-tiomorfolino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono y/o (N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono)-carbamoílo, pirrolidin-1-carbonilo, piperidin-1-carbonilo, piperazin-1-carbonilo, 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-carbonilo, morfolin-1-carbonilo, tiomorfolin-1-carbonilo, S-oxo- o S,S-dioxo-tiomorfolin-1-carbonilo, sulfo, alcano de 1 a 7 átomos de carbono-sulfonilo, alcano de 1 a 7 átomos de carbono-sulfinilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro.

$R^1$ de una manera muy particularmente preferible representa heterociclilo, hetero-arilo o arilo, en cada caso insustituido o sustituido por uno o más (de preferencia 0, 1 ó 2 sustituyentes),

en donde este heterociclilo, hetero-arilo o arilo se selecciona a partir del grupo que consiste en fenilo, 2-, 3-, 4-piridilo, 2-, 4-, 5-pirimidinilo, pirazinilo, 3-, 4-piridazinilo, 3-, 4-, 5-pirazolilo, 2-, 4-, 5-

imidazolilo, 2-, 4-, 5-tiazolilo, 3-, 4-, 5-isotiazolilo, y

en donde el sustituyente mencionado se selecciona a partir del grupo que consiste en flúor, cloro, ciano, alquilo de 1 a 4 átomos de carbono (en particular metilo, etilo), alquiloxilo de 1 a 4 átomos de carbono (en particular metoxilo), hidroxi-alquilo de 1 a 4 átomos de carbono (en particular 2-hidroxi-etilo), halo-alquilo de 1 a 4 átomos de carbono (en particular $CF_3$), alquiloxilo de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono (en particular metoxi-metilo), ciclopropilo, ciclopentilo, ciclopropiloxilo, ciclopentiloxilo o un grupo:




en donde:

$A^2$ representa un enlace individual, carbonilo, metandiilo, 1,1-etandiilo, 1,2-etandiilo;

Het representa un heterociclo saturado con 5 ó 6 átomos del anillo (en particular piperidinilo, piperazinilo, morfolinilo);

m representa 0, 1 ó 2

$R^{11}$ representa alquilo de 1 a 4 átomos de carbono (en particular metilo, etilo), alquiloxilo de 1 a 4 átomos de carbono (en particular metoxilo), alquiloxilo de 1 a 4 átomos de carbono-carbonilo (en particular terbutoxi-carbonilo), hidroxi-alquilo de 1 a 4 átomos de carbono (en particular 2-hidroxi-etilo), halo-alquilo de 1 a 4 átomos de carbono (en particular $CF_3$), alquiloxilo de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono (en particular metoxi-

metilo), ciclopropilo, ciclopropiloxilo.

En cualquiera de las fórmulas en la presente, $R^1$ es de preferencia arilo o hetero-arilo, estando cada uno insustituido o sustituido como se define en la presente.

$R^2$ de preferencia representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono.

$R^2$ de una manera particularmente preferible representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro.

$R^2$ de una manera muy particularmente preferible representa hidrógeno, flúor, cloro, metilo.

$R^3$ de preferencia representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de

carbono.

$R^3$ de una manera particularmente preferible representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro.

$R^3$ de una manera muy particularmente preferible representa hidrógeno, flúor, cloro, metilo.

Cuando $R^2$ y/o $R^3$ se conectan con $R^5$ o $R^7$ para formar una fracción cíclica fusionada con el anillo de fenilo con el que $R^2/R^3$ están unidos, el sistema de anillos fusionados resultante es de preferencia una 1,3-dihidro-indol-2-ona, opcionalmente sustituida en la posición 1 con alquilo inferior tal como metilo, o una 3,4-dihidro-1H-quinolin-2-ona.

$R^{2a}$ de preferencia representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono.

$R^{2a}$ de una manera particularmente preferible representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo,

ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro.

$R^{2a}$ de una manera muy particularmente preferible representa hidrógeno, flúor, cloro, metilo.

$R^{2a}$ más preferiblemente representa hidrógeno o metilo, todavía más preferiblemente hidrógeno.

$R^{3a}$ de preferencia representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono.

$R^{3a}$ de una manera particularmente preferible representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro.

$R^{3a}$ de una manera muy particularmente preferible representa hidrógeno, flúor, cloro, metilo.

$R^{3a}$ más preferiblemente representa hidrógeno o metilo, todavía más preferiblemente hidrógeno.

$R^{5}$ de preferencia representa hidrógeno, alquilo de 1 a 7

átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, halo-cicloalquilo de 3 a 6 átomos de carbono, o ambos $R^5$ forman junto con el átomo de carbono con el que están unidos, un ciclopropilo.

$R^5$ de una manera particularmente preferible representa hidrógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 2 átomos de carbono, ciclopropilo.

$R^5$ de una manera muy particularmente preferible representa hidrógeno, metilo o ciclopropilo.

$R^6$ y $R^7$ de preferencia representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido por uno o más sustituyentes,

en donde este heterociclo está saturado, contiene 5 ó 6 átomos del anillo, y 1, 2 ó 3 átomo heterogéneos seleccionados a partir del grupo de N, O y S, y

en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), hidroxilo, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-amino, di-alquilo de 1 a 7 átomos de carbono-amino.

$R^6$ y $R^7$ de una manera muy preferible representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido por uno a tres sustituyentes,

en donde este heterociclo se selecciona a partir del grupo de morfolinilo, piperazinilo, tiazidinilo, pirrolidinilo y

en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopropiloxilo, hidroxi-alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-amino, di-alquilo de 1 a 4 átomos de carbono-amino.

$R^6$ de preferencia representa hidrógeno, alquilo opcionalmente sustituido de 1 a 7 átomos de carbono, y

$R^7$ representa hidrógeno, alquilo opcionalmente sustituido de 1 a 7 átomos de carbono, en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), hidroxilo, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-amino, di-alquilo de 1 a 7 átomos de carbono-amino.

$R^6$ de una manera muy preferible representa hidrógeno, y

$R^7$ de una manera muy preferible representa butilo normal, butilo secundario, isobutilo, butilo terciario, propilo normal, isopropilo, etilo o metilo, en particular butilo terciario, estando cada uno opcionalmente sustituido, en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), hidroxilo, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-amino, di-alquilo de 1 a 7 átomos de carbono-amino.

$R^8$ de preferencia representa hidroxilo, alquiloxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, cicloalquilo de 3 a 6 átomos de carbono-sulfonilo, halo-cicloalquilo de 3 a 6 átomos de carbono-sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, halo-alquilo de 1 a 7 átomos de carbono-sulfinilo, cicloalquilo de 3 a 6 átomos de carbono-sulfinilo, halo-cicloalquilo de 3 a 6 átomos de carbono-sulfinilo.

$R^8$ de una manera particularmente preferible representa hidroxilo, metoxilo, etoxilo, isopropoxilo, halo-metoxilo, metil-

carbonilo, metil-sulfonilo ($H_3CSO_2$-), ciclopropil-sulfonilo.

$R^8$ de una manera muy particularmente preferible representa hidroxilo, metoxilo o metil-sulfonilo.

$R^9$ de preferencia representa hidrógeno, alquilo de 1 a 7 átomos de carbono.

$R^9$ de una manera particularmente preferible representa hidrógeno, alquilo de 1 a 4 átomos de carbono.

$R^9$ de una manera muy particularmente preferible representa hidrógeno.

$R^{10}$ de preferencia representa hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, halo-cicloalquilo de 3 a 6 átomos de carbono.

$R^{10}$ de una manera particularmente preferible representa hidrógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 2 átomos de carbono, ciclopropilo.

$R^{10}$ de una manera muy particularmente preferible representa hidrógeno o metilo.

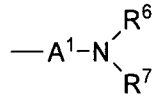
n de preferencia representa 0 ó 1.

n de una manera particularmente preferible representa 0.

n de una manera más particularmente preferible, representa 1.

En una modalidad conveniente adicional, n representa 0, y $R^8$ representa $-SO_2CH_3$.

En una modalidad conveniente todavía adicional, n representa

0 ó 1, y $R^4$ representa el grupo: 

como se define anteriormente, más preferiblemente en donde el grupo es como se define anteriormente, y $R^6$ y $R^7$, junto con el átomo de nitrógeno con el que están unidos, forman un grupo morfolinilo, piperazinilo, tiazidinilo o pirrolidinilo, estando cada uno opcionalmente sustituido, más preferiblemente $R^6$ y $R^7$ junto con el átomo de nitrógeno con el que están unidos, forman un grupo morfolinilo opcionalmente sustituido, en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), hidroxilo, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-amino, di-alquilo de 1 a 7 átomos de carbono-amino.

En una modalidad conveniente adicional, cuando menos uno de $R^2$ y $R^3$ no representan hidrógeno.

En una modalidad conveniente adicional, $R^1$ es arilo opcionalmente sustituido seleccionado a partir del grupo que consiste en fenilo, naftilo, cada uno de los cuales está insustituido o sustituido por una a tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7

átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, pirrolidino-alquilo de 1 a 7 átomos de carbono, oxo-pirrolidino-alquilo de 1 a 7 átomos de carbono, piperidino-alquilo de 1 a 7 átomos de carbono, piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, morfolino-alquilo de 1 a 7 átomos de carbono, tiomorfolino-alquilo de 1 a 7 átomos de carbono, S-mono- o S,S-dioxo-tiomorfolino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, pirrolidino, oxo-pirrolidino, piperidino,

piperazin-1-ilo, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-ilo, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-ilo, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-ilo, morfolino, tiomorfolino, S-oxo- o S,S-dioxo-tiomorfolino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono y/o (N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono)-carbamoílo, pirrolidin-1-carbonilo, piperidin-1-carbonilo, piperazin-1-carbonilo, 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-carbonilo, morfolin-1-carbonilo, tiomorfolin-1-carbonilo, S-oxo- o S,S-dioxo-tiomorfolin-1-carbonilo, sulfo, alcano de 1 a 7 átomos de carbono-sulfonilo, alcano de 1 a 7 átomos de carbono-sulfinilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro; por ejemplo, de preferencia puede ser fenilo o naftilo que está sustituido por uno o más, en especial de uno a cuatro sustituyentes seleccionados independientemente a partir del grupo que consiste en alcoxilo de 1 a 7 átomos de carbono, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono y/o alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos

de carbono)-carbamoílo, N-mono- o N,N-di-carbamoílo-{[insustituido o sustituido por N'-mono- o N,N'-di-(alquilo de 1 a 7 átomos de carbono)]}, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, piperidino, piperazino, N-alquilo de 1 a 7 átomos de carbono-piperazino, morfolino, tiomorfolino, S-oxo-tiomorfolino y S,S-dioxo-tiomorfolino, en el caso de $R^2$, arilo insustituido o sustituido es de preferencia fenilo o naftilo que está insustituido o sustituido por uno o más, en especial hasta tres, más especialmente hasta dos, sustituyentes, de preferencia no en la posición *orto*, más preferiblemente con no más de un sustituyente en la posición *meta*, más preferiblemente con un sustituyente en la posición *meta* y/o un sustituyente en la posición *para*, más preferiblemente con un sustituyente en la posición *meta* o en especial uno en la posición *para*, en donde los sustituyentes se seleccionan independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de

carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoílo, alcano de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro.

En una modalidad conveniente adicional, $R^1$ es arilo opcionalmente sustituido seleccionado a partir del grupo que consiste en fenilo, (en especial 3,4,5-)-trimetoxi-fenilo*, (en especial 3,4- o 3,5-)-dimetoxi-fenilo*, (en especial 4-)-morfolino-fenilo, (en especial 4-)-N-(2-metoxi-etil)-carbamoil-fenilo*, o (en especial 4-)-N,N-(2-dimetil-amino-etil)-carbamoil-fenilo*, (en especial 4-)-dimetil-amino-carbonil-(en especial 3-)-metil-fenilo*, (en especial 4-)-(de preferencia 4-)-(2-metoxi-etil-piperazin-(en especial 1-)-il-(en especial 3-)-metil-fenilo, (en especial 4-)-pirrolidin-1-carbonil-(en especial 3-)-metil-fenilo*, (en especial 3-)-metil-(en especial 4-)-4-metil-piperazin-1-carbonil-fenilo, (en especial 3- o 4-)-4-metil-piperazin-1-il-fenilo*, (en especial 4-)-4-etil-piperazin-1-il-(en especial 3-)-metil-fenilo*, (en especial 4-)-4-metil-piperazin-1-il-(en especial 3-)-ciano-fenilo, (en especial 4-)-piperazin-1-il-fenilo, (en especial 4-)-4-ciclopropil-piperazin-1-il-fenilo, (en especial 4-)-4-(2-dimetil-amino-etil)-piperazin-1-il-(en especial 3-)-metil-fenilo*, (en especial 4-)-4-isopropil-piperazin-1-il)-(en especial 3-)-metil-fenilo*, (en especial 4-)-N,N-dietil-amino-carbonil-(en especial 3-)-metil-fenilo*, (en especial 4-)-4-etil-piperazin-1-carbonil-(en especial 3-)-

metil-fenilo, (en especial 4-)-(4-etil-piperazin-1-il-metil)-(en especial 3-)-metil-fenilo, (en especial 4-)-N-metil-amino-carbonil-(en especial 3-)-metil-fenilo, (en especial 4-)-4-(3,3,3-trifluoro-propil)-piperazin-1-il-(en especial 3-)-metil-fenilo, (en especial 4-)-4-(2-(N',N'-dimetil-amino)-etil-amino-carbonil-(en especial 3-)-metil-fenilo, (en especial 4-)-metan-sulfonil-fenilo*, (en especial 4-)[(en especial 2-)-oxo-pirrolidin-1-il]-fenilo, (en especial 4-)N,N-dietil-amino-carbonil-(en especial 3-)-metoxi-fenilo, (en especial 3-)-4-metil-piperazin-1-il-(en especial 4-)-metil-fenilo, (en especial 3-)-4-metil-piperazin-1-il-(en especial 4-)metoxi-fenilo*, (en especial 3- o 4-)-morfolino-metil-(en especial 4- o 3-)-metil-fenilo, (en especial 2-)acetil-amino-indan-(en especial 5-)ilo, (en especial 2-)oxo-2,3-dihidro-indol-(en especial 5-)-ilo, (en especial 4-)-metil-sulfinil-fenilo, (en especial 4-)metoxi-fenilo, (en especial 4-)-metil-(en especial 3-)-metoxi-fenilo, (en especial 4-)-N-(2-metoxi-etil)-amino-carbonil-fenilo, (en especial 4-)N,N-dimetil-carbamoil-fenilo, (en especial 3-)-metan-sulfonil-amino-fenilo, (en especial 4-)metoxi-carbonil-(en especial 3-)-metoxi-fenilo, (en especial 4-)N,N-dimetil-carbamoil-(en especial 3-)-metoxi-fenilo, (en especial 4-)-(4-ciclopropil-piperazin-1-il)-(en especial 3-)-metil-fenilo*, (en especial 4-)-N-(2-(N',N'-dimetil-amino-etil)-N-metil-carbamoil-(en especial 3-)-metil-fenilo*, 1,3-dimetil-oxo-1H-piridin-5-ilo, (en especial 3- o 4-)morfolino-(en especial 4- o 3-)-metil-fenilo*, (en especial 4-)morfolino-metil-(en especial 3-)-metil-fenilo, (en especial 4-)morfolin-1-carbonil-(en especial 3-)-metil-fenilo, (en especial 4-)-N-2-(metoxi-etil)-amino-carbonil-(en especial 3-)-metil-

fenilo, (en especial 4-)-N-(3-N'.N'-dimetil-amino-propil)-amino-carbonil-(en especial 3-)-metil-fenilo, (en especial 5-)-metil-(en especial 6-)metoxi-piridin-3-ilo, (en especial 4-)-dimetil-carbamoil-(en especial 3,5-)-dimetil-fenilo, (en especial 4-)-dimetil-carbamoil-(en especial 3-)etil-fenilo, (en especial 4-(4-)N,N-dimetil-carbamoil-(en especial 3-)-metil-fenilo o (en especial 4-)morfolino-(en especial 3-)-ciano-fenilo; en donde se prefieren especialmente las fracciones marcadas con un asterisco (*), así como las fracciones en donde se da la posición después de "en especial").

En una modalidad conveniente adicional, $R^1$ es heterociclilo opcionalmente sustituido seleccionado a partir del grupo que consiste en de preferencia piridilo, pirimidilo, pirazolilo, tiofenilo, pirrolilo, imidazolilo, o *1H*-benzo-imidazolilo, cada uno de los cuales está insustituido o sustituido por una a tres fracciones independientemente seleccionadas a partir de aquéllas mencionadas anteriormente como sustituyentes para arilo $R^1$, o en especial a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono,

halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoílo, alcano de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, tiomorfolino-sulfinilo, ciano y nitro.

En una modalidad conveniente adicional, $R^1$ representa fenilo o piridilo, en cada caso opcionalmente sustituido por uno o dos sustituyentes, siendo los sustituyentes seleccionados a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono (en particular metilo), alcoxilo de 1 a 4 átomos de carbono (en particular metoxilo), halógeno (en particular flúor), N-metil-N-piperazinil-metilo, N-metil-N-piperazinil-carbonilo, 3,5-dimetil-N-piperazinilo.

La invención se refiere además a los profármacos farmacéuticamente aceptables de un compuesto de la fórmula (I).

La invención se refiere además a los metabolitos farmacéuticamente aceptables de un compuesto de la fórmula (I).

La invención se refiere en especial a los compuestos de la fórmula I dados en los Ejemplos, así como a los métodos de fabricación descritos en los mismos.

Los compuestos de la fórmula I de los mismos tienen valiosas propiedades farmacológicas, como se describe anteriormente en la presente y posteriormente en la presente. Inhiben diferentes cinasas

de proteína tirosina, y en especial la cinasa de tirosina receptora JAK2 y/o JAK3. De preferencia, los compuestos de la fórmula I exhiben selectividad para JAK2 y JAK3 sobre las cinasas JAK1 y TYK2. De una manera muy preferible, los compuestos de la fórmula I exhiben selectividad para JAK2 sobre las otras cinasas de la familia JAK, es decir, de preferencia, se exhibe selectividad para JAK2 sobre las cinasas JAK1, JAK3 y TYK2.

De preferencia, los compuestos de la fórmula I exhiben selectividad para la inhibición de JAK2 cuando se comparan con otras cinasas, por ejemplo cMet, cKit, ALK y/o PDGFRa.

Los compuestos de la fórmula I típicamente muestran valores $IC_{50}$ para la inhibición de JAK2 en el intervalo de < 0.003 a 2 micromoles/litro$^{-1}$, de preferencia de < 0.003 a 1 micromol/litro$^{-1}$, más preferiblemente de < 0.003 a 0.100 micromoles/litro$^{-1}$, todavía más preferiblemente de < 0.003 a 0.050 micromoles/litro$^{-1}$.

La eficacia de los compuestos de la invención como inhibidores de la actividad de la cinasa JAK/TYK se puede demostrar como sigue (los resultados se dan al final de la memoria descriptiva):

Se utilizaron las cuatro cinasas de la familia de cinasa JAK/TYK como proteínas de fusión con GST recombinantes purificadas, que contienen los dominios activos de cinasa. Se expresaron GST-JAK1(866-1154), GST-JAK3(811-1124), y GST-TYK2(888-1187), y se purificaron mediante cromatografía por afinidad en la unidad de biología de EPK. GST-JAK2(808-1132) se adquirió en Invitrogen (Carlsbad, EUA, #4288).

Los ensayos de cinasa se basaron en el ensayo de cambio de movilidad de Caliper utilizando los sistemas LabChip 3000. Esta tecnología es similar a la electroforesis capilar y utiliza separación del sustrato y el producto, impulsada por la carga en un chip microfluídico.

Todas las reacciones de cinasa se llevaron a cabo en placas de microtitulación de 384 cavidades en un volumen de reacción total de 18 microlitros. Las placas de ensayo se prepararon con 0.1 microlitros por cavidad del compuesto de prueba en la concentración de prueba apropiada, como se describe bajo la sección "Preparación de diluciones de compuestos". Las reacciones se iniciaron mediante la combinación de 9 microlitros de mezcla de sustrato (consistente en péptido y ATP) con 9 microlitros de dilución de cinasa. Las reacciones se incubaron durante 60 minutos a 30°C, y se detuvieron mediante la adición de 70 microlitros de regulador de paro (Hepes 100 mM, sulfóxido de dimetilo al 5 por ciento, reactivo de recubrimiento al 0.1 por ciento, EDTA 10 mM, Brij 35 al 0.015 por ciento).

Se utilizaron péptidos sintéticos fluorescentemente marcados como sustratos en todas las reacciones. Se utilizó un péptido derivado a partir de la secuencia de IRS-1 (péptido IRS-1, FITC-Ahx-KKSRGDYMTMQIG-NH2) para JAK1 y TYK2 y un péptido denominado como JAK3tide (FITC-GGEEEEYFELVKKKK-NH2) para JAK2 y JAK3. Las condiciones específicas del ensayo se describen en el Cuadro 1:

**Cuadro 1**

**Condiciones de ensayo de los ensayos de las cinasas individuales**

| Cinasa | JAK1 | JAK2 | JAK3 | TYK2 |
|---|---|---|---|---|
| Regulador | Hepes 50 mM pH 7.5, Tween 20 al 0.02 %, DTT 1 mM, BSA al 0.02 %, $MgCl_2$ 12 mM | Hepes 50 mM pH 7.5, Tween 20 al 0.02 %, DTT 1 mM, BSA al 0.02 %, $MgCl_2$ 9 mM | Hepes 50 mM pH 7.5, Tween 20 al 0.02 %, DTT 1 mM, BSA al 0.02 %, $MgCl_2$ 1.5 mM | Hepes 50 mM pH 7.5, Tween 20 al 0.02 %, DTT 1 mM, BSA al 0.02 %, $MgCl_2$ 9 mM |
| DMSO | 0.6 % | 0.6 % | 0.6 % | 0.6 % |
| Cinasa conc. | 50 nM | 1.8 nM | 6 nM | 40 nM |
| Sustrato peptídico conc. | 5 µM | 2 µM | 2 µM | 5 µM |
| ATP conc. | 40 µM | 20 µM | 80 o 18 µM | 30 µM |

Las reacciones terminadas se transfirieron al lector Caliper LabChip 3000 y se midió el cambio de cada reacción mediante la determinación de la proporción de sustrato/producto.

***Preparación de diluciones de compuestos***

Los compuestos de prueba se disolvieron en sulfóxido de dimetilo (10 mM) y se transfirieron a tubos de Matriz en forma de V o de fondo plano de 1.4 mililitros que llevaban un chip de matriz 2D único, mediante cubos del compuesto individual. Los números de estos chips se ligaron distintivamente a los números de identificación de los compuestos individuales. Las soluciones de suministro se almacenaron a –20°C si no se utilizaban inmediatamente. Para el procedimiento de prueba, los frascos se descongelaron y se identificaron mediante un escáner, en donde se generó una hoja de trabajo que guió los siguientes pasos de procesamiento.

Se hicieron diluciones de los compuestos en placas de 96 cavidades. Este formato hizo posible el ensayo de máximo 40 compuestos de prueba individuales en 8 concentraciones (puntos individuales), incluyendo 4 compuestos de referencia. El protocolo de dilución incluyó la producción de placas de pre-dilución, placas maestras, y placas de ensayo:

Placas de pre-dilución: se utilizaron placas de polipropileno de 96 cavidades como las placas de pre-dilución. Se prepararon un total de 4 placas de pre-dilución, incluyendo 10 compuestos de prueba cada una, en las posiciones de placa A1 a A10, un compuesto

estándar en A11, y un control de sulfóxido de dimetilo en A12. Todos los pasos de dilución se hicieron en un robot HamiltonSTAR.

Placas maestras: Se transfirieron 100 microlitros de las diluciones de los compuestos individuales, incluyendo el compuesto estándar y los controles de las 4 "placas de pre-dilución" hacia una "placa maestra" 384, incluyendo las siguientes concentraciones: 1'820, 564, 182, 54.6, 18.2, 5.46, 1.82 y 0.546µM, respectivamente, en sulfóxido de dimetilo al 90 por ciento.

Placas de ensayo: Entonces se prepararon placas de ensayo idénticas pasando por pipeta 100 nanolitros de cada una de las diluciones de los compuestos de las placas maestras hacia las "placas de ensayo" de 384 cavidades. En seguida, se mezclaron los compuestos con 9 microlitros de los componentes de los ensayos más 9 microlitros de enzima correspondientes a los pasos de dilución de 1:181, haciendo posible la concentración final de 10, 3.0, 1.0, 0.3, 0.1, 0.03, 0.01 y 0.003 µM, respectivamente. La preparación de las placas maestras se manejó mediante el robot Matrix PlateMate Plus, y la réplica de las placas de ensayo mediante el robot HummingBird.

Con base en estos estudios, un compuesto de la invención muestra eficacia terapéutica en especial contra trastornos dependientes de cinasa de proteína, en especial enfermedades proliferativas mediadas por la actividad de cinasa JAK/TYK.

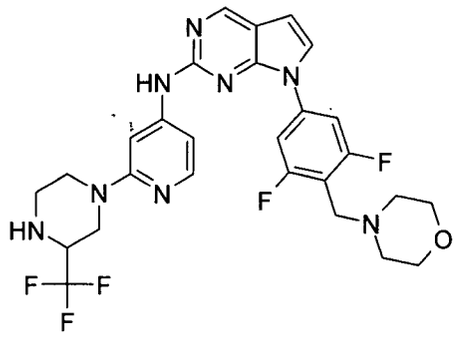
***Ensayos de translocalización nuclear de STAT:***

De una manera alternativa, la actividad de los compuestos de la invención como inhibidores de la senda de JAK/STAT se puede demostrar como sigue (los resultados se dan al final de la memoria descriptiva):

Se puede utilizar rutinariamente el ensayo de microscopio de fluorescencia automatizado celular de producción media (formato de 96 cavidades) Cellomics, para evaluar la activación funcional de las cinasas Janus (JAKs), basándose en la translocalización nuclear de su sustrato, el transductor de señales y activador de transcripción (STAT). La translocalización nuclear se puede monitorear ya sea en células de fibrosarcoma HT1080 establemente transfectadas con STAT1 fusionado con Proteína Fluorescente Verde (GFP), o bien en células de osteosarcoma U-2 OS establemente transfectadas con STAT5 fusionado con Proteína Fluorescente Verde (GFP). El estímulo de las células HT1080 con interferón-γ (IFN-γ) da como resultado la translocalización nuclear de STAT1-GFP dependiente de JAK1/JAK2, mientras que el estímulo de las células U-2 OS con eritropoietina humana recombinante (rhEpo) da como resultado la translocalización nuclear de STAT5-GFP dependiente de JAK2, ambos de los cuales se pueden cuantificar utilizando el paquete de software Cellomics Cyto/NucTrans. Este ensayo se puede utilizar para proporcionar una evaluación del diferencial nuclear-citoplásmico (NCD) de STAT-GFP utilizando el tinte Hoechst para definir los límites del núcleo.

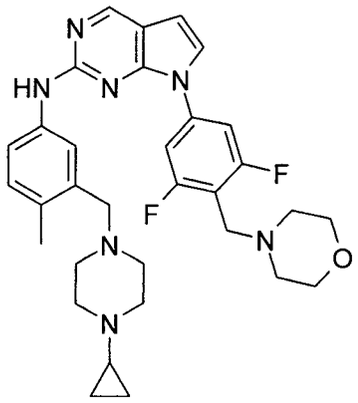
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.03 minutos. (Método B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.10

**Ejemplo 364: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-trifluoro-metil-piperazin-1-il)-piridin-4-il]-amina (racémica)**



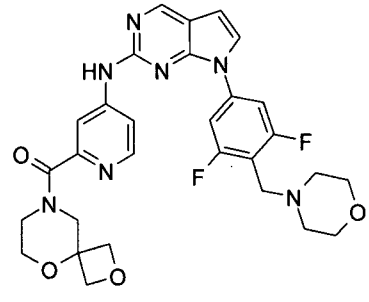
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC (mezcla racémica): $t_R$ = 3.62 minutos y 4.37 minutos (Método C); MS-ES: $(M+H)^+$ = 575

**Ejemplo 365: [3-(4-ciclopropil-piperazin-1-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



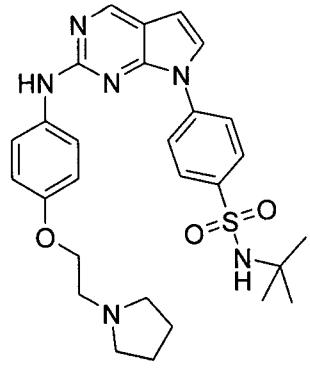
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.47 minutos. (Método B); MS-ES: $(M+H)^+$ = 549; TLC (15 por ciento de metanol / 85 por ciento de cloruro de metileno): $R_f$ = 0.15

**Ejemplo 362: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il)-metanona**



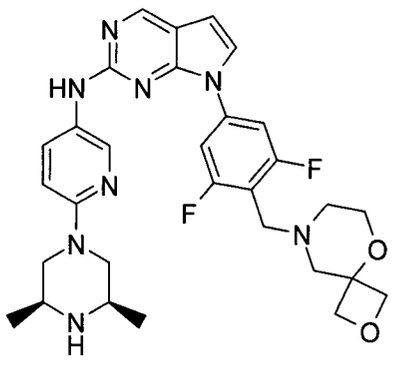
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.95 minutos. (Método B); MS-ES: $(M+H)^+$ = 578; TLC (15 por ciento de metanol / 85 por ciento de cloruro de metileno): $R_f$ = 0.47

**Ejemplo 363: N-terbutil-4-{2-[4-(2-pirrolidin-1-il-etoxi)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



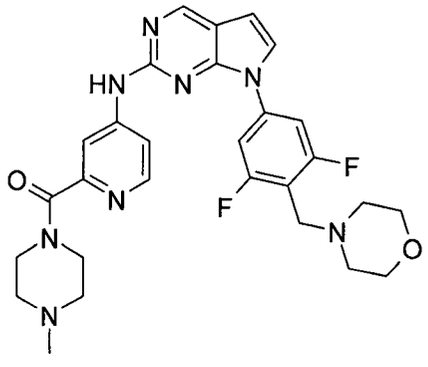
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.60 minutos. (Método B); MS-ES: $(M+H)^+$ = 573; TLC*: $R_f$ = 0.51

**Ejemplo 360: [6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



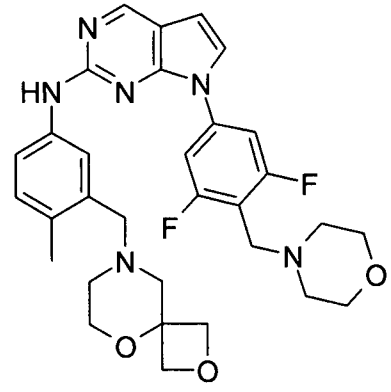
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.65 minutos. (Método B); MS-ES: $(M+H)^+$ = 577; TLC (15 por ciento de metanol / 85 por ciento de cloruro de metileno): $R_f$ = 0.16

**Ejemplo 361: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(4-metil-piperazin-1-il)-metanona**



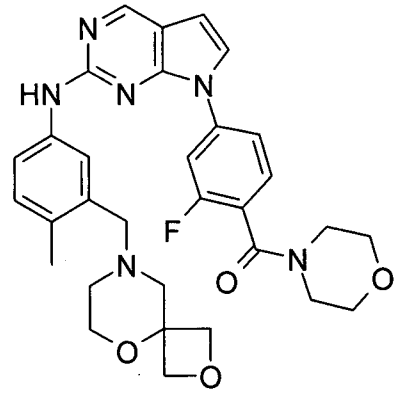
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.64 minutos. (Método B); MS-ES: $(M+H)^+$ = 479; TLC*: $R_f$ = 0.14

**Ejemplo 358: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-4-metil-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.93 minutos. (Método B); MS-ES: $(M+H)^+$ = 577; TLC*: $R_f$ = 0.58

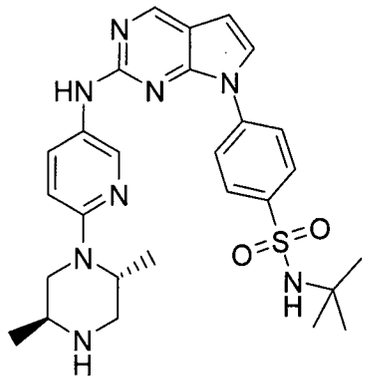
**Ejemplo 359: (4-{2-[3-(2,5-Dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



203

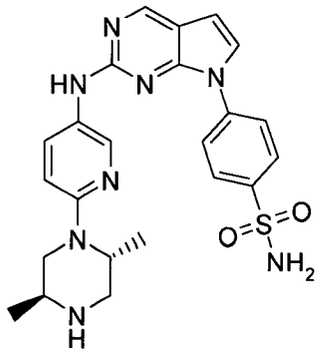
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.73 minutos. (Método B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.22

**Ejemplo 356: N-terbutil-4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida (racémica)**



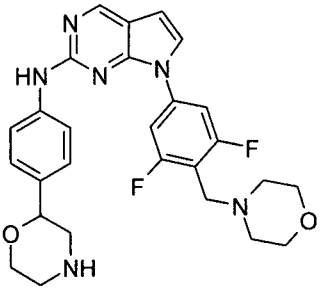
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.77 minutos. (Método B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.04

**Ejemplo 357: 4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida (racémica)**



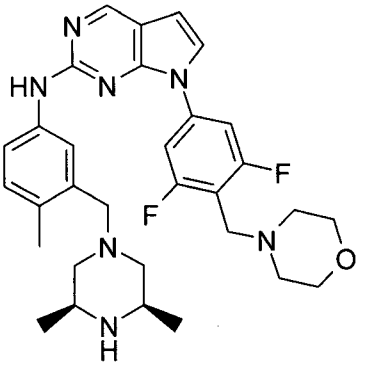
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.07 minutos. (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.22

**Ejemplo 354: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-2-il-fenil)-amina (racémica)**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de morfolina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 1M en EtOH a 60°C. HPLC: $t_R$ = 0.59 minutos (Método G); MS-ES: $(M+H)^+$ = 507

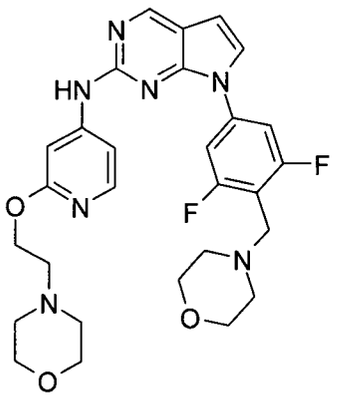
**Ejemplo 355: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina**



204

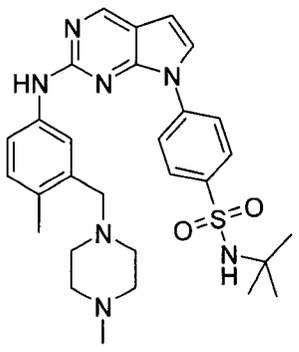
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.77 minutos. (Método B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.05

**Ejemplo 352: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(2-morfolin-4-il-etoxi)-piridin-4-il]-amina**



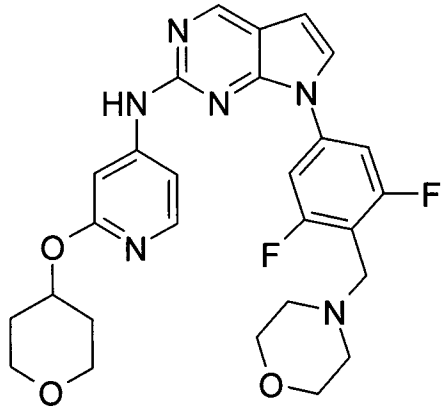
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.58 minutos (Método G); MS-ES: $(M+H)^+$ = 552

**Ejemplo 353: N-terbutil-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



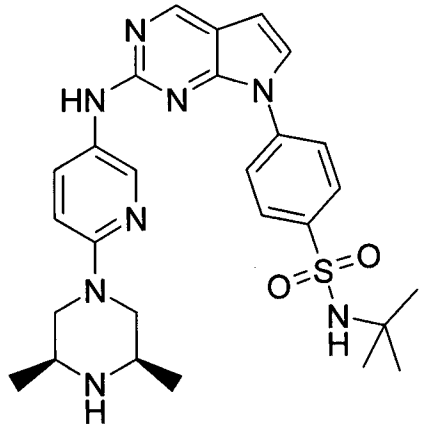
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.71 minutos. (Método B); MS-ES: $(M+H)^+$ = 464; TLC*: $R_f$ = 0.03

**Ejemplo 350: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(tetrahidro-piran-4-iloxi)-piridin-4-il]-amina**



El compuesto se prepara de una manera análoga al 2. HPLC: $t_R$ = 0.67 minutos (Método G); MS-ES: $(M+H)^+$ = 523

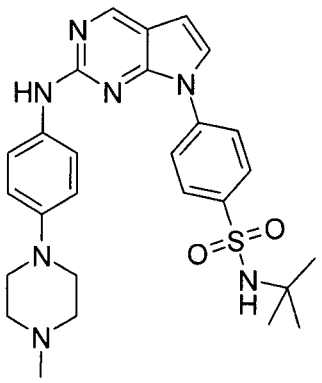
**Ejemplo 351: N-terbutil-4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



205

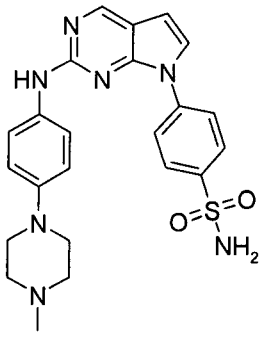
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de alcohol protegido por TBDPS en el paso 2.2. La desprotección final se logra con TBAF 1 M en tetrahidrofurano a temperatura ambiente. HPLC: $t_R$ = 0.57 minutos (Método G); MS-ES: $(M+H)^+$ = 508

**Ejemplo 348: N-terbutil-4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



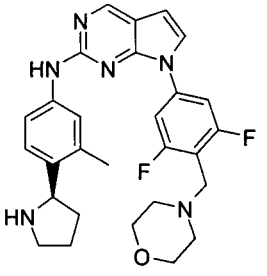
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.82 minutos. (Método B); MS-ES: $(M+H)^+$ = 520; TLC*: $R_f$ = 0.12

**Ejemplo 349: 4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



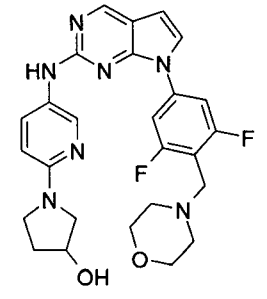
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.02 minutos. (Método B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.18

**Ejemplo 346: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((R)-3-metil-4-pirrolidin-2-il-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. La anilina protegida por Boc correspondiente se obtiene a partir del procedimiento descrito en *J. Am. Chem. Soc.* **2006**, *128*, 3538-3539, empezando a partir de la 4-bromo-3-metil-fenil-amina. HPLC: $t_R$ = 0.58 minutos (Método G); MS-ES: $(M+H)^+$ = 505

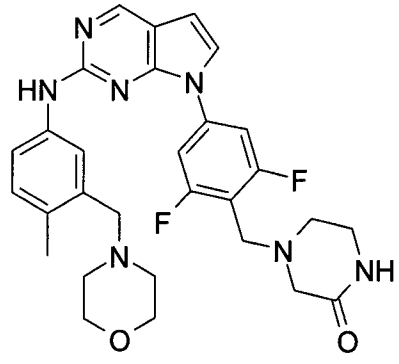
**Ejemplo 347: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-pirrolidin-3-ol (racémico)**



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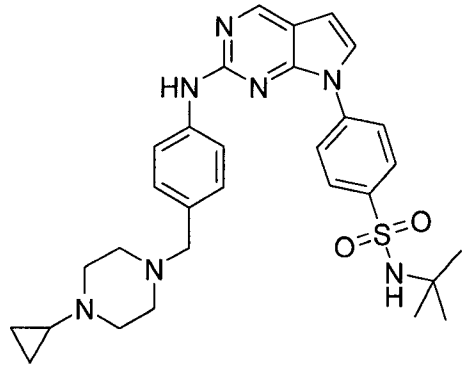
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.77 minutos. (Método B); MS-ES: $(M+H)^+$ = 561; TLC*: $R_f$ = 0.18

**Ejemplo 344: 4-{2,6-difluoro-4-[2-(4-metil-3-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-2-ona**



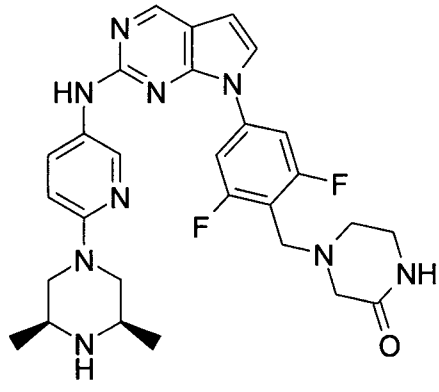
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.88 minutos. (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.35

**Ejemplo 345: N-terbutil-4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



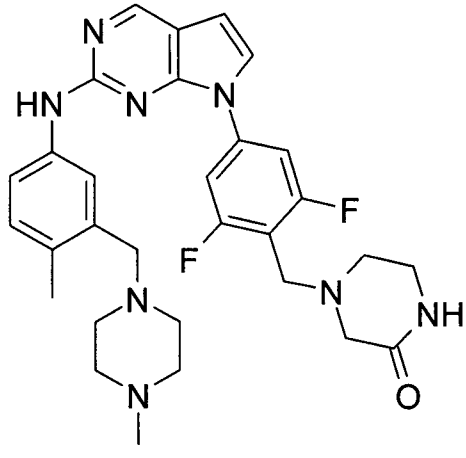
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.47 minutos. (Método B); MS-ES: $(M+H)^+$ = 533

**Ejemplo 342: 4-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.42 minutos. (Método B); MS-ES: $(M+H)^+$ = 548

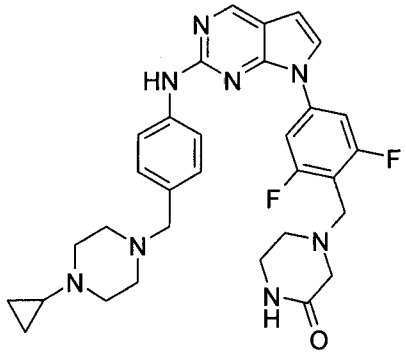
**Ejemplo 343: 4-(2,6-difluoro-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencil)-piperazin-2-ona**



707

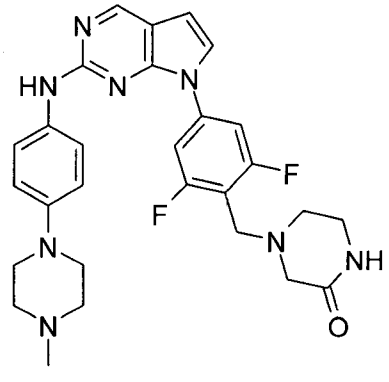
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.70 minutos. (Método B); MS-ES: $(M+H)^+$ = 575; TLC*: $R_f$ = 0.15

**Ejemplo 340: 4-(4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona**



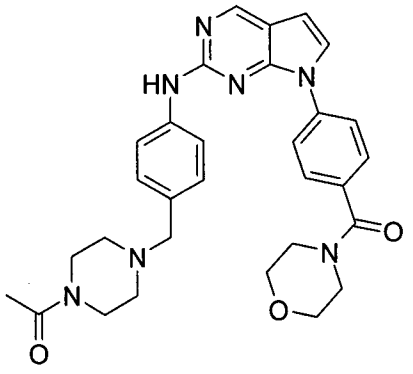
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.76 minutos. (Método B); MS-ES: $(M+H)^+$ = 573; TLC*: $R_f$ = 0.15

**Ejemplo 341: 4-(2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencil)-piperazin-2-ona**



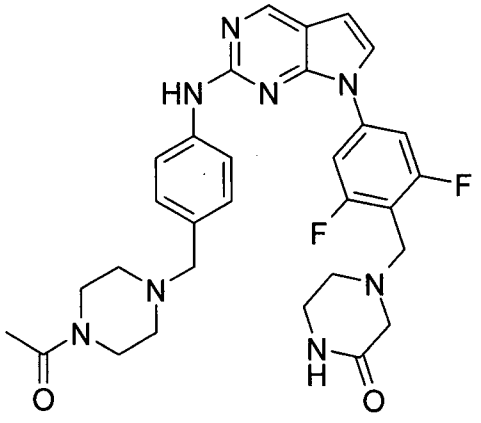
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.19 minutos. (Método B); MS-ES: $(M+H)^+$ = 544; TLC*: $R_f$ = 0.27

**Ejemplo 338: 1-[4-(4-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.02 minutos. (Método B); MS-ES: $(M+H)^+$ = 540; TLC*: $R_f$ = 0.24

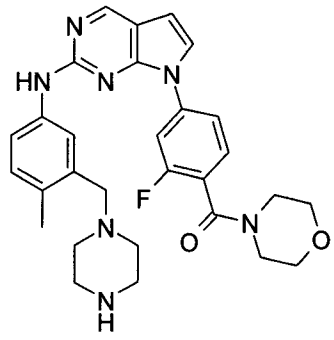
**Ejemplo 339: 4-(4-{2-[4-(4-acetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona**



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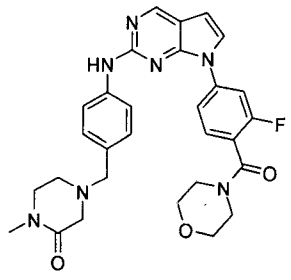
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.04 minutos. (Método B); MS-ES: $(M+H)^+$ = 491; TLC**: $R_f$ = 0.10

**Ejemplo 336: {2-fluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



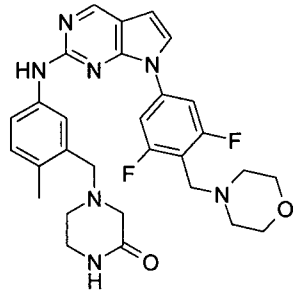
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 7.10 minutos. (Método B); MS-ES: $(M+H)^+$ = 530

**Ejemplo 337: 4-(4-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-1-metil-piperazin-2-ona**



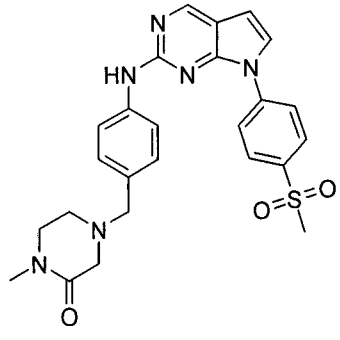
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.90 minutos. (Método B); MS-ES: $(M+H)^+$ = 477

**Ejemplo 334: 4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-2-ona**



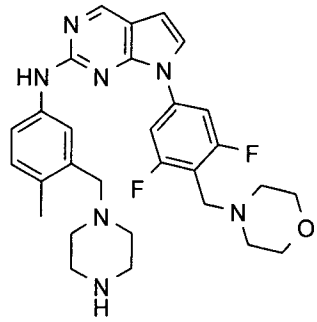
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.55 minutos. (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.39

**Ejemplo 335: 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-1-metil-piperazin-2-ona**



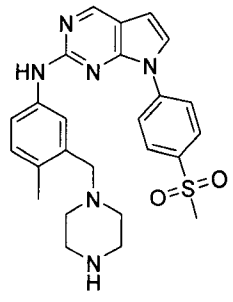
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.72 minutos. (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.35

**Ejemplo 332: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-piperazin-1-il-metil-fenil)-amina**



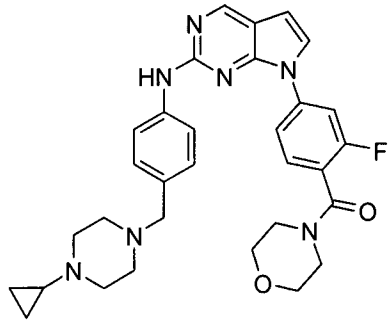
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.45 minutos. (Método B); MS-ES: $(M+H)^+$ = 534

**Ejemplo 333: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-piperazin-1-il-metil-fenil)-amina**



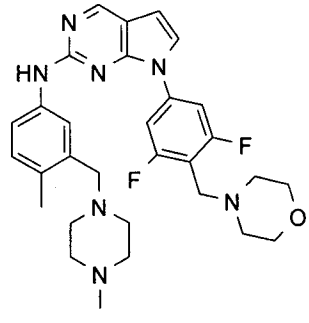
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.75 minutos. (Método B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.23

**Ejemplo 330: (4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.16 minutos. (Método B); MS-ES: $(M+H)^+$ = 556; TLC*: $R_f$ = 0.30

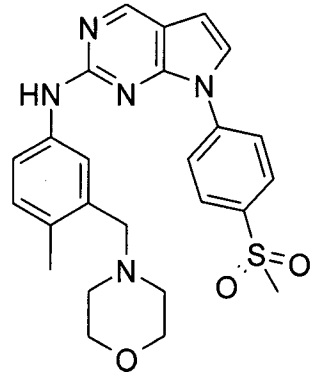
**Ejemplo 331: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil]-amina**



210

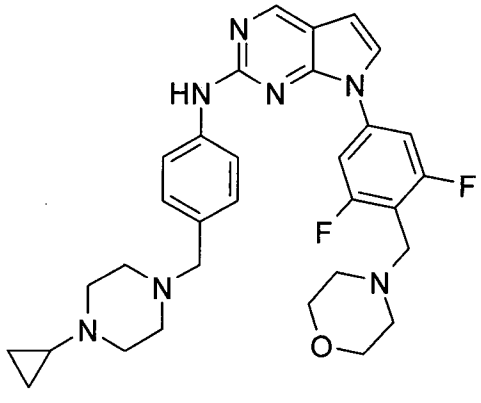
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.44 minutos. (Método B); MS-ES: $(M+H)^+$ = 531; TLC*: $R_f$ = 0.48

**Ejemplo 328: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-morfolin-4-il-metil-fenil)-amina**



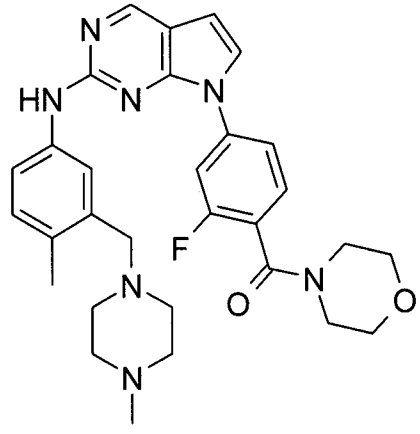
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.32 minutos. (Método B); MS-ES: $(M+H)^+$ = 478; TLC*: $R_f$ = 0.56

**Ejemplo 329: [4-(4-ciclopropil-piperazin-1-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



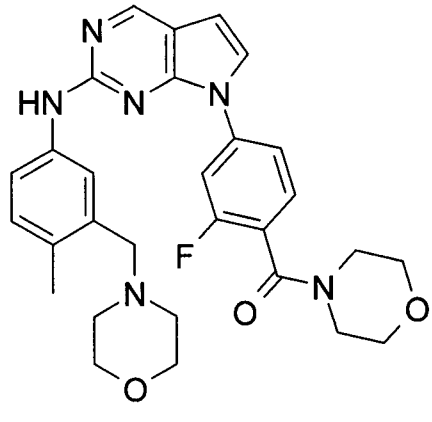
= 0.77

**Ejemplo 326: (2-fluoro-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.30 minutos. (Método B); MS-ES: $(M+H)^+$ = 544; TLC*: $R_f$ = 0.35

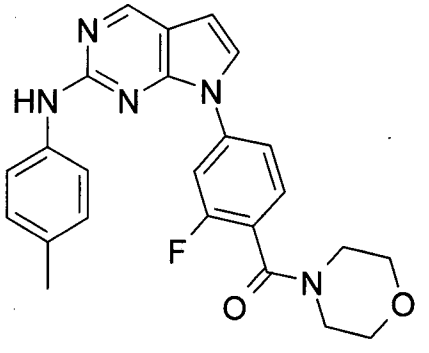
**Ejemplo 327: {2-fluoro-4-[2-(4-metil-3-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



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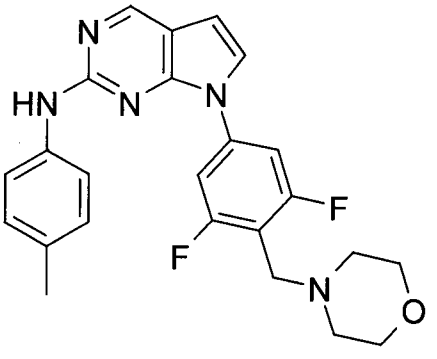
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.46 minutos. (Método B); MS-ES: $(M+H)^+$ = 576; TLC*: $R_f$ = 0.18

**Ejemplo 324: [2-fluoro-4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.47 minutos. (Método B); MS-ES: $(M+H)^+$ = 432

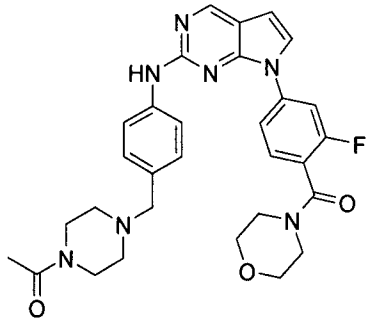
**Ejemplo 325: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.60 minutos. (Método B); MS-ES: $(M+H)^+$ = 436; TLC*: $R_f$

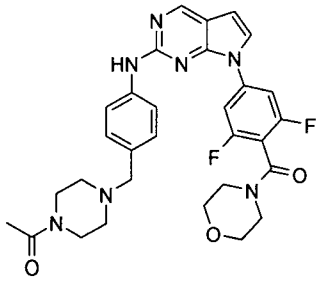
El compuesto se prepara a partir del Ejemplo 320 mediante la disociación del grupo protector de Boc bajo condiciones ácidas (HCl 4 M en dioxano). HPLC: $t_R$ = 6.13 minutos. (Método B); MS-ES: $(M+H)^+$ = 495

**Ejemplo 322: 1-[4-(4-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona**



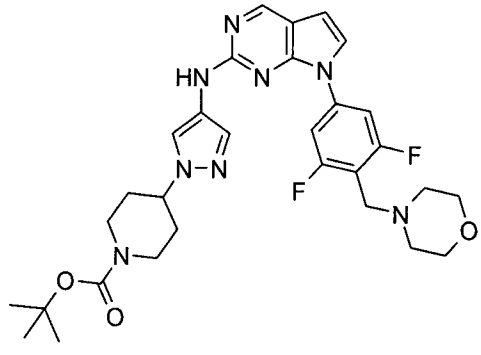
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.23 minutos. (Método B); MS-ES: $(M+H)^+$ = 558; TLC*: $R_f$ = 0.25

**Ejemplo 323: 1-[4-(4-{7-[3,5-difluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona**



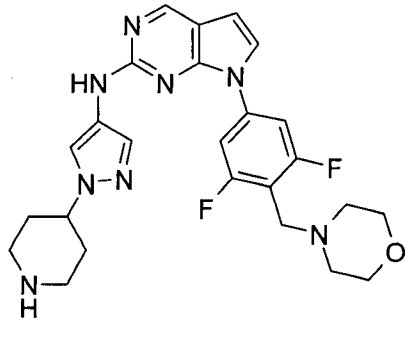
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.01 minutos. (Método B); MS-ES: $(M+H)^+$ = 505; TLC*: $R_f$ = 0.21

**Ejemplo 320: Terbutil-éster del ácido 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-pirazol-1-il}-piperidin-1-carboxílico**



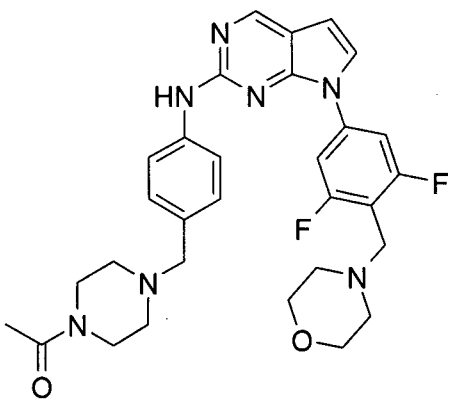
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.04 minutos. (Método B); MS-ES: $(M+H)^+$ = 595; TLC*: $R_f$ = 0.43

**Ejemplo 321: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1-piperidin-4-il-1H-pirazol-4-il)-amina**



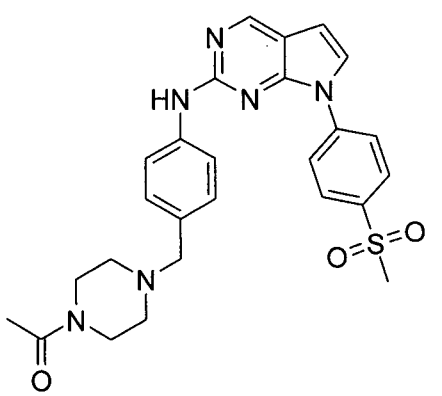
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.91 minutos. (Método B); MS-ES: $(M+H)^+$ = 492

**Ejemplo 318: 1-(4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.61 minutos. (Método B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.25

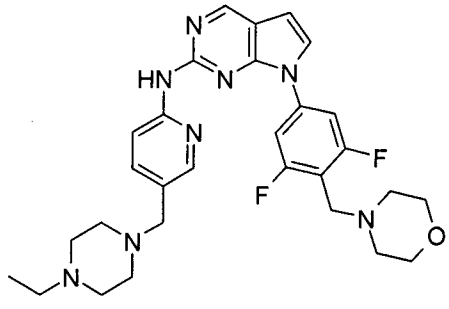
**Ejemplo 319: 1-(4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-il)-etanona**



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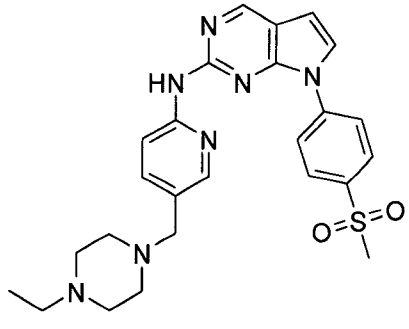
El compuesto se prepara de una manera análoga al Ejemplo 2. El producto final se obtiene mediante la disociación del grupo protector de Boc bajo condiciones ácidas (HCl 4 M en dioxano). HPLC: $t_R$ = 6.60 minutos. (Método B); MS-ES: $(M+H)^+$ = 520

**Ejemplo 316: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[5-(4-etil-piperazin-1-il-metil)-piridin-2-il]-amina**



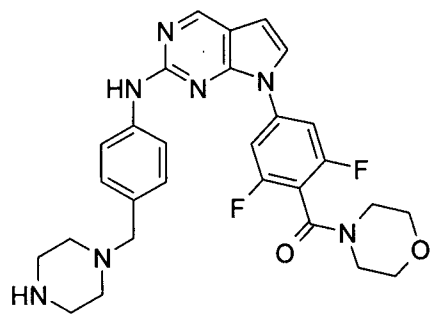
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.42 minutos. (Método B); MS-ES: $(M+H)^+$ = 549; TLC*: $R_f$ = 0.11

**Ejemplo 317: [5-(4-etil-piperazin-1-il-metil)-piridin-2-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



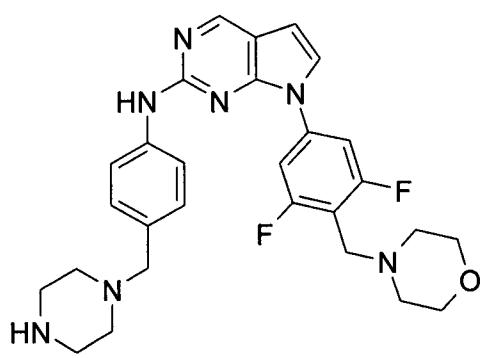
El compuesto se prepara de una manera análoga al Ejemplo 2. El producto final se obtiene mediante la disociación del grupo protector de Boc bajo condiciones ácidas (HCl 4 M en dioxano). HPLC: $t_R$ = 6.83 minutos. (Método B); MS-ES: $(M+H)^+$ = 516

**Ejemplo 314: {2,6-difluoro-4-[2-(4-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. El producto final se obtiene mediante la disociación del grupo protector de Boc bajo condiciones ácidas (HCl 4 M en dioxano). HPLC: $t_R$ = 7.00 minutos. (Método B); MS-ES: $(M+H)^+$ = 534

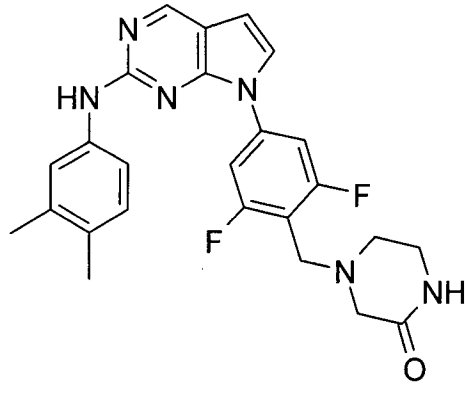
**Ejemplo 315: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-metil-fenil)-amina**



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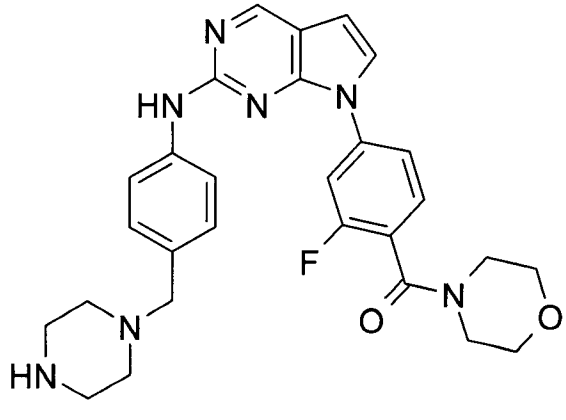
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.94 minutos. (Método B); MS-ES: $(M+H)^+$ = 436; TLC*: $R_f$ = 0.37

**Ejemplo 312: 4-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-bencil}-piperazin-2-ona**



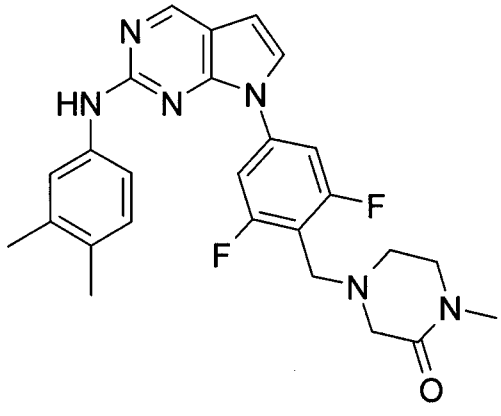
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.81 minutos. (Método B); MS-ES: $(M+H)^+$ = 463; TLC*: $R_f$ = 0.61

**Ejemplo 313: {2-fluoro-4-[2-(4-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



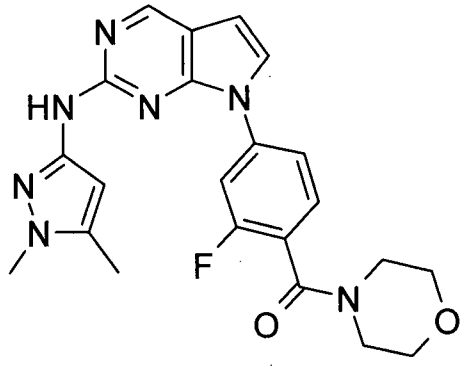
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.23 minutos. (Método B); MS-ES: $(M+H)^+$ = 478; TLC*: $R_f$ = 0.80

**Ejemplo 310: 4-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-bencil}-1-metil-piperazin-2-ona**



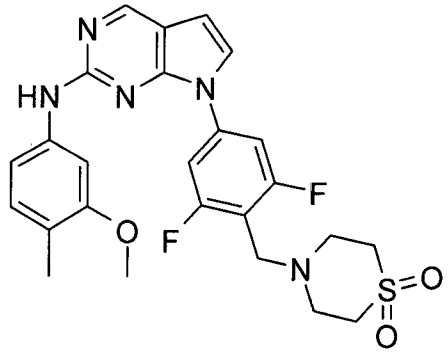
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.05 minutos. (Método B); MS-ES: $(M+H)^+$ = 477; TLC*: $R_f$ = 0.67

**Ejemplo 311: {4-[2-(1,5-dimetil-1H-pirazol-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona**



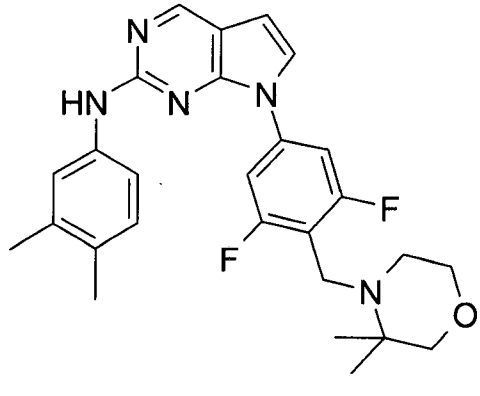
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.80 minutos. (Método B); MS-ES: $(M+H)^+$ = 466; TLC*: $R_f$ = 0.77

**Ejemplo 308: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3-metoxi-4-metil-fenil)-amina**



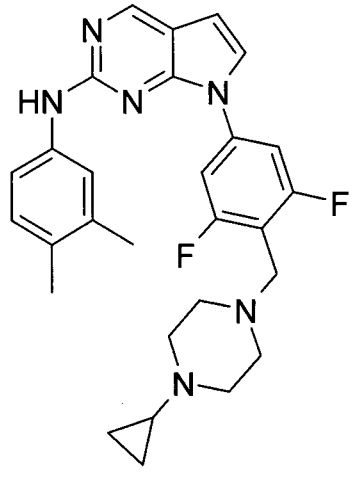
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.81 minutos. (Método B); MS-ES: $(M+H)^+$ = 514; TLC*: $R_f$ = 0.67

**Ejemplo 309: {7-[4-(3,3-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina**



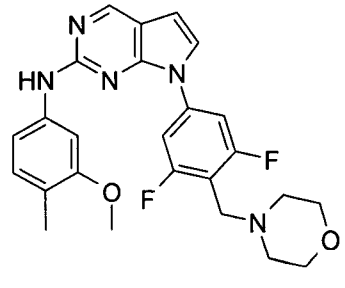
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.15 minutos. (Método B); MS-ES: $(M+H)^+$ = 491; TLC**: $R_f$ = 0.32

**Ejemplo 306: {7-[4-(4-ciclopropil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.50 minutos. (Método B); MS-ES: $(M+H)^+$ = 489; TLC**: $R_f$ = 0.50

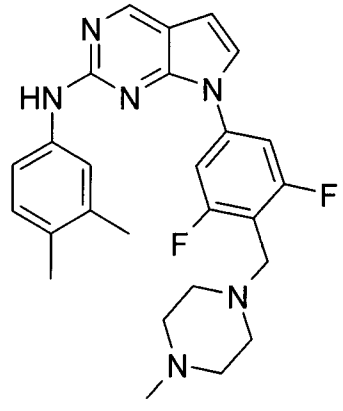
**Ejemplo 307: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metoxi-4-metil-fenil)-amina**



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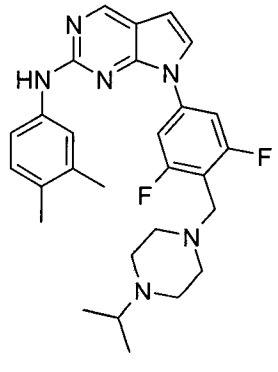
HPLC: $t_R$ = 8.67 minutos. (Método B); MS-ES: $(M+H)^+$ = 462; TLC*: $R_f$ = 0.59

**Ejemplo 304: {7-[3,5-difluoro-4-(4-metil-piperazin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina**



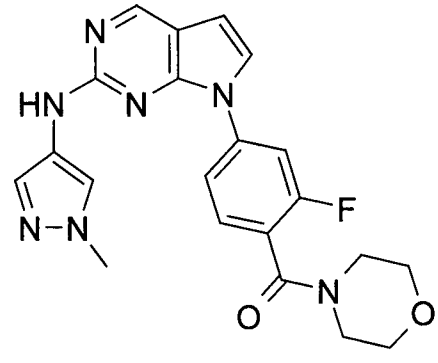
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.97 minutos. (Método B); MS-ES: $(M+H)^+$ = 463; TLC**: $R_f$ = 0.17

**Ejemplo 305: {7-[3,5-difluoro-4-(4-isopropil-piperazin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina**



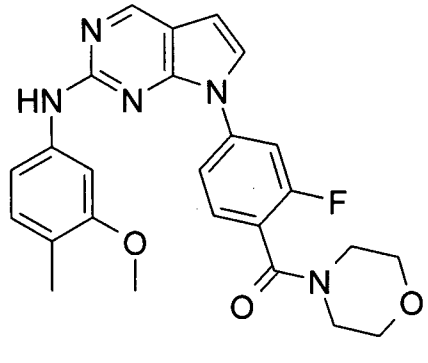
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.25 minutos. (Método B); MS-ES: $(M+H)^+$ = 418; TLC*: $R_f$ = 0.55

**Ejemplo 302: {2-fluoro-4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.23 minutos. (Método B); MS-ES: $(M+H)^+$ = 422; TLC*: $R_f$ = 0.50

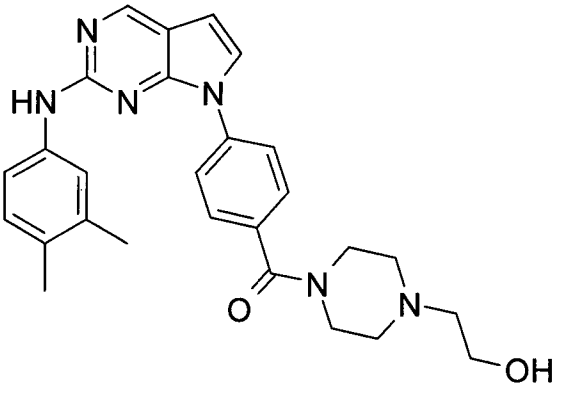
**Ejemplo 303: {2-fluoro-4-[2-(3-metoxi-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3.

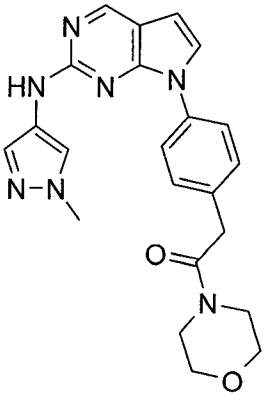
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.67 minutos. (Método B); MS-ES: $(M+H)^+$ = 487; TLC*: $R_f$ = 0.30

**Ejemplo 300: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-[4-(2-hidroxi-etil)-piperazin-1-il]-metanona**



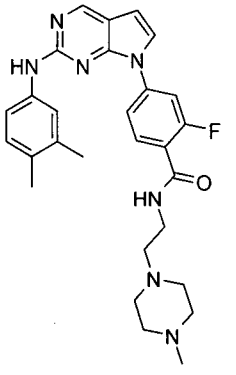
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.27 minutos. (Método B); MS-ES: $(M+H)^+$ = 471; TLC*: $R_f$ = 0.50

**Ejemplo 301: 2-{4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona**



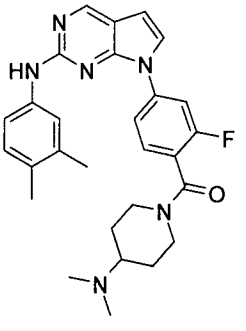
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.71 minutos. (Método B); MS-ES: $(M+H)^+$ = 489; TLC**: $R_f$ = 0.33

**Ejemplo 298: 4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-N-[2-(4-metil-piperazin-1-il)-etil]-benzamida**



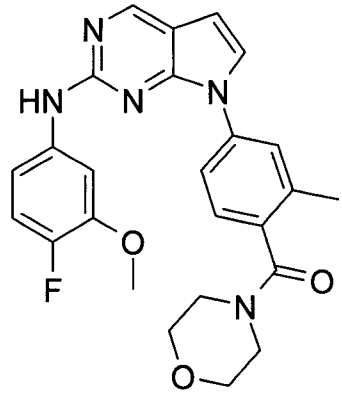
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.37 minutos. (Método B); MS-ES: $(M+H)^+$ = 502; TLC*: $R_f$ = 0.24

**Ejemplo 299: (4-dimetil-amino-piperidin-1-il)-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-metanona**



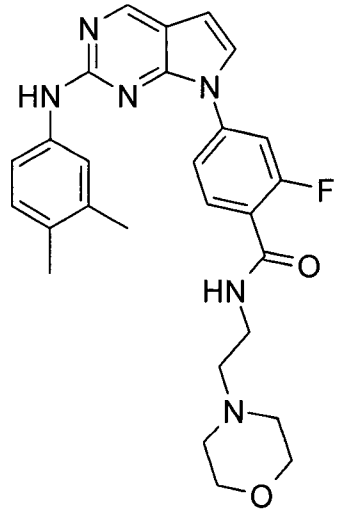
$R_f$ = 0.46

**Ejemplo 296: {4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona**



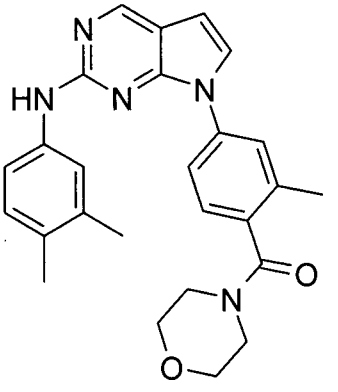
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.29 minutos. (Método B); MS-ES: $(M+H)^+$ = 462; TLC**: $R_f$ = 0.25

**Ejemplo 297: 4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-N-(2-morfolin-4-il-etil)-benzamida**



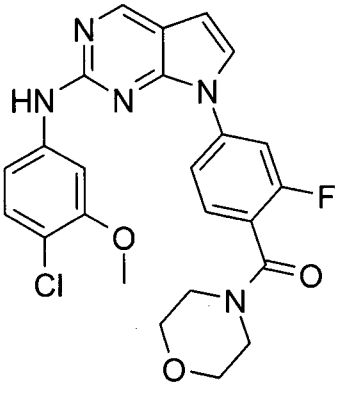
$R_f$ = 0.35

**Ejemplo 294: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.66 minutos. (Método B); MS-ES: $(M+H)^+$ = 442; TLC**: $R_f$ = 0.48

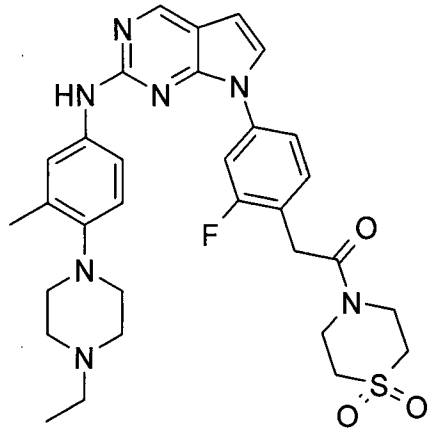
**Ejemplo 295: {4-[2-(4-cloro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.95 minutos. (Método B); MS-ES: $(M+H)^+$ = 482; TLC**:

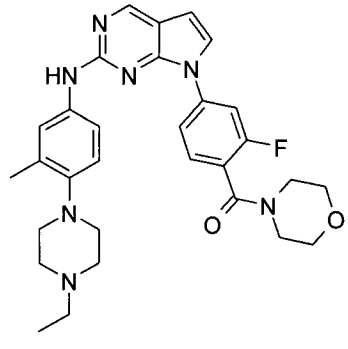
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**Ejemplo 292: 1-(1,1-dióxido-tiomorfolin-4-il)-2-(4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-etanona**



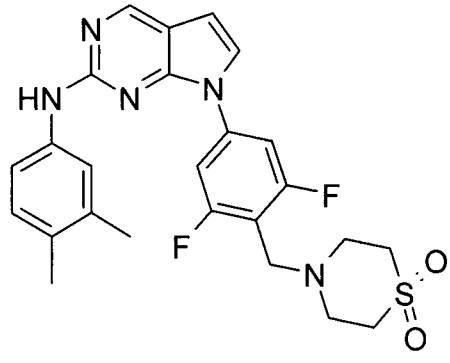
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.37 minutos. (Método B); MS-ES: $(M+H)^+$ = 606; TLC**: $R_f$ = 0.34

**Ejemplo 293: (4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



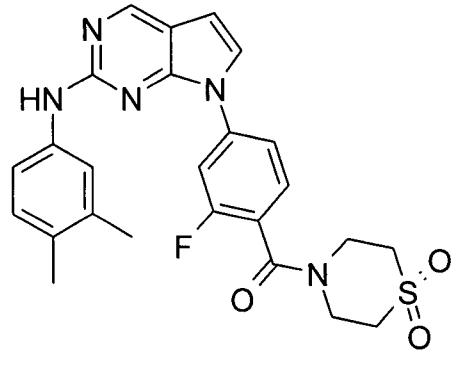
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.47 minutos. (Método B); MS-ES: $(M+H)^+$ = 544; TLC**:

**Ejemplo 290: (3,4-dimetil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.88 minutos. (Método B); MS-ES: $(M+H)^+$ = 498; TLC‡: $R_f$ = 0.32

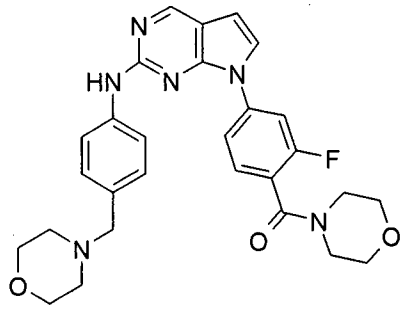
**Ejemplo 291: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-(1,1-dióxido-tiomorfolin-4-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.49 minutos. (Método B); MS-ES: $(M+H)^+$ = 494; TLC‡: $R_f$ = 0.28

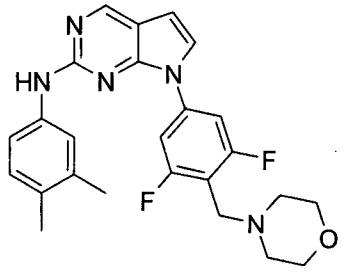
220

**Ejemplo 288: {2-fluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.22 minutos. (Método B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$ = 0.37

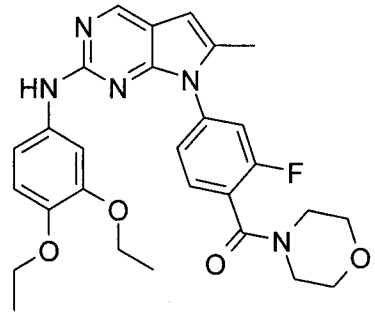
**Ejemplo 289: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4-dimetil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.85 minutos. (Método B); MS-ES: $(M+H)^+$ = 450; TLC‡: $R_f$ = 0.41

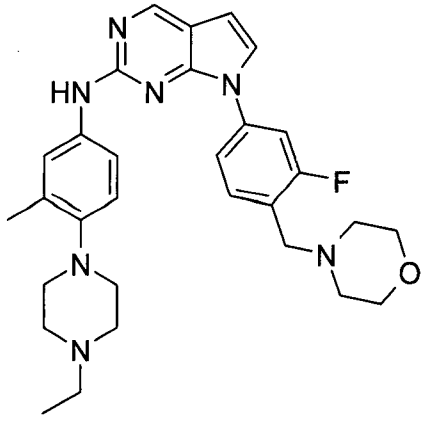
paso. Este material de partida se obtiene mediante la utilización de tributil-(1-propinil)-estaño en el acoplamiento de Stille en la síntesis para la pirrolo-pirimidina, como se ejemplifica en el esquema de reacción del Ejemplo 1. HPLC: $t_R$ = 8.46 minutos. (Método B); MS-ES: $(M+H)^+$ = 582; TLC**: $R_f$ = 0.51

**Ejemplo 287: {4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona**



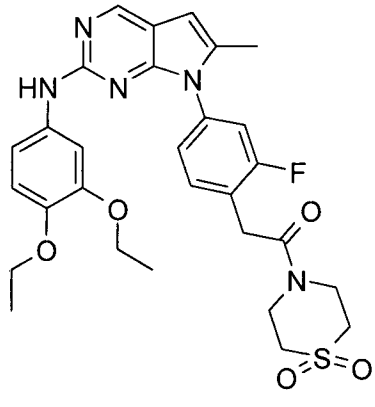
El compuesto se prepara de una manera análoga al Ejemplo 3. Pero en lugar de utilizar la 2-cloro-7H-pirrolo-[2,3-d]-pirimidina, se utiliza la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina en el primer paso. Este material de partida se obtiene mediante la utilización de tributil-(1-propinil)-estaño en el acoplamiento de Stille en la síntesis para la pirrolo-pirimidina, como se ejemplifica en el esquema de reacción del Ejemplo 1. HPLC: $t_R$ = 8.59 minutos. (Método B); MS-ES: $(M+H)^+$ = 520; TLC‡: $R_f$ = 0.22

**Ejemplo 285: [4-(4-etil-piperazin-1-il)-3-metil-fenil]-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



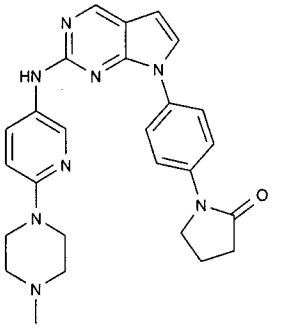
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 6.75 minutos. (Método B); MS-ES: $(M+H)^+$ = 530; TLC**: $R_f$ = 0.21

**Ejemplo 286: 2-{4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-1-(1,1-dióxido-tiomorfolin-4-il)-etanona**



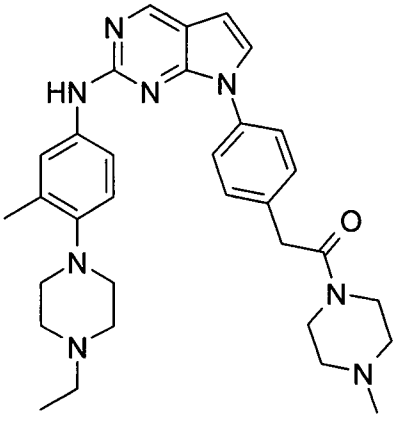
El compuesto se prepara de una manera análoga al Ejemplo 3. Pero en su lugar de utilizar la 2-cloro-7H-pirrolo-[2,3-d]-pirimidina, se utiliza la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina en el primer

**Ejemplo 283: 1-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-pirrolidin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 3.03 minutos (Método D); MS-ES: $(M+H)^+$ = 469.

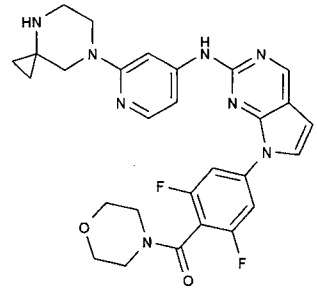
**Ejemplo 284: 2-(4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-1-(4-metil-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 6.74 minutos (Método B); MS-ES: $(M+H)^+$ = 553; TLC**: $R_f$ = 0.10

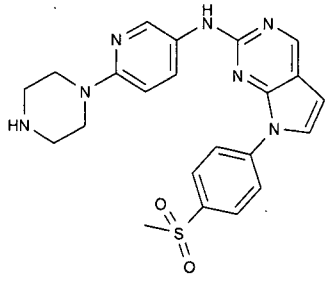
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 2.83 minutos (Método D); MS-ES: $(M+H)^+$ = 452.

**Ejemplo 281: (4-{2-[2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona**



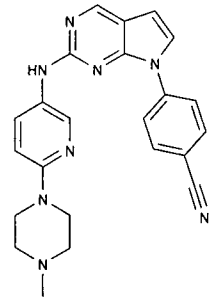
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.61 minutos (Método C); MS-ES: $(M+H)^+$ = 547.

**Ejemplo 282: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-piridin-3-il)-amina**



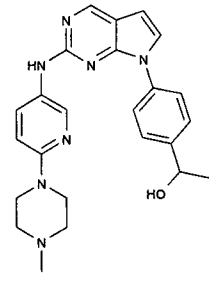
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4N en dioxano a temperatura ambiente. HPLC: $t_R$ = 4.19 minutos (Método C); MS-ES: $(M+H)^+$ = 450.

**Ejemplo 278: 4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo**



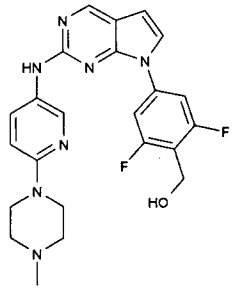
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 3.21 minutos (Método D); MS-ES: $(M+H)^+$ = 411.

**Ejemplo 279: 1-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-etanol**

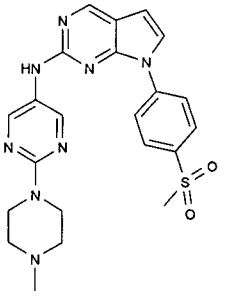


El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 2.80 minutos (Método D); MS-ES: $(M+H)^+$ = 430.

**Ejemplo 280: (2,6-difluoro-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanol**

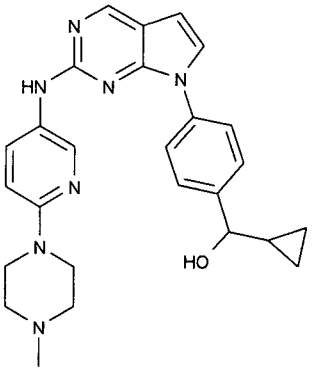


**Ejemplo 276: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(4-metil-piperazin-1-il)-pirimidin-5-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. MS-ES: $(M+H)^+$ = 465.

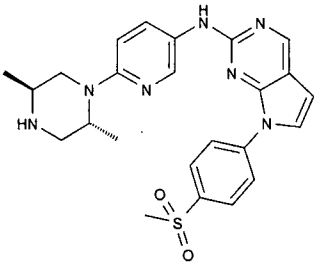
**Ejemplo 277: Ciclopropil-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanol**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 3.20 minutos (Método D); MS-ES: $(M+H)^+$ = 456.

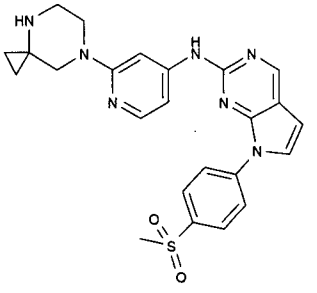
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.29 minutos (Método C); MS-ES: $(M+H)^+$ = 478.

**Ejemplo 274: [6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (racémica)**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.30 minutos (Método C); MS-ES: $(M+H)^+$ = 478.

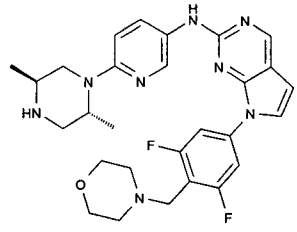
**Ejemplo 275: [2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.43 minutos (Método C); MS-ES: $(M+H)^+$ = 476.

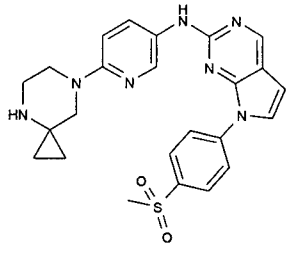
224

**Ejemplo 271: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il]-amina (racémica)**



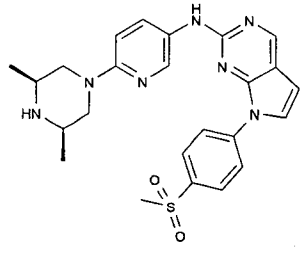
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.02 minutos (Método C); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 272: [6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**

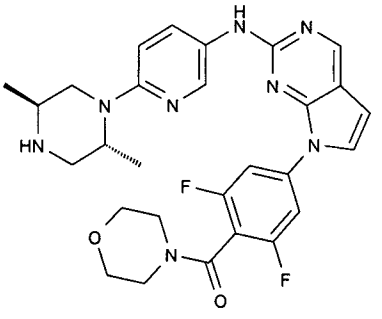


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.23 minutos (Método C); MS-ES: $(M+H)^+$ = 476.

**Ejemplo 273: [6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**

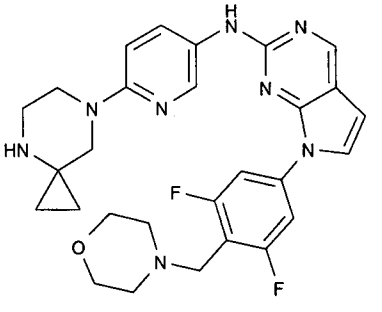


**Ejemplo 269: (4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona (racémica)**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.46 minutos (Método C); MS-ES: $(M+H)^+$ = 549.

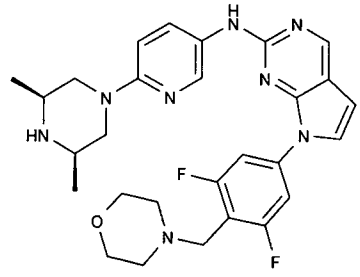
**Ejemplo 270: [6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.99 minutos (Método C); MS-ES: $(M+H)^+$ = 533.

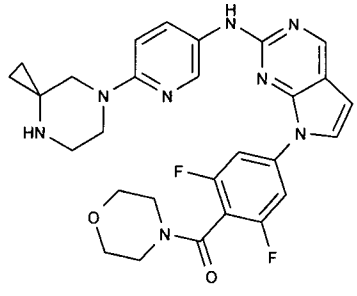
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.37 minutos (Método C); MS-ES: $(M+H)^+$ = 549.

**Ejemplo 267: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-amina**



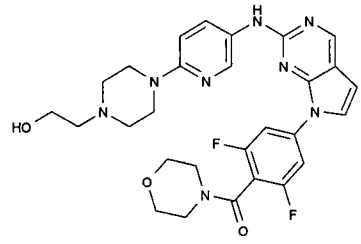
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.99 minutos (Método C); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 268: (4-{2-[6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona**



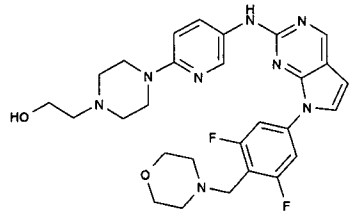
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.43 minutos (Método C); MS-ES: $(M+H)^+$ = 547.

**Ejemplo 264: [2,6-difluoro-4-(2-{6-[4-(2-hidroxi-etil)-piperazin-1-il]-piridin-3-il-amino}-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona**



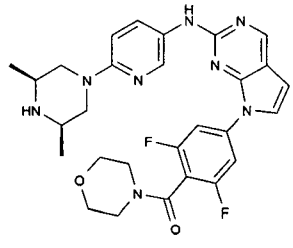
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.37 minutos (Método C); MS-ES: $(M+H)^+$ = 565.

**Ejemplo 265: 2-(4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-1-il)-etanol**



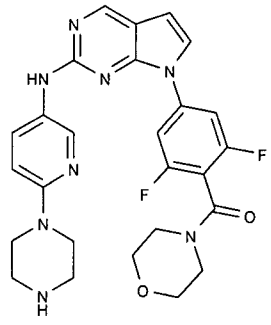
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.91 minutos (Método C); MS-ES: $(M+H)^+$ = 551.

**Ejemplo 266: (4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona**



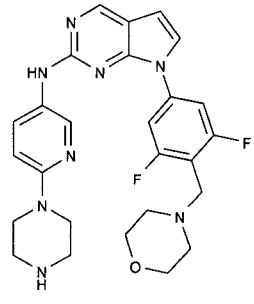
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**Ejemplo 262: {2,6-difluoro-4-[2-(6-piperazin-1-il-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



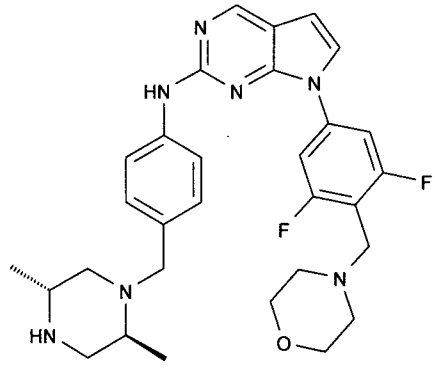
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. MS-ES: $(M+H)^+$ = 521.

**Ejemplo 263: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-piridin-3-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. MS-ES: $(M+H)^+$ = 507.

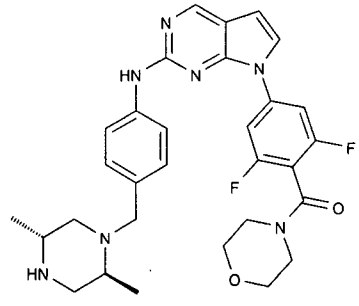
**Ejemplo 260: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-((2S,5R)-2,5-dimetil-piperazin-1-il-metil)-fenil]-amina (racémica)**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 261: (4-{2-[4-((2S,5R)-2,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona (racémica)**

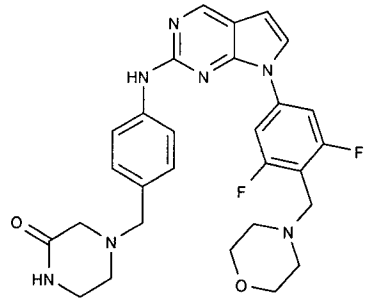


El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 1.12 minutos (Método A); MS-ES: $(M+H)^+$ = 562.

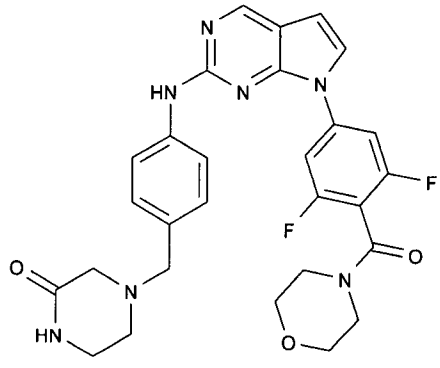
227

Ejemplo 258: 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-2-ona



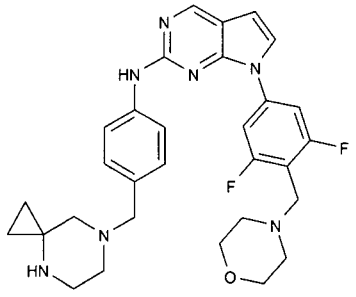
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.87 minutos (Método A); MS-ES: $(M+H)^+$ = 534.

Ejemplo 259: 4-(4-{7-[3,5-difluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-2-ona



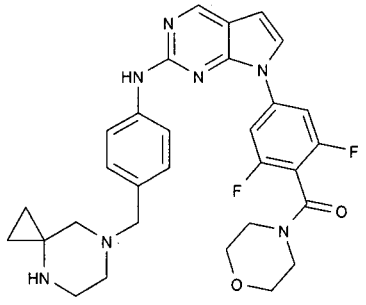
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.11 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 256: 4-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.90 minutos (Método A); MS-ES: $(M+H)^+$ = 546.

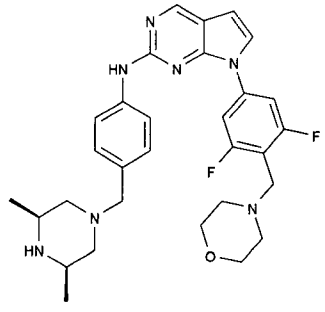
**Ejemplo 257: 4-{2-[4-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 560.

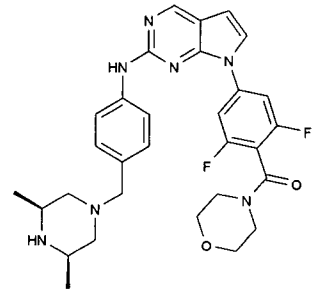
228

**Ejemplo 254: 7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.92 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

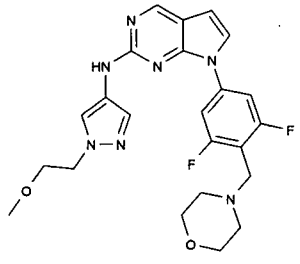
**Ejemplo 255: (4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.11 minutos (Método A); MS-ES: $(M+H)^+$ = 562.

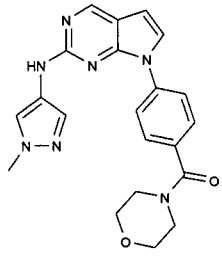
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.23 minutos (Método A); MS-ES: $(M+H)^+$ = 484.

**Ejemplo 252: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[1-(2-metoxi-etil)-1H-pirazol-4-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.90 minutos (Método A); MS-ES: $(M+H)^+$ = 470.

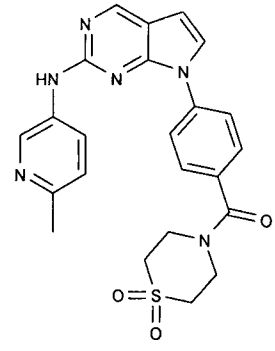
**Ejemplo 253: {4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.05 minutos (Método A); MS-ES: $(M+H)^+$ = 404.

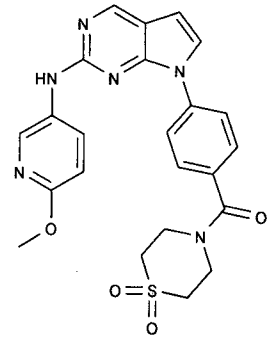
229

**Ejemplo 249: (1,1-dióxido-tiomorfolin-4-il)-{4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona**



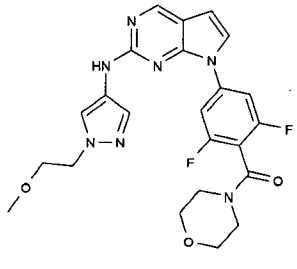
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 463.

**Ejemplo 250: (1,1-dióxido-tiomorfolin-4-il)-{4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona**

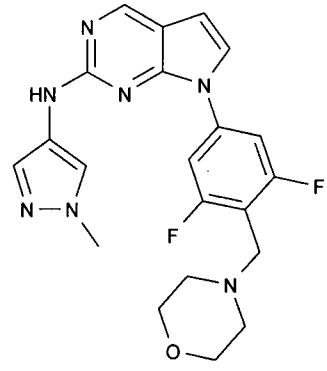


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 479.

**Ejemplo 251: (2,6-difluoro-4-{2-[1-(2-metoxi-etil)-1H-pirazol-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**

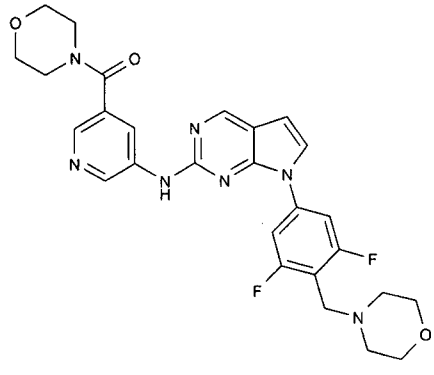


**Ejemplo 247: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1-metil-1H-pirazol-4-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.85 minutos (Método A); MS-ES: $(M+H)^+$ = 426.

**Ejemplo 248: {5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-3-il}-morfolin-4-il-metanona**

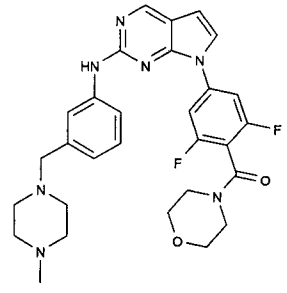


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.97 minutos (Método A); MS-ES: $(M+H)^+$ = 536.

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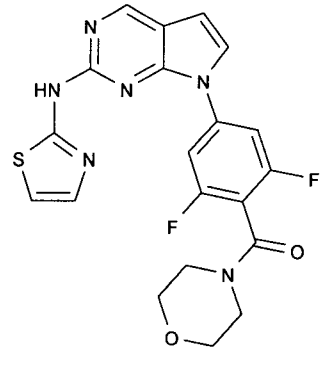
El compuesto se prepara de una manera análoga al Ejemplo 2. MS-ES: $(M+H)^+$ = 495.

**Ejemplo 245: (2,6-difluoro-4-{2-[3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



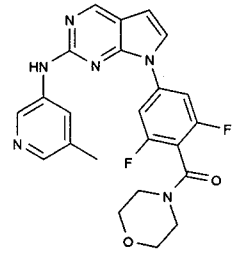
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 246: {2,6-difluoro-4-[2-(tiazol-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



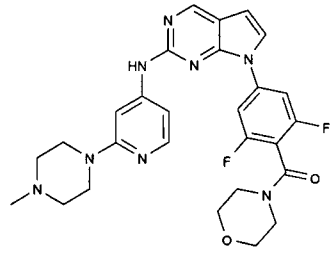
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.26 minutos (Método A); MS-ES: $(M+H)^+$ = 443.

**Ejemplo 242: {2,6-difluoro-4-[2-(5-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



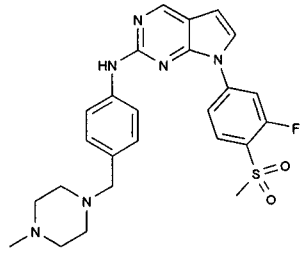
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.27 minutos (Método A); MS-ES: $(M+H)^+$ = 451.

**Ejemplo 243: (2,6-difluoro-4-{2-[2-(4-metil-piperazin-1-il)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



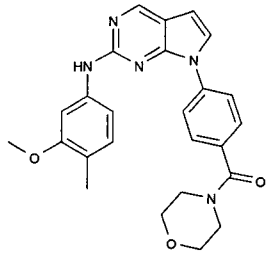
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 244: [7-(3-fluoro-4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina**



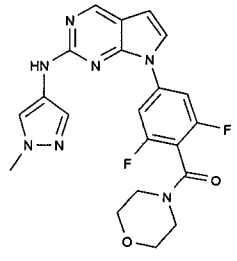
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.36 minutos (Método A); MS-ES: $(M+H)^+$ = 444.

**Ejemplo 240: {4-[2-(3-metoxi-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



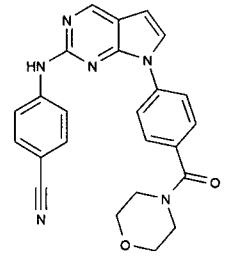
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.57 minutos (Método A); MS-ES: $(M+H)^+$ = 444.

**Ejemplo 241: {2,6-difluoro-4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



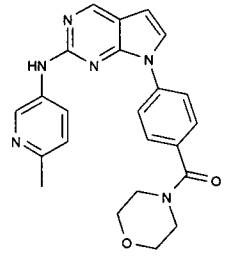
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.18 minutos (Método A); MS-ES: $(M+H)^+$ = 440.

**Ejemplo 237: 4-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-benzonitrilo**



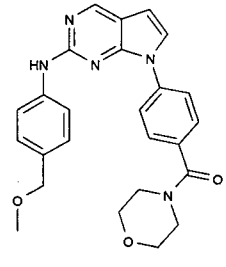
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.58 minutos (Método A); MS-ES: $(M+H)^+$ = 425.

**Ejemplo 238: {4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



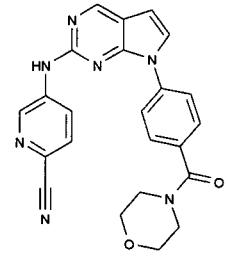
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 415.

**Ejemplo 239: {4-[2-(4-metoxi-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



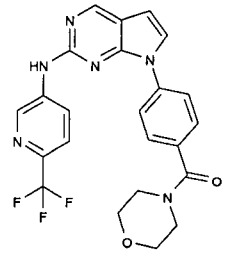
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.20 minutos (Método A); MS-ES: $(M+H)^+$ = 431.

**Ejemplo 235: 5-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-piridin-2-carbonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.55 minutos (Método A); MS-ES: $(M+H)^+$ = 426.

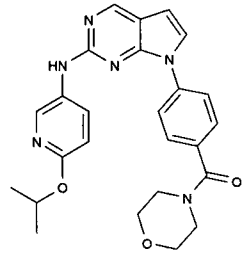
**Ejemplo 236: Morfolin-4-il-{4-[2-(6-trifluoro-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.76 minutos (Método A); MS-ES: $(M+H)^+$ = 469.

HPLC: $t_R$ = 1.57 minutos (Método A); MS-ES: $(M+H)^+$ = 458.

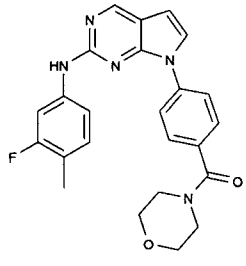
**Ejemplo 232: {4-[2-(6-isopropoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 1.42 minutos (Método A); MS-ES: $(M+H)^+$ = 459.

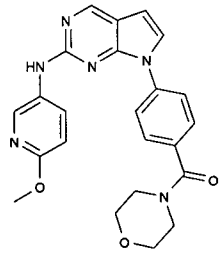
**Ejemplo 233: {4-[2-(3-fluoro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

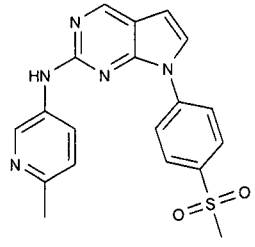
HPLC: $t_R$ = 1.64 minutos (Método A); MS-ES: $(M+H)^+$ = 432.

Ejemplo 234: {4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona



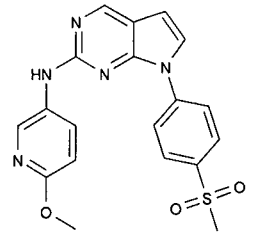
233

**Ejemplo 229: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-metil-piridin-3-il)-amina**



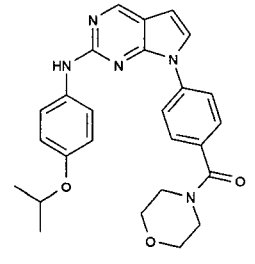
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 380.

**Ejemplo 230: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-metoxi-piridin-3-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.26 minutos (Método A); MS-ES: $(M+H)^+$ = 396.

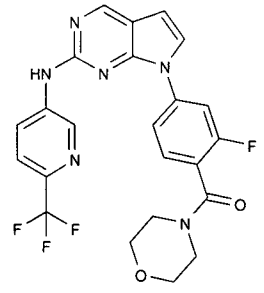
**Ejemplo 231: {4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

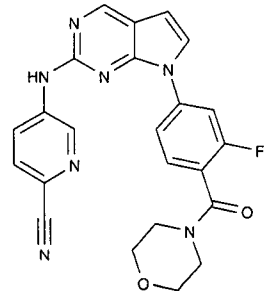
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.52 minutos (Método A); MS-ES: $(M+H)^+$ = 477.

**Ejemplo 227: {2-fluoro-4-[2-(6-trifluoro-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.91 minutos (Método A); MS-ES: $(M+H)^+$ = 487.

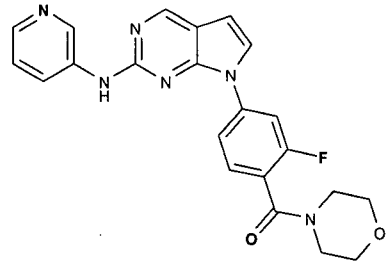
**Ejemplo 228: 5-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-piridin-2-carbonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.71 minutos (Método A); MS-ES: $(M+H)^+$ = 444.

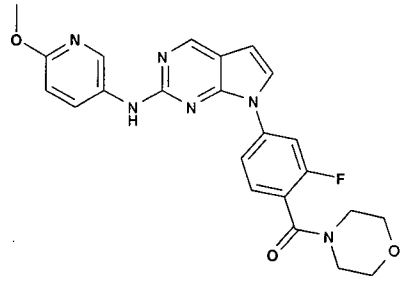
234

**Ejemplo 224: {2-fluoro-4-[2-(piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



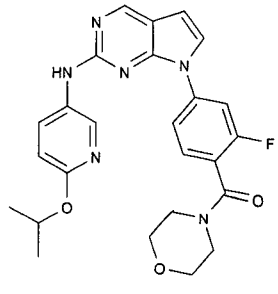
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.17 minutos (Método A); MS-ES: $(M+H)^+$ = 419.

**Ejemplo 225: {2-fluoro-4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



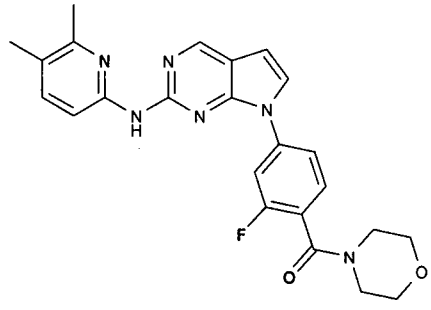
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.29 minutos (Método A); MS-ES: $(M+H)^+$ = 449.

**Ejemplo 226: {2-fluoro-4-[2-(6-isopropoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



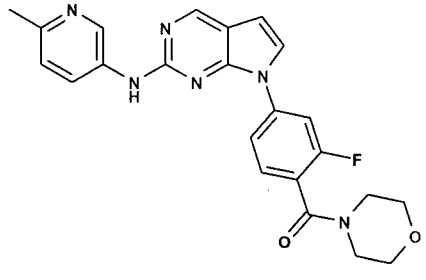
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.05 minutos (Método A); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 222: {4-[2-(5,6-dimetil-piridin-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.33 minutos (Método A); MS-ES: $(M+H)^+$ = 447.

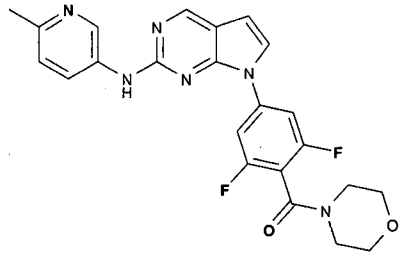
**Ejemplo 223: {2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.21 minutos (Método A); MS-ES: $(M+H)^+$ = 433.

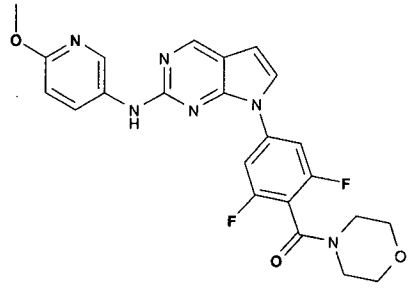
235

**Ejemplo 219: {2,6-difluoro-4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



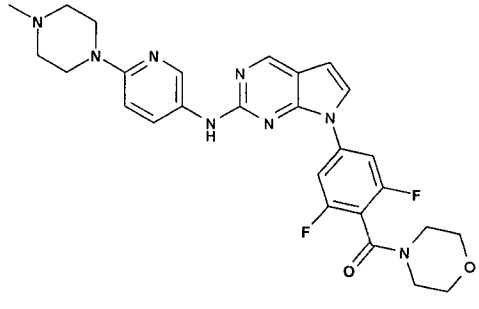
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.26 minutos (Método A); MS-ES: $(M+H)^+$ = 451.

**Ejemplo 220: {2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



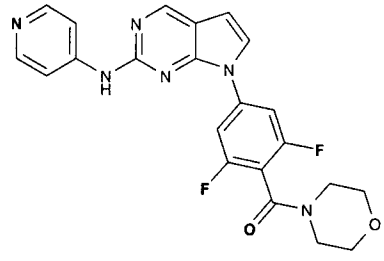
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.39 minutos (Método A); MS-ES: $(M+H)^+$ = 467.

**Ejemplo 221: {2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



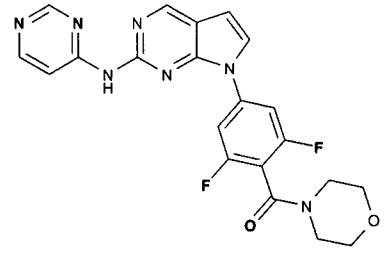
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.22 minutos (Método A); MS-ES: $(M+H)^+$ = 437.

**Ejemplo 217: {2,6-difluoro-4-[2-(piridin-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.24 minutos (Método A); MS-ES: $(M+H)^+$ = 437.

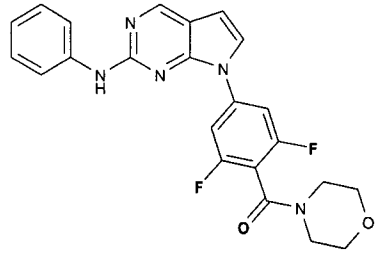
**Ejemplo 218: {2,6-difluoro-4-[2-(pirimidin-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 438.

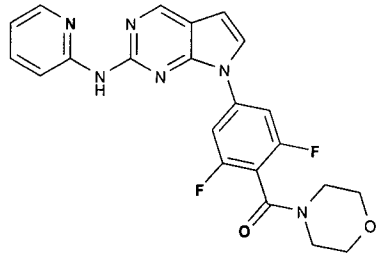
236

**Ejemplo 214: [2,6-difluoro-4-(2-fenil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona**



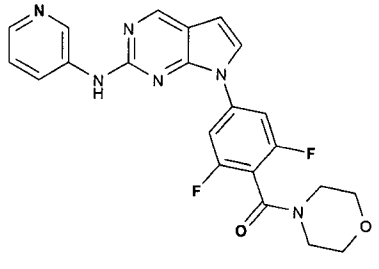
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.60 minutos (Método A); MS-ES: $(M+H)^+$ = 436.

**Ejemplo 215: {2,6-difluoro-4-[2-(piridin-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**

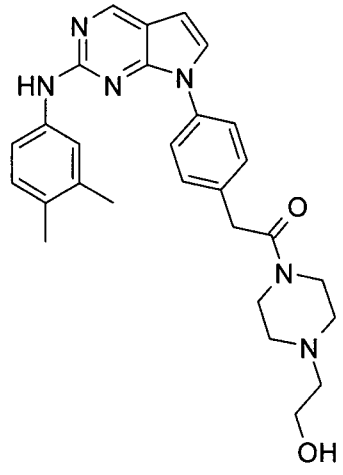


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.24 minutos (Método A); MS-ES: $(M+H)^+$ = 437.

**Ejemplo 216: {2,6-difluoro-4-[2-(piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**

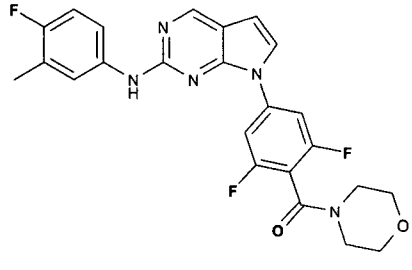


**Ejemplo 212: 2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-[4-(2-hidroxi-etil)-piperazin-1-il]-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3 (esquema 3). HPLC: $t_R$ = 7.59 minutos. (Método B); MS-ES: $(M+H)^+$ = 485; TLC**: $R_f$ = 0.17

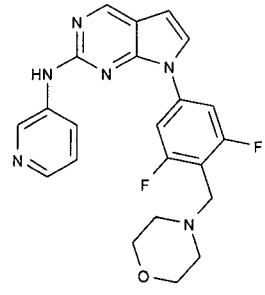
**Ejemplo 213: {2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.78 minutos (Método A); MS-ES: $(M+H)^+$ = 468.

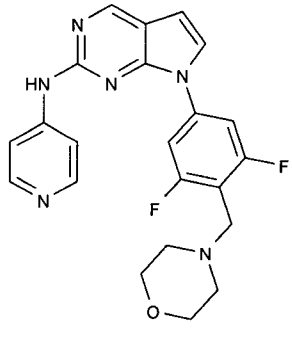
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.95 minutos (Método A); MS-ES: $(M+H)^+$ = 423.

**Ejemplo 210: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-3-il-amina**



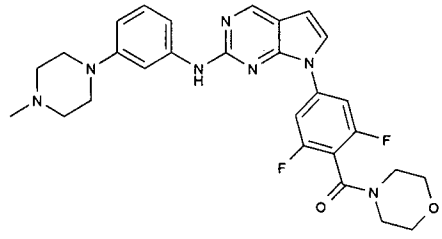
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 423.

**Ejemplo 211: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-4-il-amina**



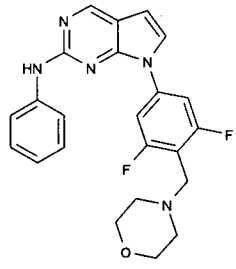
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.96 minutos (Método A); MS-ES: $(M+H)^+$ = 423.

**Ejemplo 207: (2,6-difluoro-4-{2-[3-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



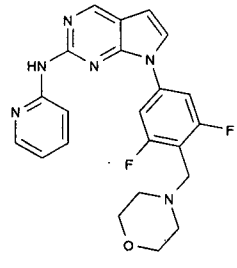
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.20 minutos (Método A); MS-ES: $(M+H)^+$ = 534.

**Ejemplo 208: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-fenil-amina**



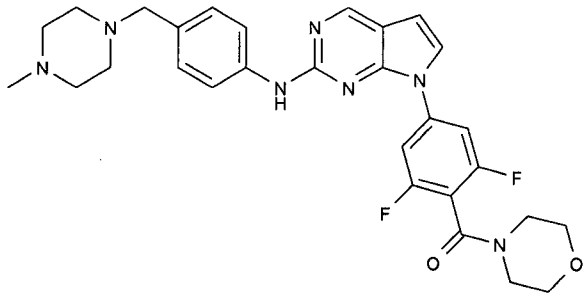
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.16 minutos (Método A); MS-ES: $(M+H)^+$ = 422.

**Ejemplo 209: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-2-il-amina**



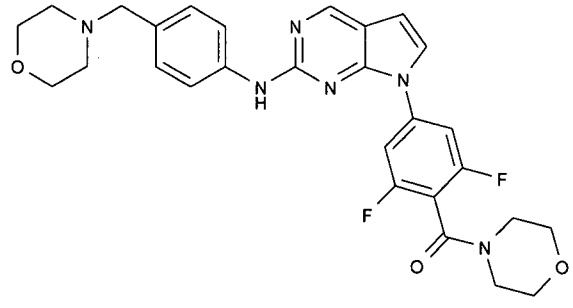
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**Ejemplo 205: (2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



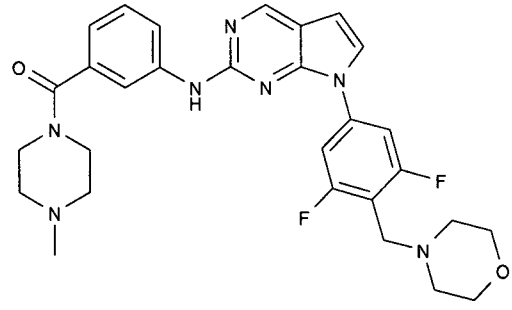
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.10 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 206: {2,6-difluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



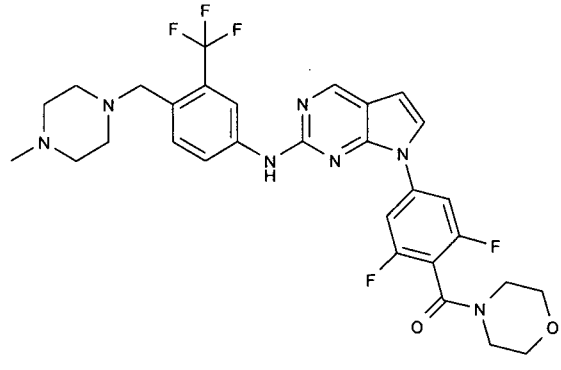
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.17 minutos (Método A); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 203: {3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.89 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

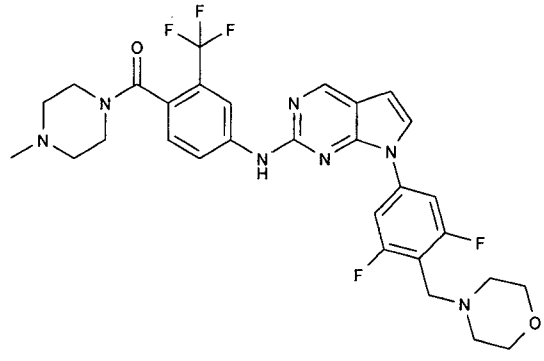
**Ejemplo 204: (2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il-metil)-3-trifluoro-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.43 minutos (Método A); MS-ES: $(M+H)^+$ = 616.

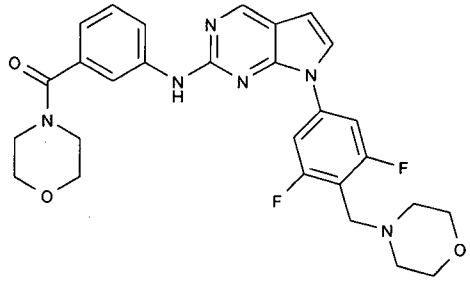
239

**Ejemplo 201: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-trifluoro-metil-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 616.

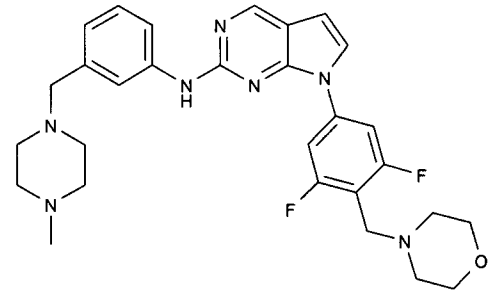
**Ejemplo 202: {3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 535.

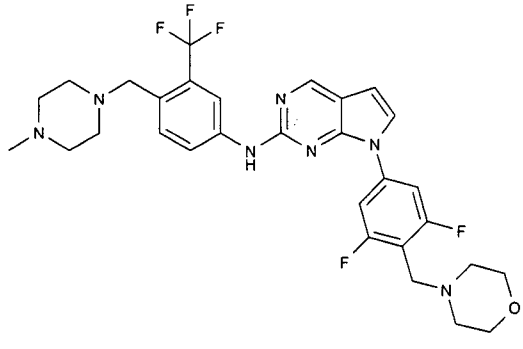
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.94 minutos (Método A); MS-ES: $(M+H)^+$ = 521.

**Ejemplo 199: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il-metil)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 534.

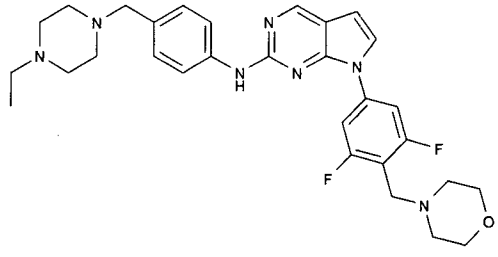
**Ejemplo 200: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-3-trifluoro-metil-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.17 minutos (Método A); MS-ES: $(M+H)^+$ = 602.

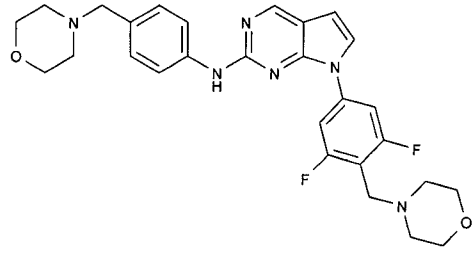
240

**Ejemplo 196: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-etil-piperazin-1-il-metil)-fenil]-amina**



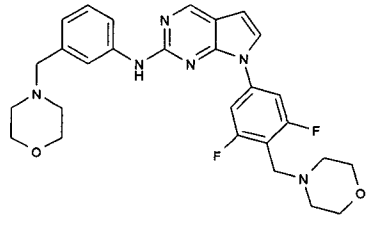
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.92 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 197: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-4-il-metil-fenil)-amina**

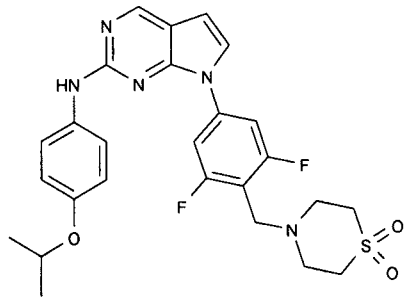


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.94 minutos (Método A); MS-ES: $(M+H)^+$ = 521.

**Ejemplo 198: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-morfolin-4-il-metil-fenil)-amina**

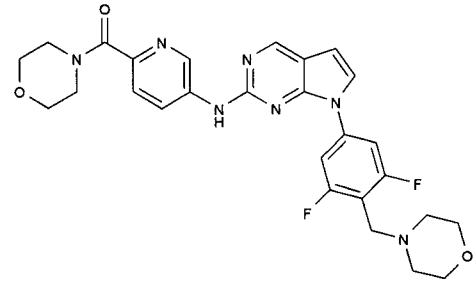


**Ejemplo 194: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.73 minutos (Método A); MS-ES: $(M+H)^+$ = 528.

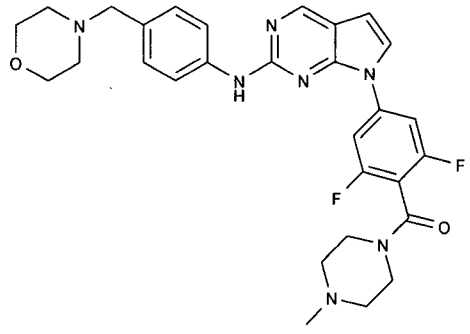
**Ejemplo 195: {5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.07 minutos (Método A); MS-ES: $(M+H)^+$ = 536.

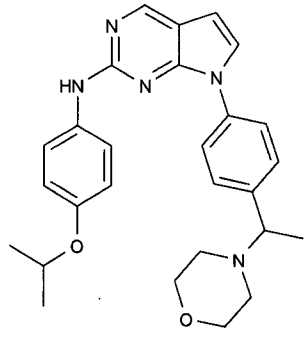
241

**Ejemplo 192: {2,6-difluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



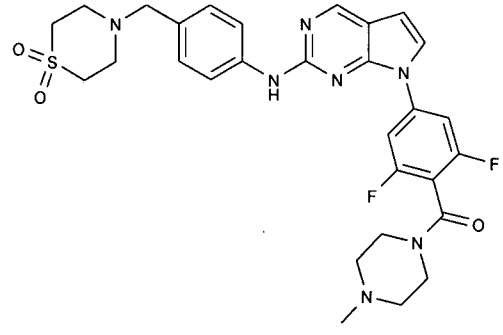
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.96 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 193: (4-isopropoxi-fenil)-{7-[4-(1-morfolin-4-il-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina (racémica)**



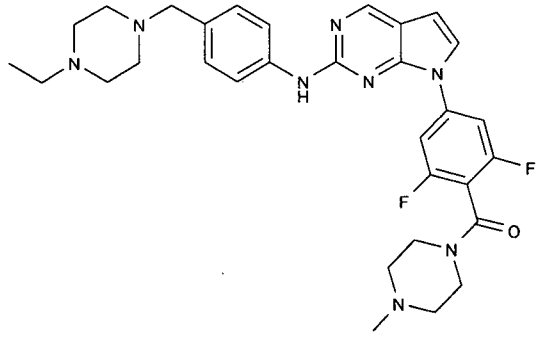
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.28 minutos (Método A); MS-ES: $(M+H)^+$ = 458.

**Ejemplo 190: (4-{2-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.98 minutos (Método A); MS-ES: $(M+H)^+$ = 596.

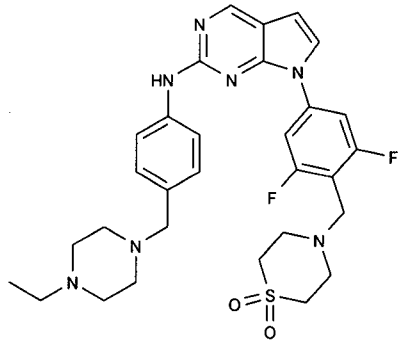
**Ejemplo 191: (4-{2-[4-(4-etil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 575.

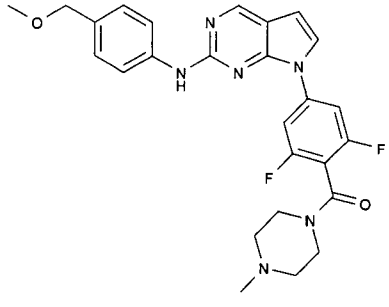
242

**Ejemplo 188: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[4-(4-etil-piperazin-1-il-metil)-fenil]-amina**



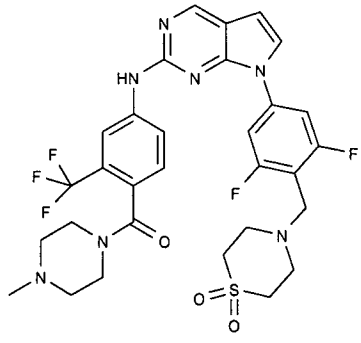
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.14 minutos (Método A); MS-ES: $(M+H)^+$ = 596.

**Ejemplo 189: {2,6-difluoro-4-[2-(4-metoxi-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



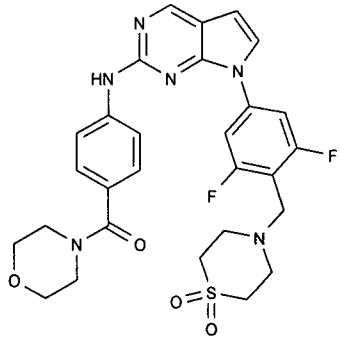
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.18 minutos (Método A); MS-ES: $(M+H)^+$ = 493.

**Ejemplo 186: (4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-trifluoro-metil-fenil)-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.35 minutos (Método A); MS-ES: $(M+H)^+$ = 664.

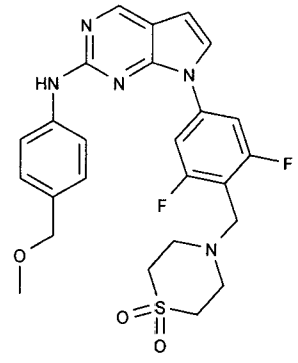
**Ejemplo 187: (4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.36 minutos (Método A); MS-ES: $(M+H)^+$ = 583.

213

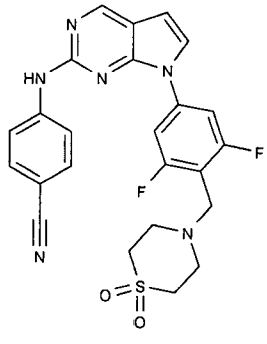
**Ejemplo 184: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-metoxi-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 1.52 minutos (Método A); MS-ES: $(M+H)^+$ = 514.

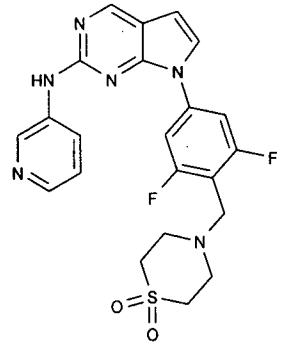
**Ejemplo 185: 4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-benzonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 2.

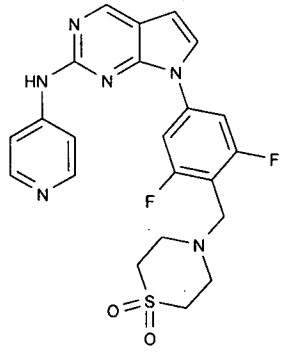
HPLC: $t_R$ = 1.78 minutos (Método A); MS-ES: $(M+H)^+$ = 495.

**Ejemplo 182: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-3-il-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.17 minutos (Método A); MS-ES: $(M+H)^+$ = 471.

**Ejemplo 183: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-4-il-amina**

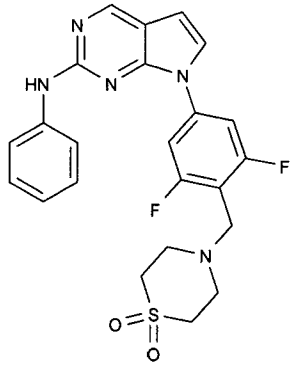


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.21 minutos (Método A); MS-ES: $(M+H)^+$ = 471.

244

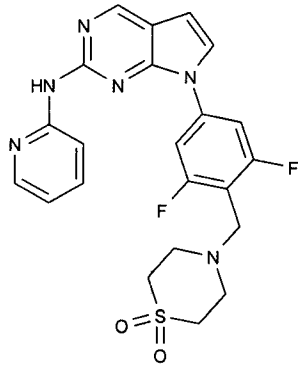
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.21 minutos (Método A); MS-ES: $(M+H)^+$ = 450.

**Ejemplo 180: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-fenil-amina**



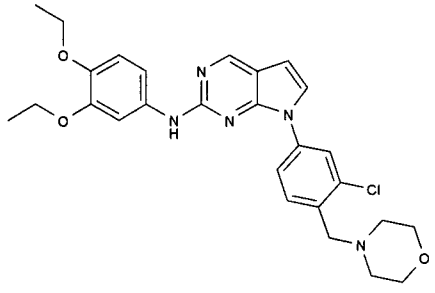
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.53 minutos (Método A); MS-ES: $(M+H)^+$ = 470.

**Ejemplo 181: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-2-il-amina**



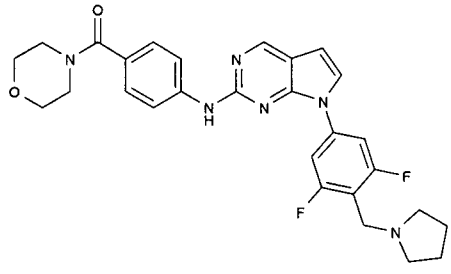
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.20 minutos (Método A); MS-ES: $(M+H)^+$ = 471.

**Ejemplo 177: [7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4-dietoxi-fenil)-amina**



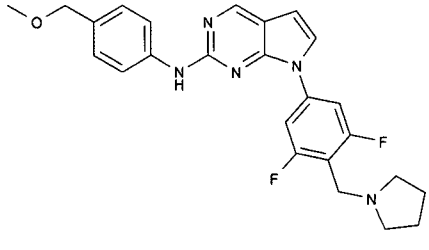
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.28 minutos (Método A); MS-ES: $(M+H)^+$ = 508.

**Ejemplo 178: {4-[7-(3,5-difluoro-4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 519.

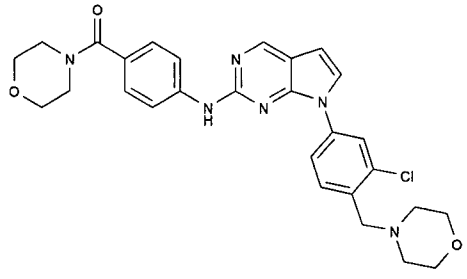
**Ejemplo 179: [7-(3,5-difluoro-4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina**



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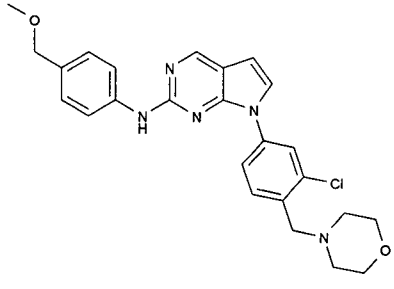
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 520.

**Ejemplo 175: {4-[7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



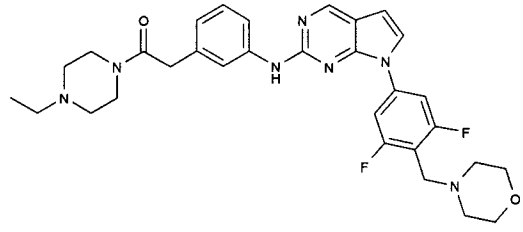
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 533.

**Ejemplo 176: [7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina**



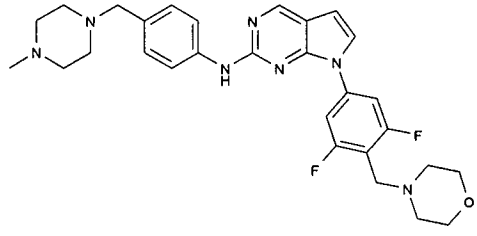
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.19 minutos (Método A); MS-ES: $(M+H)^+$ = 464.

**Ejemplo 172: 2-{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-1-(4-etil-piperazin-1-il)-etanona**



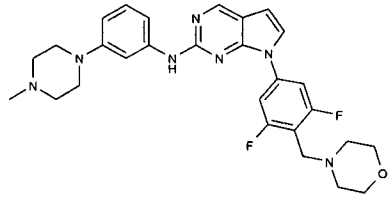
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 576.

**Ejemplo 173: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 534.

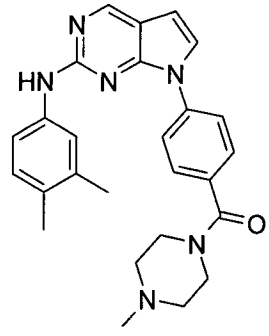
**Ejemplo 174: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il)-fenil]-amina**



246

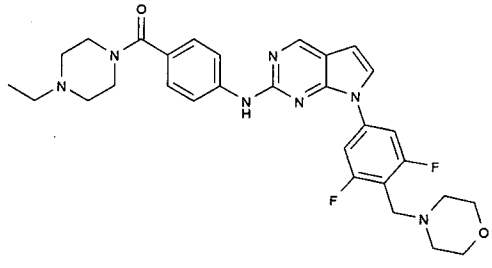
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.54 minutos. (Método B); MS-ES: $(M+H)^+$ = 428; TLC*: $R_f$ = 0.66

**Ejemplo 170: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.36 minutos. (Método B); MS-ES: $(M+H)^+$ = 441; TLC**: $R_f$ = 0.18

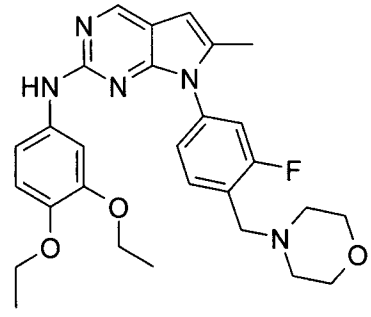
**Ejemplo 171: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-etil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.93 minutos (Método A); MS-ES: $(M+H)^+$ = 562.

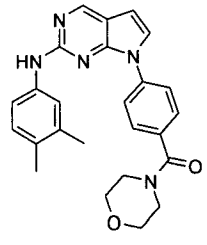
tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.52 minutos. (Método B); MS-ES: (M+H)+ = 529; TLC*: $R_f$ = 0.50

**Ejemplo 168: (3,4-dietoxi-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.49 minutos. (Método B); MS-ES: $(M+H)^+$ = 506; TLC***: $R_f$ = 0.24

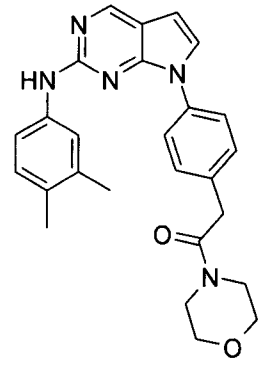
**Ejemplo 169: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



247

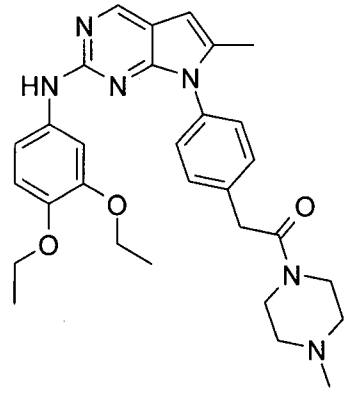
= 0.43

**Ejemplo 166: 2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona**



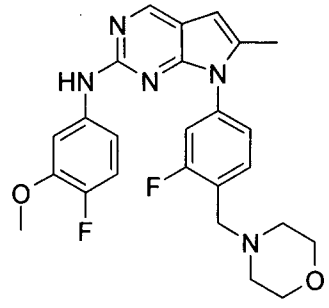
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.63 minutos. (Método B); MS-ES: $(M+H)^+$ = 442; TLC**: $R_f$ = 0.30

**Ejemplo 167: 2-{4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



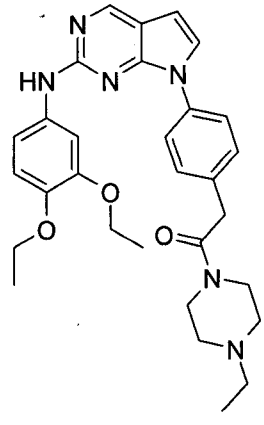
El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó

**Ejemplo 164: (4-fluoro-3-metoxi-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.23 minutos. (Método B); MS-ES: $(M+H)^+$ = 466; TLC***: $R_f$ = 0.32

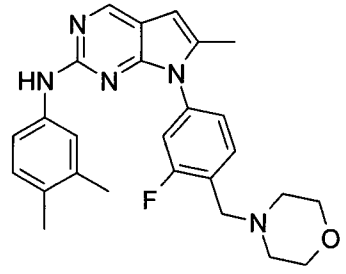
**Ejemplo 165: 2-{4-[2-(3,4-dietoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-etil-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.53 minutos. (Método B); MS-ES: $(M+H)^+$ = 529; TLC*: $R_f$

El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.31 minutos. (Método B); MS-ES: $(M+H)^+$ = 489; TLC***: $R_f$ = 0.20

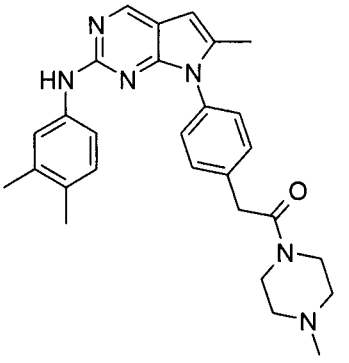
**Ejemplo 163: (3,4-dimetil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**




El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.58 minutos. (Método B); MS-ES: $(M+H)^+$ = 446; TLC***: $R_f$ = 0.40

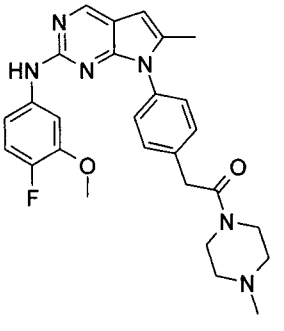
$R_f$ = 0.21

**Ejemplo 161: 2-{4-[2-(3,4-dimetil-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. Pero durante la síntesis del núcleo de pirrolo-pirimidina, se utilizó tributil-(1-propinil)-estaño en lugar del tributil-(2-etoxi-vinil)-estanano, como se describe en el Ejemplo 1, para obtener la 2-cloro-6-metil-7H-pirrolo-[2,3-d]-pirimidina. HPLC: $t_R$ = 7.76 minutos. (Método B); MS-ES: $(M+H)^+$ = 469; TLC**: $R_f$ = 0.31

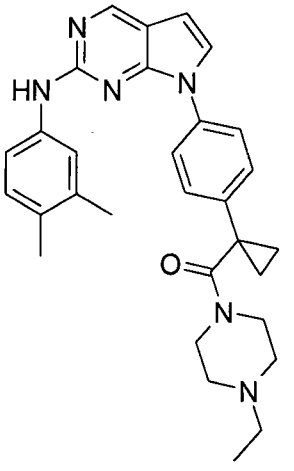
**Ejemplo 162: 2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



249

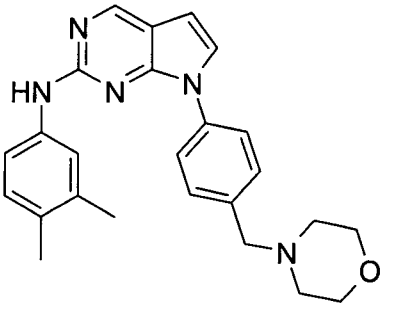
= 0.57

**Ejemplo 159: (1-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-etil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.20 minutos. (Método B); MS-ES: $(M+H)^+$ = 495; TLC**: $R_f$ = 0.11

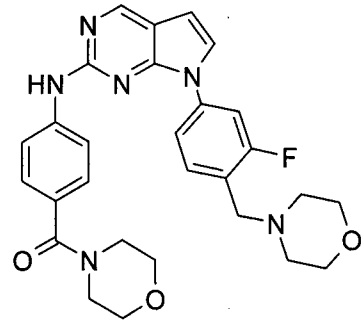
**Ejemplo 160: (3,4-dimetil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.80 minutos. (Método B); MS-ES: $(M+H)^+$ = 414; TLC**:

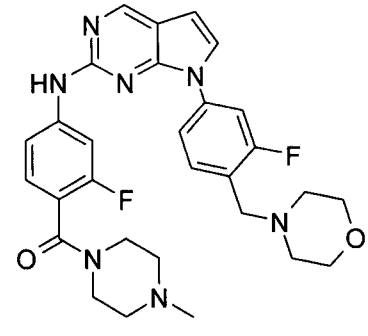
HPLC: $t_R$ = 8.51 minutos. (Método B); MS-ES: $(M+H)^+$ = 508; TLC**: $R_f$ = 0.67

**Ejemplo 157: {4-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.03 minutos. (Método B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$ = 0.29

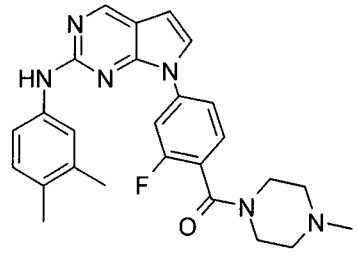
**Ejemplo 158: {2-fluoro-4-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 6.71 minutos. (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$

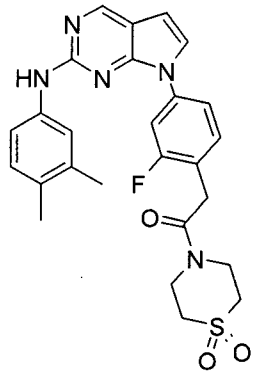
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.26 minutos. (Método B); MS-ES: $(M+H)^+$ = 479; TLC**: $R_f$ = 0.23

**Ejemplo 155: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.45 minutos. (Método B); MS-ES: $(M+H)^+$ = 459; TLC**: $R_f$ = 0.31

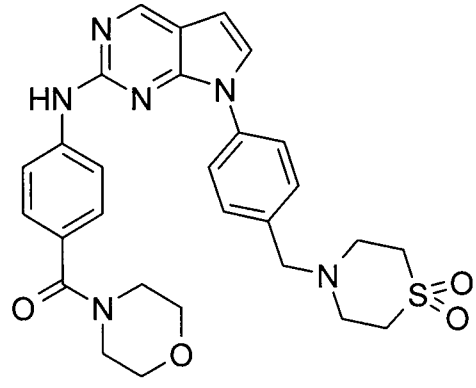
**Ejemplo 156: 2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-1-(1,1-dióxido-1-tiomorfolin-4-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3.

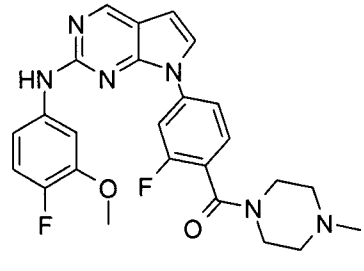
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.76 minutos. (Método B); MS-ES: $(M+H)^+$ = 446; TLC‡: $R_f$ = 0.26

**Ejemplo 153: (4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.03 minutos. (Método B); MS-ES: $(M+H)^+$ = 547; TLC**: $R_f$ = 0.29

**Ejemplo 154: {2-fluoro-4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



Organizacion y
Digitalizacion CSA Ltda

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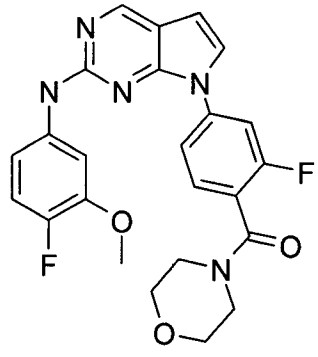
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Tomo 2/2

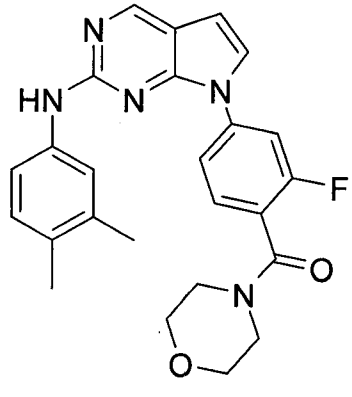
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.21 minutos. (Método B); MS-ES: $(M+H)^+$ = 475; TLC*: $R_f$ = 0.36

**Ejemplo 151: {2-fluoro-4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



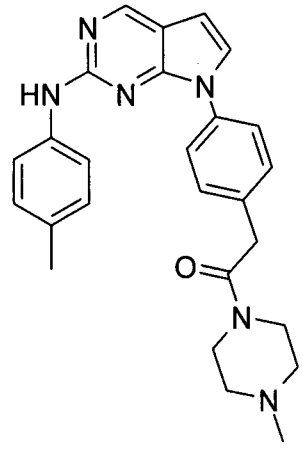
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.40 minutos. (Método B); MS-ES: $(M+H)^+$ = 466; TLC‡: $R_f$ = 0.16

**Ejemplo 152: {4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona**



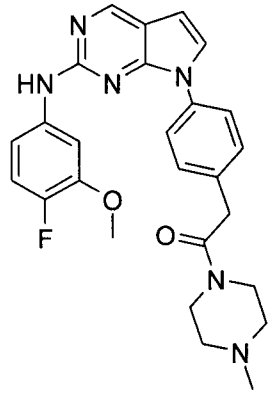
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.50 minutos. (Método B); MS-ES: $(M+H)^+$ = 455; TLC*: $R_f$ = 0.36

**Ejemplo 149: 1-(4-metil-piperazin-1-il)-2-[4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona**



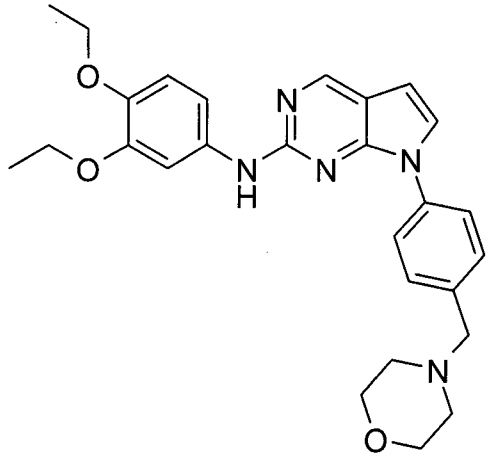
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.25 minutos. (Método B); MS-ES: $(M+H)^+$ = 441; TLC*: $R_f$ = 0.37

**Ejemplo 150: 2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



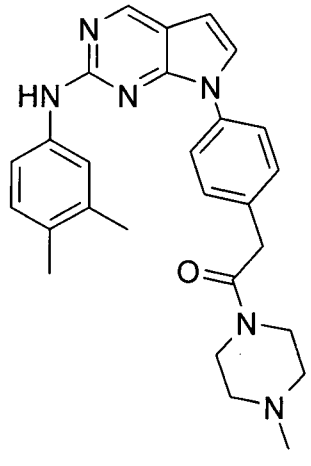
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.28 minutos. (Método B); MS-ES: $(M+H)^+$ = 400; TLC‡: $R_f$ = 0.17

**Ejemplo 147: (3,4-dietoxi-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



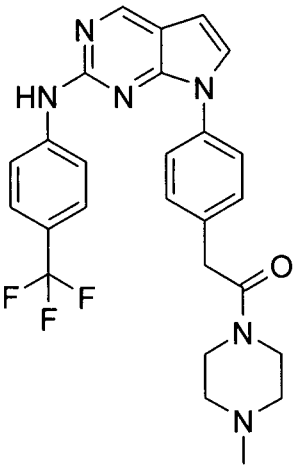
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.47 minutos. (Método B); MS-ES: $(M+H)^+$ = 474

**Ejemplo 148: 2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



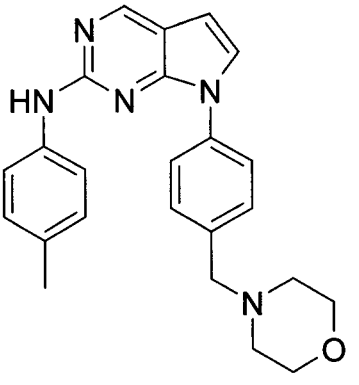
= 0.12

**Ejemplo 145: 1-(4-metil-piperazin-1-il)-2-{4-[2-(4-trifluoro-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona**



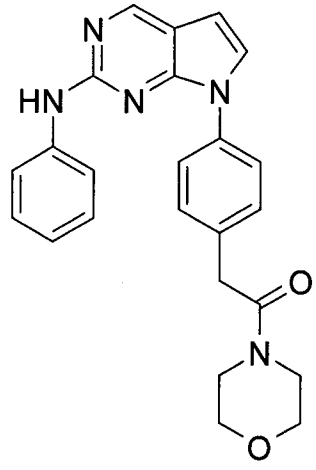
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.15 minutos. (Método B); MS-ES: $(M+H)^+$ = 495; TLC*: $R_f$ = 0.29

**Ejemplo 146: [7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina**



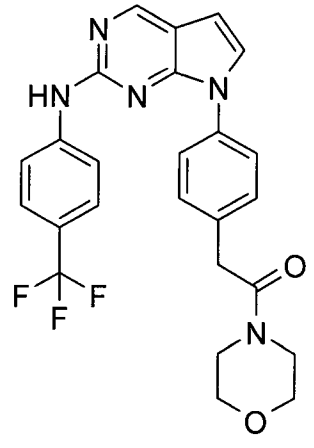
253

**Ejemplo 143: 1-morfolin-4-il-2-[4-(2-fenil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona**



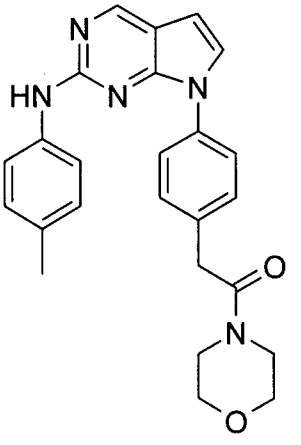
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.04 minutos. (Método B); MS-ES: $(M+H)^+$ = 414; TLC‡: $R_f$ = 0.11

**Ejemplo 144: 1-morfolin-4-il-2-{4-[2-(4-trifluoro-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona**



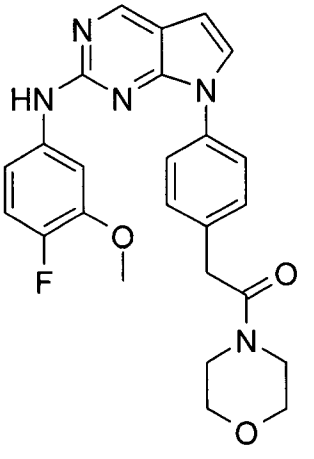
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 9.22 minutos. (Método B); MS-ES: $(M+H)^+$ = 482; TLC‡: $R_f$

**Ejemplo 141: 1-morfolin-4-il-2-[4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.36 minutos. (Método B); MS-ES: $(M+H)^+$ = 428; TLC‡: $R_f$ = 0.14

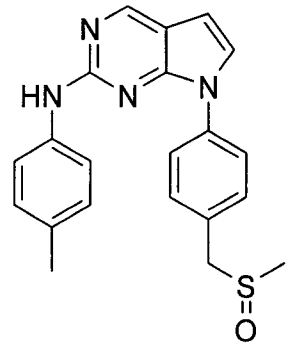
**Ejemplo 142: 2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.27 minutos. (Método B); MS-ES: $(M+H)^+$ = 462; TLC‡: $R_f$ = 0.23

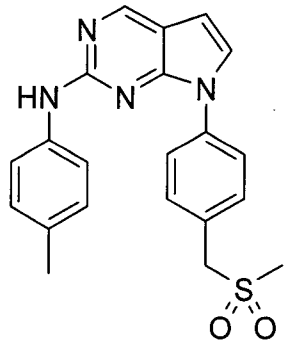
254

**Ejemplo 139: [7-(4-metan-sulfinil-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 7.96 minutos. (Método B); MS-ES: $(M+H)^+$ = 377; TLC***: $R_f$ = 0.22

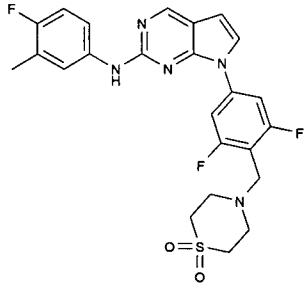
**Ejemplo 140: [7-(4-metan-sulfonil-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 8.23 minutos. (Método B); MS-ES: $(M+H)^+$ = 393; TLC***: $R_f$ = 0.42

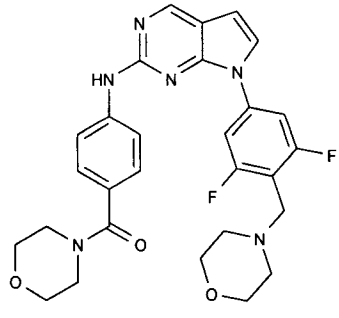
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.38 minutos (Método A); MS-ES: $(M+H)^+$ = 447.

**Ejemplo 137: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina**



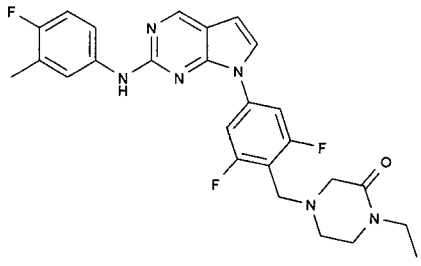
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.71 minutos (Método A); MS-ES: $(M+H)^+$ = 502.

**Ejemplo 138: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



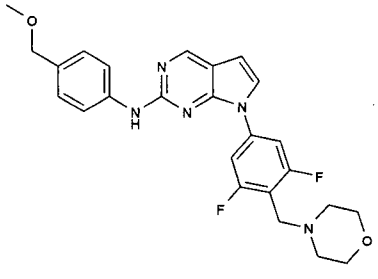
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 535.

**Ejemplo 134: 4-{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-1-etil-piperazin-2-ona**



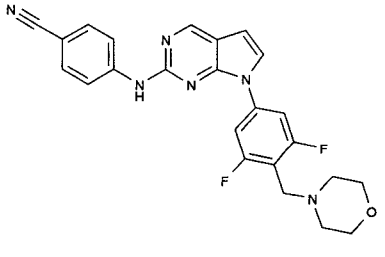
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.43 minutos (Método A); MS-ES: $(M+H)^+$ = 495.

**Ejemplo 135: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina**



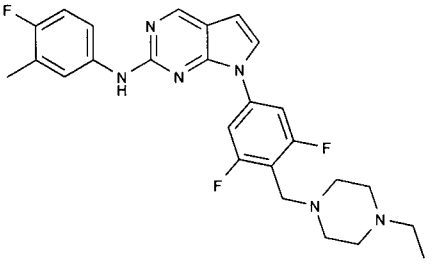
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 466.

**Ejemplo 136: 4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzonitrilo**



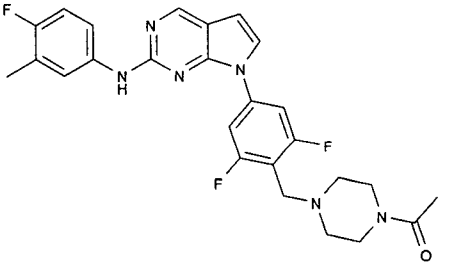
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.39 minutos (Método A); MS-ES: $(M+H)^+$ = 454.

**Ejemplo 132: {7-[4-(4-etil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.35 minutos (Método A); MS-ES: $(M+H)^+$ = 481.

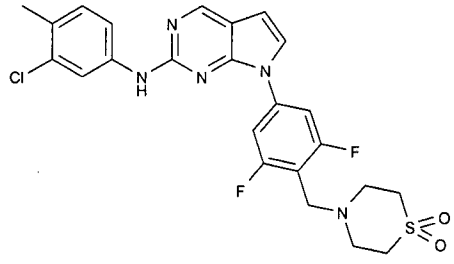
**Ejemplo 133: 1-(4-{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.26 minutos (Método A); MS-ES: $(M+H)^+$ = 495.

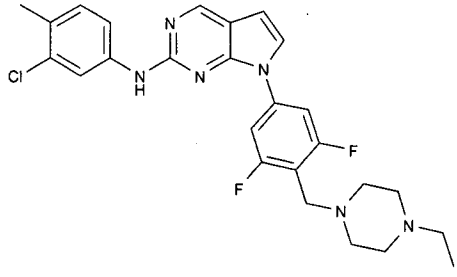
256

**Ejemplo 129: (3-cloro-4-metil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



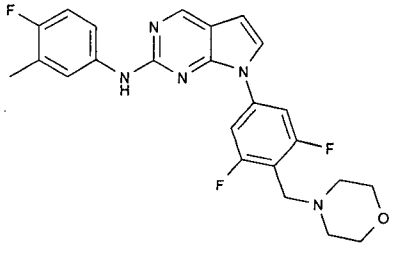
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.96 minutos (Método A); MS-ES: $(M+H)^+$ = 518.

**Ejemplo 130: (3-cloro-4-metil-fenil)-{7-[4-(4-etil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



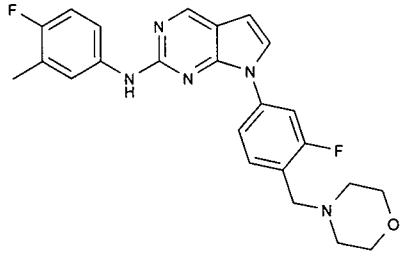
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.51 minutos (Método A); MS-ES: $(M+H)^+$ = 497.

**Ejemplo 131: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-fluoro-3-metil-fenil)-amina**



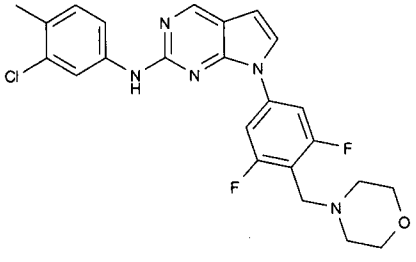
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.32 minutos (Método A); MS-ES: $(M+H)^+$ = 480.

**Ejemplo 127: (4-fluoro-3-metil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



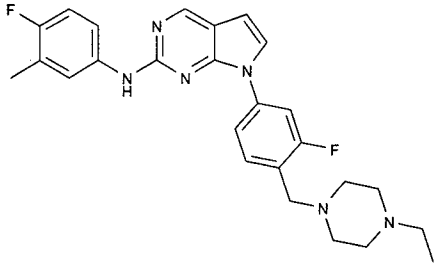
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.26 minutos (Método A); MS-ES: $(M+H)^+$ = 436.

**Ejemplo 128: (3-cloro-4-metil-fenil)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



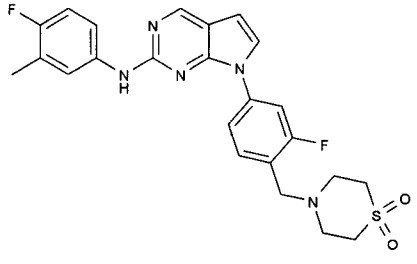
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.48 minutos (Método A); MS-ES: $(M+H)^+$ = 470.

**Ejemplo 124: {7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina**



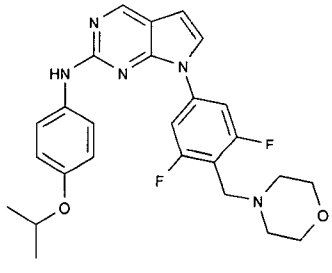
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.24 minutos (Método A); MS-ES: $(M+H)^+$ = 463.

**Ejemplo 125: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina**



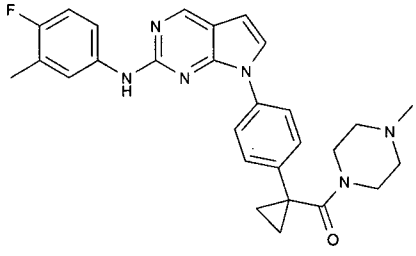
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.53 minutos (Método A); MS-ES: $(M+H)^+$ = 484.

**Ejemplo 126: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina**



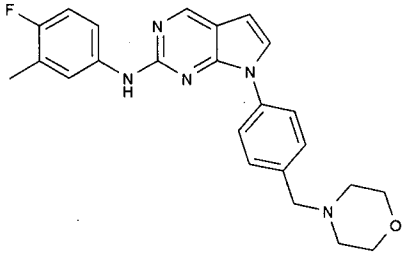
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.73 minutos (Método A); MS-ES: $(M+H)^+$ = 500.

**Ejemplo 122: (1-{4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.33 minutos (Método A); MS-ES: $(M+H)^+$ = 485.

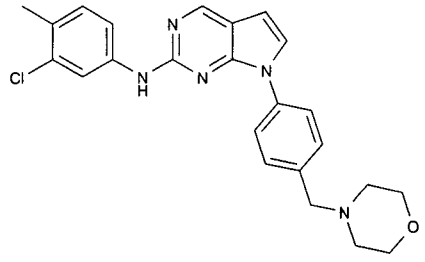
**Ejemplo 123: (4-fluoro-3-metil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.18 minutos (Método A); MS-ES: $(M+H)^+$ = 418.

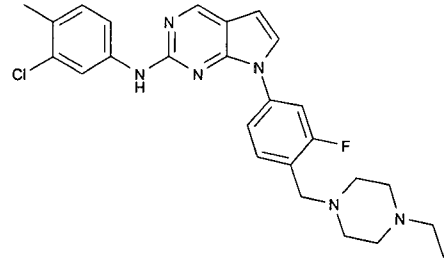
252

**Ejemplo 119: (3-cloro-4-metil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



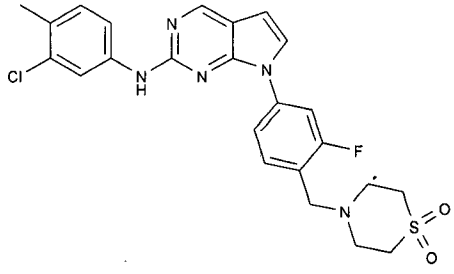
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.33 minutos (Método A); MS-ES: $(M+H)^+$ = 434.

**Ejemplo 120: (3-cloro-4-metil-fenil)-{7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



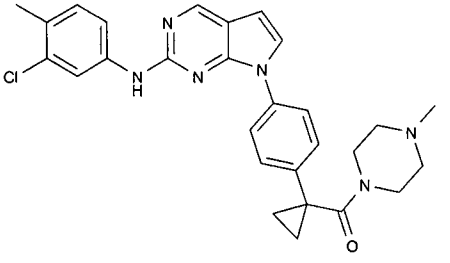
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.38 minutos (Método A); MS-ES: $(M+H)^+$ = 479.

**Ejemplo 121: (3-cloro-4-metil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



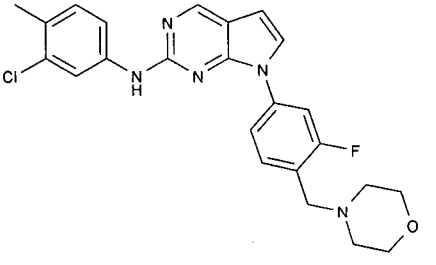
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 2.03 minutos (Método A); MS-ES: $(M+H)^+$ = 484.

**Ejemplo 117: (1-{4-[2-(3-cloro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona**



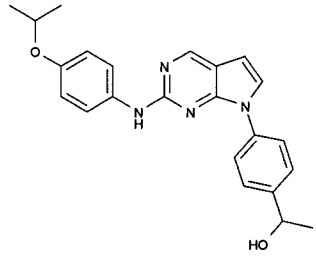
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.47 minutos (Método A); MS-ES: $(M+H)^+$ = 501.

**Ejemplo 118: (3-cloro-4-metil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



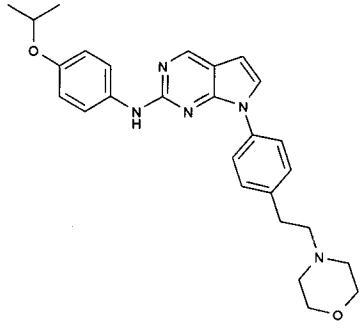
El compuesto se prepara de una manera análoga al Ejemplo 3. MS-ES: $(M+H)^+$ = 452.

**Ejemplo 114: 1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanol**



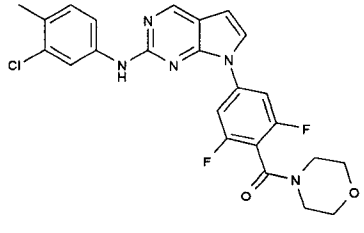
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.63 minutos (Método A); MS-ES: $(M+H)^+$ = 389.

**Ejemplo 115: (4-isopropoxi-fenil)-{7-[4-(2-morfolin-4-il-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**

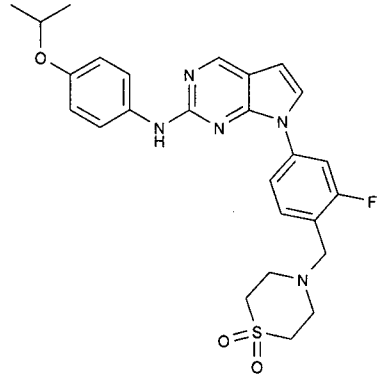


El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.27 minutos (Método A); MS-ES: $(M+H)^+$ = 458.

**Ejemplo 116: {4-[2-(3-cloro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-fenil}-morfolin-4-il-metanona**

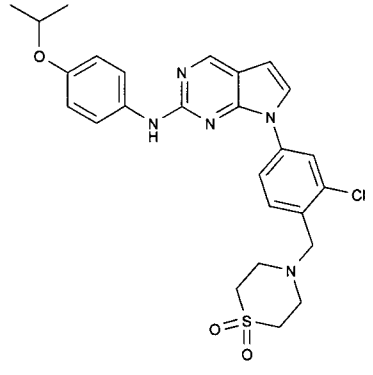


**Ejemplo 112: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.55 minutos (Método A); MS-ES: $(M+H)^+$ = 510.

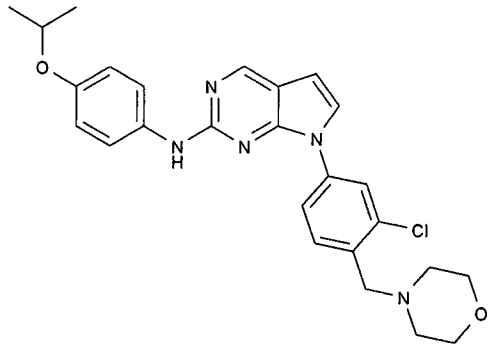
**Ejemplo 113: {7-[3-cloro-4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.73 minutos (Método A); MS-ES: $(M+H)^+$ = 526.

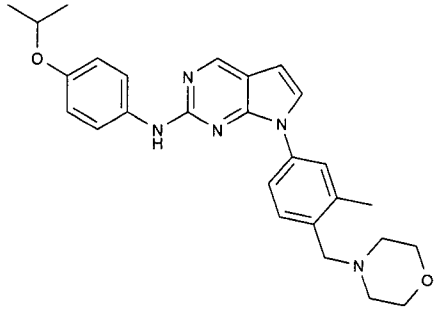
260

**Ejemplo 110: [7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina**



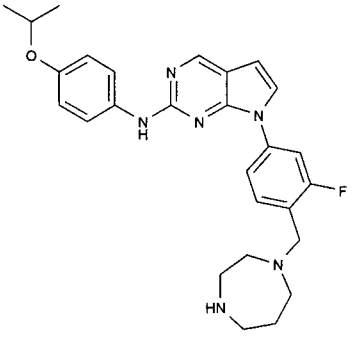
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.33 minutos (Método A); MS-ES: $(M+H)^+$ = 478.

**Ejemplo 111: (4-isopropoxi-fenil)-[7-(3-metil-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



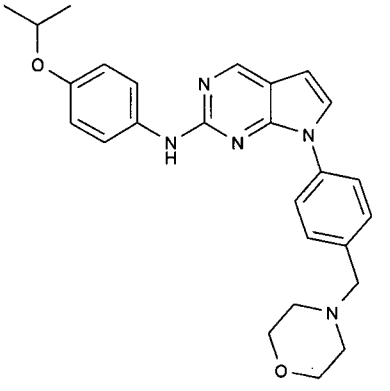
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.28 minutos (Método A); MS-ES: $(M+H)^+$ = 458.

**Ejemplo 108: 7-(4-[1,4]-diazepan-1-il-metil-3-fluoro-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.14 minutos (Método A); MS-ES: $(M+H)^+$ = 475.

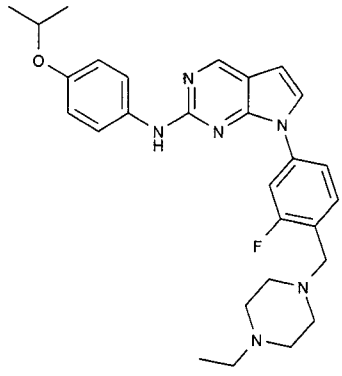
**Ejemplo 109: (4-isopropoxi-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.23 minutos (Método A); MS-ES: $(M+H)^+$ = 444.

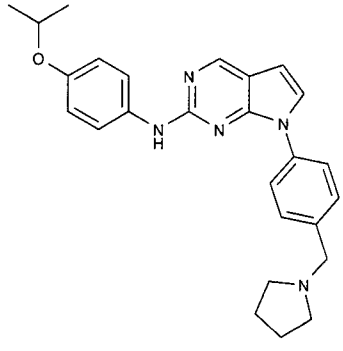
261

**Ejemplo 106: {7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.25 minutos (Método A); MS-ES: $(M+H)^+$ = 489.

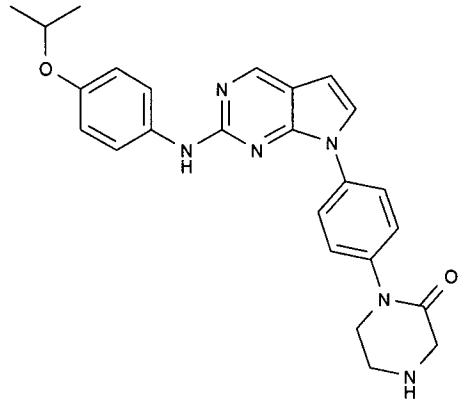
**Ejemplo 107: (4-isopropoxi-fenil)-[7-(4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.27 minutos (Método A); MS-ES: $(M+H)^+$ = 428.

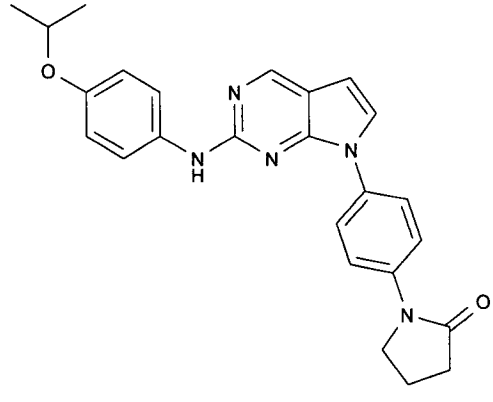
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.36 minutos (Método A); MS-ES: $(M+H)^+$ = 511.

**Ejemplo 104: 1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 443.

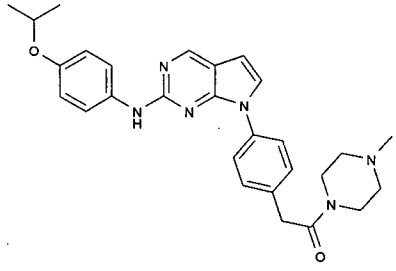
**Ejemplo 105: 1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-pirrolidin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.72 minutos (Método A); MS-ES: $(M+H)^+$ = 428.

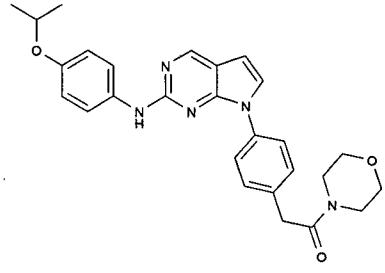
262

**Ejemplo 101: 2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



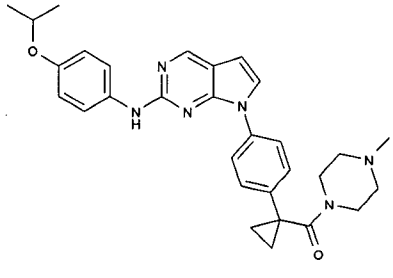
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.27 minutos (Método A); MS-ES: $(M+H)^+$ = 485.

**Ejemplo 102: 2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona**



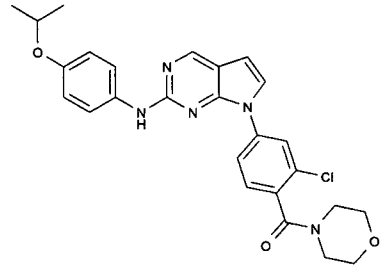
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.60 minutos (Método A); MS-ES: $(M+H)^+$ = 472.

**Ejemplo 103: (1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona**



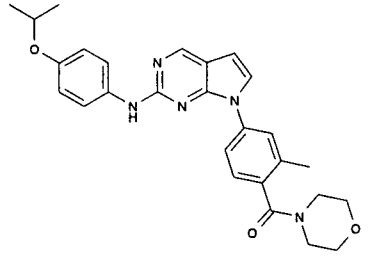
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.64 minutos (Método A); MS-ES: $(M+H)^+$ = 476.

**Ejemplo 99: {2-cloro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.69 minutos (Método A); MS-ES: $(M+H)^+$ = 492.

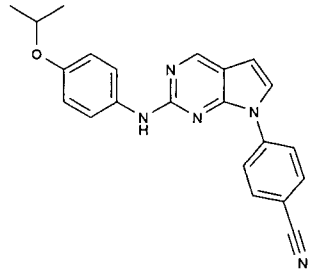
**Ejemplo 100: {4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.61 minutos (Método A); MS-ES: $(M+H)^+$ = 472.

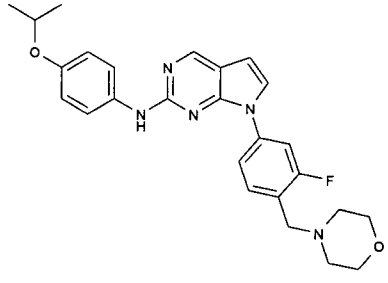
263

**Ejemplo 96: 4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzonitrilo**



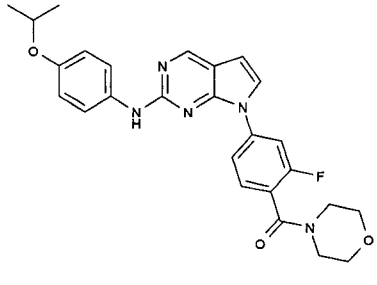
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.90 minutos (Método A); MS-ES: $(M+H)^+$ = 370.

**Ejemplo 97: [7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina**



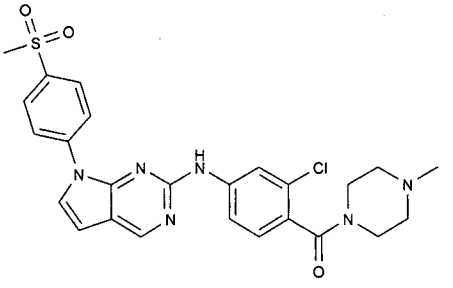
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.27 minutos (Método A); MS-ES: $(M+H)^+$ = 462.

**Ejemplo 98: {2-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



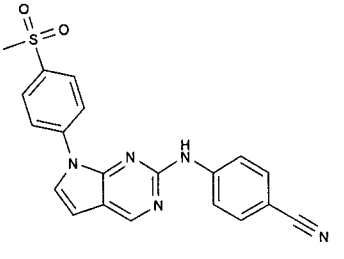
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.02 minutos (Método A); MS-ES: $(M+H)^+$ = 477.

**Ejemplo 94: {2-cloro-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 525.

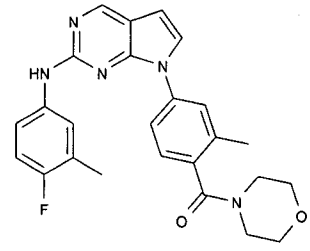
**Ejemplo 95: 4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.77 minutos (Método A); MS-ES: $(M+H)^+$ = 390.

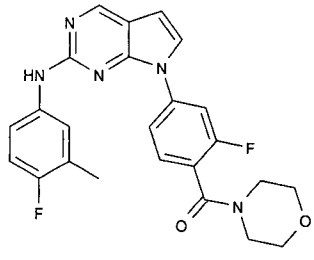
264

**Ejemplo 91: {4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona**



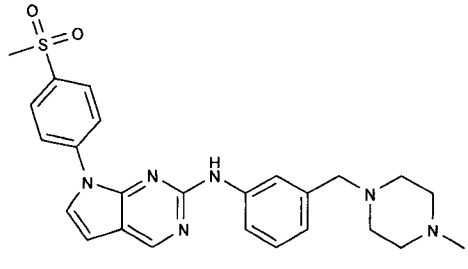
El compuesto se prepara de una manera análoga al Ejemplo 3. MS-ES: $(M+H)^+$ = 446.

**Ejemplo 92: {2-fluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



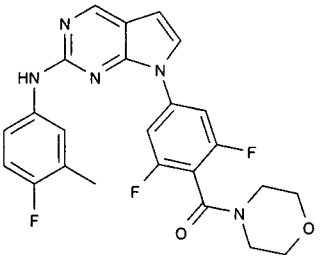
El compuesto se prepara de una manera análoga al Ejemplo 3. MS-ES: $(M+H)^+$ = 450.

**Ejemplo 93: 7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il-metil)-fenil]-amina**



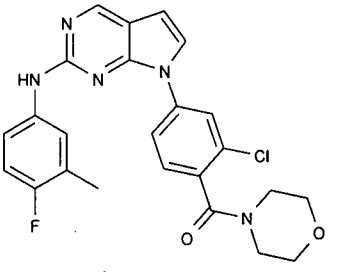
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.24 minutos (Método A); MS-ES: $(M+H)^+$ = 463.

**Ejemplo 89: {2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



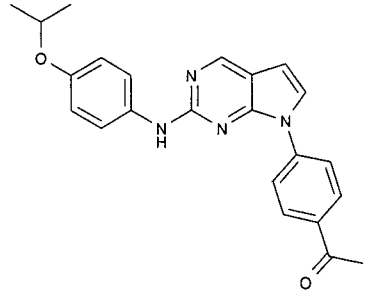
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.78 minutos (Método A); MS-ES: $(M+H)^+$ = 468.

**Ejemplo 90: {2-cloro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



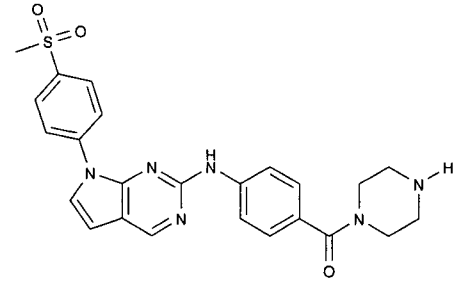
El compuesto se prepara de una manera análoga al Ejemplo 3. MS-ES: $(M+H)^+$ = 466.

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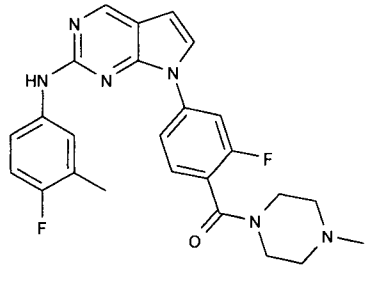
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.83 minutos (Método A); MS-ES: $(M+H)^+$ = 387.

**Ejemplo 87: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-piperazin-1-il-metanona**

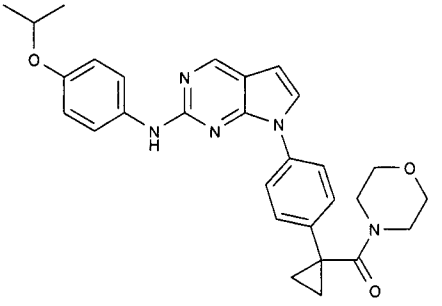


El compuesto se prepara mediante el tratamiento del Ejemplo 69 con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. MS-ES: $(M+H)^+$ = 477.

**Ejemplo 88: {2-fluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**

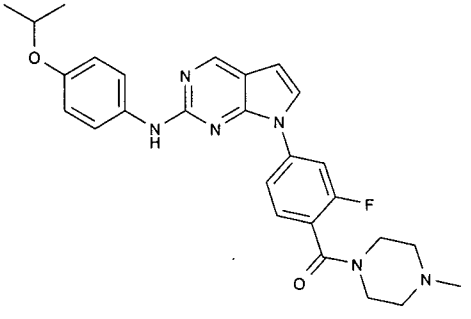


Ejemplo 84: (1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-morfolin-4-il-metanona



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.69 minutos (Método A); MS-ES: $(M+H)^+$ = 498.

**Ejemplo 85: {2-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



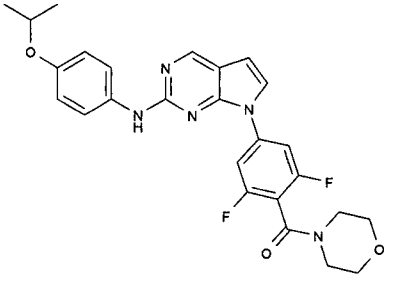
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.23 minutos (Método A); MS-ES: $(M+H)^+$ = 489.

**Ejemplo 86: 1,1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona**

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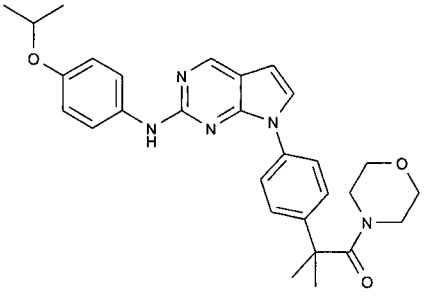
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.67 minutos (Método A); MS-ES: $(M+H)^+$ = 397.

**Ejemplo 82: {2,6-difluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



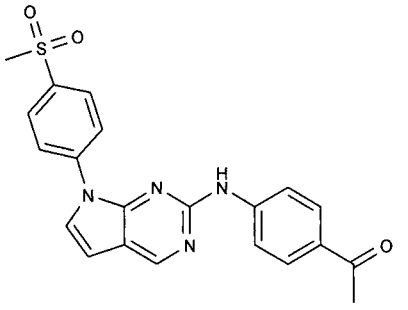
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.76 minutos (Método A); MS-ES: $(M+H)^+$ = 494.

**Ejemplo 83: 2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-2-metil-1-morfolin-4-il-propan-1-ona**



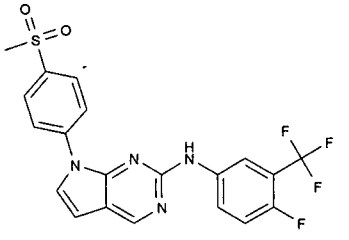
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.79 minutos (Método A); MS-ES: $(M+H)^+$ = 500.

**Ejemplo 79: 1-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-etanona**



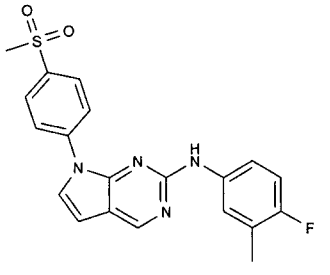
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.61 minutos (Método A); MS-ES: $(M+H)^+$ = 407.

**Ejemplo 80: (4-fluoro-3-trifluoro-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



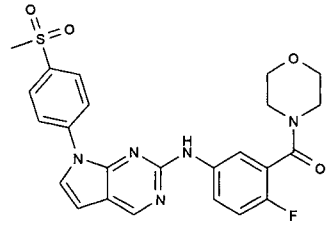
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 2.01 minutos (Método A); MS-ES: $(M+H)^+$ = 451.

**Ejemplo 81: (4-fluoro-3-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



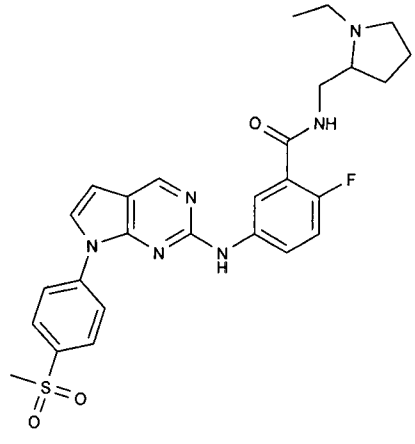
267

**Ejemplo 77: {2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.38 minutos (Método A); MS-ES: $(M+H)^+$ = 496.

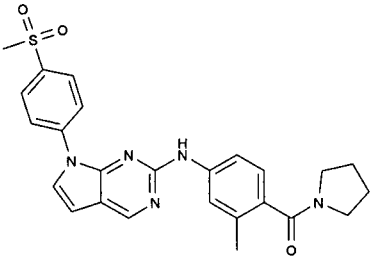
**Ejemplo 78: N-(1-etil-pirrolidin-2-il-metil)-2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.14 minutos (Método A); MS-ES: $(M+H)^+$ = 537.

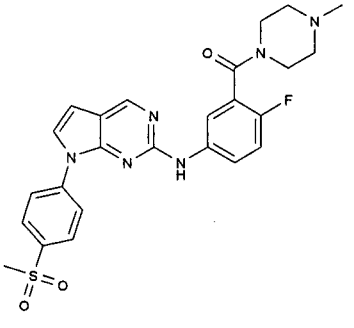
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.31 minutos (Método A); MS-ES: $(M+H)^+$ = 492.

**Ejemplo 75: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-pirrolidin-1-il-metanona**

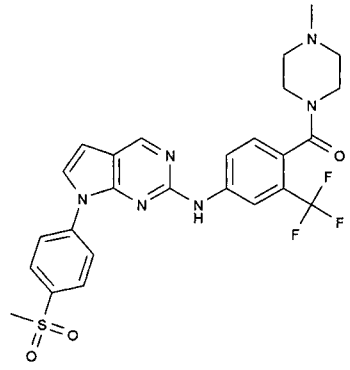


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.42 minutos (Método A); MS-ES: $(M+H)^+$ = 476.

**Ejemplo 76: {2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**

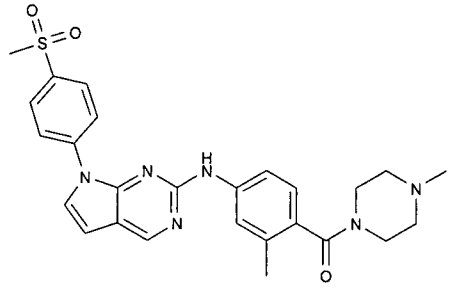


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.06 minutos (Método A); MS-ES: $(M+H)^+$ = 509.



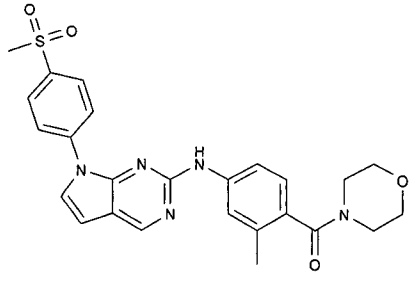
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.23 minutos (Método A); MS-ES: $(M+H)^+$ = 559.

**Ejemplo 73: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(4-metil-piperazin-1-il)-metanona**

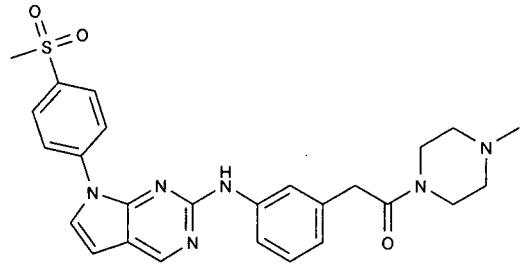


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.02 minutos (Método A); MS-ES: $(M+H)^+$ = 505.

**Ejemplo 74: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-morfolin-4-il-metanona**

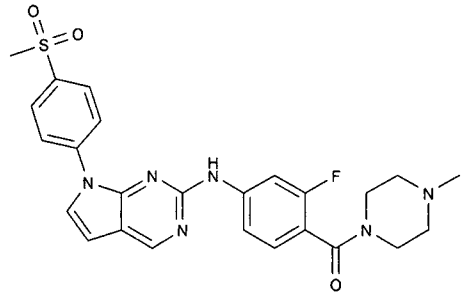


**Ejemplo 70: 2-{3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-1-(4-metil-piperazin-1-il)-etanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.03 minutos (Método A); MS-ES: $(M+H)^+$ = 505.

**Ejemplo 71: {2-fluoro-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**

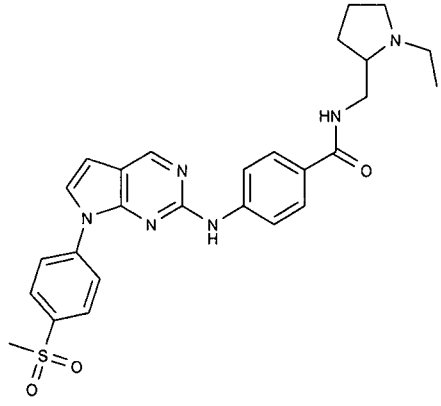


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 509.

**Ejemplo 72: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-trifluoro-metil-fenil}-(4-metil-piperazin-1-il)-metanona**

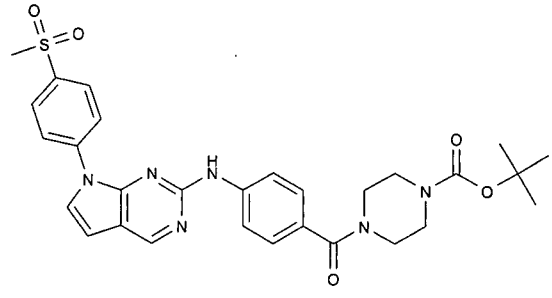
269

**Ejemplo 68: N-(1-etil-pirrolidin-2-il-metil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida**



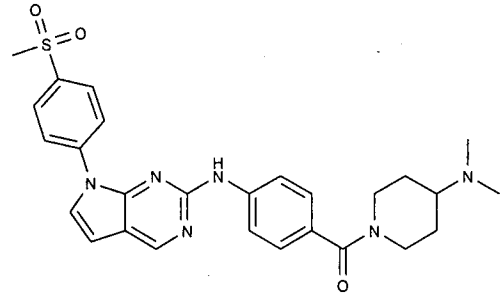
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.18 minutos (Método A); MS-ES: $(M+H)^+$ = 519.

**Ejemplo 69: Terbutil-éster del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzoil}-piperazin-1-carboxílico**



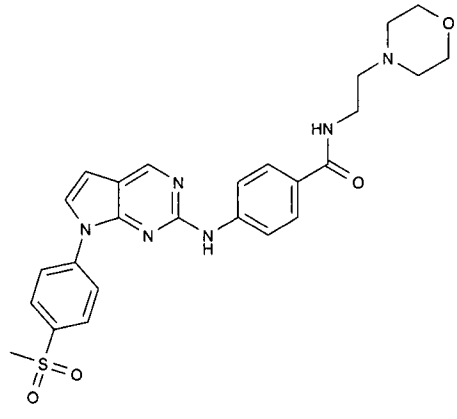
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.80 minutos (Método A); MS-ES: $(M+H)^+$ = 577.

**Ejemplo 66: (4-dimetil-amino-piperidin-1-il)-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.02 minutos (Método A); MS-ES: $(M+H)^+$ = 519.

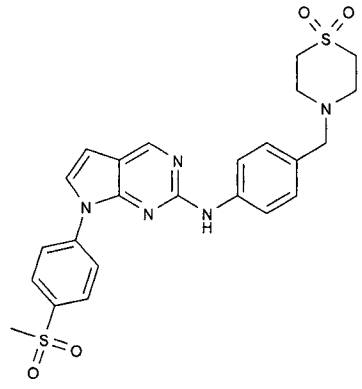
**Ejemplo 67: 4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-(2-morfolin-4-il-etil)-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.10 minutos (Método A); MS-ES: $(M+H)^+$ = 521.

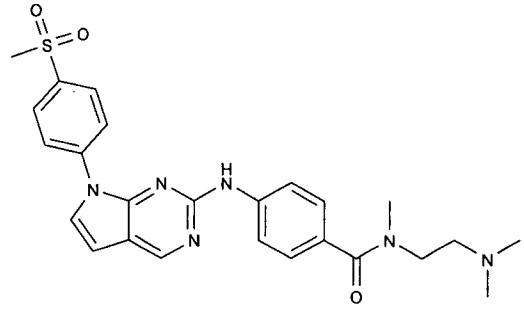
270

**Ejemplo 64: [4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.11 minutos (Método A); MS-ES: $(M+H)^+$ = 512.

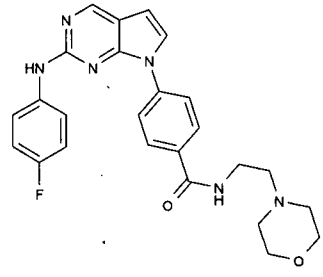
**Ejemplo 65: N-(2-dimetil-amino-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-metil-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.04 minutos (Método A); MS-ES: $(M+H)^+$ = 493.

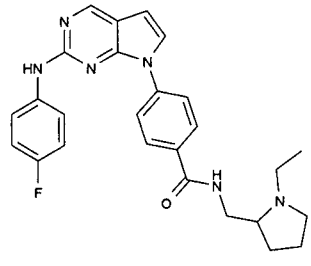
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.42 minutos (Método A); MS-ES: $(M+H)^+$ = 418.

**Ejemplo 62: 4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-N-(2-morfolin-4-il-etil)-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 461.

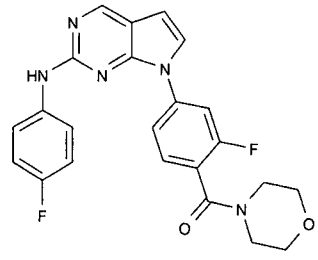
**Ejemplo 63: N-(1-etil-pirrolidin-2-il-metil)-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.23 minutos (Método A); MS-ES: $(M+H)^+$ = 459.

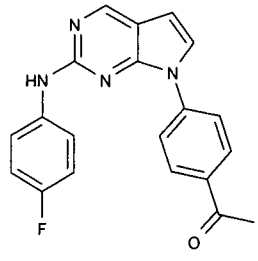
271

**Ejemplo 59: {2-fluoro-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



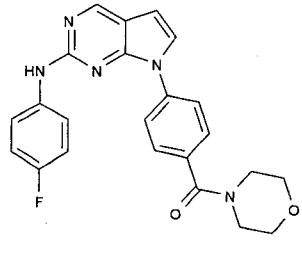
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.54 minutos (Método A); MS-ES: $(M+H)^+$ = 436.

**Ejemplo 60: 1-{4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona**



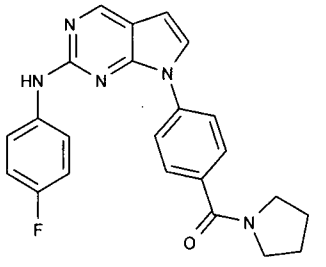
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.71 minutos (Método A); MS-ES: $(M+H)^+$ = 347.

**Ejemplo 61: {4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



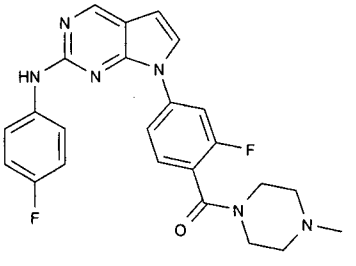
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.06 minutos (Método A); MS-ES: $(M+H)^+$ = 431.

**Ejemplo 57: {4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-pirrolidin-1-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.56 minutos (Método A); MS-ES: $(M+H)^+$ = 402.

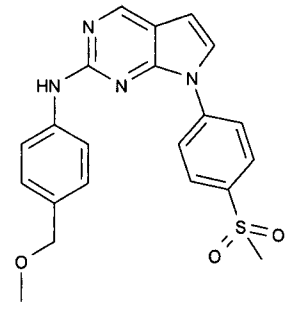
**Ejemplo 58: {2-fluoro-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.11 minutos (Método A); MS-ES: $(M+H)^+$ = 449.

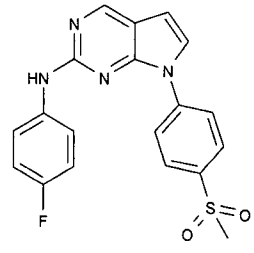
272

**Ejemplo 54: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina**



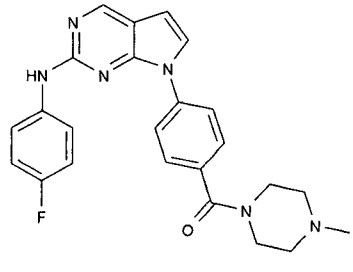
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.46 minutos (Método A); MS-ES: $(M+H)^+$ = 409.

**Ejemplo 55: (4-fluoro-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**

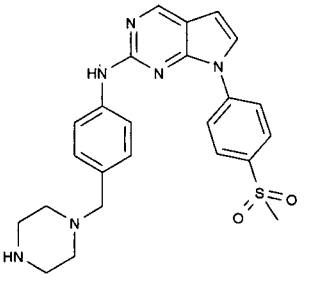


El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.52 minutos (Método A); MS-ES: $(M+H)^+$ = 383.

**Ejemplo 56: {4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona**

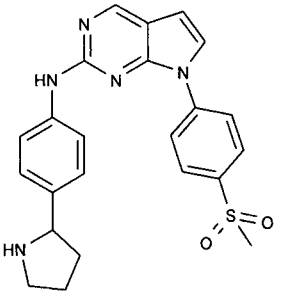


**Ejemplo 52: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-metil-fenil)-amina**



El compuesto se prepara mediante el tratamiento del Ejemplo 45 con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 464.

**Ejemplo 53: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-pirrolidin-2-il-fenil)-amina**

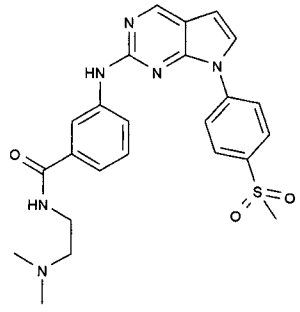


El compuesto se prepara mediante el tratamiento del Ejemplo 46 con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 434.

273

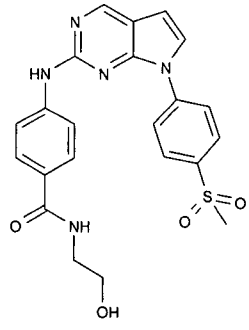
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.32 minutos (Método A); MS-ES: $(M+H)^+$ = 478.

**Ejemplo 50: N-(2-dimetil-amino-etil)-3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida**

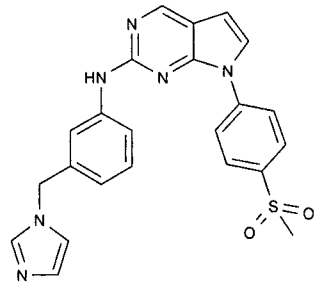


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.04 minutos (Método A); MS-ES: $(M+H)^+$ = 479.

**Ejemplo 51: N-(2-hidroxi-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida**

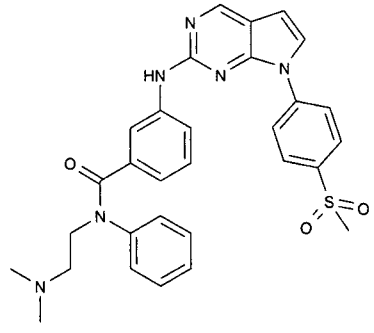


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.17 minutos (Método A); MS-ES: $(M+H)^+$ = 452.



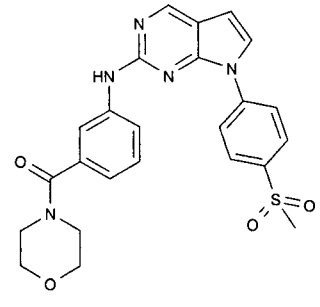
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 445.

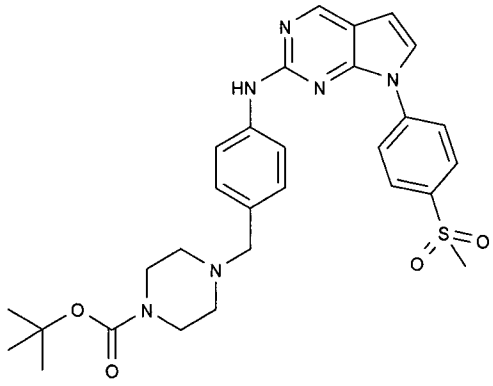
**Ejemplo 48: N-(2-dimetil-amino-etil)-3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-fenil-benzamida**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.28 minutos (Método A); MS-ES: $(M+H)^+$ = 555.

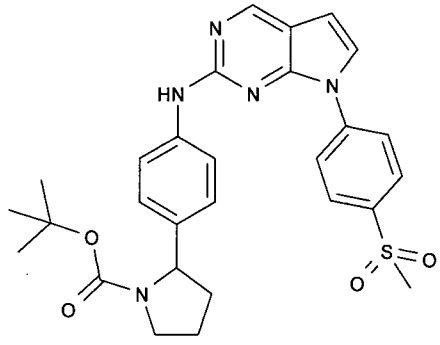
**Ejemplo 49: {3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**





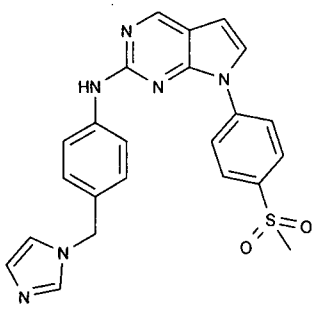
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.41 minutos (Método A); MS-ES: $(M+H)^+$ = 563.

**Ejemplo 46: Terbutil-éster del ácido 2-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-pirrolidin-1-carboxílico**



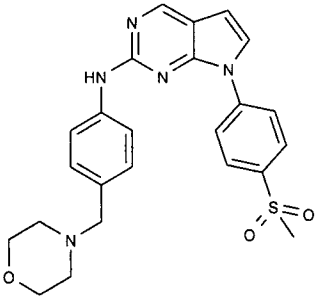
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.92 minutos (Método A); MS-ES: $(M+H)^+$ = 534.

**Ejemplo 47: (3-imidazol-1-il-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.06 minutos (Método A); MS-ES: $(M+H)^+$ = 445.

**Ejemplo 44: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-4-il-metil-fenil)-amina**

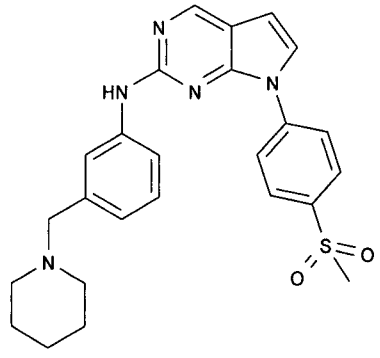


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 464.

**Ejemplo 45: Terbutil-éster del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-carboxílico**

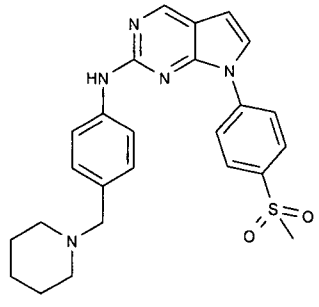
275

**Ejemplo 41: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-piperidin-1-il-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.16 minutos (Método A); MS-ES: $(M+H)^+$ = 462.

**Ejemplo 42: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperidin-1-il-metil-fenil)-amina**

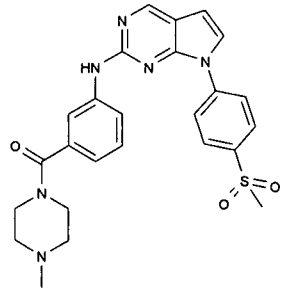


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.15 minutos (Método A); MS-ES: $(M+H)^+$ = 462.

**Ejemplo 43: (4-imidazol-1-il-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**

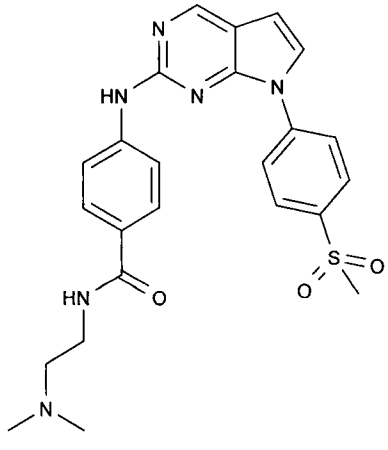
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.98 minutos (Método A); MS-ES: $(M+H)^+$ = 477.

**Ejemplo 39: {3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**

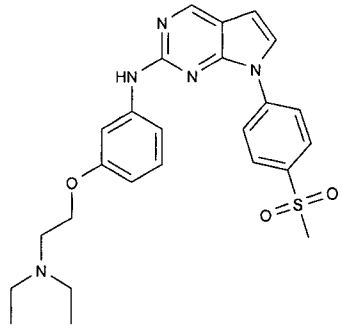


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.02 minutos (Método A); MS-ES: $(M+H)^+$ = 491.

**Ejemplo 40: N-(2-dimetil-amino-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida**

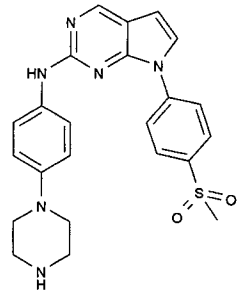


El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.10 minutos (Método A); MS-ES: $(M+H)^+$ = 479.



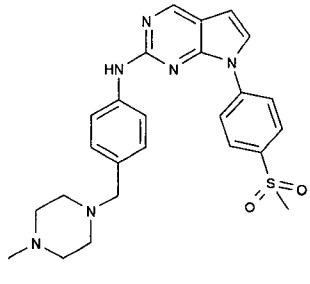
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.20 minutos (Método A); MS-ES: $(M+H)^+$ = 480.

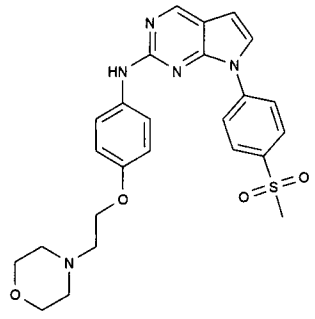
**Ejemplo 37: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 0.98 minutos (Método A); MS-ES: $(M+H)^+$ = 449.

**Ejemplo 38: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina**

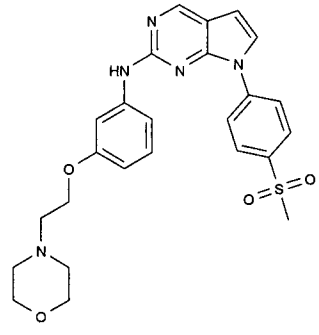




El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.01 minutos (Método A); MS-ES: $(M+H)^+$ = 494.

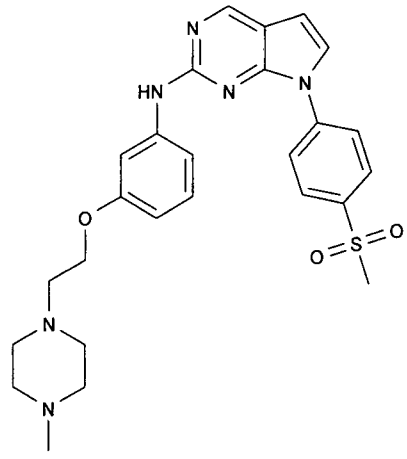
**Ejemplo 35: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(2-morfolin-4-il-etoxi)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1.

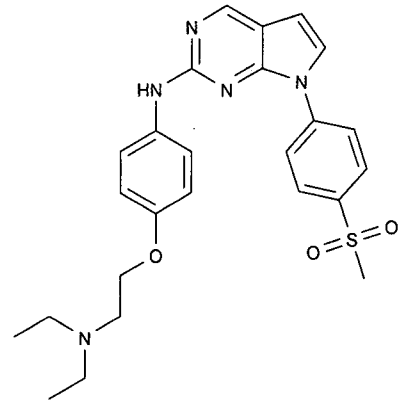
HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 494.

**Ejemplo 36: [3-(2-dietil-amino-etoxi)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.05 minutos (Método A); MS-ES: $(M+H)^+$ = 507.

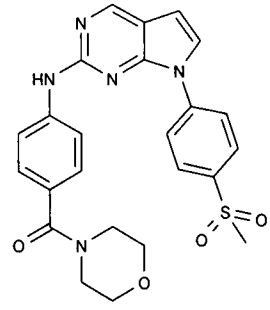
**Ejemplo 33: [4-(2-dietil-amino-etoxi)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 480.

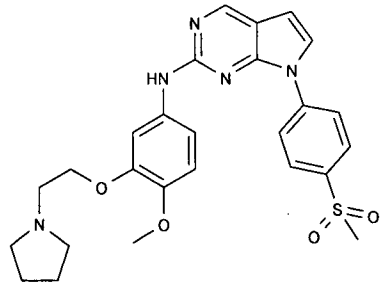
**Ejemplo 34: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(2-morfolin-4-il-etoxi)-fenil]-amina**

**Ejemplo 30: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.33 minutos (Método A); MS-ES: $(M+H)^+$ = 478.

**Ejemplo 31: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(2-pirrolidin-1-il-etoxi)-fenil]-amina**

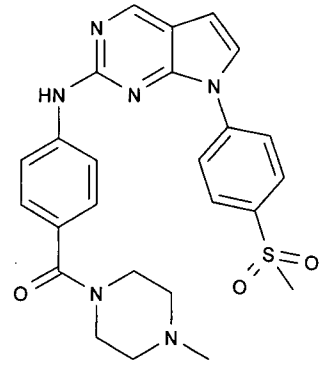


El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.13 minutos (Método A); MS-ES: $(M+H)^+$ = 508.

**Ejemplo 32: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{3-[2-(4-metil-piperazin-1-il)-etoxi]-fenil}-amina**

278

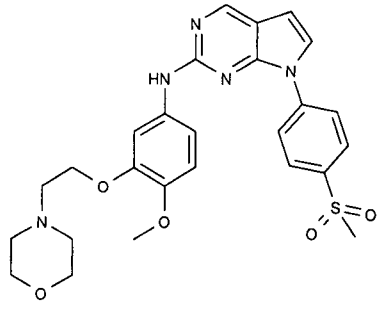
**Ejemplo 28: {4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 1.02 minutos (Método A); MS-ES: $(M+H)^+$ = 491.

**Ejemplo 29: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(2-morfolin-4-il-etoxi)-fenil]-amina**

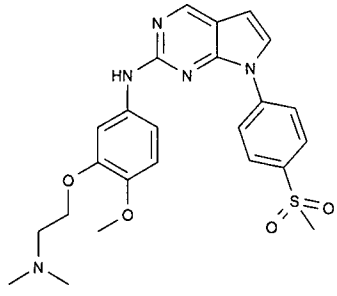


El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.11 minutos (Método A); MS-ES: $(M+H)^+$ = 524.

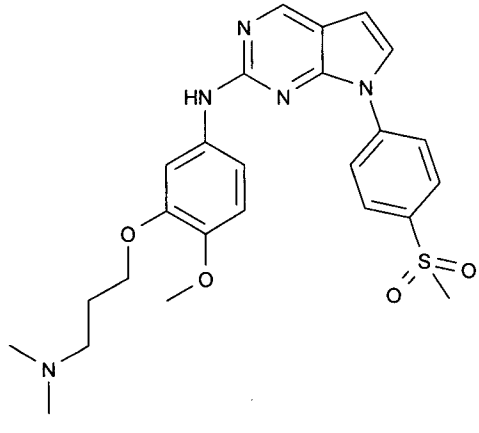
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.07 minutos (Método A); MS-ES: $(M+H)^+$ = 493.

**Ejemplo 26: [3-(2-dimetil-amino-etoxi)-4-metoxi-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 482.

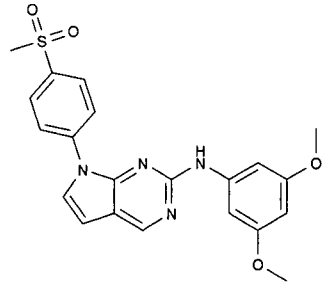
**Ejemplo 27: [3-(3-dimetil-amino-propoxi)-4-metoxi-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.10 minutos (Método A); MS-ES: $(M+H)^+$ = 496.

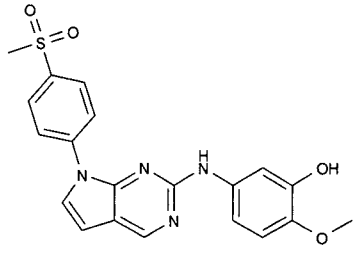
279

**Ejemplo 23: (3,5-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



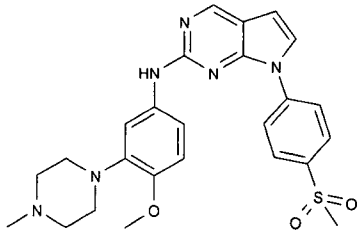
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.62 minutos (Método A); MS-ES: $(M+H)^+$ = 425.

**Ejemplo 24: 5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metoxi-fenol**



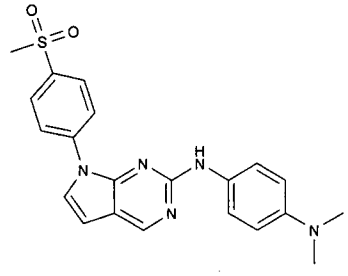
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.22 minutos (Método A); MS-ES: $(M+H)^+$ = 411.

**Ejemplo 25: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(4-metil-piperazin-1-il)-fenil]-amina**



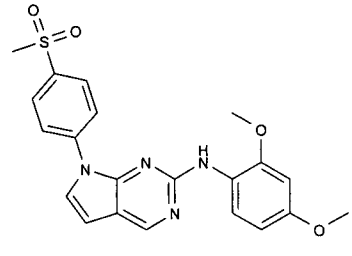
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.41 minutos (Método A); MS-ES: $(M+H)^+$ = 395.

**Ejemplo 21: N-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-N',N'-dimetil-bencen-1,4-diamina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.07 minutos (Método A); MS-ES: $(M+H)^+$ = 408.

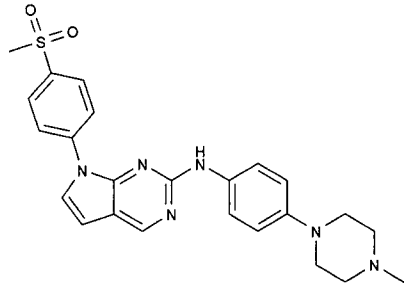
**Ejemplo 22: (2,4-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. MS-ES: $(M+H)^+$ = 425.

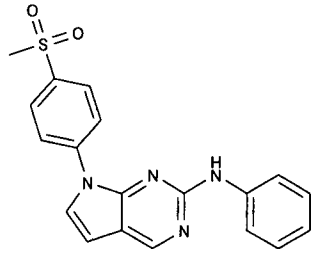
280

**Ejemplo 18: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il)-fenil]-amina**



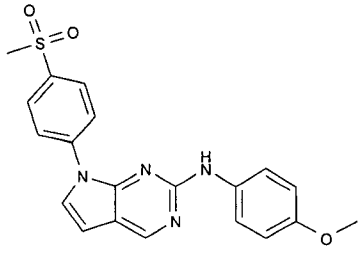
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 0.98 minutos (Método A); MS-ES: $(M+H)^+$ = 463.

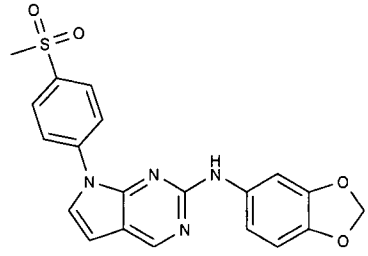
**Ejemplo 19: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-fenil-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.46 minutos (Método A); MS-ES: $(M+H)^+$ = 365.

**Ejemplo 20: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-fenil)-amina**

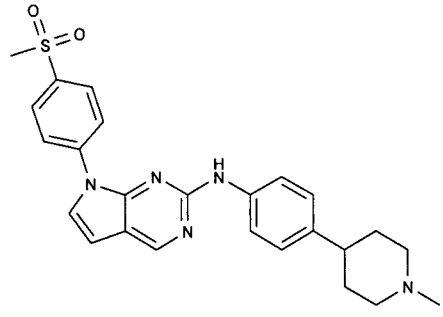




El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.42 minutos (Método A); MS-ES: $(M+H)^+$ = 409.

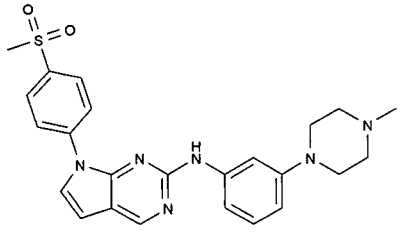
**Ejemplo 16: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(1-metil-piperidin-4-il)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.08 minutos (Método A); MS-ES: $(M+H)^+$ = 462.

**Ejemplo 17: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il)-fenil]-amina**

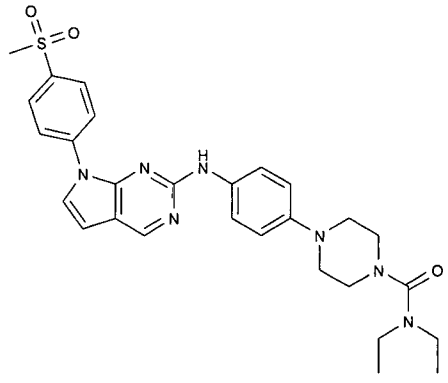


El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.09 minutos (Método A); MS-ES: $(M+H)^+$ = 463.

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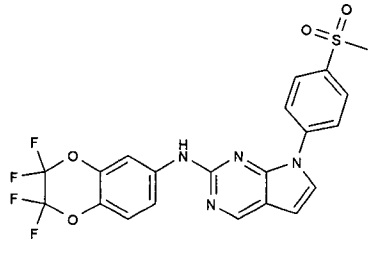
**Ejemplo 13: Dietil-amida del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-piperazin-1-carboxílico**



El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 1.44 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 14: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2,2,3,3-tetrafluoro-2,3-dihidro-benzo-[1,4]-dioxin-6-il)-amina**



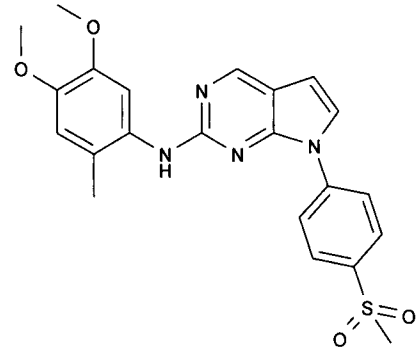
El compuesto se prepara de una manera análoga al Ejemplo 1.

HPLC: $t_R$ = 2.30 minutos (Método A); MS-ES: $(M+H)^+$ = 495.

**Ejemplo 15: Benzo-[1,3]-dioxol-5-il-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**

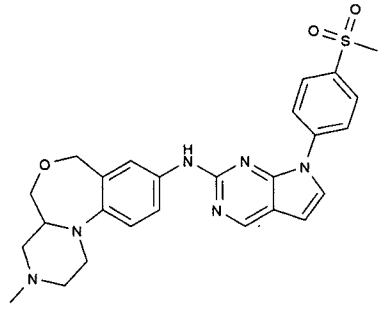
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.69 minutos (Método A); MS-ES: $(M+H)^+$ = 484.

**Ejemplo 11: (4,5-dimetoxi-2-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



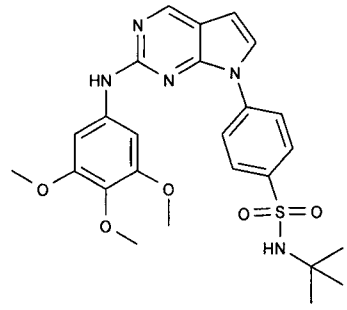
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.32 minutos (Método A); MS-ES: $(M+H)^+$ = 439.

**Ejemplo 12: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metil-1,2,3,4,4a,5-hexahidro-7H-6-oxa-3,11b-diaza-dibenzo-[a,c]-ciclohepten-9-il)-amina**



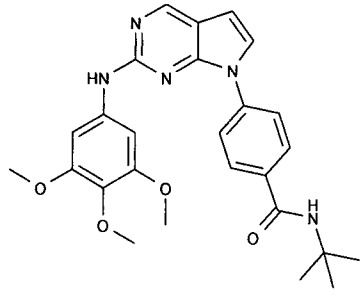
El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.06 minutos (Método A); MS-ES: $(M+H)^+$ = 505.

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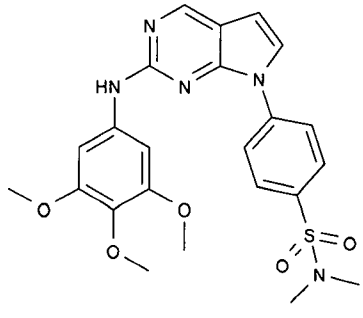
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.83 minutos (Método A); MS-ES: $(M+H)^+$ = 512.

**Ejemplo 9: N-terbutil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida**

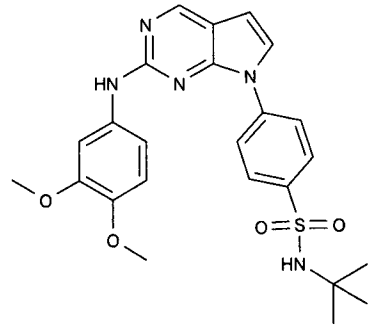


El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.81 minutos (Método A); MS-ES: $(M+H)^+$ = 476.

**Ejemplo 10: N,N-dimetil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida**

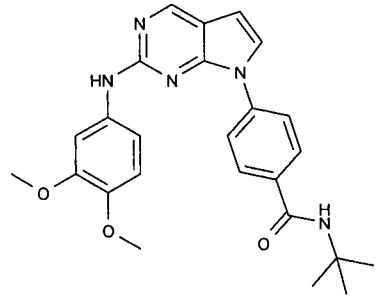


**Ejemplo 6: N-terbutil-4-[2-(3,4-dimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.73 minutos (Método A); MS-ES: $(M+H)^+$ = 482.

**Ejemplo 7: N-terbutil-4-[2-(3,4-dimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida**

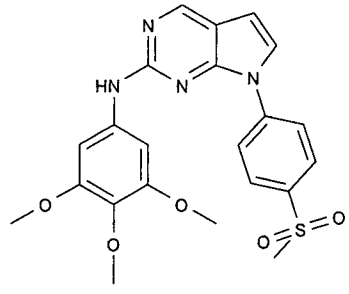


El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.71 minutos (Método A); MS-ES: $(M+H)^+$ = 446.

**Ejemplo 8: N-terbutil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida**

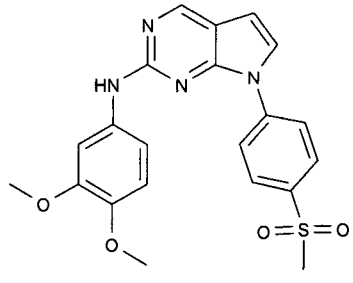
HPLC de preparación en fase inversa (Waters), para proporcionar el compuesto del título (**3**) como un sólido grisáceo. HPLC: $t_R$ = 1.67 minutos (Método A); MS-ES: $(M+H)^+$ = 423.

**Ejemplo 4: [7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4,5-trimetoxi-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 1. HPLC: $t_R$ = 1.48 minutos (Método A); MS-ES: $(M+H)^+$ = 455.

**Ejemplo 5: (3,4-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.37 minutos (Método A); MS-ES: $(M+H)^+$ = 425.

miligramos, 4.33 milimoles) en BuOH (10 mililitros), se le agrega 4-isopropoxi-anilina (1.31 gramos, 8.66 milimoles), y HCl acuoso concentrado (al 37 por ciento, 1.28 mililitros, 13.0 milimoles). La mezcla de reacción se calienta a 140°C durante 24 horas, se enfría a temperatura ambiente, y se concentra bajo presión reducida. El residuo se disuelve en EtOAc, y la capa orgánica se lava con una solución acuosa saturada de $Na_2CO_3$ (2 veces). La capa orgánica se seca sobre $Na_2SO_4$, se filtra, y se concentra bajo presión reducida. El residuo sólido se tritura con hexano, para proporcionar el compuesto del título como un sólido grisáceo.

Paso 3.2: (4-isopropoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (**3**)

En un tubo sellado, la (4-isopropoxi-fenil)-(7H-pirrolo-[2,3-d]-pirimidin-2-il)-amina (350 miligramos, 1.17 milimoles), 4-bromo-fenil-metil-sulfona (552 miligramos, 2.35 milimoles), CuI (68.4 miligramos, 0.352 milimoles), y $K_3PO_4$ (763 miligramos, 3.52 milimoles), se suspenden en 1,4-dioxano (10 mililitros). Entonces se agrega el trans-1,2-diamino-ciclohexano (42.7 microlitros, 0.352 milimoles) a temperatura ambiente. El frasco de reacción se inunda con argón, y la mezcla se calienta a 110°C durante 6 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluye con EtOAc, y la capa orgánica se lava con una solución acuosa saturada de NaCl (3 veces). La capa orgánica se seca sobre $Na_2SO_4$, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante

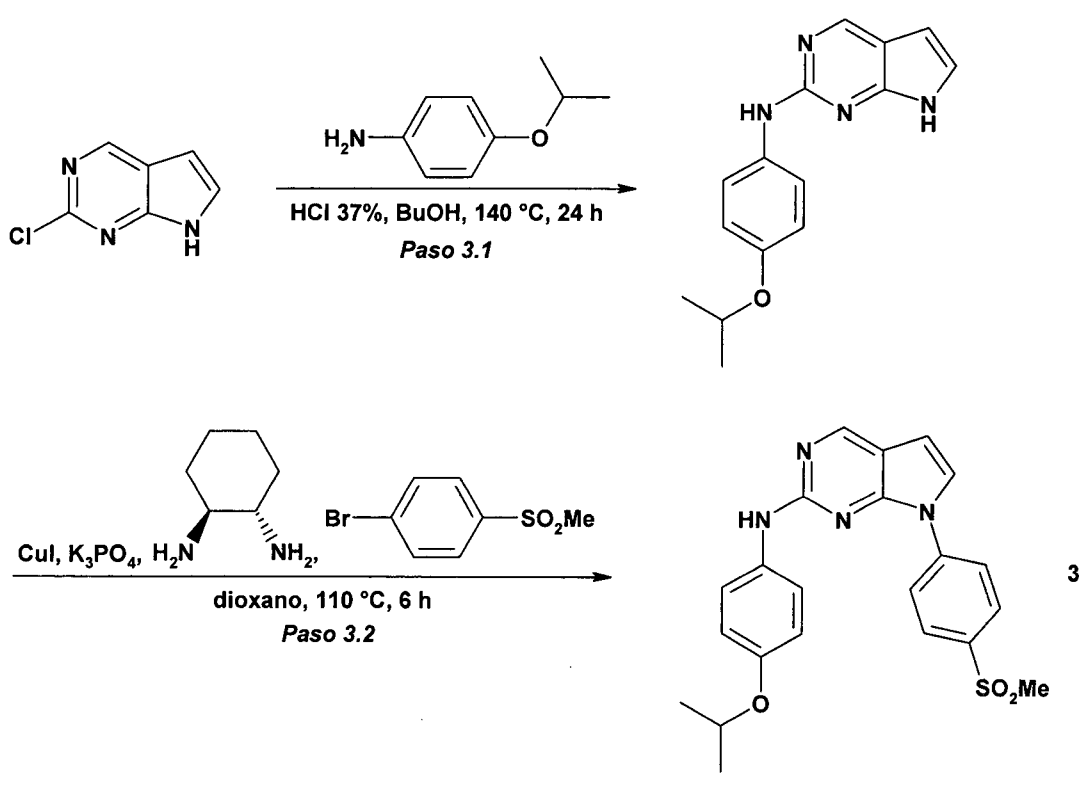
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mediante HPLC de preparación en fase inversa (Waters), para proporcionar el compuesto del título (**2**) como un sólido blanco. HPLC: $t_R$ = 0.89 minutos (Método A); MS-ES: $(M+H)^+$ = 548.

**Ejemplo 3: (4-isopropoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (3)**

El compuesto se prepara de acuerdo con el Esquema 3.

**Esquema 3**




Paso 3.1: (4-isopropoxi-fenil)-(7H-pirrolo-[2,3-d]-pirimidin-2-il)-amina

A una suspensión de 2-cloro-7H-pirrolo-[2,3-d]-pirimidina (700

trans-1,2-diamino-ciclohexano (45.0 microlitros, 0.371 milimoles) a temperatura ambiente. El frasco de reacción se inunda con argón, y la mezcla se calienta a 110°C durante 5 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluye con EtOAc, y la capa orgánica se lava con una solución acuosa saturada de $Na_2CO_3$ (2 veces). La capa orgánica se seca sobre $Na_2SO_4$, se filtra, y se concentra bajo presión reducida. El residuo se purifica mediante cromatografía en columna ($SiO_2$, elución en gradiente, hexano / EtOAc, 100:0 → 30:70), para proporcionar el compuesto del título como un sólido blanco.

Paso 2.2: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona (**2**)

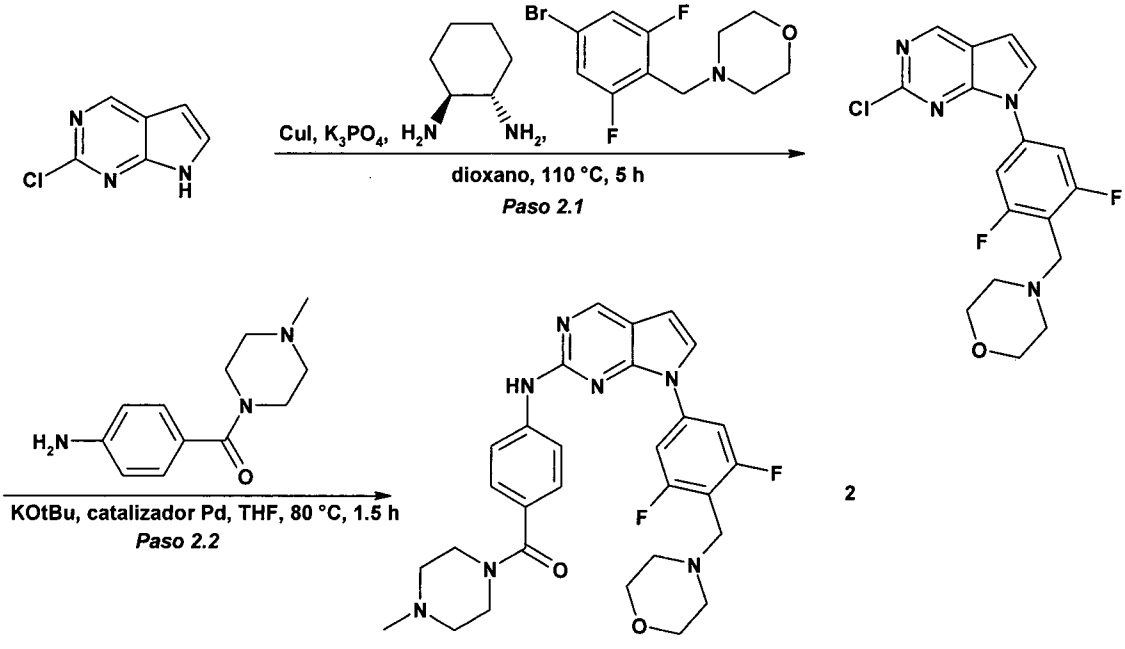
En un tubo sellado, la 2-cloro-7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidina (50.0 miligramos, 0.130 milimoles), (4-amino-fenil)-(4-metil-piperazin-1-il)-metanona (42.1 miligramos, 0.182 milimoles), KOtBu (21.1 miligramos, 0.182 milimoles), y SK-CC02-A (12.5 miligramos, 0.020 milimoles, catalizador de Pd Complejo de cloruro de 2-(dimetil-amino-metil)-ferroceno-1-il-paladio(II) - dinorbornil-fosfina, Fluka No. 44696), se suspenden en tetrahidrofurano (2 mililitros) bajo argón. La mezcla de reacción se agita a 80°C durante 1.5 horas, se enfría a temperatura ambiente, y entonces se filtra a través de un tapón de Celite. El filtrado se concentra bajo presión reducida. El residuo se purifica

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**Ejemplo 2: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona (2)**

El compuesto se prepara de acuerdo con el Esquema 2.

**Esquema 2**




Paso 2.1: 2-cloro-7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidina

En un tubo sellado, la 2-cloro-7H-pirrolo-[2,3-d]-pirimidina (200 miligramos, 1.24 milimoles), 4-(4-bromo-2,6-difluoro-bencil)-morfolina (418 miligramos, 1.36 milimoles), CuI (72.1 miligramos, 0.371 milimoles), y $K_3PO_4$ (804 miligramos, 3.71 milimoles), se suspenden en 1,4-dioxano (8 mililitros). Entonces, se agrega el

(30 mililitros). Entonces se agrega el trans-1,2-diamino-ciclohexano (149 microlitros, 1.23 milimoles) a temperatura ambiente. El frasco de reacción se inunda con argón, y la mezcla se calienta a 110°C durante 3 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se concentra bajo presión reducida. El residuo se suspende en EtOAc, y se lava con una solución acuosa saturada de NaCl (3 veces). La capa orgánica se seca sobre $MgSO_4$, se filtra, y se concentra bajo presión reducida. El residuo sólido se tritura con pequeñas cantidades de EtOAc, para proporcionar el compuesto del título como un sólido color café.

Paso 1.6: (3,4-dietoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (**1**)

A una suspensión de la 2-cloro-7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidina (30.0 miligramos, 0.093 milimoles) en BuOH (1.5 mililitros), se le agrega 3,4-dietoxi-anilina (41.0 miligramos, 0.220 milimoles), y HCl acuoso concentrado (al 37 por ciento, 23.0 microlitros, 0.232 milimoles). La mezcla de reacción se calienta a 140°C durante 24 horas, se enfría a temperatura ambiente, y se concentra bajo presión reducida. El residuo se purifica mediante HPLC de preparación en fase inversa (Waters), para proporcionar el compuesto del título (**1**) como un sólido amarillo. HPLC: $t_R$ = 1.61 minutos (Método A); MS-ES: $(M+H)^+$ = 453.

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capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran, y se concentran bajo presión reducida. El residuo se purifica mediante cromatografía en columna ($SiO_2$, elución en gradiente, EtOAc / éter de petróleo, 1:10 → 1:4), para proporcionar el compuesto del título como un sólido amarillo.

Paso 1.4: 2-cloro-7H-pirrolo-[2,3-d]-pirimidina

A una solución de la 2-cloro-5-(2-etoxi-vinil)-pirimidin-4-il-amina (38.0 gramos, 0.19 moles) en EtOH (1000 mililitros), se le agrega HCl acuoso concentrado (al 37 por ciento, 100 gramos, 1.00 moles) a temperatura ambiente. La mezcla de reacción se calienta a reflujo durante 3 horas, y entonces se evapora a sequedad bajo presión reducida. Al residuo se le agrega una solución acuosa de carbonato de sodio (al 5 por ciento, 500 mililitros), y la mezcla se extrae con EtOAc (3 veces). Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran, y se concentran bajo presión reducida. El residuo se recristaliza a partir de hexano/éter (4/1, 250 mililitros) para dar el compuesto del título como un sólido grisáceo.

Paso 1.5: 2-cloro-7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidina

En un tubo sellado, la 2-cloro-7H-pirrolo-[2,3-d]-pirimidina (600 miligramos, 3.56 milimoles), 4-bromo-fenil-metil-sulfona (700 miligramos, 4.10 milimoles), CuI (239 miligramos, 1.23 milimoles), y $K_3PO_4$ (2.67 gramos, 12.3 milimoles), se suspenden en 1,4-dioxano

nuevamente hasta la temperatura ambiente, y se agita durante 55 horas. Se concentra bajo presión reducida, y el residuo se suspende en $H_2O$ (500 mililitros). La capa acuosa se extrae con EtOAc (3 veces), y las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran, y se concentran bajo presión reducida, para proporcionar el compuesto del título como un sólido blanco.

Paso 1.2: 1-etoxi-propeno

A una solución de etoxi-etino (120 gramos, 0.69 moles, al 40 por ciento en hexano) en tolueno (1500 mililitros), se le agrega lentamente hidruro de tributil-estaño (190 gramos, 0.65 moles), y AIBN (4.6 gramos, 0.028 moles). La mezcla de reacción se calienta a 100°C durante 16 horas. La mezcla de reacción se concentra bajo presión reducida y se seca bajo un alto vacío. El aceite residual color café (pureza del 80 por ciento del compuesto del título) se utiliza para el siguiente paso sin purificación.

Paso 1.3: 2-cloro-5-(2-etoxi-vinil)-pirimidin-4-il-amina

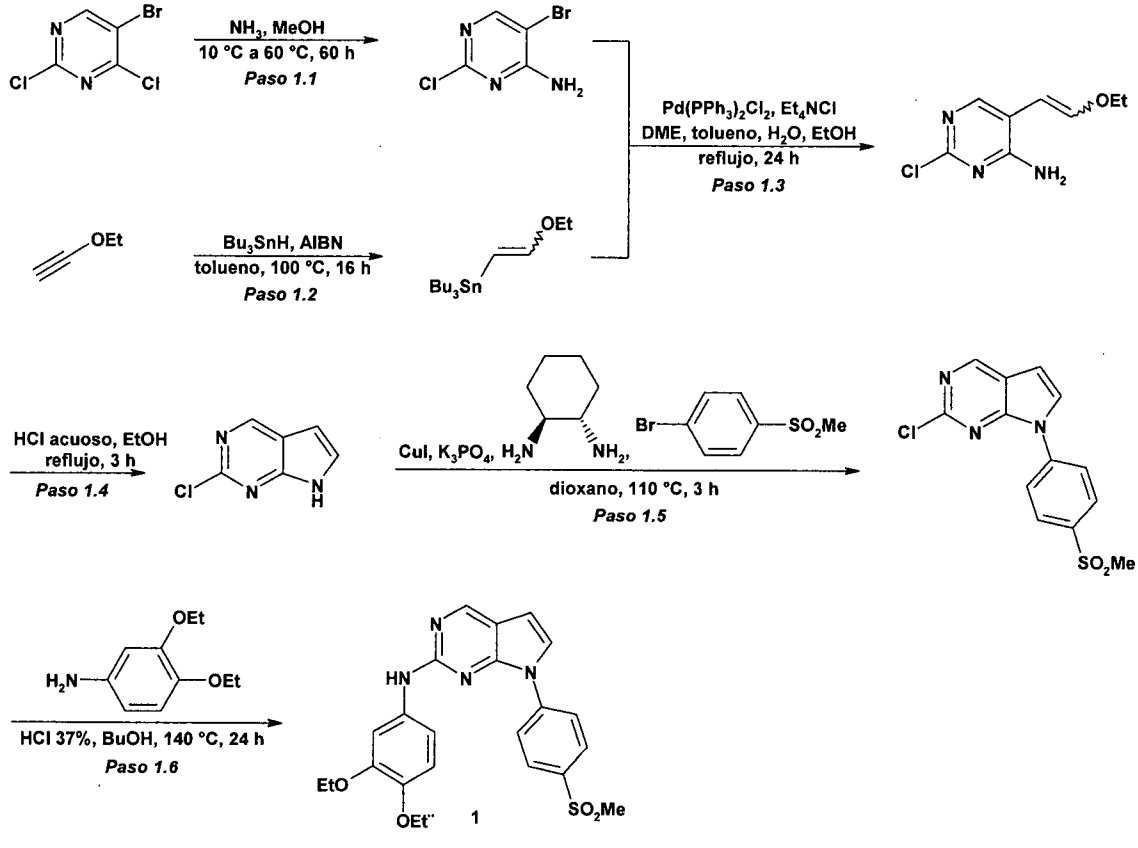
La 5-bromo-2-cloro-pirimidin-4-il-amina (88.0 gramos, 0.43 moles), 1-etoxi-propeno (220 gramos, 0.49 moles), $Pd(PPh_3)_2Cl_2$ (35.0 gramos, 0.05 moles), y $Et_4NCl$ (67.0 gramos, 0.40 moles) se suspenden en solvente (750 mililitros, DME/tolueno/$H_2O$/EtOH, 10:1:3:6) bajo nitrógeno. La mezcla de reacción se calienta a reflujo durante 24 horas, se enfría a temperatura ambiente, y entonces se diluye con agua. La capa acuosa se extrae con EtOAc (3 veces). Las

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**Ejemplo 1: (3,4-dietoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (1)**

El compuesto se prepara de acuerdo con el Esquema 1.

**Esquema 1**




Paso 1.1: 5-bromo-2-cloro-pirimidin-4-il-amina

La 2,4-dicloro-5-bromo-pirimidina (200 gramos, 0.88 moles) se agrega lentamente a $NH_3$ (1000 mililitros, 7 M en MeOH) mientras que la mezcla de reacción se mantiene debajo de 10°C. La mezcla de reacción se agita a temperatura ambiente durante 2 horas, se calienta hasta 60°C durante 2 horas, y entonces se enfría

NaOH, seguida por un procesamiento acuoso con dicloro-metano / bicarbonato. El material resultante se purifica mediante cromatografía en columna sobre sílice, y entonces se protege con Boc, con el anhídrido de Boc en dicloro-metano a temperatura ambiente.

El compuesto intermediario (B) se obtiene a partir de la reducción de la (S)-5-fenil-morfolin-3-ona (C) con hidruro de litio y aluminio en tetrahidrofurano a temperatura ambiente. El compuesto derivado de morfolina (C) se obtiene a partir del cierre de anillo de la 2-cloro-N-((S)-2-hidroxi-1-fenil-etil)-acetamida (D) en la presencia de hidruro de sodio en tetrahidrofurano / tolueno, 1:1, desde 0°C hasta la temperatura ambiente. El compuesto intermediario (D) resulta a partir de la adición lenta del cloruro de cloro-acetilo (F) disuelto en dicloro-metano hasta el (S)-2-amino-2-fenil-etanol (E) en tetrahidrofurano en la presencia de $Et_3N$ a 0°C a temperatura ambiente.

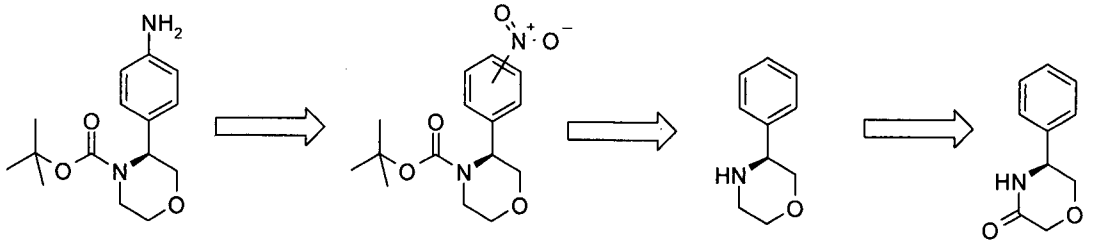
Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

terbutil-éster del ácido 2-(4-amino-fenil)-morfolin-4-carboxílico (racémico)

terbutil-éster del ácido (S)-3-(3-amino-fenil)-morfolin-4-carboxílico

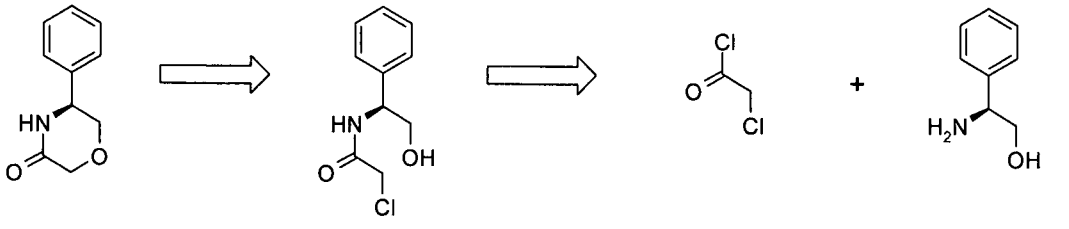
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Procedimiento General **XI** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para el terbutil-éster del ácido (S)-3-(4-amino-fenil)-morfolin-4-carboxílico):



Terbutil-éster del ácido (S)-3-(4-amino-fenil)-morfolin-4-carboxílico

(A) (B) (C)



(C) (D) (F) (E)

El compuesto mostrado a la izquierda anteriormente, el terbutil-éster del ácido (S)-3-(4-amino-fenil)-morfolin-4-carboxílico, se obtiene a partir de la hidrogenación del Intermediario (A) con hidrato de hidrazina en etanol, en la presencia de Níquel de Raney, bajo una atmósfera de argón a temperatura ambiente, seguida por la separación de los regioisómeros de $NO_2$. Para obtener el compuesto intermediario (A) (mezcla de regioisómeros), se gotea lentamente una solución de la (S)-3-fenil-morfolina (B) en dicloro-metano en ácido nítrico en vaporización en dicloro-metano a -45°C. Después de 1 hora, la reacción se apaga lentamente con una solución acuosa de

temperatura ambiente en la presencia de di-isopropil-etil-amina. El compuesto intermediario (B) se obtiene a partir de la reacción de la N-(2-hidroxi-metil-piridin-4-il)-acetamida (D) con cloruro de metan-sulfonilo en la presencia de $Et_3N$ en dicloro-metano (o con $SOCl_2$ en 1,2-dicloro-etano con una pequeña cantidad de dimetil-formamida para el análogo de cloruro del (B)). El intermediario (D) se obtiene a partir del tratamiento del (4-cloro-piridin-2-il)-metanol con acetamida en la presencia de $Pd(OAc)_2$, 4,5-bis-difenil-fosfanil-9,9-dimetil-9H-xanteno, y carbonato de cesio en dioxano y dimetil-formamida a 130°C en el horno de microondas durante 1 hora.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

2-(cis-3,5-dimetil-piperazin-1-il-metil)-piridin-4-il-amina

2-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-piridin-4-il-amina

4-(4-amino-piridin-2-il-metil)-1-metil-piperazin-2-ona

2-(3,3-difluoro-pirrolidin-1-il-metil)-piridin-4-il-amina

2-(4-ciclopropil-piperazin-1-il-metil)-piridin-4-il-amina

2-(3-trifluoro-metil-piperazin-1-il-metil)-piridin-4-il-amina (racémica)

terbutil-éster del ácido 4-(4-amino-piridin-2-il-metil)-3-oxo-piperazin-1-carboxílico

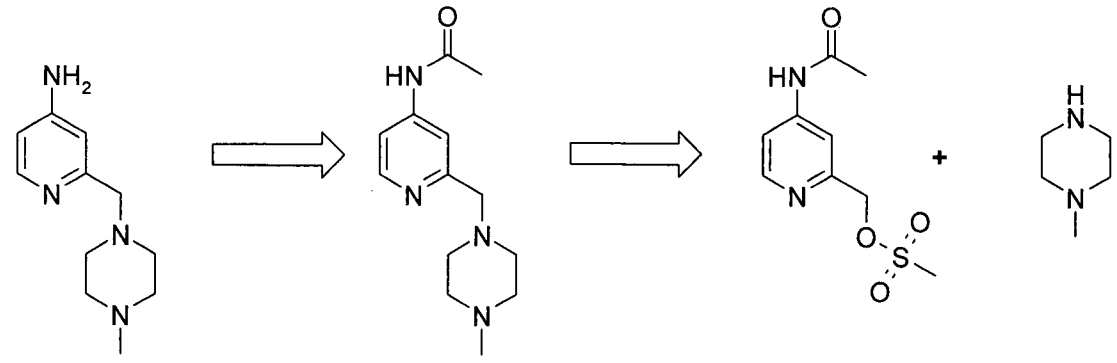
1-(4-amino-piridin-2-il-metil)-pirrolidin-3-ol

2-(3-metoxi-pirrolidin-1-il-metil)-piridin-4-il-amina

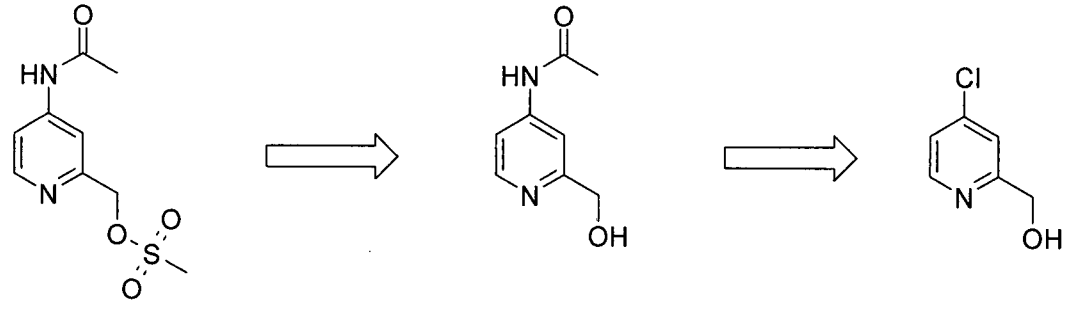
2-(3-dimetil-amino-pirrolidin-1-il-metil)-piridin-4-il-amina

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Procedimiento General **X** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la 2-(4-metil-piperazin-1-il-metil)-piridin-4-il-amina):



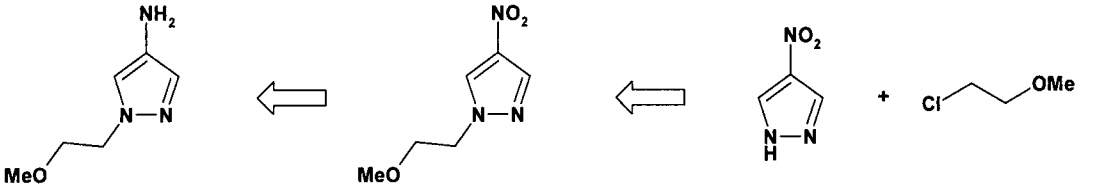
2-(4-Metil-piperazin-1-ilmetil)-piridin-4-ilamina (A) (B) (C)



(B) (D) (E)

El compuesto mostrado a la izquierda anteriormente, 2-(4-metil-piperazin-1-il-metil)-piridin-4-il-amina), se obtiene mediante el tratamiento del Intermediario (A), N-[2-(4-metil-piperazin-1-il-metil)-piridin-4-il]-acetamida, con KOH en EtOH / agua, 2:1, a 100°C durante 4 horas. El compuesto intermediario (A) se obtiene mediante la reacción de la N-metil-piperazina (C) con el 4-acetil-amino-piridin-2-il-metil-éster del ácido metan-sulfónico (B) en dicloro-metano a

Procedimiento General **IX** para la síntesis de bloques de construcción de amino-pirazol (en la siguiente fórmula se ejemplifican para la 1-(2-metoxi-etil)-1H-pirazol-4-il-amina):




1-(2-metoxi-etil)-1H-pirazol-4-ilamina (A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, 1-(2-metoxi-etil)-1H-pirazol-4-il-amina, se obtiene mediante el tratamiento del Intermediario (A), 1-(2-metoxi-etil)-4-nitro-1H-pirazol, con formato de amonio y Pd/C en metanol a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante la alquilación del 4-nitro-1H-pirazol (B) con el 1-cloro-2-metoxi-etano (C) en la presencia de NaH en N,N-dimetil-formamida a 95°C.

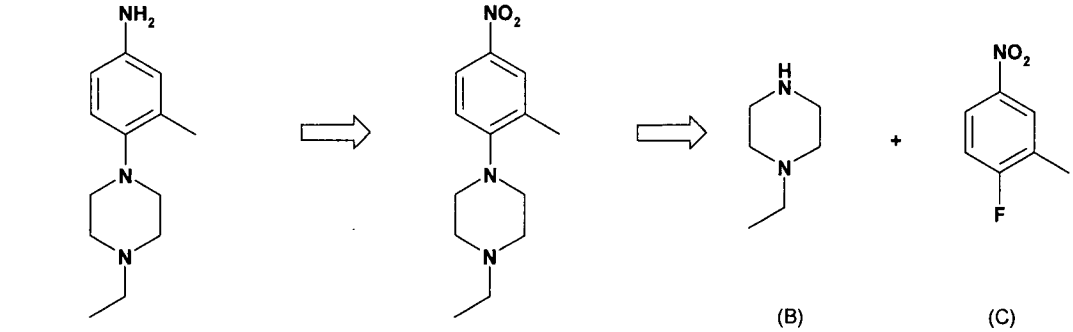
El siguiente amino-pirazol utilizado en los Ejemplos que se encuentran más adelante, se sintetiza de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

terbutil-éster del ácido 4-(4-amino-pirazol-1-il)-piperidin-1-carboxílico

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5-(4-metil-piperazin-1-il)-piridin-2-il-amina

Procedimiento General **VIII** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la 4-(4-etil-piperazin-1-il)-3-metil-fenil-amina):




4-(4-Etil-piperazin-1-il)-3-metil -fenilamina

El compuesto mostrado a la izquierda anteriormente, 4-(4-etil-piperazin-1-il)-3-metil-fenil-amina, se obtiene mediante el tratamiento del Intermediario (A), 1-etil-4-(2-metil-4-nitro-fenil)-piperazina, con $H_2$ (o formato de amonio) y Pd/C en metanol (y tetrahidrofurano) a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante la reacción de la N-etil-piperazina (B) con el 1-fluoro-2-metil-4-nitro-benceno (C) en dimetil-acetamida (DMA) a 110°C durante 20 horas.

piperazin-1-carboxílico

6-(cis-3,5-dimetil-piperazin-1-il)-5-trifluoro-metil-piridin-3-il-amina

6-(cis-3,5-dimetil-piperazin-1-il)-5-metoxi-piridin-3-il-amina

4-(4-amino-piridin-2-il)-piperazin-2-ona

terbutil-éster del ácido 4-(5-amino-3-cloro-piridin-2-il)-piperazin-1-carboxílico

1-(4-amino-piridin-2-il)-3,3-dimetil-piperazin-2-ona

4-(4-amino-piridin-2-il)-1-metil-piperazin-2-ona

6-(6,6-difluoro-[1,4]-diazepan-1-il)-5-metil-piridin-3-il-amina (B obtenida de la Publicación Internacional Número WO2003 042172, página 51)

6-(2-morfolin-4-il-etoxi)-piridin-3-il-amina

terbutil-éster del ácido 3-(5-amino-piridin-2-iloxi)-azetidin-1-carboxílico

6-(tetrahidro-piran-4-iloxi)-piridin-3-il-amina

6-(2-metoxi-etoxi)-piridin-3-il-amina

6-(tetrahidro-piran-4-il-metoxi)-piridin-3-il-amina

6-[2-(terbutil-difenil-silaniloxi)-etoxi]-piridin-3-il-amina

terbutil-éster del ácido 3-(5-amino-piridin-2-iloxi)-pirrolidin-1-carboxílico

6-[3-(terbutil-difenil-silaniloxi)-pirrolidin-1-il]-piridin-3-il-amina

2-(tetrahidro-piran-4-iloxi)-piridin-4-il-amina

2-(2-morfolin-4-il-etoxi)-piridin-4-il-amina

2-(3-trifluoro-metil-piperazin-1-il)-piridin-4-il-amina (racémica)

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(racémica)

6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il-amina

2-[4-(5-amino-piridin-2-il)-piperazin-1-il]-etanol

2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il-amina

2-(4-metil-piperazin-1-il)-pirimidin-5-il-amina

6-isopropoxi-piridin-3-il-amina

terbutil-éster del ácido 4-(4-amino-piridin-2-iloxi-metil)-piperidin-1-carboxílico

6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il-amina

5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amina

2-(4-ciclopropil-piperazin-1-il)-piridin-4-il-amina

6-(4-ciclopropil-piperazin-1-il)-piridin-3-il-amina

6-[4-(2-dimetil-amino-etil)-piperazin-1-il]-piridin-3-il-amina

6-(3-trifluoro-metil-piperazin-1-il)-piridin-3-il-amina (racémica)

terbutil-éster del ácido 4-(5-amino-piridin-2-il)-3-oxo-piperazin-1-carboxílico

terbutil-éster del ácido 4-(5-amino-3-metil-piridin-2-il)-piperazin-1-carboxílico

6-(3,3-dimetil-piperazin-1-il)-5-metil-piridin-3-il-amina

5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amina

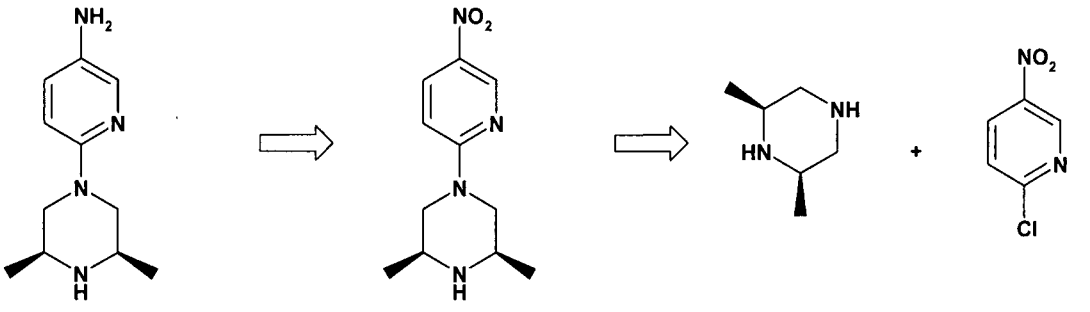
5-amino-2-(cis-3,5-dimetil-piperazin-1-il)-nicotinonitrilo

4-(5-amino-3-cloro-piridin-2-il)-piperazin-2-ona

1-(5-amino-piridin-2-il)-3,3-dimetil-piperazin-2-ona

1-(5-amino-3-metil-piridin-2-il)-3,3-dimetil-piperazin-2-ona

terbutil-éster del ácido 4-(5-amino-3-metil-piridin-2-il)-3-oxo-




6-(cis-3,5-Dimetil-piperazin-1-il) -piridin-3-ilamina (A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, 6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amina, se obtiene mediante el tratamiento del Intermediario (A), cis-3,5-dimetil-1-(5-nitro-piridin-2-il)-piperazina, con $H_2$ (o formato de amonio) y Pd/C (o Níquel de Raney) en metanol (y tetrahidrofurano) a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante la reacción de la cis-2,6-dimetil-piperazina (B) con la 2-cloro-5-nitro-piridina (C) en la presencia de $Et_3N$ en tetrahidrofurano desde la temperatura ambiente hasta 70°C.

De una manera alternativa, en el caso de que el (B) sea un alcohol, 2-bromo-5-nitro-piridina, o 1-óxido de 2-cloro-4-nitro-piridina para algunos de los derivados *meta*-sustituidos, se utiliza como el (C) en la presencia de KOtBu o $Cs_2CO_3$, o NaH en dimetil-acetamida o tetrahidrofurano desde la temperatura ambiente hasta 80°C.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amina

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amina

4-metil-3-(4-metil-pirazol-1-il-metil)-fenil-amina

2-[1-(5-amino-2-metil-bencil)-1H-pirazol-4-il]-etanol

De una manera alternativa, el (A) se obtiene mediante la reacción del 2-bromo-metil-1-metil-4-nitro-benceno (C) con azida de sodio en etanol / agua, 1:2, a temperatura ambiente durante la noche, seguida por la formación de triazol con dimetil-prop-2-inil-amina en terbutanol / agua, 1:1, en la presencia de sulfato de cobre (I) (0.15 equivalentes) y L-(+)-ascorbato de sodio (0.3 equivalentes).

3-(4-dimetil-amino-metil-[1,2,3]-triazol-1-il-metil)-4-metil-fenil-amina

[1-(5-amino-2-metil-bencil)-1H-[1,2,3]-triazol-4-il]-metanol

De una manera alternativa, el (B) se obtiene a partir de la reacción del terbutil-éster del ácido 3-oxo-piperazin-1-carboxílico activado con hidruro de sodio y con (2-bromo-etil)-dimetil-amina en N,N-dimetil-formamida. El material resultante se desprotege entonces del Boc en dioxano con HCl para dar el (B) como la sal de HCl.

4-(5-amino-2-metil-bencil)-1-(2-dimetil-amino-etil)-piperazin-2-ona

Procedimiento General **VII** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la 6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amina):

4-metil-3-pirazol-1-il-metil-fenil-amina

4-metil-3-[1,2,4]-triazol-4-il-metil-fenil-amina

3-(3-metoxi-pirrolidin-1-il-metil)-4-metil-fenil-amina

terbutil-éster del ácido 3-(5-amino-2-metil-benciloxi)-azetidin-1-carboxílico

[1-(5-amino-2-metil-bencil)-pirrolidin-3-il]-dimetil-amina

3-(7-Aza-biciclo-[2.2.1]-hept-7-il-metil)-4-metil-fenil-amina

terbutil-éster del ácido 4-(4-amino-2-metil-bencil)-piperazin-1-carboxílico

4-(cis-3,5-dimetil-piperazin-1-il-metil)-3-metil-fenil-amina

4-(3,3-difluoro-pirrolidin-1-il-metil)-fenil-amina

6-(4-metil-piperazin-1-il-metil)-piridin-3-il-amina

4-(3,3-dimetil-piperazin-1-il-metil)-fenil-amina

4-(3-trifluoro-metil-piperazin-1-il-metil)-fenil-amina (racémica)

4-(cis-3,5-dimetil-piperazin-1-il-metil)-2-fluoro-fenil-amina

1-(4-amino-bencil)-azetidin-3-ol

6-morfolin-4-il-metil-piridin-3-il-amina

6-piperazin-1-il-metil-piridin-3-il-amina

4-cloro-3-(4-metil-piperazin-1-il-metil)-fenil-amina

terbutil-éster del ácido 4-(4-amino-bencil)-3-oxo-piperazin-1-carboxílico

4-(5-amino-piridin-2-il-metil)-1-metil-piperazin-2-ona

4-(3-metoxi-pirrolidin-1-il-metil)-fenil-amina

1-(5-amino-piridin-2-il-metil)-pirrolidin-3-ol (racémico)

4-metil-3-(7-metil-2,7-diaza-espiro-[4.4]-non-2-il-metil)-fenil-

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3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amina

3-(2,5-Dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-4-metil-fenil-amina

3-(4-ciclopropil-piperazin-1-il-metil)-4-metil-fenil-amina

terbutil-éster del ácido 4-(4-amino-piridin-2-il-metil)-piperazin-1-carboxílico

3-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-4-metil-fenil-amina

3-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amina (racémica)

3-(3,3-dimetil-piperazin-1-il-metil)-4-metil-fenil-amina

3-(3,3-difluoro-pirrolidin-1-il-metil)-4-metil-fenil-amina

1-(5-amino-2-metil-bencil)-azetidin-3-ol

4-(5-amino-2-metil-bencil)-1-metil-piperazin-2-ona

3-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-4-metil-fenil-amina

terbutil-éster del ácido 4-(5-amino-2-metil-bencil)-3-oxo-piperazin-1-carboxílico

1-(5-amino-2-cloro-bencil)-azetidin-3-ol

terbutil-éster del ácido 4-(5-amino-2-cloro-bencil)-piperazin-1-carboxílico

4-metil-3-(3-trifluoro-metil-piperazin-1-il-metil)-fenil-amina (racémica)

3-(3-metoxi-azetidin-1-il-metil)-4-metil-fenil-amina

1-(5-amino-2-metil-bencil)-pirrolidin-3-ol

3-imidazol-1-il-metil-4-metil-fenil-amina

ambiente.

Cuando sea necesario, el bromuro de bencilo (sustituido) (C) se sintetiza a partir del ácido carboxílico correspondiente (D) mediante reducción hasta el alcohol y la conversión hasta el compuesto de halógeno.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

4-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-fenil-amina (racémica)

4-(4-amino-bencil)-piperazin-2-ona

4-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-fenil-amina

terbutil-éster del ácido 4-(4-amino-bencil)-piperazin-1-carboxílico

1-[4-(4-amino-bencil)-piperazin-1-il]-etanona

4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amina

4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amina

4-metil-3-morfolin-4-il-metil-fenil-amina

5-(4-etil-piperazin-1-il-metil)-piridin-2-il-amina

4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amina

terbutil-éster del ácido 4-(5-amino-2-metil-bencil)-piperazin-1-carboxílico

4-(5-amino-2-metil-bencil)-piperazin-2-ona

4-(4-amino-bencil)-1-metil-piperazin-2-ona

4-(4-metil-piperazin-1-il-metil)-fenil-amina

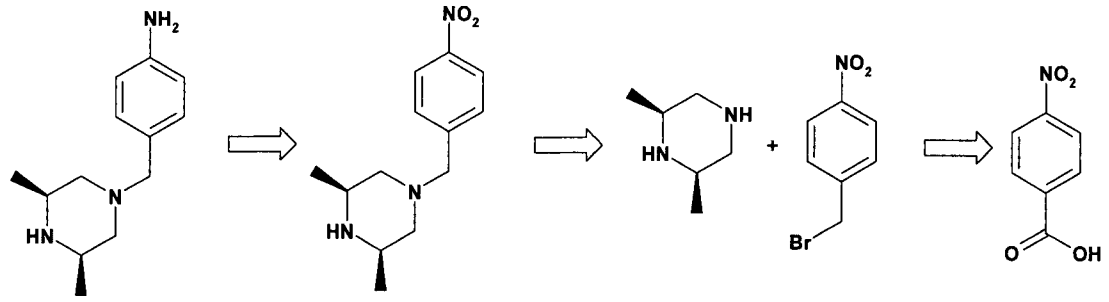
4-(2-dietil-amino-etoxi)-fenil-amina

4-(2-morfolin-4-il-etoxi)-fenil-amina

4-(2-pirrolidin-1-il-etoxi)-fenil-amina

3,5-dimetil-4-(2-morfolin-4-il-etoxi)-fenil-amina

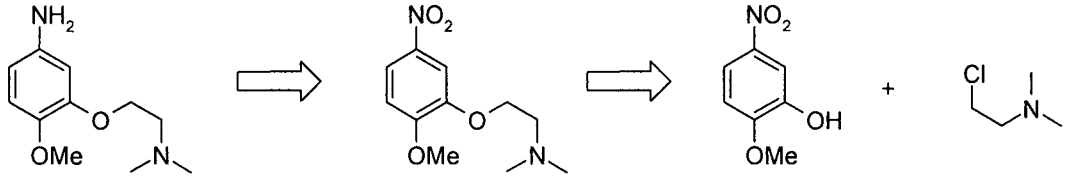
Procedimiento General **VI** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la 4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amina):




4-(cis-3,5-Dimetil-piperazin-1-ilmetil)-fenilamina (A) (B) (C) (D)

El compuesto mostrado a la izquierda anteriormente, 4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amina, se obtiene mediante el tratamiento del Intermediario (A), cis-3,5-dimetil-1-(4-nitro-bencil)-piperazina, con hidrato de $SnCl_2$ en metanol, a temperatura ambiente. De una manera alternativa, la reducción del grupo nitro se puede lograr con Pd/C o Níquel de Raney y $H_2$ o $NH_4CO_2H$ en metanol a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante la reacción de la cis-2,6-dimetil-piperazina (B) con 1-bromo-metil-4-nitro-benceno (C) en la presencia de $Et_3N$ o di-isopropil-etil-amina en N,N-dimetil-formamida a temperatura

Procedimiento General **V** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la 3-(2-dimetil-amino-etoxi)-4-metoxi-fenil-amina):




3-(2-Dimetilamino-etoxi)-4-methxi-fenilamina (A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, 3-(2-dimetil-amino-etoxi)-4-metoxi-fenil-amina, se obtiene mediante el tratamiento del Intermediario (A), [2-(2-metoxi-5-nitro-fenoxi)-etil]-dimetil-amina, con Pd/C y $NH_4CO_2H$ en metanol/tetrahidrofurano a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante la alquilación del 2-metoxi-5-nitro-fenol (B) con la (2-cloro-etil)-dimetil-amina (C) en la presencia de NaH en N,N-dimetil-formamida a 150°C.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

3-(3-dimetil-amino-propoxi)-4-metoxi-fenil-amina

4-metoxi-3-(2-pirrolidin-1-il-etoxi)-fenil-amina

4-metoxi-3-(2-morfolin-4-il-etoxi)-fenil-amina

3-(2-morfolin-4-il-etoxi)-fenil-amina

3-[2-(4-metil-piperazin-1-il)-etoxi]-fenil-amina

3-(2-dietil-amino-etoxi)-fenil-amina

de hexafluorofosfato de 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-tetrametil-uronio y N-metil-morfolina en dicloro-metano a temperatura ambiente. El Intermediario (A) se obtiene en un buen rendimiento.

El uso del grupo protector de Boc no es necesario para la preparación de ciertos bloques de construcción de anilina.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

4-amino-N-(2-dimetil-amino-etil)-N-metil-benzamida

4-amino-N-(2-dimetil-amino-etil)-benzamida

4-amino-N-(2-hidroxi-etil)-benzamida

(5-amino-piridin-2-il)-morfolin-4-il-metanona

(3-amino-fenil)-morfolin-4-il-metanona

(3-amino-fenil)-(4-metil-piperazin-1-il)-metanona

3-amino-N-(2-dimetil-amino-etil)-benzamida

2-(3-amino-fenil)-1-(4-metil-piperazin-1-il)-etanona

2-(3-amino-fenil)-1-(4-etil-piperazin-1-il)-etanona

(4-amino-fenil)-(4-etil-piperazin-1-il)-metanona

(5-amino-piridin-3-il)-morfolin-4-il-metanona

(3-amino-fenil)-(cis-3,5-dimetil-piperazin-1-il)-metanona

(3-amino-fenil)-(4-ciclopropil-piperazin-1-il)-metanona

(5-amino-piridin-2-il)-(4-metil-piperazin-1-il)-metanona

(4-amino-piridin-2-il)-(4-metil-piperazin-1-il)-metanona

(4-amino-piridin-2-il)-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il)-metanona

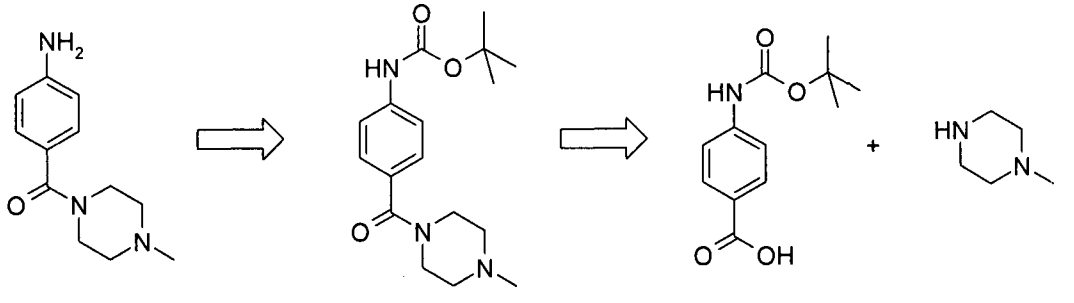
4-amino-piridin-2-il)-(cis-3,5-dimetil-piperazin-1-il)-metanona

terbutil-éster del ácido 4-(4-amino-piridin-2-carbonil)-piperazin-1-carboxílico

(5-amino-2-metil-fenil)-(4-metil-piperazin-1-il)-metanona

(5-amino-2-metil-fenil)-(cis-3,5-dimetil-piperazin-1-il)-metanona

Procedimiento General **IV** para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la (4-amino-fenil)-(4-metil-piperazin-1-il)-metanona):




(4-Amino-fenil)-(4-metil-piperazin-1-il)-metanona (A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, (4-amino-fenil)-(4-metil-piperazin-1-il)-metanona, se obtiene mediante el tratamiento del Intermediario (A), terbutil-éster del ácido [4-(4-metil-piperazin-1-carbonil)-fenil]-carbámico, con ácido trifluoro-acético en dicloro-metano a temperatura ambiente. El compuesto intermediario (A) se obtiene mediante el acoplamiento del ácido 4-terbutoxi-carbonil-amino-benzoico (B) y N-metil-piperazina (C) en la presencia

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con cloruro de tionilo o cloruro de oxalilo en dicloro-metano o dicloro-etano.

De una manera alternativa, se puede lograr la formación del enlace de amida mediante el acoplamiento derivado del ácido carboxílico apropiado (B) y la amina apropiada, en la presencia de TBTU y $Et_3N$ en tetrahidrofurano a 0°C a temperatura ambiente.

Las siguientes anilinas utilizadas en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados correspondientes:

4-amino-N-(1-metil-piperidin-4-il)-benzamida

(4-amino-fenil)-(4-dimetil-amino-piperidin-1-il)-metanona

4-amino-N-(2-morfolin-4-il-etil)-benzamida

4-amino-N-(1-etil-pirrolidin-2-il-metil)-benzamida

(4-amino-2-fluoro-fenil)-(4-metil-piperazin-1-il)-metanona

(4-amino-2-cloro-fenil)-(4-metil-piperazin-1-il)-metanona

(4-amino-2-metil-fenil)-(4-metil-piperazin-1-il)-metanona

(4-amino-2-trifluoro-metil-fenil)-(4-metil-piperazin-1-il)-metanona

(4-amino-2-metil-fenil)-morfolin-4-il-metanona

(4-amino-2-metil-fenil)-pirrolidin-1-il-metanona

(5-amino-2-fluoro-fenil)-(4-metil-piperazin-1-il)-metanona

(5-amino-2-fluoro-fenil)-morfolin-4-il-metanona

5-amino-N-(1-etil-pirrolidin-2-il-metil)-2-fluoro-benzamida

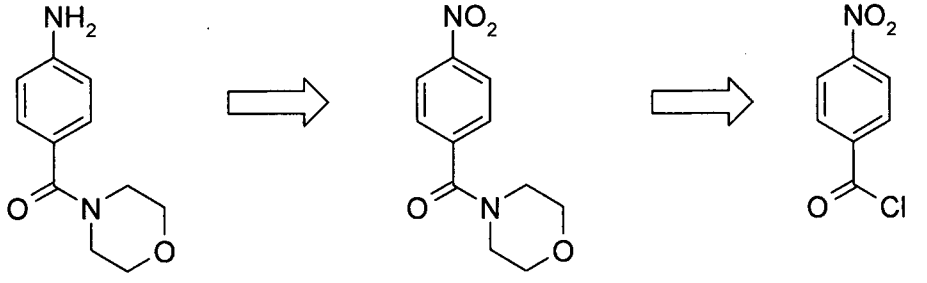
terbutil-éster del ácido 4-(4-amino-benzoil)-piperazin-1-carboxílico

1-(4-bromo-2,6-difluoro-bencil)-pirrolidin-2-ona

1-(4-bromo-2,6-difluoro-bencil)-3-metoxi-azetidina

4-(4-bromo-2,6-difluoro-bencil)-morfolin-3-ona

Procedimiento General III para la síntesis de bloques de construcción de anilina (en la siguiente fórmula se ejemplifican para la (4-amino-fenil)-morfolin-4-il-metanona):



(4-Amino-fenil)-morfolin-4-il-metanona (A) (B)

El compuesto mostrado a la izquierda anteriormente, (4-amino-fenil)-morfolin-4-il-metanona, se obtiene mediante la hidrogenación del compuesto de nitro correspondiente (A), la morfolin-4-il-(4-nitro-fenil)-metanona, con Pd/C o Níquel de Raney y $H_2$ o $NH_4CO_2H$ en metanol a temperatura ambiente. De una manera alternativa, la reducción del grupo nitro se puede lograr con $SnCl_2$ en EtOH a 90°C. El compuesto intermediario de nitro (A) se obtiene mediante la reacción del cloruro de 4-nitro-benzoílo (B) y morfolina, y $Et_3N$ en dicloro-metano, a temperatura ambiente. El Intermediario (A) se obtiene en un buen rendimiento. Cuando sean necesarios, se obtienen los análogos del (B) a partir de los derivados de ácido carboxílico correspondientes calentados a reflujo durante 2 horas

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utilizando los materiales de partida apropiados correspondientes:

4-(4-bromo-2-fluoro-bencil)-morfolina

4-(4-bromo-2-cloro-bencil)-morfolina

4-(4-bromo-2-metil-bencil)-morfolina

4-(4-bromo-2,6-difluoro-bencil)-morfolina

4-[1-(4-bromo-fenil)-etil]-morfolina

4-(6-bromo-piridin-3-il-metil)-morfolina

4-(5-bromo-piridin-2-il-metil)-morfolina

4-[2-(4-bromo-fenil)-etil]-morfolina

1-(4-bromo-2-fluoro-bencil)-4-etil-piperazina

1-(4-bromo-2,6-difluoro-bencil)-4-etil-piperazina

4-(4-bromo-2,6-difluoro-bencil)-1-etil-piperazin-2-ona

1-[4-(4-bromo-2,6-difluoro-bencil)-piperazin-1-il]-etanona

1,1-dióxido de 4-(4-bromo-2,6-difluoro-bencil)-tiomorfolina

1,1-dióxido de 4-(4-bromo-2-fluoro-bencil)-tiomorfolina

1,1-dióxido de 4-(4-bromo-2-cloro-bencil)-tiomorfolina

1-(4-bromo-2,6-difluoro-bencil)-4-metil-piperazina

1-(4-bromo-2,6-difluoro-bencil)-4-isopropil-piperazina

1-(4-bromo-2,6-difluoro-bencil)-4-ciclopropil-piperazina

4-(4-bromo-2,6-difluoro-bencil)-3,3-dimetil-morfolina

4-(4-bromo-2,6-difluoro-bencil)-1-metil-piperazin-2-ona

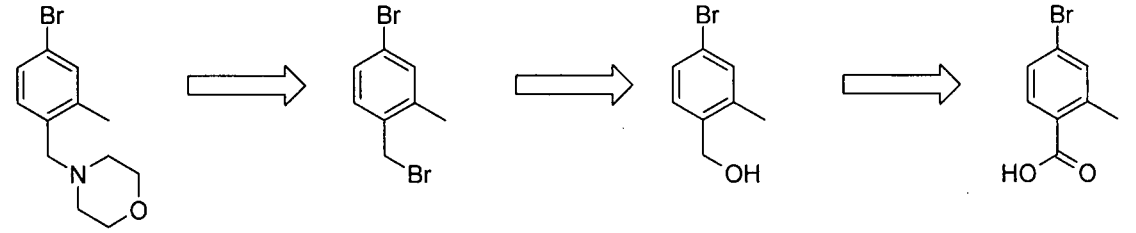
4-(4-bromo-2,6-difluoro-bencil)-piperazin-2-ona

8-(4-bromo-2,6-difluoro-bencil)-2,5-dioxa-8-aza-espiro-[3.5]-nonano

4-(4-bromo-2,6-difluoro-bencil)-cis-2,6-dimetil-morfolina

(4-bromo-3-fluoro-fenil)-morfolin-4-il-metanona

Procedimiento General **II** para la síntesis de bloques de construcción de bromuro de arilo (en la siguiente fórmula se ejemplifican para la 4-(4-bromo-2-metil-bencil)-morfolina):




4-(4-Bromo-2-metil-bencil)-morfolina (A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, 4-(4-bromo-2-metil-bencil)-morfolina, se obtiene mediante la reacción del bromuro de bencilo correspondiente (A), el 4-bromo-1-bromo-metil-2-metil-benceno, con morfolina en N,N-dimetil-formamida a temperatura ambiente. El producto se obtiene en un alto rendimiento. El Intermediario de bromuro de bencilo (A) se obtiene mediante la reacción del (4-bromo-2-metil-fenil)-metanol (B) con $PPh_3$ y $CBr_4$ en dicloro-metano a temperatura ambiente. El Intermediario (A) se obtiene en un alto rendimiento. El Intermediario de alcohol bencílico B se obtiene mediante la reducción del ácido carboxílico correspondiente (C), el ácido 4-bromo-2-metil-benzoico, con hidruro de litio y aluminio en tetrahidrofurano. El Intermediario (B) se obtiene en un buen rendimiento.

Los siguientes bromuros de arilo utilizados en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga,

(4-bromo-fenil)-(1,1-dióxido-tiomorfolin-4-il)-metanona

(5-bromo-piridin-2-il)-(1,1-dióxido-tiomorfolin-4-il)-metanona

(6-bromo-piridin-3-il)-(1,1-dióxido-tiomorfolin-4-il)-metanona

(4-bromo-2,6-difluoro-fenil)-(1,1-dióxido-tiomorfolin-4-il)-metanona

(4-bromo-2,6-difluoro-fenil)-morfolin-4-il-metanona

(4-bromo-2,6-difluoro-fenil)-(4-metil-piperazin-1-il)-metanona

(4-bromo-2-cloro-fenil)-morfolin-4-il-metanona

(4-bromo-2-metil-fenil)-morfolin-4-il-metanona

(4-bromo-3-fluoro-fenil)-morfolin-4-il-metanona

(6-bromo-piridin-3-il)-morfolin-4-il-metanona

(5-bromo-piridin-2-il)-morfolin-4-il-metanona

(3-bromo-fenil)-(4-metil-piperazin-1-il)-metanona

2-(4-bromo-fenil)-2-metil-1-morfolin-4-il-propan-1-ona

[1-(4-bromo-fenil)-ciclopropil]-morfolin-4-il-metanona

[1-(4-bromo-fenil)-ciclopropil]-(4-metil-piperazin-1-il)-metanona

(5-bromo-piridin-2-il)-morfolin-4-il-metanona

(5-bromo-piridin-2-il)-(4-metil-piperazin-1-il)-metanona

2-(4-bromo-fenil)-1-[4-(2-hidroxi-etil)-piperazin-1-il]-etanona

4-bromo-2-fluoro-N-(2-morfolin-4-il-etil)-benzamida

4-bromo-2-fluoro-N-[2-(4-metil-piperazin-1-il)-etil]-benzamida

(4-bromo-2-fluoro-fenil)-(4-dimetil-amino-piperidin-1-il)-metanona

(4-bromo-fenil)-[4-(2-hidroxi-etil)-piperazin-1-il]-metanona

(4-bromo-2-fluoro-fenil)-(1,1-dióxido-tiomorfolin-4-il)-metanona

Intermediario de cloruro de ácido (A) se obtiene mediante la reacción del ácido (4-bromo-fenil)-acético (B) y cloruro de oxalilo (C) en dicloro-metano a temperatura ambiente, y utilizando dimetil-formamida como iniciador de la reacción. El Intermediario (A) se obtiene en un buen rendimiento.

De una manera alternativa, se puede lograr la formación del enlace de amida mediante el acoplamiento del ácido carboxílico apropiado (B) y la amina apropiada, en la presencia de hexafluorofosfato de 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-tetrametil-uronio y N-metil-morfolina en N,N-dimetil-formamida a temperatura ambiente.

Los siguientes bromuros de arilo utilizados en los Ejemplos que se encuentran más adelante, se sintetizan de una manera análoga, utilizando los materiales de partida apropiados:

2-(4-bromo-fenil)-1-(4-metil-piperazin-1-il)-etanona

(4-bromo-2-fluoro-fenil)-morfolin-4-il-metanona

(4-bromo-2-fluoro-fenil)-(4-metil-piperazin-1-il)-metanona

2-(4-bromo-2-fluoro-fenil)-1-(1,1-dióxido-tiomorfolin-4-il)-etanona

[1-(4-bromo-fenil)-ciclopropil]-(4-etil-piperazin-1-il)-metanona

(4-bromo-fenil)-morfolin-4-il-metanona

(4-bromo-fenil)-(4-metil-piperazin-1-il)-metanona

(4-bromo-fenil)-pirrolidin-1-il-metanona

4-bromo-N-(2-morfolin-4-il-etil)-benzamida

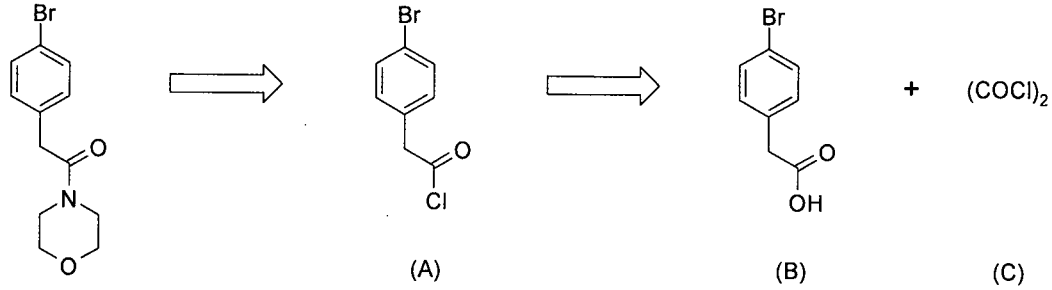
4-bromo-N-(1-etil-pirrolidin-2-il-metil)-benzamida

| | |
|---|---|
| $t_R$ | tiempo de retención |
| UV | Ultravioleta |

**Materiales de Partida:**

Varios bromuros de arilo y anilinas, como se utilizan de acuerdo con los Esquemas 1 a 3, se adquirieron en fuentes comerciales cuando fue practicable. De otra manera, los bromuros de arilo y las anilinas/amino-heterociclos se preparan de acuerdo con los Procedimientos Generales ejemplificados:

Procedimiento General I para la síntesis de bloques de construcción de bromuro de arilo (en la siguiente fórmula se ejemplifican para la 2-(4-bromo-fenil)-1-morfolin-4-il-etanona):




2-(4-Bromo-fenil)-1-morfolin-4-il-etanona

(A) (B) (C)

El compuesto mostrado a la izquierda anteriormente, 2-(4-bromo-fenil)-1-morfolin-4-il-etanona, se obtiene mediante la reacción del cloruro de ácido correspondiente (A), cloruro de (4-bromo-fenil)-acetilo, con morfolina y $Et_3N$ en dicloro-metano, a temperatura ambiente. El producto se obtiene en un alto rendimiento. El

| | |
|---|---|
| DIPEA | di-isopropil-etil-amina |
| DME | 1,2-dimetoxi-etano |
| DMF | N,N-dimetil-formamida |
| DMSO | sulfóxido de dimetilo |
| h | hora(s) |
| HATU | hexafluorofosfato de 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-tetrametil-uronio |
| HPLC | Cromatografía de líquidos de alto rendimiento |
| HV | alto vacío |
| Isolute | Isolute® HM-N por International Solvent Technology Ltd., Reino Unido. |
| LAH | hidruro de litio y aluminio |
| mL | mililitro(s) |
| min | minuto(s) |
| MS-ES | Espectrometría de masas por electropulverización |
| MW | microondas |
| $R_f$ | proporción de frentes en la TLC |
| rt | temperatura ambiente |
| TBTU | tetrafluoro borato de [(benzotriazol-1-iloxi)-dimetil-amino-metilen]-dimetil-amonio |
| TBDPS | terbutil-difenil-sililo |
| TFA | ácido trifluoro-acético |
| THF | tetrahidrofurano |
| TLC | Cromatografía de capa delgada |

300

ácido trifluoro-acético al 0.1 por ciento.

Velocidad de flujo: 1.0 mililitro/minuto.

Gradiente: Del 2 al 100 por ciento de B en 7.0 minutos, luego 2 minutos con el 100 por ciento de B.

**Método G**

Columna: Acquity UPLC BEH C18 / 2.1*50 milímetros / 1.7 micras.

Temperatura de la columna: 40°C

Eluyentes: A: $H_2O$, B: acetonitrilo, ambos conteniendo ácido trifluoro-acético al 0.1 por ciento.

Velocidad de flujo: 1.0 mililitro/minuto.

Gradiente: 0.1 minuto con el 2 por ciento de B; del 2 al 100 por ciento de B en 1.5 minutos; 0.4 minutos con el 100 por ciento de B.

**Abreviaturas**

| | |
|---|---|
| AIBN | α,α'-azo-isobutironitrilo |
| Ar | Argón |
| Bn | bencilo |
| Boc | terbutoxi-carbonilo |
| DCM | dicloro-metano |

Eluyentes: A: $H_2O$, B: acetonitrilo, ambos conteniendo ácido trifluoro-acético al 0.1 por ciento.

Velocidad de flujo: 1.0 mililitro/minuto.

Gradiente: del 20 al 100 por ciento de B en 7.0 minutos.

**Método E**

Sistema: Agilent Serie 1100 con Waters Micromass ZQ.

Columna: XBridge C18, 3 x 30 milímetros, 2.5 micras.

Eluyentes: A: $H_2O$, conteniendo acetonitrilo al 5 por ciento y HCOOH al 0.8 por ciento.
B: acetonitrilo, conteniendo HCOOH al 0.6 por ciento.

Velocidad de flujo: De 1.4 a 2.4 mililitros/minuto.

Gradiente: Del 10 al 95 por ciento de B en 2.4 minutos (E1) o del 1 al 95 por ciento de B en 2.9 minutos (E2).

**Método F**

Columna: Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD.

Temperatura de la columna: 30°C

Eluyentes: A: $H_2O$, B: acetonitrilo, ambos conteniendo

de flujo: 1 mililitro/minuto.

Gradiente: Agua (ácido trifluoro-acético al 0.1 por ciento)/acetonitrilo (ácido trifluoro-acético al 0.1 por ciento) = 98/2 durante 1 minuto hasta el 100 por ciento de acetonitrilo (ácido trifluoro-acético al 0.1 por ciento) en 10 minutos. Se queda al 100 por ciento durante 2 minutos (tiempo de ejecución total: 13 min).

**Método C**

Columna: Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD.

Temperatura de la columna: 30°C

Eluyentes: A: $H_2O$, B: acetonitrilo, ambos conteniendo ácido trifluoro-acético al 0.1 por ciento.

Velocidad de flujo: 1.0 mililitro/minuto.

Gradiente: Del 2 al 100 por ciento de B en 7.0 minutos.

**Método D**

Columna: Macherey-Nagel CC125/4 Nucleosil 100-3 C18 HD.

Temperatura de la columna: 30°C

metileno

‡ 50 por ciento de hexano / 50 por ciento de acetato de etilo

† 66 por ciento de hexano / 33 por ciento de acetato de etilo

Si no se indica de otra manera, las condiciones de HPLC analítica son como sigue:

**Método A**

| | |
|---|---|
| Columna: | SunFire C18 20 x 4.6 milímetros, 3.5 micras. |
| Temperatura de la columna: | 40°C |
| Eluyentes: | A: $H_2O$, B: acetonitrilo, ambos conteniendo ácido trifluoro-acético al 0.1 por ciento. |
| Velocidad de flujo: | 3.0 mililitros/minuto. |
| Gradiente | Del 5 al 100 por ciento de B en 4.0 minutos. |

**Método B**

| | |
|---|---|
| Columna: | Column Engineering, Inc., Matrix, C18, 3 micras, 150 x 4.6 milímetros (Lote # 205). Detección mediante absorción ultravioleta a 215 y 254 nanómetros. |
| Temperatura de la columna: | 35°C |
| Eluyentes: | A: $H_2O$, B: acetonitrilo, ambos conteniendo ácido trifluoro-acético al 0.1 por ciento. |
| Velocidad | |

técnica, y/o están comercialmente disponibles. Los materiales de partida novedosos, así como los procesos para su preparación, de la misma manera son una modalidad de la presente invención. En las modalidades preferidas, se utilizan los materiales de partida y se selecciona la reacción, de tal manera que se haga posible la obtención de los compuestos preferidos.

En los materiales de partida (incluyendo los intermediarios), los cuales también se pueden utilizar y/u obtener como sales cuando sea apropiado y conveniente, los sustituyentes son de preferencia como se definen para un compuesto de la fórmula I.

Los siguientes ejemplos ilustran la invención sin limitar su alcance.

Las temperaturas se miden en grados Celsius. A menos que se indique de otra manera, las reacciones tienen lugar a temperatura ambiente.

Los valores $R_f$ en la TLC indican la proporción de la distancia movida por cada sustancia a la distancia movida por el frente de eluyente. Los valores $R_f$ para la TLC se miden en placas de TLC de 5 x 10 centímetros, gel de sílice $F_{254}$, Merck, Darmstadt, Alemania; los sistemas de solventes están marcados en los Ejemplos como sigue:

* 10 por ciento de metanol / 90 por ciento de cloruro de metileno ($CH_2Cl_2$)

** 5 por ciento de metanol / 95 por ciento de cloruro de metileno

*** 2 por ciento de metanol / 98 por ciento de cloruro de

alcalinos, o hidróxidos de metales alcalinos, típicamente carbonato de potasio o hidróxido de sodio.

Las mezclas estereoisoméricas, por ejemplo las mezclas de diaestereómeros, se pueden separar en sus isómeros correspondientes de una manera conocida por sí misma, por medio de métodos de separación adecuados. Por ejemplo, las mezclas diaestereoméricas se pueden separar en sus diaestereómeros individuales por medio de cristalización fraccionaria, cromatografía, distribución de solvente, y procedimientos similares. Esta separación puede tener lugar ya sea al nivel de un compuesto de partida, o bien en un compuesto de la fórmula I mismo. Los enantiómeros se pueden separar a través de la formación de sales diaestereoméricas, por ejemplo mediante formación de sal con un ácido quiral puro en enantiómeros, o por medio de cromatografía, por ejemplo mediante HPLC, utilizando sustratos cromatográficos con ligandos quirales.

Se debe enfatizar que también pueden tener lugar reacciones análogas a las conversiones mencionadas en este capítulo al nivel de los Intermediarios apropiados (y por lo tanto, son útiles en la preparación de los materiales de partida correspondientes).

**Materiales de Partida:**

Los materiales de partida de las fórmulas II, III y IV, así como otros materiales de partida mencionados en la presente, por ejemplo, más adelante, se pueden preparar de acuerdo con, o en analogía a, los métodos que son conocidos en la materia, se conocen en la

apropiado, tal como cloruro de metileno, por ejemplo, a temperaturas en el intervalo de -20°C a 50°C, por ejemplo, a aproximadamente la temperatura ambiente, convirtiendo de esta manera uno (en especial en la posición *para*) de los grupos amino vicinales en un grupo formil-amino. En un segundo paso, los grupos amino y formil-amino se hacen reaccionar entonces para obtener –N=C-N- mediante calentamiento en la presencia de un ácido, en especial ácido acético, por ejemplo, a temperaturas en el intervalo de 50°C a 110°C, por ejemplo a aproximadamente 100°C.

Las sales de un compuesto de la fórmula I con un grupo formador de sal, se pueden preparar de una manera conocida por sí misma. De esta manera, se pueden obtener sales de adición de ácido de los compuestos de la fórmula I mediante el tratamiento con un ácido o con un reactivo de intercambio de aniones adecuado. Una sal con dos moléculas de ácido (por ejemplo un dihaluro de un compuesto de la fórmula I) también se puede convertir en una sal con una molécula de ácido por compuesto (por ejemplo, un monohaluro); esto se puede hacer mediante calentamiento hasta obtener una fusión, o, por ejemplo, mediante calentamiento como un sólido bajo un alto vacío a una temperatura elevada, por ejemplo de 130°C a 170°C, expulsándose una molécula del ácido por molécula de un compuesto de la fórmula I. Las sales usualmente se pueden convertir hasta los compuestos libres, por ejemplo, mediante el tratamiento con compuestos básicos adecuados, por ejemplo con carbonatos de metales alcalinos, carbonatos ácidos de metales

piridil)-N,N,N',N'-tetrametil-uronio (TPTU); tetrafluoro-borato de O-benzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (TBTU); hexafluoro-fosfato de (benzotriazol-1-iloxi)-tripirrolidino-fosfonio (PyBOP), hexafluoro-fosfato de O-(1H-6-cloro-benzotriazol-1-il)-1,1,3,3-tetrametil-uronio, clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida / hidroxi-benzotriazol o / 1-hidroxi-7-aza-benzotriazol (EDC/HOBT o EDC/HOAt) o HOAt solo, o con (1-cloro-2-metil-propenil)-dimetil-amina. Para una revisión de algunos otros posibles agentes de acoplamiento, véase por ejemplo, Klauser; Bodansky, *Synthesis* (1972), 453-463. La mezcla de reacción de preferencia se agita a una temperatura de entre aproximadamente -20°C y 50°C, en especial entre 0°C y 30°C, por ejemplo, a temperatura ambiente.

En un compuesto de la fórmula I, en donde $R^1$ o en especial $R^4$ lleva dos grupos amino vicinales, los dos átomos de nitrógeno de los dos grupos amino se pueden puentear mediante un grupo –CH= (formando, por consiguiente, junto con los dos átomos de carbono que enlazan los grupos amino originales y el enlace entre ellos, un anillo de 1H-imidazolo templado a $R^1$ o $R^4$; por ejemplo, (diamino vicinal)-fenilo se puede convertir en benzo-imidazolilo de acuerdo con este método. La reacción de preferencia tiene lugar haciendo reaccionar primeramente el compuesto de la fórmula I que lleva los dos grupos amino vicinales, con ácido fórmico, por ejemplo, en la presencia de un agente de acoplamiento como se menciona en el párrafo anterior, tal como clorhidrato de EDC, una base, tal como N,N-dimetil-amino-piridina (DMAP) y de preferencia un solvente

a 7 átomos de carbono-sulfonil-amino, mediante la reacción con un haluro de alcanoílo de 1 a 7 átomos de carbono, o un haluro de alcano de 1 a 7 átomos de carbono-sulfonilo correspondiente, por ejemplo, un cloruro correspondiente, en la presencia de una base de nitrógeno terciario, tal como trietil-amina o piridina, en ausencia o en la presencia de un solvente apropiado, tal como cloruro de metileno, por ejemplo a temperaturas en el intervalo de -20°C a 50°C, por ejemplo, a aproximadamente la temperatura ambiente.

En un compuesto de la fórmula I, en donde $R^1$ o en especial $R^4$ lleva un sustituyente de ciano, el ciano se puede convertir hasta un grupo amino-metilo, por ejemplo, mediante hidrogenación, en la presencia de un catalizador de metal apropiado, tal como Níquel de Raney o Cobalto de Raney, en un solvente apropiado, por ejemplo, un alcanol inferior, tal como metanol y/o etanol, por ejemplo a temperaturas en el intervalo de -20°C a 50°C, por ejemplo, a aproximadamente la temperatura ambiente.

En un compuesto de la fórmula I, en donde $R^1$ o en especial $R^4$ lleva un sustituyente de carboxilo (COOH), éste último se puede convertir en un grupo amida, por ejemplo, un grupo N-alquilo de 1 a 7 átomos de carbono-carbamoílo, mediante la reacción con la amina correspondiente, por ejemplo, en la presencia de un agente de acoplamiento que forme un derivado reactivo preferido del grupo carboxilo *in situ*, por ejemplo diciclohexil-carbodi-imida/1-hidroxi-benzo-triazol (DCC/HOBT); cloruro de bis-(2-oxo-3-oxazolidinil)-fosfínico (BOPCl); tetrafluoro-borato de O-(1,2-dihidro-2-oxo-1-

reacciones mencionadas anteriormente y más adelante.

La protección de estos grupos funcionales mediante tales grupos protectores, los grupos protectores mismos, y sus reacciones de remoción se describen, por ejemplo, en los trabajos de referencia convencionales, tales como J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres y Nueva York 1973, en T. W. Greene, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999, en "The Peptides"; Volumen 3 (Editores: E. Gross y J. Meienhofer), Academic Press, Londres y Nueva York 1981, en "Methoden der organischen Chemie" (*Métodos de química orgánica*), Houben Weil, 4a. Edición, Volumen 15/I, Georg Thieme Verlag, Stuttgart 1974, en H.-D. Jakubke y H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Aminoácidos, péptidos, proteínas*), Verlag Chemie, Weinheim, Deerfield Beach, y Basilea 1982, y en Jochen Lehmann, "Chemie der Kohlenhidrate: Monosaccharide und Derivate" (*Química de carbohidratos: monosacáridos y derivados*), Georg Thieme Verlag, Stuttgart 1974.

**Reacciones y Conversiones Opcionales**

Un compuesto de la fórmula I se puede convertir en un compuesto diferente de la fórmula I.

Por ejemplo, en un compuesto de la fórmula I, en donde $R^1$ o en especial $R^4$ lleva un sustituyente de amino o amino-alquilo de 1 a 7 átomos de carbono, el amino se puede convertir en acil-amino, por ejemplo, alcanoílo de 1 a 7 átomos de carbono-amino, o alcano de 1

los grupos que se utilizan usualmente en la síntesis de los compuestos peptídicos, y también de cefalosporinas y penicilinas, así como derivados de ácidos nucleicos y azúcares. Los grupos protectores son los grupos que ya no están presentes en los compuestos finales una vez que se remueven, mientras que los grupos que permanecen como sustituyentes no son los grupos protectores en el sentido utilizado en la presente, los cuales son grupos que se agregan en la etapa de un material de partida o de un intermediario, y se remueven para obtener un compuesto final. También en el caso de las conversiones de un compuesto de la fórmula I en un compuesto diferente de la fórmula I, se pueden introducir y remover los grupos protectores, si esto es útil o se requiere.

Los grupos protectores pueden ya estar presentes en los precursores y deben proteger a los grupos funcionales concernidos contra las reacciones secundarias indeseadas, tales como acilaciones, eterificaciones, esterificaciones, oxidaciones, solvólisis, y reacciones similares. Es una característica de los grupos protectores que se prestan fácilmente, es decir, sin reacciones secundarias indeseadas, a la remoción, típicamente mediante acetólisis, protonólisis, solvólisis, reducción, fotólisis, o también mediante la actividad enzimática, por ejemplo bajo condiciones análogas a las condiciones fisiológicas, y que no están presentes en los productos finales. El especialista sabe, o puede establecer fácilmente, cuáles grupos protectores son adecuados con las

utilizar en cantidades equimolares; de una manera alternativa, un compuesto se puede utilizar en exceso, por ejemplo, para funcionar como un solvente, o para cambiar el equilibrio, o, en términos generales, para acelerar las velocidades de reacción. Se pueden agregar auxiliares de reacción, tales como ácidos, bases o catalizadores, en las cantidades adecuadas, como se conoce en este campo, requeridas por una reacción, y en línea con los procedimientos generalmente conocidos.

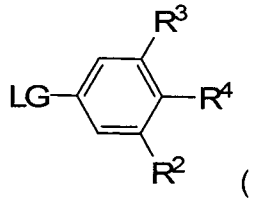
**Reacción de Buchwald**

Esta reacción, también conocida como aminación de Buchwald o reacción de Buchwald-Hartwig, se conoce en general en este campo. Esta reacción es catalizada por metales de transición, en particular por complejos o sales de Cu o Pd; tiene lugar en la presencia de uno o más compuestos básicos (tales como una amina o un alcóxido alcalino), y uno o más diluyentes (tales como diluyentes apróticos polares). Se pueden encontrar detalles adicionales en los Ejemplos.

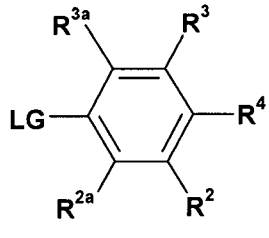
**Grupos Protectores**

Si se protegen o se necesitan proteger uno o más grupos funcionales diferentes, por ejemplo carboxilo, hidroxilo, amino, sulfhidrilo o similares, en un material de partida, como se describe en la presente, o cualquier otro precursor, debido a que no deban tomar parte en la reacción o no deban alterar la reacción, éstos son

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(IV')




(IV)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente (tal como tosilato, mesilato o halógeno, en particular bromuro), para obtener un compuesto de la fórmula I;

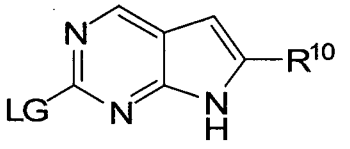
y, si se desea, convertir un compuesto de la fórmula I obtenido de acuerdo con el método A) o con el método B) en un compuesto diferente de la fórmula I, y/o convertir una sal que se pueda obtener de un compuesto de la fórmula I en una sal diferente del mismo, y/o convertir un compuesto libre que se pueda obtener de la fórmula I en una sal del mismo, y/o separar un isómero que se pueda obtener de un compuesto de la fórmula I de uno o más isómeros diferentes que se puedan obtener de la fórmula I.

**Condiciones de Reacción**

Cuando se dan temperaturas anteriormente en la presente o más adelante en la presente, se debe agregar "aproximadamente", debido a que son tolerables las desviaciones menores de los valores numéricos dados, por ejemplo, las variaciones de ±10 por ciento. Todas las reacciones pueden tener lugar en la presencia de uno o más diluyentes y/o solventes. Los materiales de partida se puede n

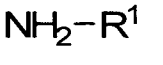
o

método B) hacer reaccionar, en un primer paso, un compuesto de la fórmula II:



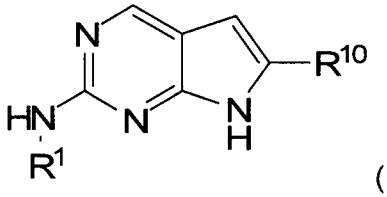
(II)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente (tal como tosilato, mesilato o halógeno, en particular cloruro) con un compuesto de la fórmula III:



(III)

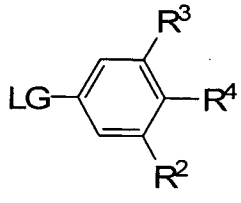
en donde $R^1$ es como se define en la fórmula I, ya sea en una reacción de Buchwald catalizada por Pd, o bien bajo condiciones ácidas, para obtener un compuesto de la fórmula (V):



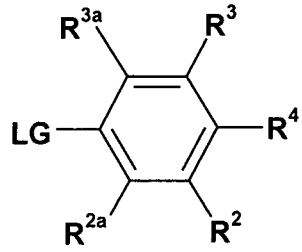
(V)

en donde los sustituyentes son como se definen anteriormente para un compuesto de la fórmula I, y hacer reaccionar, en un segundo paso, el compuesto obtenido de la fórmula V con un compuesto de la fórmula IV:

mesilato o halógeno, en particular cloruro), con un compuesto de la fórmula IV o IV':

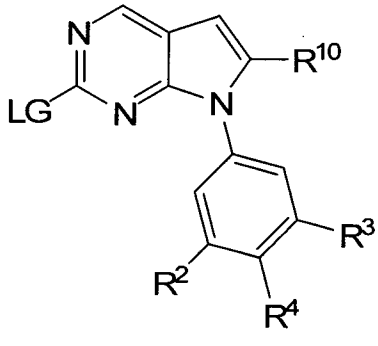


(IV')

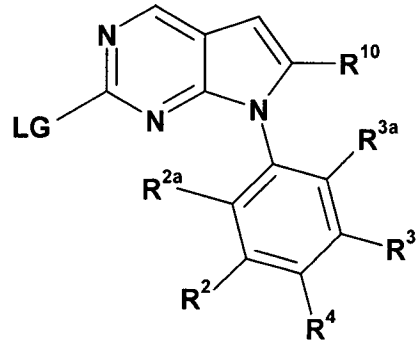


(IV)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente (tal como tosilato, mesilato o halógeno, en particular bromuro) en una reacción de Buchwald catalizada por Cu, para obtener un compuesto de la fórmula (VI) o (VI'):

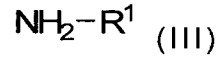


(VI')



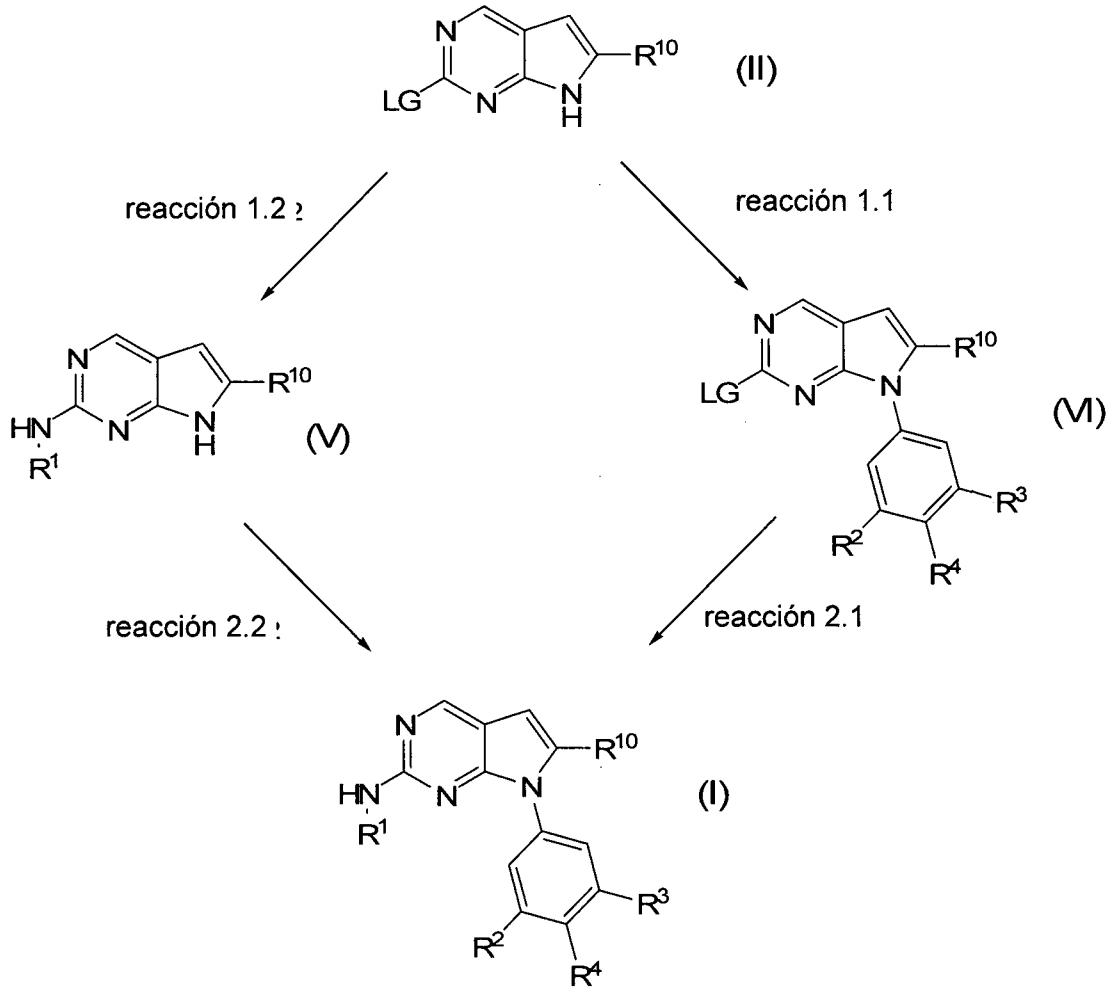
(VI)

en donde los sustituyentes son como se definen anteriormente, con un compuesto de la fórmula I, y hacer reaccionar, en un segundo paso, el compuesto obtenido de la fórmula VI, con un compuesto de la fórmula (III):



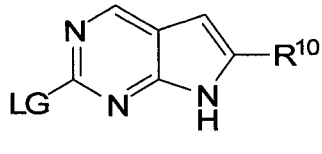
(III)

en donde $R^1$ es como se define en la fórmula I, para obtener un compuesto de la fórmula I;




De preferencia, un proceso para la fabricación de un compuesto de la fórmula I comprende cualquiera de:

Método a) hacer reaccionar, en un primer paso, un compuesto de la fórmula II:



(II)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente (tal como tosilato,

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composiciones farmacéuticas que comprenden: (a) una cantidad efectiva del compuesto de la fórmula I, y sales farmacéuticamente aceptables, pro-fármacos farmacéuticamente aceptables, y metabolitos farmacéuticamente activos del mismo; y (b) uno o más excipientes y/o diluyentes farmacéuticamente aceptables.

En un aspecto adicional, la invención se refiere a una composición farmacéutica para el tratamiento de una enfermedad, por ejemplo, de tumores sólidos o líquidos en animales de sangre caliente, incluyendo seres humanos, la cual comprende una dosis efectiva en el tratamiento de esta enfermedad, de un compuesto de la fórmula I como se describe anteriormente, o una sal farmacéuticamente aceptable de este compuesto, junto con un vehículo farmacéuticamente aceptable (= material portador).

Un compuesto de la fórmula I o I' se puede preparar mediante procesos que, aunque no se aplican hasta ahora para los nuevos compuestos de la presente invención, en donde, por consiguiente, forman nuevos procesos, son conocidos por sí mismos, y el siguiente esquema ilustra los métodos para dicha preparación.

En un aspecto adicional, la invención se refiere a un compuesto de la fórmula I o una sal farmacéuticamente aceptable de este compuesto, para utilizarse en un método para el tratamiento de un sujeto que lo necesite, en especial para el tratamiento de una enfermedad mediada por la cinasa de proteína tirosina, más especialmente en un paciente que requiera de dicho tratamiento.

En un aspecto adicional, la invención se refiere a un método para el tratamiento de una enfermedad que responda a la inhibición de la cinasa JAK-2 y/o JAK-3, el cual comprende administrar un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, en donde los radicales y símbolos tienen los significados definidos anteriormente, en especial en una cantidad efectiva contra esta enfermedad, a un animal de sangre caliente que requiera dicho tratamiento.

En un aspecto adicional, la invención se refiere a una composición farmacéutica, la cual comprende un compuesto de la fórmula I como ingrediente activo, en asociación con cuando menos un vehículo o diluyente farmacéutico. Estas composiciones se pueden fabricar de una manera convencional.

En un aspecto adicional, la invención se refiere a un método para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina, en un sujeto que necesite dicho tratamiento, el cual comprende administrar a este sujeto, una cantidad terapéuticamente efectiva del compuesto de la fórmula I.

En un aspecto adicional, la invención se refiere a

aproximadamente 70 kilogramos, es de preferencia de aproximadamente 3 miligramos a aproximadamente 5 gramos, más preferiblemente de aproximadamente 10 miligramos a aproximadamente 1.5 gramos por persona al día, divididos de preferencia en 1 a 3 dosis individuales, las cuales, por ejemplo, pueden ser del mismo tamaño. Usualmente, los niños reciben la mitad de la dosis para adultos.

En un aspecto adicional, la invención se refiere a un compuesto de la fórmula I o una sal farmacéuticamente aceptable, como un medicamento / para utilizarse como un medicamento, en particular para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

En un aspecto adicional, la invención se refiere al uso de un compuesto de la fórmula I o una sal farmacéuticamente aceptable, como ingrediente activo en un medicamento, en particular para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

En un aspecto adicional, la invención se refiere al uso de un compuesto de la fórmula I o una sal farmacéuticamente aceptable, como un medicamento, en particular para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

En un aspecto adicional, la invención se refiere al uso de un compuesto de la fórmula I o una sal farmacéuticamente aceptable, para la fabricación de un medicamento para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

osmótica, y/o reguladores del pH. Las presentes composiciones farmacéuticas, las cuales, si se desea, pueden comprender otras sustancias farmacológicamente activas, se preparan de una manera conocida por sí misma, por ejemplo por medio de procesos convencionales de mezcla, granulación, confitería, disolución, o liofilización, y comprenden de aproximadamente el 1 por ciento al 99 por ciento, en especial de aproximadamente el 1 por ciento a aproximadamente el 20 por ciento de ingrediente(s) activo(s).

La dosificación del ingrediente activo para aplicarse a un animal de sangre caliente depende de una variedad de factores, incluyendo el tipo, la especie, la edad, el peso, el sexo y la condición médica del paciente; la gravedad de la condición que se vaya a tratar; la vía de administración; la función renal y hepática del paciente; y el compuesto particular empleado. Un médico, clínico, o veterinario de una experiencia ordinaria puede determinar fácilmente y prescribir la cantidad efectiva del fármaco requerida para prevenir, contrarrestar, o detener el progreso de la condición. La precisión óptima para alcanzar la concentración del fármaco dentro del intervalo que produzca eficacia sin toxicidad, requiere de un régimen basado en la cinética de la disponibilidad del fármaco para los sitios objetivo. Esto involucra una consideración de la distribución, el equilibrio, y la eliminación de un fármaco. La dosis de un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, para administrarse a animales de sangre caliente, por ejemplo seres humanos de un peso corporal de

La invención se refiere también a composiciones farmacéuticas que comprenden una cantidad efectiva, en especial una cantidad efectiva en el tratamiento de una de las enfermedades anteriormente mencionadas (= trastornos), de un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, junto con uno o más vehículos farmacéuticamente aceptables que sean adecuados para administración tópica, enteral, por ejemplo oral o rectal, o parenteral, y los cuales pueden ser inorgánicos u orgánicos, sólidos o líquidos. Para administración oral se pueden utilizar en especial tabletas o cápsulas de gelatina que comprendan al ingrediente activo junto con diluyentes, por ejemplo lactosa, dextrosa, manitol, y/o glicerol, y/o lubricantes y/o polietilenglicol. Las tabletas también pueden comprender aglutinantes, por ejemplo silicato de magnesio y aluminio, almidones, tales como almidón de maíz, de trigo, o de arroz, gelatina, metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona, y si se desea, desintegrantes, por ejemplo almidones, ágar, ácido algínico o una sal del mismo, tal como alginato de sodio, y/o mezclas efervescentes, o adsorbentes, tintes, saborizantes, y edulcorantes. También es posible utilizar los compuestos farmacológicamente activos de la presente invención en la forma de composiciones parenteralmente administrables o en la forma de soluciones para infusión. Las composiciones farmacéuticas se pueden esterilizar y/o pueden comprender excipientes, por ejemplo, conservadores, estabilizantes, compuestos humectantes y/o emulsionantes, solubilizantes, sales para regular la presión

adicional, a una combinación que comprende una cantidad terapéuticamente efectiva de un compuesto de la fórmula I en forma libre o en forma de sal farmacéuticamente aceptable, y una segunda sustancia de fármaco, para su administración simultánea o en secuencia.

La invención también proporciona, en un aspecto adicional, una preparación farmacéutica (composición), la cual comprende un compuesto de la fórmula I como se define en la presente, o una sal farmacéuticamente aceptable de este compuesto, o un hidrato o solvato del mismo, y cuando menos un vehículo farmacéuticamente aceptable, y / o diluyentes, y opcionalmente una o más sustancias de fármaco adicionales.

Los compuestos de la invención se pueden administrar por cualquier vía convencional, en particular parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables, enteralmente, por ejemplo, oralmente, por ejemplo en la forma de tabletas o cápsulas, tópicamente, por ejemplo, en la forma de lociones, geles, ungüentos o cremas, o en una forma nasal o de supositorio. La administración tópica es, por ejemplo, a la piel. Una forma adicional de administración tópica es a los ojos. Las composiciones farmacéuticas que comprenden un compuesto de la invención en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se pueden fabricar de una manera convencional mezclando con un vehículo o diluyente farmacéuticamente aceptable.

crecimiento endotelial vascular, por ejemplo, PTK787 o Avastin®, o la cinasa de tirosina receptora del factor de crecimiento derivado de plaquetas, por ejemplo, STI571 (Glivec®), una citoquina, un regulador de crecimiento negativo, tal como TGF-ß o IFN-ß, un inhibidor de aromatasa, por ejemplo, letrozol (Femara®) o anastrozol, un inhibidor de la interacción de un dominio SH2 con una proteína fosforilada, anti-estrógenos, inhibidores de topoisomerasa I, tales como irinotecano, inhibidores de topoisomerasa II, los agentes activos en microtúbulos, por ejemplo, paclitaxel o una epotilona, los agentes alquilantes, anti-metabolitos anti-proliferativos, tales como gemcitabina o capecitabina, compuestos de platina, tales como carboplatina o cisplatina, bisfosfonatos, por ejemplo, AREDIA® o ZOMETA®, y anticuerpos monoclonales, por ejemplo, contra HER2, tales como trastuzumab.

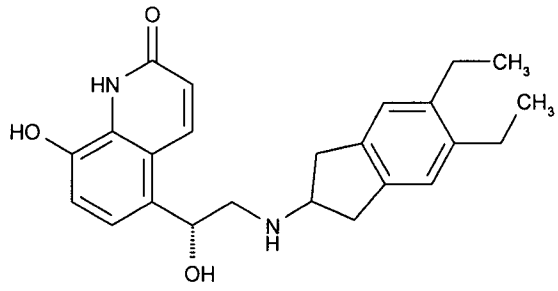
La estructura de los agentes activos identificados por números de código, nombres genéricos o comerciales, se puede tomar de la edición actual del compendio estándar "The Merck Index" o de las bases de datos, por ejemplo, Patents International (por ejemplo, IMS World Publications). El contenido correspondiente de las mismas se incorpora a la presente como referencia.

Los compuestos anteriormente mencionados, los cuales se pueden utilizar en combinación con un compuesto de la fórmula I, se pueden preparar y administrar como se describe en la técnica, tal como en los documentos citados anteriormente.

Por consiguiente, la invención se refiere, en un aspecto

Otras combinaciones útiles de los compuestos de la invención con fármacos anti-inflamatorios son aquéllas con antagonistas de los receptores de quimiocina, por ejemplo, CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 y CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, en particular los antagonistas de CCR-5, tales como los antagonistas Schering-Plough SC-351125, SCH-55700 y SCH-D, los antagonistas Takeda, tales como cloruro de N-[[4-[[[6,7-dihidro-2-(4-metil-fenil)-5H-benzo-ciclohepten-8-il]-carbonil]-amino]-fenil]-metil]-tetrahidro-N,N-dimetil-2H-piran-4-aminio (TAK-770), y los antagonistas de CCR-5 descritos en la Patente de los Estados Unidos de Norteamérica Número US 6166037 (en particular en las reivindicaciones 18 y 19), en la Publicación Internacional Número WO 00/66558 (en particular en la reivindicación 8), en la Publicación Internacional Número WO 00/66559 (en particular en la reivindicación 9), y en las Publicaciones Internacionales Números WO 04/018425 y WO 04/026873.

Los agentes terapéuticos para la posible combinación son en especial uno o más compuestos anti-proliferativos, citostáticos, o citotóxicos, por ejemplo uno o varios agentes seleccionados a partir del grupo que incluye, pero no se limita a, un inhibidor de la biosíntesis de poliamina, un inhibidor de una cinasa de proteína, en especial de una cinasa de proteína serina/treonina, tal como la cinasa C de proteína, o de una cinasa de proteína tirosina, tal como la cinasa de tirosina receptora del factor de crecimiento epidérmico, por ejemplo, Iressa®, la cinasa de tirosina receptora del factor de




y las sales farmacéuticamente aceptables del mismo, así como los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación Internacional Número WO 04/16601, y también los compuestos de de la Publicación Internacional Número WO 04/033412.

Los fármacos broncodilatadores adecuados incluyen los compuestos anti-colinérgicos o anti-muscarínicos, en particular bromuro de ipratropio, bromuro de oxitropio, sales de tiotropio y CHF 4226 (Chiesi), y glicopirrolato, pero también aquéllos descritos en las Patentes Números WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, US 5171744, US 3714357, WO 03/33495 y WO 04/018422.

Las sustancias de fármaco anti-histamínicas adecuadas incluyen clorhidrato de cetirizina, acetaminofeno, fumarato de clemastina, prometazina, loratidina, desloratidina, difenhidramina y clorhidrato de fexofenadina, activastina, astemizol, azelastina, ebastina, epinastina, mizolastina y tefenadina así como las que se dan a conocer en las Patentes Números WO 03/099807, WO 04/026841 y JP 2004107299.

04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/ 019944, WO 04/019945, WO 04/045607 y WO 04/037805; los agonistas de A2a, tales como aquéllos que se dan a conocer en las Patentes Números EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/ 039762, WO 04/039766, WO 04/045618 y WO 04/046083; los antagonistas de A2b, tales como aquéllos descritos en la Publicación Internacional Número WO 02/42298; y los agonistas del adreno-receptor beta-2, tales como albuterol (salbutamol), metaproterenol, terbutalina, salmeterol, fenoterol, procaterol, y en especial, formoterol, y las sales farmacéuticamente aceptables de los mismos, y los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación Internacional Número WO 0075114, cuyo documento se incorpora a la presente como referencia, de preferencia los compuestos de los Ejemplos de la misma, en especial un compuesto de la fórmula:

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dipropionato de beclametasona, propionato de fluticasona, ciclesonida o furoato de mometasona, o los esteroides descritos en las Publicaciones Internacionales Números WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (en especial aquéllos de los Ejemplos 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 y 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, los agonistas del receptor glucocorticoide no esteroideos, tales como aquéllos descritos en las Publicaciones Internacionales Números WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229; antagonistas de LTB4, tales como LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 y aquéllos descritos en la Patente de los Estados Unidos de Norteamérica Número US 5451700; los antagonistas de LTD4, tales como montelukast y zafirlukast; los inhibidores de PDE4, tales como cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofilina (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), y aquéllos que se dan a conocer en las Publicaciones Internacionales Números WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/ 005258, WO

limitan a, alcaloides de plantas, los compuestos y antagonistas hormonales; modificadores de la respuesta biológica, de preferencia linfocinas o interferones; oligonucleótidos anti-sentido o derivados de oligonucleótidos; shARN o siARN; o compuestos diversos, o compuestos con un mecanismo de acción diferente o desconocido.

Los compuestos de la invención también son útiles como compuestos co-terapéuticos para utilizarse en combinación con otras sustancias de fármaco, tales como sustancias de fármaco anti-inflamatorias, broncodilatadoras, o antihistamínicas, en particular en el tratamiento de enfermedades inflamatorias, tales como aquéllas mencionadas anteriormente en la presente, por ejemplo como potenciadores de la actividad terapéutica de tales fármacos, o como un medio para reducir la dosificación requerida o los efectos secundarios potenciales de estos fármacos. Un compuesto de la invención se puede mezclar con la otra sustancia de fármaco en una composición farmacéutica, o se puede administrar por separado, antes, de una manera simultánea con, o después de la otra sustancia de fármaco. De conformidad con lo anterior, la invención incluye una combinación de un compuesto de la invención como se describe anteriormente en la presente, con una sustancia de fármaco anti-inflamatoria o anti-histamínica, estando el compuesto mencionado de la invención y dicha sustancia de fármaco en la misma o diferente composición farmacéutica.

Los fármacos anti-inflamatorios adecuados incluyen esteroides, en particular glucocorticosteroides, tales como budesonida,

ANGIOSTATINA, descrita por O'Reilly y colaboradores, *Cell*, Volumen 79, páginas 315-328 (1994); ENDOSTATINA, descrita por O'Reilly y colaboradores, *Cell*, Volumen 88, páginas 277-285 (1997); amidas del ácido antranílico; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; o anticuerpos contra el factor de crecimiento endotelial vascular o anticuerpos contra el receptor del factor de crecimiento endotelial vascular, por ejemplo, rhuMAb y RHUFab, aptámero del factor de crecimiento endotelial vascular, por ejemplo, Macugon; inhibidores de FLT-4, inhibidores de FLT-3, anticuerpo IgG1 de VEGFR-2, Angiozima (RPI 4610) y Bevacizumab (Avastin$^{MR}$).

"Terapia fotodinámica", como se utiliza en la presente, se refiere a la terapia que utiliza ciertos productos químicos conocidos como compuestos fotosensibilizantes para tratar o prevenir cánceres. Los ejemplos de la terapia fotodinámica incluyen el tratamiento con compuestos, tales como, por ejemplo, VISUDYNE y porfímero-sodio.

"Esteroides angiostáticos", como se utilizan en la presente, se refieren a los compuestos que bloquean o inhiben la angiogénesis, tales como, por ejemplo, anecortave, triamcinolona, hidrocortisona, 11-α-epihidrocortisol, cortexolona, 17α-hidroxi-progesterona, corticosterona, desoxi-corticosterona, testosterona, estrona y dexametasona.

"Implantes que contienen corticosteroides", como se utiliza en la presente, incluye, pero no se limita a, compuestos, tales como, por ejemplo, fluocinolona, dexametasona.

"Otros compuestos quimioterapéuticos" incluyen, pero no se

mercapto-purina (en especial en combinación con ara-C contra leucemia linfocítica aguda) y/o pentostatina. Los inhibidores de reductasa de ribonucleótido son en especial hidroxiurea o los derivados de 2-hidroxi-1H-isoindol-1,3-diona, tales como PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 o PL-8 mencionados en Nandy y colaboradores, *Acta Oncologica*, Volumen 33, Número 8, páginas 953-961 (1994).

El término "inhibidores de descarboxilasa de S-adenosil-metionina", como se utiliza en la presente, incluye, pero no se limita a, los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,461,076.

También se incluyen en particular los compuestos, proteínas, o anticuerpos monoclonales del factor de crecimiento endotelial vascular que se dan a conocer en la Publicación Internacional Número WO 98/35958, por ejemplo, 1-(4-cloro-anilino)-4-(4-piridil-metil)-ftalazina o una sal farmacéuticamente aceptable de la misma, por ejemplo, el succinato, o en las Patentes Números WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 y EP 0 769 947; aquéllos descritos por Prewett y colaboradores, *Cancer Res*, Volumen 59, páginas 5209-5218 (1999); Yuan y colaboradores, *Proc Natl Acad Sci EUA*, Volumen 93, páginas 14765-14770 (1996); Zhu y colaboradores, *Cancer Res*, Volumen 58, páginas 3209-3214 (1998); y Mordenti y colaboradores, *Toxicol Pathol*, Volumen 27, Número 1, páginas 14-21 (1999); en las Publicaciones Internacionales Números WO 00/37502 y WO 94/10202;

3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida, o una sal farmacéuticamente aceptable de la misma, en especial la sal de lactato.

"Antagonistas del receptor de somatostatina", como se utilizan en la presente, se refieren a los compuestos que dirigen, tratan, o inhiben al receptor de somatostatina, tales como octreotida, y SOM230.

"Planteamientos que dañan las células tumorales" se refieren a planteamientos tales como radiación ionizante. El término "radiación ionizante" referido anteriormente y más adelante en la presente, significa la radiación ionizante que se presenta como rayos electromagnéticos (tales como rayos-X y rayos gamma), o bien partículas (tales como partículas alfa y beta). La radiación ionizante se proporciona en, pero no limitándose a, terapia de radiación y se conoce en este campo. Véase Hellman, Principles of Radiation Therapy, Cancer, en *Principles and Practice of Oncology*, Devita y colaboradores, Editores, 4a. Edición, Volumen 1, páginas 248-275 (1993).

El término "Aglutinantes EDG", como se utiliza en la presente, se refiere a una clase de inmunosupresores que modulan la recirculación de los linfocitos, tal como FTY720.

El término "inhibidores de reductasa de ribonucleótido" incluye, pero no se limita a, los análogos de nucleósido de pirimidina o purina incluyendo, pero no limitándose a, fludarabina y/o citosina arabinosida (ara-C), 6-tioguanina, 5-fluoro-uracilo, cladribina, 6-

compuestos de la fórmula (I) se pueden utilizar en combinación con las terapias convencionales de leucemia, en especial en combinación con las terapias empleadas para el tratamiento de leucemia mieloide aguda. En particular, los compuestos de la fórmula (I) se pueden administrar en combinación con, por ejemplo, los inhibidores de farnesil-transferasa y/u otros fármacos útiles para el tratamiento de leucemia mieloide aguda, tales como Daunorrubicina, Adriamicina, Ara-C, VP-16, Teniposida, Mitoxantrona, Idarrubicina, Carboplatino, y PKC412.

El término "compuestos anti-leucémicos" incluye, por ejemplo, Ara-C, un análogo de pirimidina, el cual es el derivado de 2'-alfa-hidroxi-ribosa (arabinosida) de desoxicitidina. También se incluye el análogo de purina de la hipoxantina, 6-mercapto-purina (6-MP) y fosfato de fludarabina.

Los compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de la desacetilasa de histona (HDAC), tales como butirato de sodio y ácido hidroxámico de suberoil-anilida (SAHA), inhiben la actividad de las enzimas conocidas como desacetilasas de histona. Los inhibidores de desacetilasa de histona específicos incluyen MS275, SAHA, FK228 (anteriormente FR901228), Tricostatina A y los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 6,552,065, en particular, *N*-hidroxi-3-[4-[[[2-(2-metil-1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida, o una sal farmacéuticamente aceptable de la misma, y *N*-hidroxi-3-[4-[(2-hidroxi-etil)-{2-(1*H*-indol-

especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de la cinasa receptora Flt-3R, por ejemplo, PKC412, midostaurina, un derivado de estaurosporina, SU11248 y MLN518.

El término "inhibidores de HSP90", como se utiliza en la presente, incluye, pero no se limita a, los compuestos que dirigen, reducen, o inhiben la actividad intrínseca de la ATPasa de HSP90; que degradan, dirigen, reducen, o inhiben las proteínas clientes de HSP90 por medio de la senda de proteasoma de ubiquitina. Los compuestos que dirigen, reducen, o inhiben la actividad intrínseca de la ATPasa de HSP90 son en especial los compuestos, proteínas o anticuerpos que inhiben la actividad de ATPasa de HSP90, por ejemplo, 17-alil-amino,17-desmetoxi-geldanamicina (17AAG), un derivado de geldanamicina; otros compuestos relacionados con geldanamicina; radicicol e inhibidores de desacetilasa de histona.

El término "anticuerpos anti-proliferativos", como se utiliza en la presente, incluye, pero no se limita a, trastuzumab (Herceptin$^{MR}$), trastuzumab-DM1, erbitux, bevacizumab (Avastin$^{MR}$), rituximab (Rituxan®), PRO64553 (anti-CD40) y Anticuerpo 2C4. Anticuerpos significan, por ejemplo, anticuerpos monoclonales intactos, anticuerpos policlonales, anticuerpos multiespecíficos formados a partir de cuando menos 2 anticuerpos intactos, y fragmentos de anticuerpos, siempre que éstos exhiban la actividad biológica deseada.

Para el tratamiento de leucemia mieloide aguda (AML), los

amino-peptidasa de metionina son, por ejemplo, bengamida o un derivado de la misma.

El término "inhibidor de proteasoma", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad del proteasoma. Los compuestos que dirigen, reducen, o inhiben la actividad del proteasoma incluyen, por ejemplo, Bortezomid (Velcade$^{MR}$) y MLN 341.

El término "inhibidor de metaloproteinasa de matriz" o ("inhibidor de MMP"), como se utiliza en la presente, incluye, pero no se limita a, inhibidores peptidomiméticos y no peptidomiméticos de colágeno, derivados de tetraciclina, por ejemplo, el inhibidor peptidomimético de hidroxamato batimastato y su análogo oralmente biodisponible marimastato (BB-2516), prinomastato (AG3340), metastato (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B o AAJ996.

El término "compuestos utilizados en el tratamiento de malignidades hematológicas", como se utiliza en la presente, incluye, pero no se limita a, inhibidores de cinasa de tirosina tipo FMS, por ejemplo, los compuestos que dirigen, reducen, o inhiben la actividad de los receptores de cinasa de tirosina tipo FMS (Flt-3R); interferón, 1-b-D-arabino-furanosil-citosina (ara-c) y bisulfano; e inhibidores de ALK, por ejemplo, los compuestos que dirigen, reducen, o inhiben la cinasa de linfoma anaplásico.

Los compuestos que dirigen, reducen, o inhiben la actividad de los receptores de cinasa de tirosina tipo FMS (Flt-3R) son en

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inhiben el objetivo de mamífero de rapamicina (mTOR), y que poseen una actividad anti-proliferativa, tal como sirolimus (Rapamune®), everolimus (Certican$^{MR}$), CCI-779 y ABT578.

El término "inhibidor de heparanasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la degradación del sulfato de heparina. El término incluye, pero no se limita a, PI-88.

El término "modificador de la respuesta biológica", como se utiliza en la presente, se refiere a una linfocina o interferones, por ejemplo, interferón γ.

El término "inhibidor de las isoformas oncogénicas Ras", por ejemplo, H-Ras, K-Ras, o N-Ras, como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad oncogénica de Ras, por ejemplo, un "inhibidor de farnesil-transferasa" por ejemplo, L-744832, DK8G557 o R115777 (Zarnestra).

El término "inhibidor de telomerasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la telomerasa. Los compuestos que dirigen, reducen, o inhiben la actividad de telomerasa, son en especial los compuestos que inhiben al receptor de telomerasa, por ejemplo, telomestatina.

El término "inhibidor de amino-peptidasa de metionina", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la amino-peptidasa de metionina. Los compuestos que dirigen, reducen, o inhiben la actividad de la

etoricoxib, valdecoxib o un ácido 5-alquil-2-aril-amino-fenil-acético, por ejemplo, ácido 5-metil-2-(2'-cloro-6'-fluoro-anilino)-fenil-acético, lumiracoxib.

El término "bisfosfonatos", como se utiliza en la presente, incluye, pero no se limita a, ácido etridónico, clodrónico, tiludrónico, pamidrónico, alendrónico, ibandrónico, risedrónico, y zoledrónico. "El ácido etridónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada DIDRONEL. El "ácido clodrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada BONEFOS. El "ácido tiludrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada SKELID. El "ácido pamidrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AREDIA$^{MR}$. El "ácido alendrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FOSAMAX. El "ácido ibandrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada BONDRANAT. El "ácido risedrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ACTONEL. El "ácido zoledrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOMETA.

El término "inhibidores de mTOR" se refiere a compuestos que

inhiben la actividad de c-Met, en especial compuestos que inhiben la actividad de cinasa del receptor c-Met, o anticuerpos que se dirigen al dominio extracelular de c-Met o que se enlazan con HGF.

Otros compuestos anti-angiogénicos incluyen los compuestos que tienen otro mecanismo para su actividad, por ejemplo, no relacionados con la inhibición de cinasa de proteína o de lípido, por ejemplo, talidomida (THALOMID) y TNP-470.

El término "Compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido" incluye, pero no se limita a, inhibidores de fosfatasa 1, fosfatasa 2A, o CDC25, por ejemplo, ácido ocadaico o un derivado del mismo.

El término "Compuestos que inducen los procesos de diferenciación celular" incluye, pero no se limita a, por ejemplo, ácido retinoico, α-, γ-, o δ-tocoferol, o α-, γ-, o δ-tocotrienol.

Los compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido son, por ejemplo, inhibidores de fosfatasa 1, fosfatasa 2A, o CDC25, por ejemplo, ácido ocadaico o un derivado del mismo.

Los compuestos que inducen los procesos de diferenciación celular son, por ejemplo, ácido retinoico, α- γ- o δ-tocoferol o α- γ- o δ-tocotrienol.

El término "inhibidor de ciclo-oxigenasa", como se utiliza en la presente, incluye, pero no se limita a, por ejemplo, inhibidores de Cox-2, 2-aril-amino-fenil-acético sustituido por 5-alquilo y sus derivados, tales como celecoxib (CELEBREX), rofecoxib (VIOXX),

epidérmico (EGFR, ErbB2, ErbB3, ErbB4 como homo- o hetero-dímeros) y sus mutantes, tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de receptores del factor de crecimiento epidérmico, que son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de cinasa de tirosina receptora del factor de crecimiento epidérmico, por ejemplo, el receptor de EGF, ErbB2, ErbB3 y ErbB4, o que se enlazan con el factor de crecimiento epidérmico o con los ligandos relacionados con el factor de crecimiento epidérmico, y son en particular los compuestos, proteínas, o anticuerpos monoclonales genérica y específicamente dados a conocer en la Publicación Internacional Número WO 97/02266, por ejemplo, el compuesto del Ejemplo 39, o en las Patentes Números EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 y, en especial, WO 96/30347 (por ejemplo, el compuesto conocido como CP 358774), WO 96/33980 (por ejemplo, el compuesto ZD 1839) y WO 95/03283 (por ejemplo, el compuesto ZM105180); por ejemplo, trastuzumab (Herceptin$^{MR}$), cetuximab (Erbitux$^{MR}$), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 o E7.6.3, y derivados de 7H-pirrolo-[2,3-d]-pirimidina, los cuales se dan a conocer en la Publicación Internacional Número WO 03/013541; y

m) compuestos que dirigen, reducen, o inhiben la actividad del receptor c-Met, tales como compuestos que dirigen, reducen, o

los Estados Unidos de Norteamérica Número US 5,093,330, por ejemplo, midostaurina; los ejemplos de compuestos adicionales incluyen, por ejemplo, UCN-01, safingol, BAY 43-9006, Briostatina 1, Perifosina; Ilmofosina; RO 318220 y RO 320432; GO 6976; Isis 3521; LY333531/LY379196; compuestos de isoquinolina, tales como aquéllos que se dan a conocer en la Publicación Internacional Número WO 00/09495; FTIs; PD184352 o QAN697 (un inhibidor de P13K) o AT7519 (un inhibidor de CDK);

k) compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, tales como los compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, incluyendo mesilato de Imatinib (GLEEVEC) o tirfostina. Una tirfostina es de preferencia un compuesto de bajo peso molecular (Mr < 1500), o una sal farmacéuticamente aceptable del mismo, en especial un compuesto seleccionado a partir de la clase de benciliden-malonitrilo, o de la clase de compuestos de S-aril-bencen-malonitrilo o de quinolina de bisustrato, más especialmente cualquier compuesto seleccionado a partir del grupo que consiste en Tirfostina A23/RG-50810; AG 99; Tirfostina AG 213; Tirfostina AG 1748; Tirfostina AG 490; Tirfostina B44; enantiómero de Tirfostina B44 (+); Tirfostina AG 555; AG 494; Tirfostina AG 556, AG957, y adafostina (adamantil-éster del ácido 4-{[(2,5-dihidroxifenil)metil]amino}benzoico; NSC 680410, adafostina);

l) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasas de tirosina receptoras del factor de crecimiento

la familia de cinasa de tirosina receptora Axl;

f) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Ret;

g) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Kit/SCFR, por ejemplo, imatinib;

h) compuestos que dirigen, reducen, o inhiben la actividad de las cinasas de tirosina receptoras C-kit - (parte de la familia de PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora c-Kit, en especial los compuestos que inhiben al receptor c-Kit, por ejemplo, imatinib;

i) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl, sus productos de fusión genética (por ejemplo, cinasa BCR-Abl) y mutantes, tales como los compuestos dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl y sus productos de fusión genética, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib o nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 a partir de ParkeDavis; o dasatinib (BMS-354825);

j) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia de cinasas de serina/treonina de la cinasa C de proteína (PKC) y Raf, los miembros de la familia MEK, SRC, JAK, FAK, PDK1, PKB/Akt, y Ras/MAPK, y/o los miembros de la familia de cinasa dependiente de ciclina (CDK), y son en especial los derivados de estaurosporina que se dan a conocer en la Patente de

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proteína o de lípido"; o "compuestos anti-angiogénicos adicionales", como se utiliza en la presente, incluye, pero no se limita a, inhibidores de cinasa de proteína tirosina y/o de cinasa de serina y/o treonina, o inhibidores de cinasa de lípido, por ejemplo,

a) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento derivado de plaquetas (PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de PDGFR, en especial los compuestos que inhiben al receptor del factor de crecimiento derivado de plaquetas, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib, SU101, SU6668 y GFB-111;

b) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento de fibroblastos (FGFR);

c) compuestos que dirigen, reducen, o inhiben la actividad del receptor del factor de crecimiento tipo insulina I (IGF-IR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de IGF-IR, en especial los compuestos que inhiben la actividad de cinasa del receptor de IGF-I, tales como los compuestos que se dan a conocer en la Publicación Internacional Número WO 02/092599, o anticuerpos que se dirigen al dominio extracelular del receptor de IGF-I o sus factores de crecimiento;

d) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Trk, o inhibidores de efrina B4;

e) compuestos que dirigen, reducen, o inhiben la actividad de

Esto incluye los compuestos que se dan a conocer en la Publicación Internacional Número WO 02/22577, en especial N-hidroxi-3-[4-[[(2-hidroxi-etil)[2-(1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida, N-hidroxi-3-[4-[[[2-(2-metil-1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida y las sales farmacéuticamente aceptables de las mismas. Además incluye en especial el ácido hidroxámico de suberoil-anilida (SAHA).

El término "anti-metabolito anti-neoplásico" incluye, pero no se limita a, 5-Fluoro-uracilo o 5-FU, capecitabina, gemcitabina, compuestos desmetilantes del ADN, tales como 5-azacitidina y decitabina, metotrexato y edatrexato, y antagonistas de ácido fólico, tales como pemetrexed. La capecitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada XELODA. La gemcitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada GEMZAR.

El término "compuesto de platina", como se utiliza en la presente, incluye, pero no se limita a, carboplatina, cisplatina, cisplatino y oxaliplatina. La carboplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CARBOPLAT. La oxaliplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ELOXATIN.

El término "compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido"; o una "actividad de fosfatasa de

epotilona B o D o derivados de las mismas. El paclitaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, TAXOL. El docetaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada TAXOTERE. El sulfato de vinblastina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VINBLASTIN R.P. El sulfato de vincristina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMISTIN. La discodermolida se puede obtener, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,010,099. También se incluyen los derivados de epotilona que se dan a conocer en las Patentes Números WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 y WO 00/31247. Se prefieren en especial Epotilona A y/o B.

El término "compuesto alquilante", como se utiliza en la presente, incluye, pero no se limita a, ciclofosfamida, ifosfamida, melfalano o nitrosourea (BCNU o Gliadel). La ciclofosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CICLOSTIN. La ifosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HOLOXAN.

El término "inhibidores de desacetilasa de histona" o "inhibidores de HDAC" se refiere a compuestos que inhiben el desacetilasa de histona y que poseen una actividad anti-proliferativa.

doxorrubicina (incluyendo la formulación liposomal, por ejemplo, CAELYX), daunorrubicina, epirrubicina, idarrubicina y nemorrubicina, las antraquinonas mitoxantrona y losoxantrona, y las podofilotoxinas etoposida y teniposida. La etoposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ETOPOPHOS. La teniposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VM 26-BRISTOL. La doxorrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ADRIBLASTIN o ADRIAMYCIN. La epirrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMORUBICIN. La idarrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZAVEDOS. La mitoxantrona se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOVANTRON.

El término "compuesto activo en microtúbulos" se refiere a los compuestos estabilizantes de microtúbulos y desestabilizantes de microtúbulos, y a los inhibidores de la polimerización de microtubulina, incluyendo, pero no limitándose a, taxanos, por ejemplo, paclitaxel y docetaxel, alcaloides vinca, por ejemplo, vinblastina, en especial sulfato de vinblastina, vincristina, en especial sulfato de vincristina, y vinorelbina, discodermolidas, colquicina, y epotilonas y derivados de las mismas, por ejemplo,

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refiere a cualquier sustancia que sea capaz de inhibir los efectos biológicos de las hormonas androgénicas e incluye, pero no se limita a, bicalutamida (CASODEX), que se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,636,505.

El término "agonista de gonadorelina", como se utiliza en la presente, incluye, pero no se limita a, abarelix, goserelina y acetato de goserelina. La goserelina se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 4,100,274, y se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOLADEX. El abarelix se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,843,901.

El término "inhibidor de topoisomerasa I", como se utiliza en la presente, incluye, pero no se limita a, topotecano, gimatecano, irinotecano, camptotecina y sus análogos, 9-nitro-camptotecina y el conjugado de camptotecina macromolecular PNU-166148 (el compuesto A1 de la Publicación Internacional Número WO99/ 17804). El irinotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CAMPTOSAR. El topotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HYCAMTIN.

El término "inhibidor de topoisomerasa II", como se utiliza en la presente, incluye, pero no se limita a, las antraciclinas, tales como

ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FEMARA o FEMAR. La amino-glutetimida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ORIMETEN. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un inhibidor de aromatasa, es en particular útil para el tratamiento de los tumores positivos para el receptor de hormonas, por ejemplo, tumores de mama.

El término "anti-estrógeno", como se utiliza en la presente, se refiere a un compuesto que antagoniza el efecto de los estrógenos al nivel del receptor de estrógeno. El término incluye, pero no se limita a, tamoxifeno, fulvestrant, raloxifeno y clorhidrato de raloxifeno. El tamoxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOLVADEX. El clorhidrato de raloxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada EVISTA. El fulvestrant se puede formular como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,659,516 o se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FASLODEX. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un anti-estrógeno, es en particular útil para el tratamiento de los tumores positivos para el receptor de estrógeno, por ejemplo, tumores de mama.

El término "anti-andrógeno", como se utiliza en la presente, se

tratamiento de tumores, incluyendo cirugía, radiación ionizante, terapia fotodinámica, implantes, por ejemplo, con corticosteroides, hormonas, o se pueden utilizar como radiosensibilizantes. También, en el tratamiento anti-inflamatorio y/o anti-proliferativo, se incluye la combinación con fármacos anti-inflamatorios. También es posible la combinación con sustancias de fármaco anti-histamínicas, fármacos broncodilatadores, fármacos anti-inflamatorios no esteroideos (NSAID) o antagonistas de los receptores de quimiocina.

El término "inhibidor de aromatasa", como se utiliza en la presente, se refiere a un compuesto que inhibe la producción de estrógeno, es decir, la conversión de los sustratos androstenodiona y testosterona hasta estrona y estradiol, respectivamente. El término incluye, pero no se limita a, esteroides, en especial atamestano, exemestano y formestano y, en particular, no esteroides, en especial amino-glutetimida, rogletimida, pirido-glutetimida, trilostano, testolactona, quetoconazol, vorozol, fadrozol, anastrozol y letrozol. El exemestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AROMASIN. El formestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada LENTARON. El fadrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AFEMA. El anastrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ARIMIDEX. El letrozol se puede administrar, por

MMP; inhibidores de mTOR; anti-metabolitos anti-neoplásicos; compuestos de platina; compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido y otros compuestos anti-angiogénicos; compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido; agonistas de gonadorelina; anti-andrógenos; inhibidores de amino-peptidasa de metionina; bisfosfonatos; modificadores de la respuesta biológica; anticuerpos anti-proliferativos; inhibidores de heparanasa; inhibidores de las isoformas oncogénicas Ras; inhibidores de telomerasa; inhibidores de proteasoma; compuestos utilizados en el tratamiento de malignidades hematológicas; compuestos que dirigen, reducen, o inhiben la actividad de Flt-3; inhibidores de Hsp90, tales como 17-AAG (17-alil-amino-geldanamicina, NSC330507), 17-DMAG (17-dimetil-amino-etil-amino-17-desmetoxi-geldanamicina, C707545), IPI-504, CNF1010, CNF2024, CNF1010 de Conforma Therapeutics; temozolomida (TEMODAL®); inhibidores de proteína de huso de cinesina, tales como SB715992 o SB743921 de GlaxoSmithKline, o pentamidina/clorpromazina de CombinatoRx; inhibidores de MEK, tales como ARRY142886 de Array PioPharma, AZD6244 de AstraZeneca, PD181461 de Pfizer, leucovorina, Aglutinantes EDG, los compuestos anti-leucemia, inhibidores de reductasa de ribonucleótido, inhibidores de descarboxilasa de S-adenosil-metionina, anticuerpos anti-proliferativos u otros compuestos quimioterapéuticos. Además, de una manera alternativa o en adición, se pueden utilizar en combinación con otros planteamientos de

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en la materia.

Un compuesto de la fórmula I se puede administrar solo o en combinación con uno o más agentes terapéuticos diferentes, tomando la posible terapia de combinación la forma de combinaciones fijas, o la administración de un compuesto de la invención y escalonándose uno o más agentes terapéuticos diferentes o dándose independientemente unos de otros, o la administración combinada de combinaciones fijas y uno o más agentes terapéuticos diferentes. Un compuesto de la fórmula I además o en adición, se puede administrar en especial para la terapia de tumores en combinación con quimioterapia, radioterapia, inmunoterapia, intervención quirúrgica, o una combinación de las mismas. Igualmente es posible la terapia a largo plazo, así como la terapia adyuvante en el contexto de otras estrategias de tratamiento, como se describe anteriormente. Otros posibles tratamientos son terapia para mantener el estado del paciente después de la regresión del tumor, o inclusive terapia quimiopreventiva, por ejemplo en los pacientes en riesgo.

Por consiguiente, un compuesto de la fórmula I se puede utilizar con ventaja en combinación con otros compuestos anti-proliferativos. Estos compuestos anti-proliferativos incluyen, pero no se limitan a, inhibidores de aromatasa; anti-estrógenos; inhibidores de topoisomerasa I; inhibidores de topoisomerasa II; compuestos activos en microtúbulos; compuestos alquilantes; inhibidores de desacetilasa de histona; compuestos que inducen los procesos de diferenciación celular; inhibidores de ciclo-oxigenasa; inhibidores de

Con el fin de generar los valores $IC_{50}$, se puede utilizar el diferencial nuclear-citoplásmico de STAT-GFP de las células no tratadas como una línea base, y se puede utilizar la siguiente ecuación para determinar el incremento de porcentaje en la translocalización nuclear: Porcentaje = 100 * (Compuesto NCD previamente tratado y estimulado - NCD No tratado) / (NCD previamente tratado y estimulado con DMSO – NCD No tratado).

En estos ensayos, los compuestos de la fórmula (I) en términos generales inhiben las cinasas JAK2 en el intervalo de 1 a 10 000 nM.

La actividad de los compuestos de la fórmula I también se puede determinar *in vivo:*

**JAK-2 *in vivo***

El ensayo se puede llevar a cabo como es descrito por G. Wernig, T. Mercher, R. Okabe, R.L. Levina, B. H. Lee, D.G. Gilliland, *Blood*, primera Edición en papel, publicado en línea el 14 de Febrero de 2006; DOI 10, 1182/blood-2005-12-4824.

Con base en estos estudios, un compuesto de la fórmula I de acuerdo con la invención muestra eficacia terapéutica en especial contra los trastornos dependientes de la cinasa de proteína, en especial las enfermedades proliferativas mediadas por la actividad de la cinasa JAK2.

En adición, otras cinasas de proteína pueden ser inhibidas por los compuestos de esta invención, tales como Tyk2, c-src, Flt-3, KDR y otras, para cada una de las cuales se conocen sistemas de prueba

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Xenón y un microscopio invertido Zeiss Axiovert, utilizando el cubo de filtro dicroico/de emisión XF100, y los filtros de excitación de acoplamiento, amplificación 10x, y un objetivo de apertura numérica 0.3. La adquisición y análisis de la imagen se puede llevar a cabo utilizando un protocolo a la medida basado en la Bioaplicación de 'NuclearTranslocation' (Translocalización Nuclear). Para cada cavidad, se pueden adquirir múltiples imágenes (campos) hasta que se cuenten un mínimo de 1000 células utilizando dos (2) canales: Canal 1 (Hoechst) = foco + máscara nuclear, Canal 2 (GFP) = cuantificación de señal en áreas de máscara, como se ilustra más adelante.

Primero se pueden identificar los núcleos basándose en el teñido Hoechst, y entonces una máscara generada para cada núcleo sirve como una plantilla para generar un círculo (erosionado hacia dentro por 1 pixel), y un anillo tipo collar de 3 pixeles de anchura (desfasamiento hacia fuera por 1 pixel), en donde se cuantifica la intensidad nuclear y citoplásmica de la proteína fluorescente verde, respectivamente, en el canal correspondiente. El análisis de alto contenido proporciona numerosas mediciones por célula, y se puede seleccionar el diferencial de intensidad de proteína fluorescente verde entre la máscara nuclear y la máscara citoplásmica, como una medida de la relocalización sub-celular de STAT-GFP. Los valores resultantes se pueden promediar para todas las células en el cavidad, para devolver una sola medición más la desviación estándar.

minuto. Las placas entonces se pueden lavar una vez en suero regulado con fosfato, y finalmente se agregan 200 microlitros de suero regulado con fosfato por cavidad. Las placas, siendo finalmente cubiertas con un adhesivo negro, se pueden leer directamente, o bien se pueden almacenar a 4°C para la toma de imágenes posterior. Cuando sea apropiado, los compuestos se pueden agregar 30 minutos antes del estímulo con IFN-γ.

Las U-2 OS se pueden sembrar a una densidad celular de 12'000 células por cavidad, en placas Packard View-Plates$^{MR}$ de 96 cavidades, negras, de fondo transparente. Al día siguiente, se puede remover el medio, y es reemplazado con medio que contiene ya sea el vehículo (sulfóxido de dimetilo), o concentraciones crecientes de los compuestos de prueba durante 30 minutos a 37°C. Las células se pueden estimular entonces durante 1 hora mediante la adición de 10 microlitros por cavidad de 50 Unidades/mililitro de rhEpo, para obtener 5 Unidades/mililitro de rhEpo como la concentración final. En seguida de los tratamientos, las células se pueden fijar y procesar como se describe anteriormente.

***Medición de translocalización nuclear de STAT-GFP mediante toma de imágenes y análisis del microscopio de fluorescencia automatizado Cellomics:***

Las placas se pueden leer en un lector de placas de microscopio de fluorescencia automatizado Cellomics® ArrayscanII equipado con una fuente de iluminación de luz blanca de Mercurio-

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***Preparación de suministros de compuestos:***

Los compuestos se pueden disolver en sulfóxido de dimetilo hasta una concentración final de suministro de 10 mM, y se almacenan como alícuotas a 4°C. Los compuestos se pueden diluir previamente en sulfóxido de dimetilo al 100 por ciento a 10 mM, 3 mM, 1 mM, 0.3 mM, 0.1 mM, 0.03 mM, 0.01 mM, y 0.003 mM. Subsiguientemente, los compuestos se pueden diluir en el medio, y se agregan en 50 microlitros a las células. Las concentraciones finales de los compuestos probadas pueden ser de 10 µM, 3 µM, 1 µM, 0.3 µM, 0.1 µM, 0.03 µM, 0.01 µM y 0.003 µM, y la concentración final de sulfóxido de dimetilo puede ser del 0.1 por ciento.

***Ensayos de translocalización nuclear de STAT-GFP Cellomics:***

Las células HT1080 STAT1-GFP se pueden sembrar a una densidad de 10'000 células por cavidad en placas Packard View-Plates$^{MR}$ de 96 cavidades, negras, de fondo transparente. De 16 a 24 horas después, las células se pueden tratar durante 2 horas con 100 nanogramos/mililitro de IFN-γ, se lavan dos veces en suero regulado con fosfato previamente calentado, y se fijan en 200 microlitros de solución de fijación previamente calentada (suero regulado con fosfato, formaldehído al 3.7 por ciento) durante 10 minutos. Las placas se pueden lavar dos veces en 200 microlitros de suero regulado con fosfato, y se incuban, protegidas de la luz, en 100 microlitros de solución de teñido de ADN (suero regulado con fosfato, 0.5 microgramos/mililitro de Hoechst-33342) durante 1

***Generación de células de fibrosarcoma HT1080 que expresan establemente GFP-STAT1:***

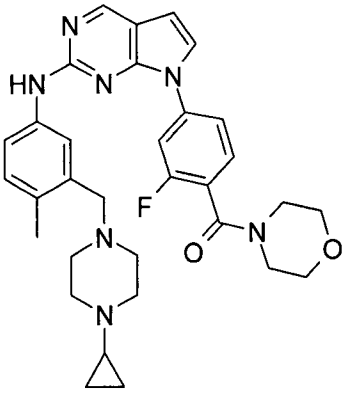
Las células de fibrosarcoma HT1080 se pueden obtener a partir de ATCC, y se pueden cultivar en un Medio de Eagle Modificado alfa, con suero fetal de becerro al 10 por ciento. Las células se pueden transfectar con pEGFP-N2 STAT1 utilizando el reactivo de transfección Fugene 6, siguiendo el protocolo de los fabricantes. 24 horas después de la transfección, el medio puede ser reemplazado y seleccionado en 1 miligramo/mililitro de Geneticina.

***Generación de células U2OS que expresan establemente STAT5a-GFP y EpoR:***

Las células de osteosarcoma U-2 OS se pueden obtener a partir de ATCC, y se pueden cultivar en un medio RPMI estándar complementado con suero fetal de becerro al 10 por ciento y L-glutamina 2 mM. Las células se pueden transfectar establemente con STAT5a-GFP utilizando Lipofectamina, siguiendo el protocolo de los fabricantes. 24 horas después de la transfección, el medio puede ser reemplazado y seleccionado en 400 microgramos/mililitro de Geneticina. Subsiguientemente, las células se pueden transfectar establemente con EpoR utilizando Lipofectamina, siguiendo el protocolo de los fabricantes. 24 horas después de la transfección, el medio puede ser reemplazado, y las células se seleccionan en 100 microgramos/mililitro de Higromicina B.

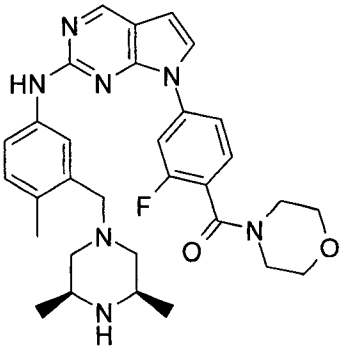
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.94 minutos. (Método B); MS-ES: $(M+H)^+$ = 574; TLC*: $R_f$ = 0.38

**Ejemplo 366: (4-{2-[3-(4-ciclopropil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



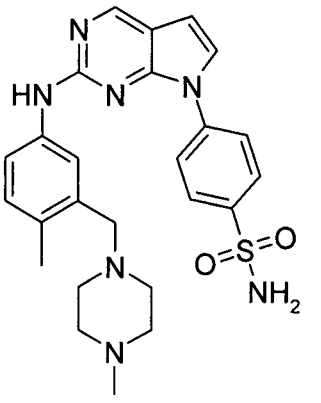
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.62 minutos. (Método B); MS-ES: $(M+H)^+$ = 570; TLC*: $R_f$ = 0.55

**Ejemplo 367: (4-{2-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



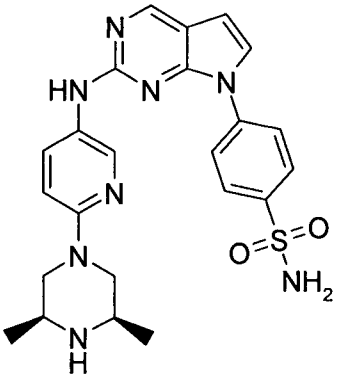
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.41 minutos (Método B); MS-ES: $(M+H)^+$ = 558

**Ejemplo 368: 4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.84 minutos (Método B); MS-ES: $(M+H)^+$ = 492; TLC*: $R_f$ = 0.03

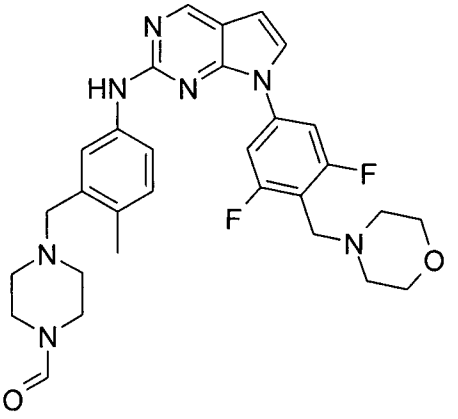
**Ejemplo 369: 4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



El compuesto se prepara de una manera análoga al Ejemplo 2.

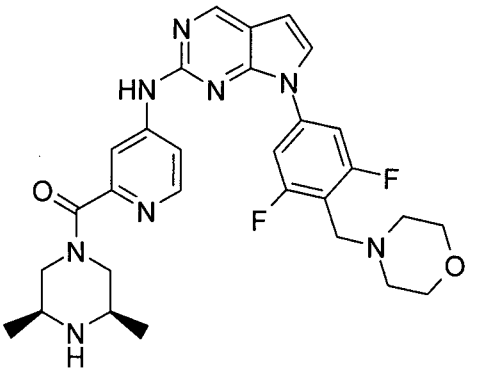
HPLC: $t_R$ = 6.67 minutos (Método B); MS-ES: $(M+H)^+$ = 479; TLC (50 por ciento de metanol / 50 por ciento de cloruro de metileno): $R_f$ = 0.26

**Ejemplo 370: 4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-1-carbaldehído**



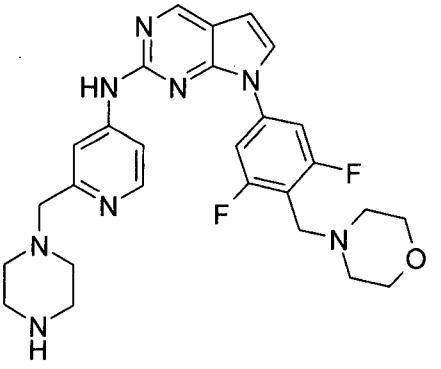
El compuesto se obtiene mediante el tratamiento de la [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-piperazin-1-il-metil-fenil)-amina (Ejemplo 332) con 4-nitro-fenil-éster del ácido fórmico en la presencia de trietil-amina en tetrahidrofurano. HPLC: $t_R$ = 6.84 minutos (Método B); MS-ES: $(M+H)^+$ = 562

**Ejemplo 371: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(cis-3,5-dimetil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.53 minutos (Método B); MS-ES: $(M+H)^+$ = 563; TLC (15 por ciento de metanol / 85 por ciento de cloruro de metileno): $R_f$ = 0.28

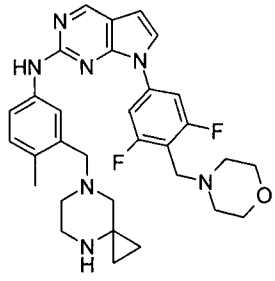
**Ejemplo 372: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2-piperazin-1-il-metil-piridin-4-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso

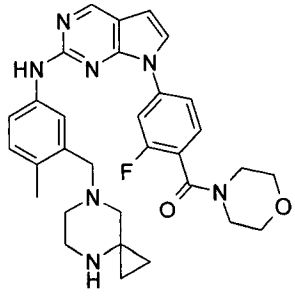
2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.52 minutos (Método B); MS-ES: $(M+H)^+$ = 521; TLC (64 por ciento de metanol / 32 por ciento de cloruro de metileno / 4 por ciento de amoníaco acuoso al 24 por ciento): $R_f$ = 0.49

**Ejemplo 373: [3-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



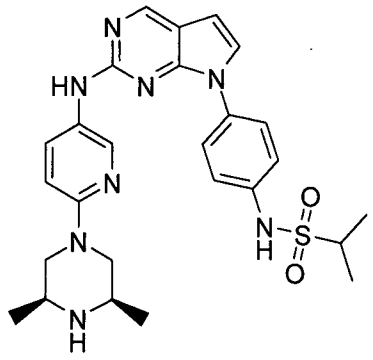
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.62 minutos (Método B); MS-ES: $(M+H)^+$ = 560

**Ejemplo 374: (4-{2-[3-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



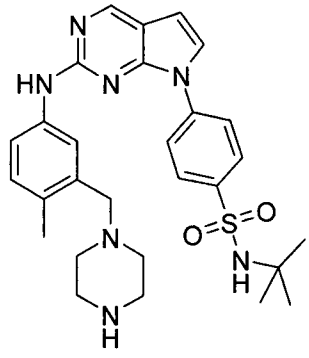
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.33 minutos (Método B); MS-ES: $(M+H)^+$ = 556

**Ejemplo 375: (4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-amida del ácido propan-2-sulfónico**



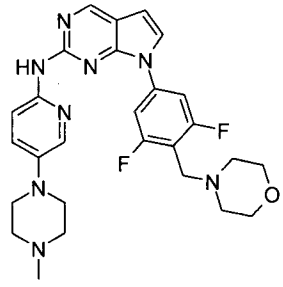
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.26 minutos (Método B); MS-ES: $(M+H)^+$ = 521; TLC (50 por ciento de metanol / 50 por ciento de cloruro de metileno): $R_f$ = 0.30

**Ejemplo 376: N-terbutil-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida**



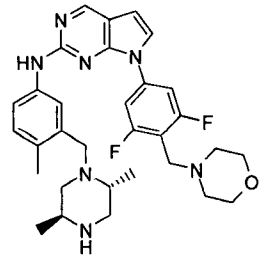
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 7.86 minutos (Método B); MS-ES: $(M+H)^+$ = 534; TLC (50 por ciento de metanol / 50 por ciento de cloruro de metileno): $R_f$ = 0.09

**Ejemplo 377: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[5-(4-metil-piperazin-1-il)-piridin-2-il]-amina**



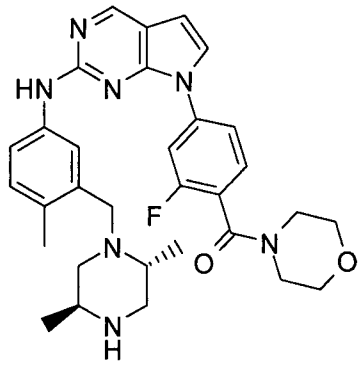
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.90 minutos (Método C); MS-ES: $(M+H)^+$ = 521

**Ejemplo 378: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina (racémica)**



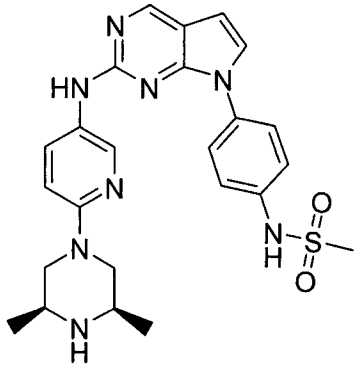
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.73 minutos (Método B); MS-ES: $(M+H)^+$ = 562; TLC (metanol al 100 por ciento): $R_f$ = 0.11

**Ejemplo 379: (4-{2-[3-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona (racémica)**



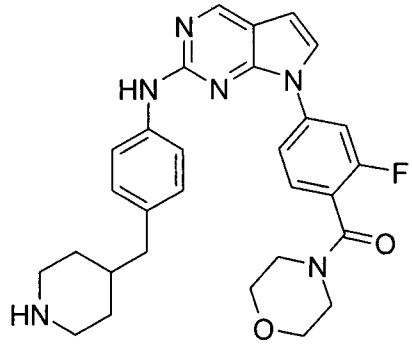
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.38 minutos (Método B); MS-ES: $(M+H)^+$ = 558; TLC (metanol al 100 por ciento): $R_f$ = 0.12

**Ejemplo 380: N-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metan-sulfonamida**



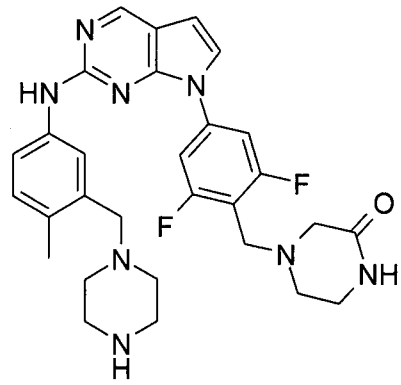
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.89 minutos (Método B); MS-ES: $(M+H)^+$ = 493; TLC (50 por ciento de metanol / 50 por ciento de cloruro de metileno): $R_f$ = 0.25

**Ejemplo 381: {2-fluoro-4-[2-(4-piperidin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



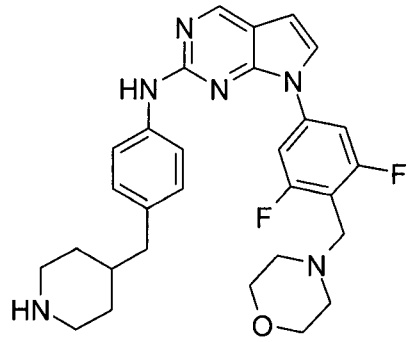
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperidina protegido por trifluoro-acetilo en el paso 2.2. La desprotección final se logra con $K_2CO_3$ en metanol / agua a temperatura ambiente. La anilina correspondiente se obtiene mediante el procedimiento descrito en la Publicación Internacional Número WO98/05292 páginas 104-105, compuesto (111), seguido por reducción de nitro. HPLC: $t_R$ = 7.52 minutos (Método B); MS-ES: $(M+H)^+$ = 515; TLC (50 por ciento de metanol / 50 por ciento de cloruro de metileno): $R_f$ = 0.06

**Ejemplo 382: 4-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.64 minutos (Método B); MS-ES: $(M+H)^+$ = 547

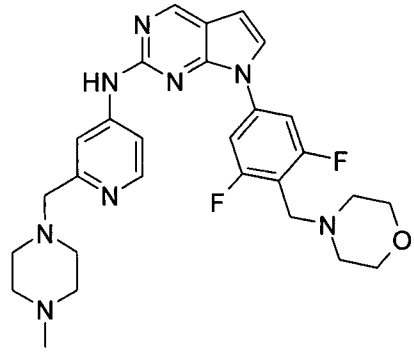
**Ejemplo 383: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperidin-4-il-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperidina protegido por trifluoro-acetilo en

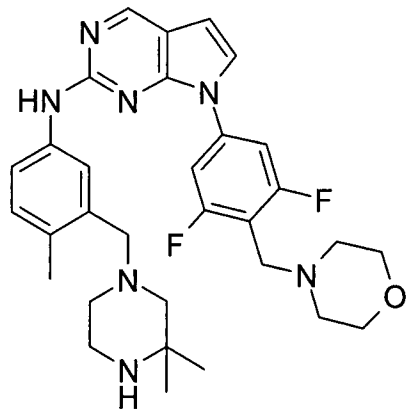
el paso 2.2. La desprotección final se logra con $K_2CO_3$ en metanol / agua a temperatura ambiente. La anilina correspondiente se obtiene mediante el procedimiento descrito en la Publicación Internacional Número WO98/05292 páginas 104-105, compuesto (111), seguido por reducción de nitro. HPLC: $t_R$ = 6.93 minutos (Método B); MS-ES: $(M+H)^+$ = 519; TLC (49 por ciento de metanol / 49 por ciento de cloruro de metileno / 2 por ciento de amoníaco 7N en metanol): $R_f$ = 0.06

**Ejemplo 384: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(4-metil-piperazin-1-il-metil)-piridin-4-il]-amina**



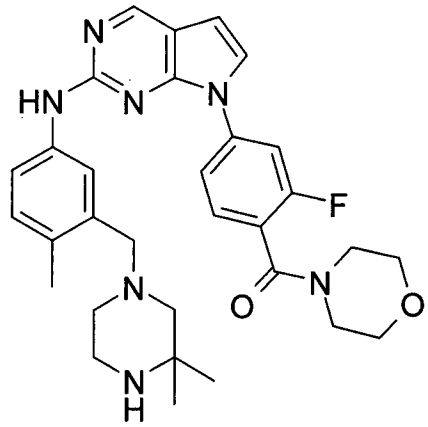
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.57 minutos (Método B); MS-ES: $(M+H)^+$ = 535

**Ejemplo 385: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3,3-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.03 minutos (Método B); MS-ES: $(M+H)^+$ = 562

**Ejemplo 386: (4-{2-[3-(3,3-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**

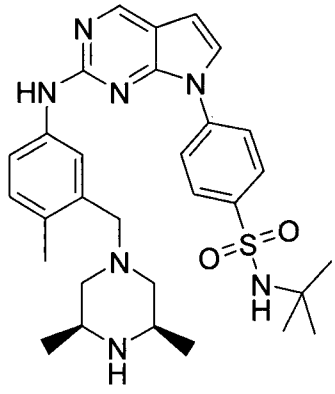


El compuesto se prepara de una manera análoga al Ejemplo 2.

333

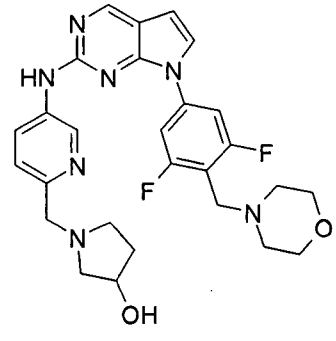
HPLC: $t_R$ = 7.82 minutos (Método B); MS-ES: $(M+H)^+$ = 558

**Ejemplo 387: N-terbutil-4-{2-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



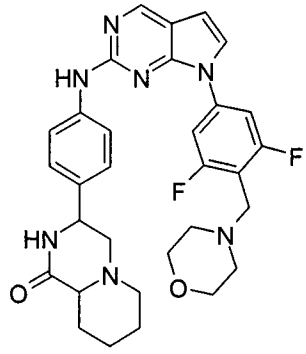
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.06 minutos (Método B); MS-ES: $(M+H)^+$ = 562; TLC (33 por ciento de metanol / 67 por ciento de cloruro de metileno): $R_f$ = 0.23

**Ejemplo 388: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-pirrolidin-3-ol (racémico)**



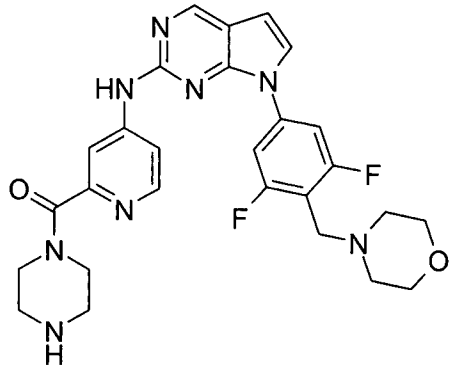
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.00 minutos (Método C); MS-ES: $(M)^+$ = 521

**Ejemplo 389: 3-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-hexahidro-pirido-[1,2-a]-pirazin-1-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.60 minutos (Método G); MS-ES: $(M+H)^+$ = 574

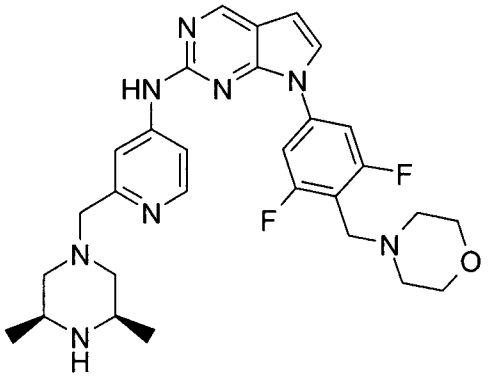
**Ejemplo 390: {4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-1-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2,

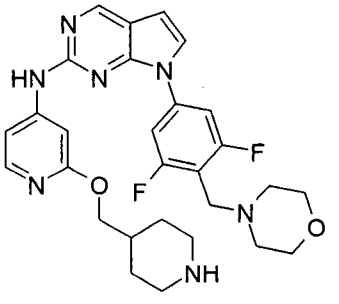
utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.37 minutos (Método B); MS-ES: $(M+H)^+$ = 535

**Ejemplo 391: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(cis-3,5-dimetil-piperazin-1-il-metil)-piridin-4-il]-amina**



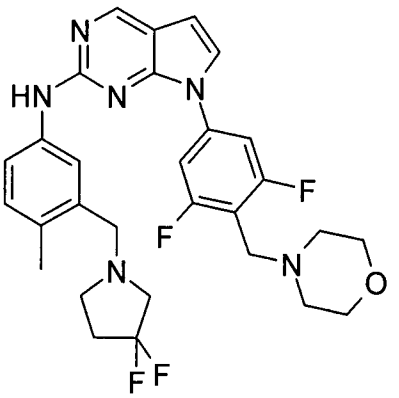
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.75 minutos (Método B); MS-ES: $(M+H)^+$ = 549

**Ejemplo 392: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(piperidin-4-il-metoxi)-piridin-4-il]-amina**



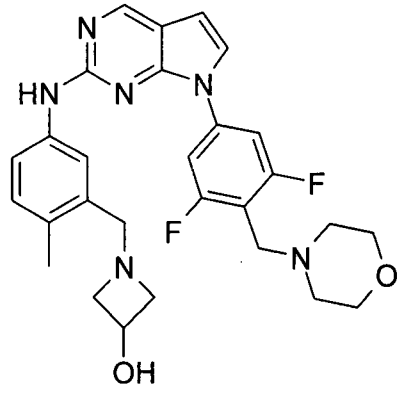
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.67 minutos (Método B); MS-ES: $(M+H)^+$ = 536; TLC (33 por ciento de metanol / 66 por ciento de cloruro de metileno / 1 por ciento de amoníaco acuoso al 24 por ciento): $R_f$ = 0.28

**Ejemplo 393: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3,3-difluoro-pirrolidin-1-il-metil)-4-metil-fenil]-amina**



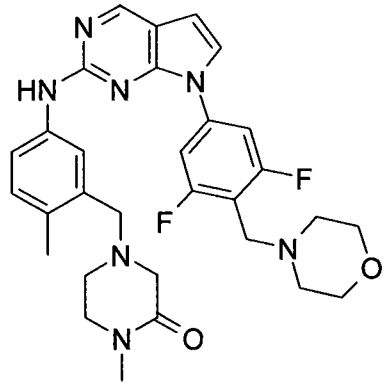
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.08 minutos (Método B); MS-ES: $(M+H)^+$ = 555; TLC*: $R_f$ = 0.63

**Ejemplo 394: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-azetidin-3-ol**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.67 minutos (Método B); MS-ES: $(M+H)^+$ = 521; TLC (20 por ciento de metanol / 80 por ciento de cloruro de metileno): $R_f$ = 0.36

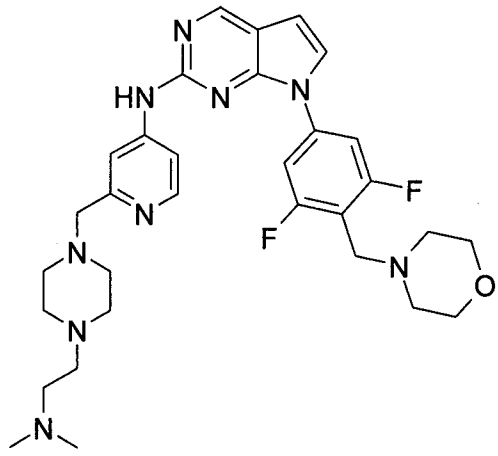
**Ejemplo 395: 4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1-metil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 6.83 minutos (Método B); MS-ES: $(M+H)^+$ = 562

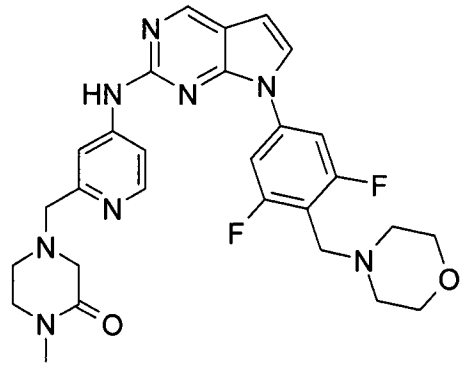
**Ejemplo 396: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{2-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-piridin-4-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 6.51 minutos (Método B); MS-ES: $(M+H)^+$ = 592

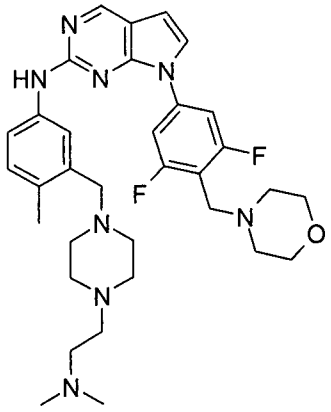
**Ejemplo 397: 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-1-metil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 7.00 minutos (Método B); MS-ES: $(M+H)^+$ = 579

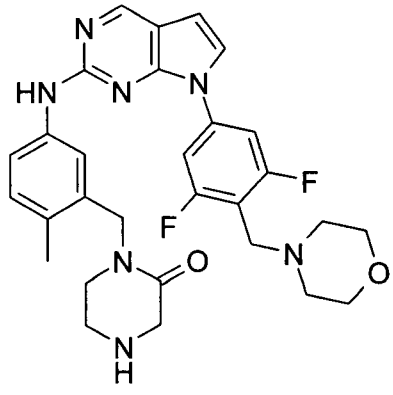
**Ejemplo 398: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{3-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-4-metil-fenil}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

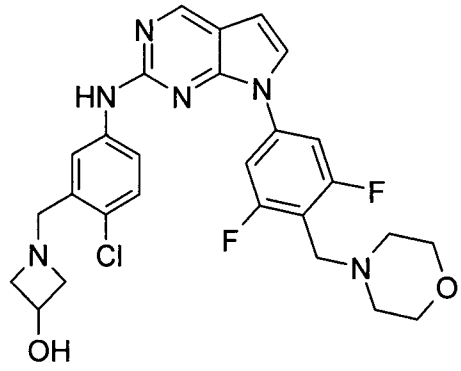
HPLC: $t_R$ = 6.81 minutos (Método B); MS-ES: $(M+H)^+$ = 605

**Ejemplo 399: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-2-ona**



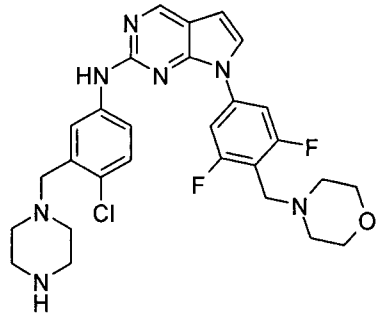
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.76 minutos (Método B); MS-ES: $(M+H)^+$ = 548; TLC*: $R_f$ = 0.27

**Ejemplo 400: 1-{2-cloro-5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-azetidin-3-ol**



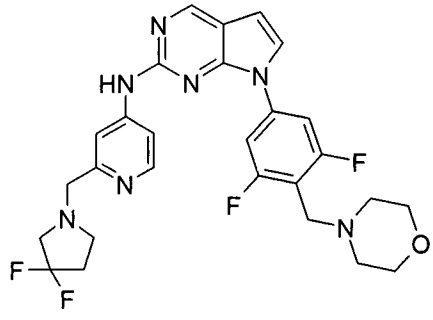
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.04 minutos (Método B); MS-ES: $(M+H)^+$ = 541

**Ejemplo 401: (4-cloro-3-piperazin-1-il-metil-fenil)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



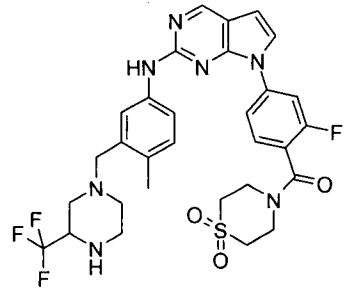
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.93 minutos (Método B); MS-ES: $(M+H)^+$ = 554

**Ejemplo 402: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3,3-difluoro-pirrolidin-1-il-metil)-piridin-4-il]-amina**



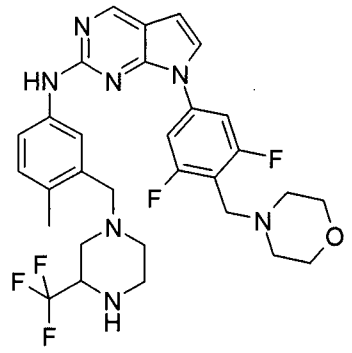
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.71 minutos (Método B); MS-ES: $(M+H)^+$ = 542

**Ejemplo 403: (1,1-dióxido-tiomorfolin-4-il)-(2-fluoro-4-{2-[4-metil-3-(3-trifluoro-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanona (racémica)**



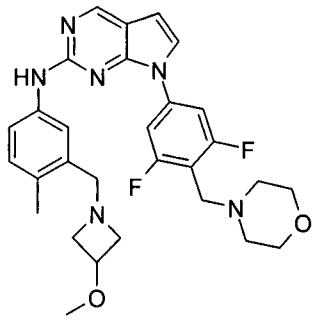
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.74 minutos (Método B); MS-ES: $(M+H)^+$ = 646; TLC*: $R_f$ = 0.41

**Ejemplo 404: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(3-trifluoro-metil-piperazin-1-il-metil)-fenil]-amina (racémica)**



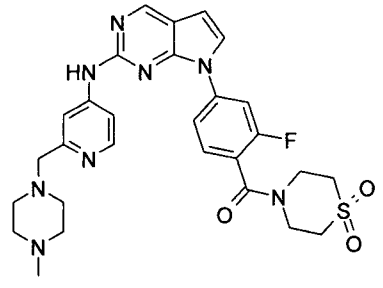
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.25 minutos (Método B); MS-ES: $(M+H)^+$ = 602; TLC*: $R_f$ = 0.31

**Ejemplo 405: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3-metoxi-azetidin-1-il-metil)-4-metil-fenil]-amina**



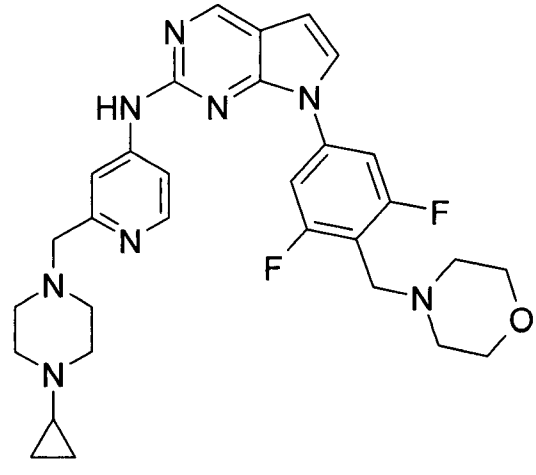
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.02 minutos (Método B); MS-ES: $(M+H)^+$ = 535; TLC*: $R_f$ = 0.19

**Ejemplo 406: (1,1-dióxido-tiomorfolin-4-il)-(2-fluoro-4-{2-[2-(4-metil-piperazin-1-il-metil)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanona**



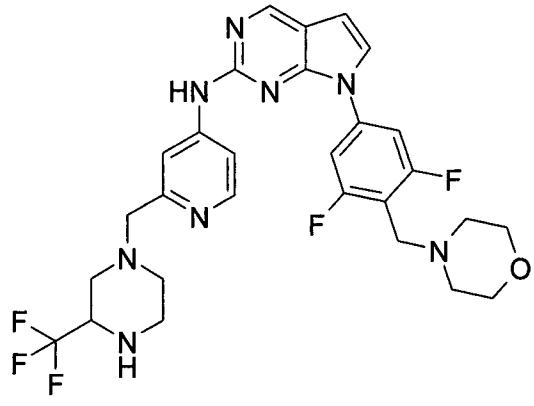
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.18 minutos (Método B); MS-ES: $(M+H)^+$ = 579

**Ejemplo 407: [2-(4-ciclopropil-piperazin-1-il-metil)-piridin-4-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



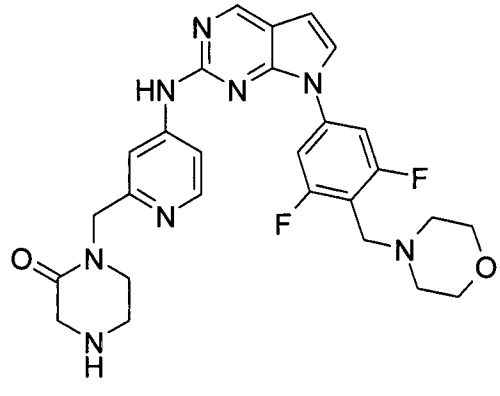
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.81 minutos (Método B); MS-ES: $(M+H)^+$ = 561

**Ejemplo 408: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-trifluoro-metil-piperazin-1-il-metil)-piridin-4-il]-amina (racémica)**



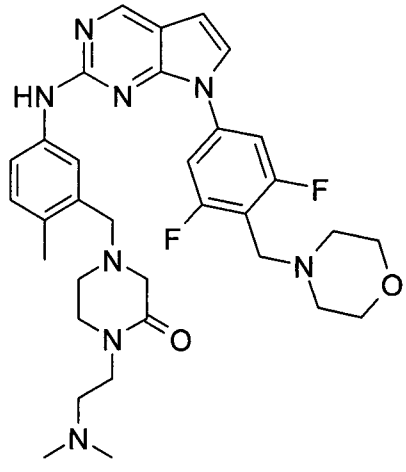
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.85 minutos (Método B); MS-ES: $(M+H)^+$ = 589

**Ejemplo 409: 1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-piperazin-2-ona**



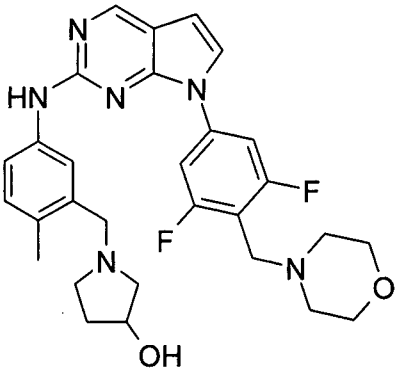
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.38 minutos (Método B); MS-ES: $(M+H)^+$ = 535

**Ejemplo 410: 4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1-(2-dimetil-amino-etil)-piperazin-2-ona**



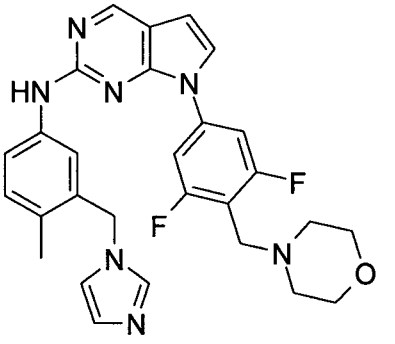
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.86 minutos (Método B); MS-ES: $(M+H)^+$ = 619; TLC*: $R_f$ = 0.14

**Ejemplo 411: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-pirrolidin-3-ol (racémico)**



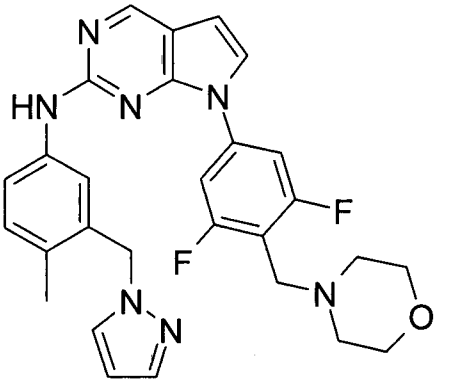
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.81 minutos (Método B); MS-ES: $(M+H)^+$ = 535; TLC* con el 1 por ciento de amoníaco acuoso al 24 por ciento: $R_f$ = 0.66

**Ejemplo 412: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-imidazol-1-il-metil-4-metil-fenil)-amina**



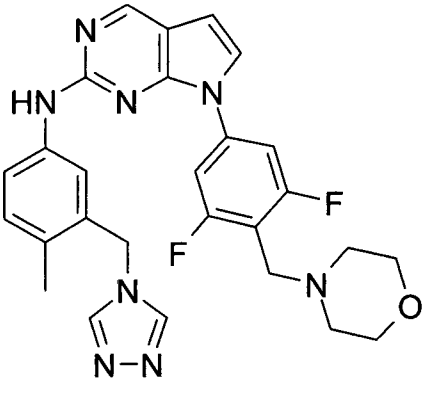
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.90 minutos (Método B); MS-ES: $(M+H)^+$ = 516; TLC*: $R_f$ = 0.52

**Ejemplo 413: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-pirazol-1-il-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.81 minutos (Método B); MS-ES: $(M+H)^+$ = 516; TLC*: $R_f$ = 0.77

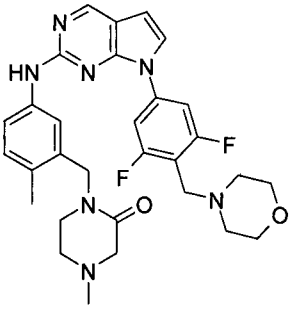
**Ejemplo 414: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-[1,2,4]-triazol-4-il-metil-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.30 minutos (Método B); MS-ES: $(M+H)^+$ = 517; TLC*: $R_f$

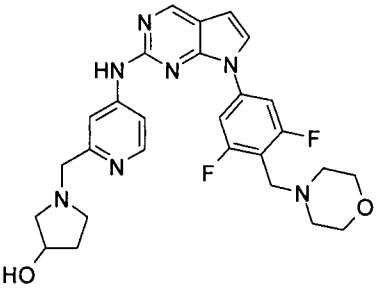
= 0.40

**Ejemplo 415: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-4-metil-piperazin-2-ona**



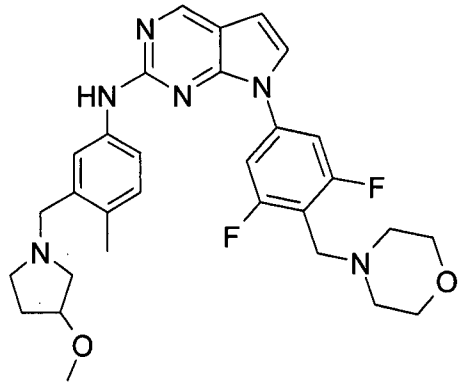
El compuesto se obtiene a partir de la reacción de la 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-2-ona (Ejemplo 399) con formaldehído y ciano-borohidruro de sodio en metanol y dicloro-metano, 2:1, a temperatura ambiente. HPLC: $t_R$ = 6.91 minutos (Método B); MS-ES: $(M+H)^+$ = 562; TLC*: $R_f$ = 0.28

**Ejemplo 416: 1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-pirrolidin-3-ol (racémico)**



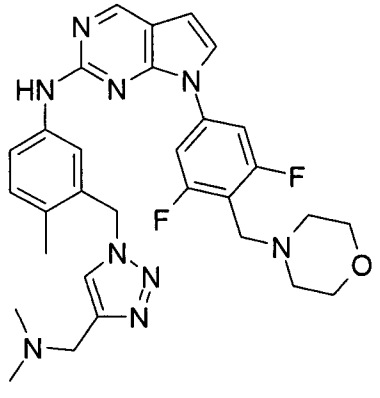
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.45 minutos (Método B); MS-ES: $(M+H)^+$ = 522

**Ejemplo 417: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-l]-[3-(3-metoxi-pirrolidin-1-il-metil)-4-metil-fenil]-amina (racémica)**



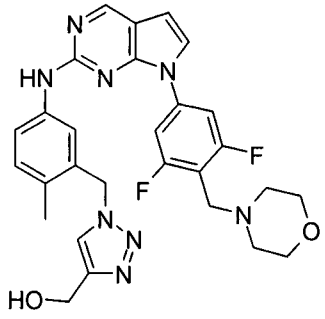
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.22 minutos (Método B); MS-ES: $(M+H)^+$ = 549

**Ejemplo 418: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-dimetil-amino-metil-[1,2,3]-triazol-1-il-metil)-4-metil-fenil]-amina**



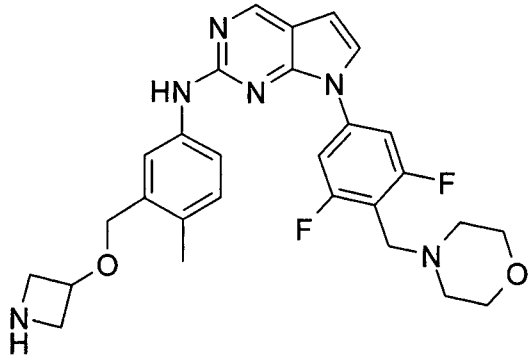
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.11 minutos (Método B); MS-ES: $(M+H)^+$ = 574; TLC*: $R_f$ = 0.19

**Ejemplo 419: (1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1H-[1,2,3]-triazol-4-il)-metanol**



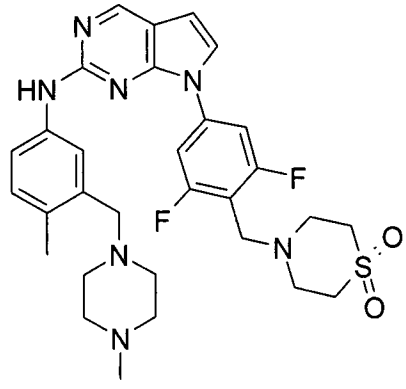
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.19 minutos (Método B); MS-ES: $(M+H)^+$ = 547; TLC*: $R_f$ = 0.31

**Ejemplo 420: [3-(Azetidin-3-iloxi-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



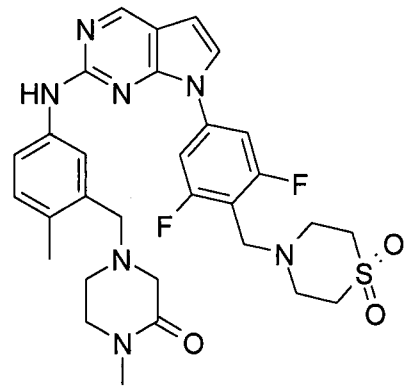
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 6.98 minutos (Método B); MS-ES: $(M+H)^+$ = 521

**Ejemplo 421: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil]-amina**



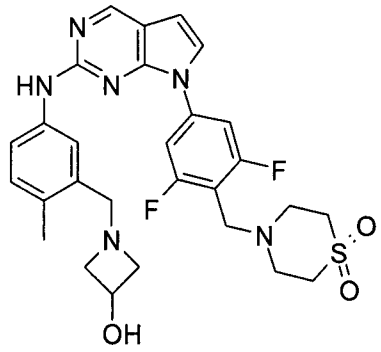
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.63 minutos (Método B); MS-ES: $(M+H)^+$ = 596; TLC*: $R_f$ = 0.17

**Ejemplo 422: 4-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-1-metil-piperazin-2-ona**



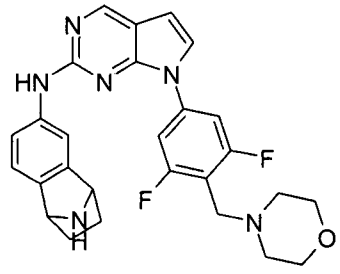
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.71 minutos (Método B); MS-ES: $(M+H)^+$ = 610; TLC*: $R_f$ = 0.23

**Ejemplo 423: 1-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-azetidin-3-ol**



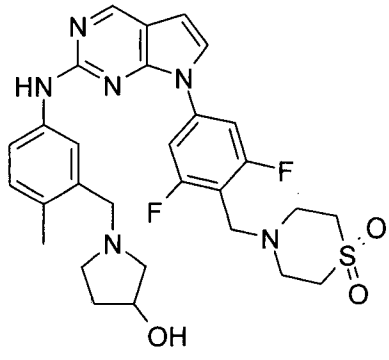
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.55 minutos (Método B); MS-ES: $(M+H)^+$ = 569; TLC*: $R_f$ = 0.14

**Ejemplo 424: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1,2,3,4-tetrahidro-1,4-epiazano-naftalen-6-il)-amina**



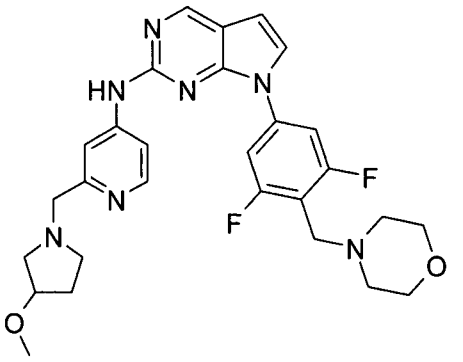
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano, y luego ácido trifluoro-acético a temperatura ambiente. El bloque de construcción de anilina se obtiene a partir de la Publicación Internacional Número WO 2007/072158, página 45, Esquema 4. HPLC: $t_R$ = 6.78 minutos (Método B); MS-ES: $(M+H)^+$ = 489; TLC (33 por ciento de metanol / 67 por ciento de cloruro de metileno): $R_f$ = 0.52

**Ejemplo 425: 1-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-pirrolidin-3-ol (racémico)**



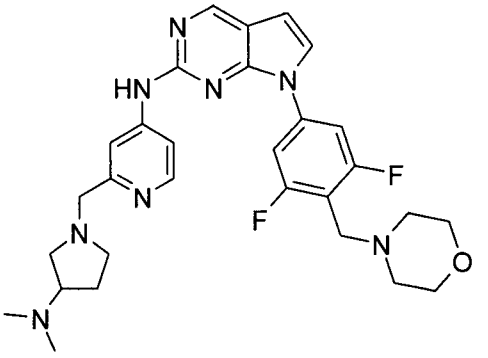
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.68 minutos (Método B); MS-ES: $(M+H)^+$ = 583; TLC*: $R_f$ = 0.10

**Ejemplo 426: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-metoxi-pirrolidin-1-il-metil)-piridin-4-il]-amina (racémica)**



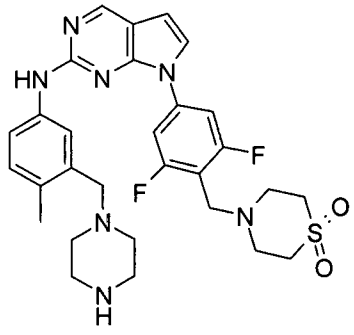
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.77 minutos (Método B); MS-ES: $(M+H)^+$ = 536

**Ejemplo 427: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-dimetil-amino-pirrolidin-1-il-metil)-piridin-4-il]-amina (racémica)**



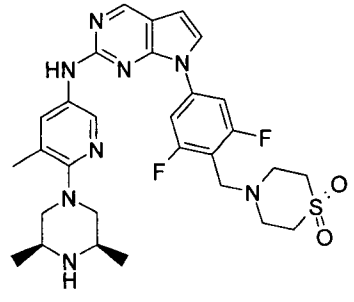
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.79 minutos (Método B); MS-ES: $(M+H)^+$ = 549

**Ejemplo 428: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-metil-3-piperazin-1-il-metil-fenil)-amina**



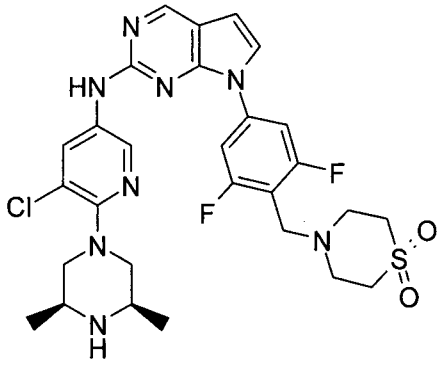
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 4M en dioxano a temperatura ambiente. HPLC: $t_R$ = 7.43 minutos (Método B); MS-ES: $(M+H)^+$ = 582; TLC*: $R_f$ = 0.15

**Ejemplo 429: [6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



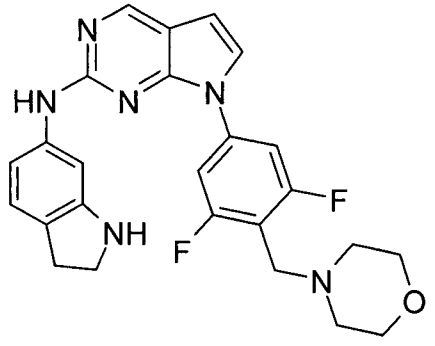
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.74 minutos (Método B); MS-ES: $(M+H)^+$ = 597; TLC*: $R_f$ = 0.06

**Ejemplo 430: [5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.33 minutos (Método B); MS-ES: $(M+H)^+$ = 617; TLC*: $R_f$ = 0.15

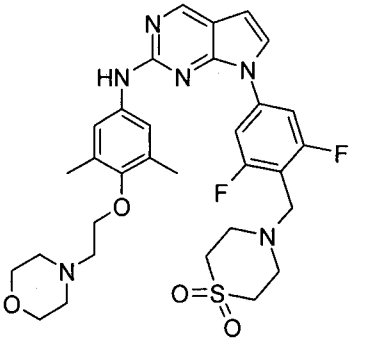
**Ejemplo 431: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2,3-dihidro-1H-indol-6-il)-amina**



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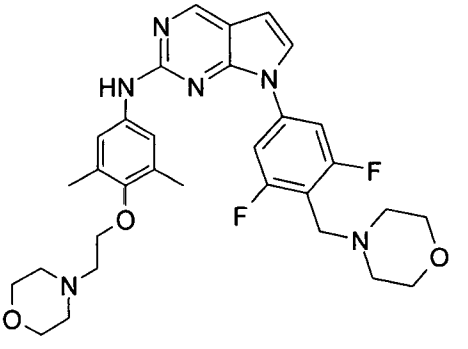
El compuesto se prepara de una manera análoga al Ejemplo 2 con el derivado de anilina obtenido a partir de la hidrogenación del 6-nitro-2,3-dihidro-1H-indol. HPLC: $t_R$ = 6.71 minutos (Método B); MS-ES: $(M+H)^+$ = 463; TLC**: $R_f$ = 0.24

**Ejemplo 432: [3,5-dimetil-4-(2-morfolin-4-il-etoxi)-fenil]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



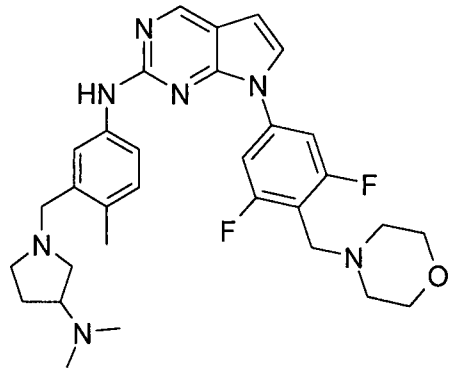
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.86 minutos (Método B); MS-ES: $(M+H)^+$ = 627

**Ejemplo 433: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3,5-dimetil-4-(2-morfolin-4-il-etoxi)-fenil]-amina**



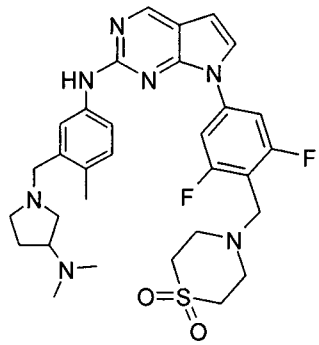
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.04 minutos (Método B); MS-ES: $(M+H)^+$ = 579

**Ejemplo 434: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3-dimetil-amino-pirrolidin-1-il-metil)-4-metil-fenil]-amina (racémica)**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.78 minutos (Método B); MS-ES: $(M+H)^+$ = 562

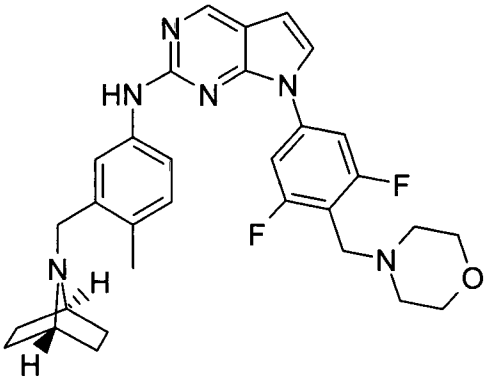
**Ejemplo 435: [3-(3-dimetil-amino-pirrolidin-1-il-metil)-4-metil-fenil]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina (racémica)**



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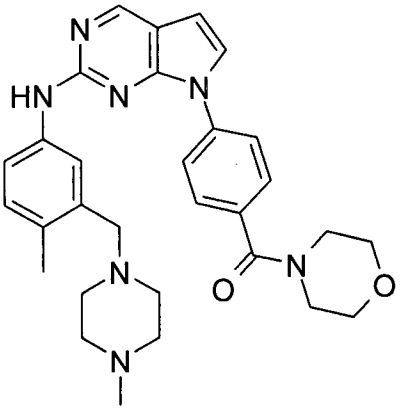
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.57 minutos (Método B); MS-ES: $(M+H)^+$ = 610

**Ejemplo 436: [3-(7-Aza-biciclo-[2.2.1]-hept-7-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



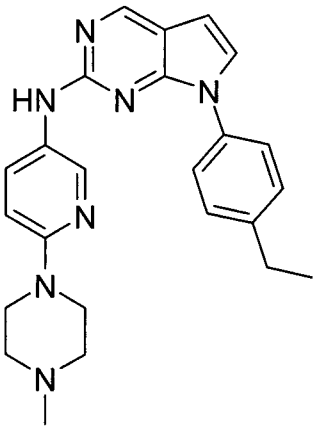
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.37 minutos (Método B); MS-ES: $(M+H)^+$ = 545

**Ejemplo 437: (4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona**



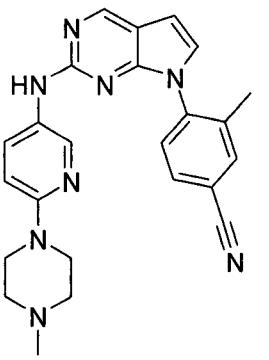
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.10 minutos (Método B); MS-ES: $(M+H)^+$ = 526; TLC*: $R_f$ = 0.23

**Ejemplo 438: [7-(4-etil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 4.79 minutos (Método F); MS-ES: $(M+H)^+$ = 414

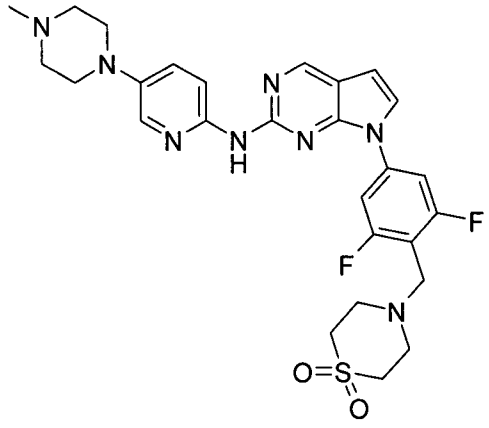
**Ejemplo 439: 3-metil-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 3.

HPLC: $t_R$ = 4.45 minutos (Método F); MS-ES: $(M+H)^+$ = 425

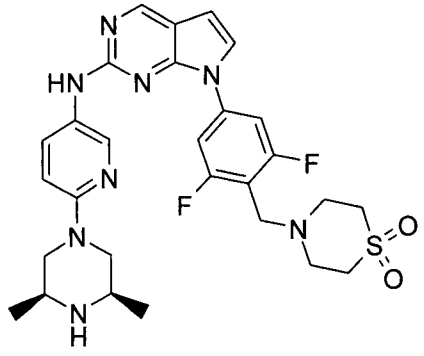
**Ejemplo 440: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[5-(4-metil-piperazin-1-il)-piridin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.29 minutos (Método F); MS-ES: $(M+H)^+$ = 569

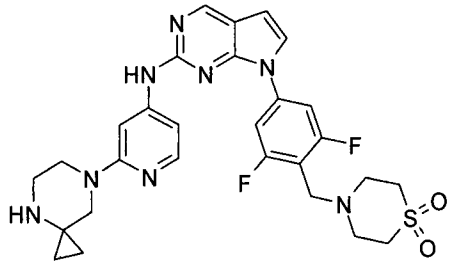
**Ejemplo 441: [6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

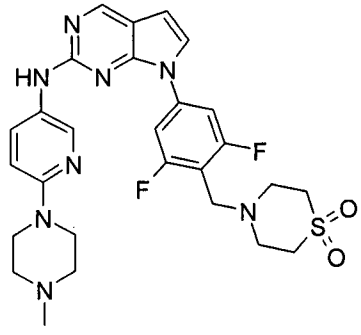
HPLC: $t_R$ = 4.40 minutos (Método F); MS-ES: $(M+H)^+$ = 583; TLC (20 por ciento de metanol / 80 por ciento de cloruro de metileno): $R_f$ = 0.32

**Ejemplo 442: [2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.48 minutos (Método F); MS-ES: $(M+H)^+$ = 581; TLC (20 por ciento de metanol / 80 por ciento de cloruro de metileno): $R_f$ = 0.38

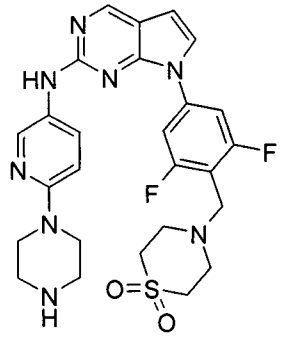
**Ejemplo 443: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina**



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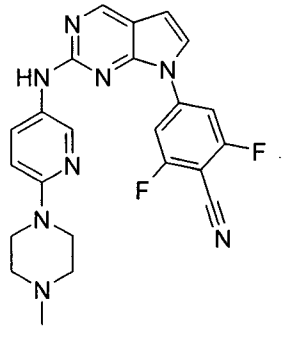
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.36 minutos (Método F); MS-ES: $(M+H)^+$ = 569

**Ejemplo 444: {7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(6-piperazin-1-il-piridin-3-il)-amina**



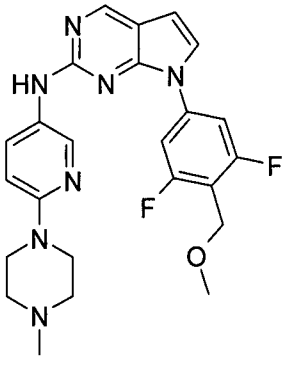
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 4.29 minutos (Método F); MS-ES: $(M+H)^+$ = 555

**Ejemplo 445: 2,6-difluoro-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo**



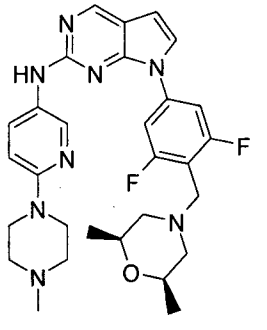
El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 4.74 minutos (Método F); MS-ES: $(M+H)^+$ = 447

**Ejemplo 446: [7-(3,5-difluoro-4-metoxi-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 3. El bromuro de arilo correspondiente se obtiene a partir de la reacción del (4-bromo-2,6-difluoro-fenil)-metanol con yodo-metano en la presencia de hidruro de sodio en tetrahidrofurano. HPLC: $t_R$ = 4.69 minutos (Método F); MS-ES: $(M+H)^+$ = 466

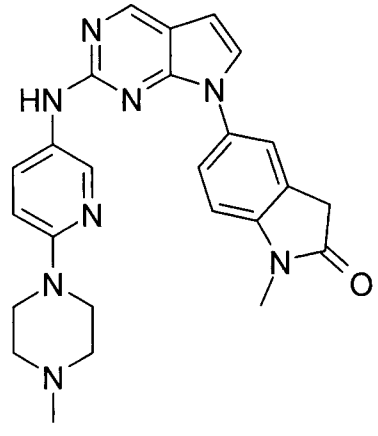
**Ejemplo 447: {7-[4-(cis-2,6-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.14 minutos (Método F); MS-ES: $(M+H)^+$ = 549

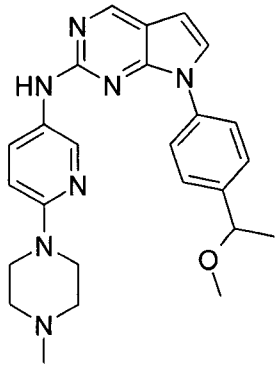
**Ejemplo 448: 1-metil-5-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-1,3-dihidro-indol-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 3.

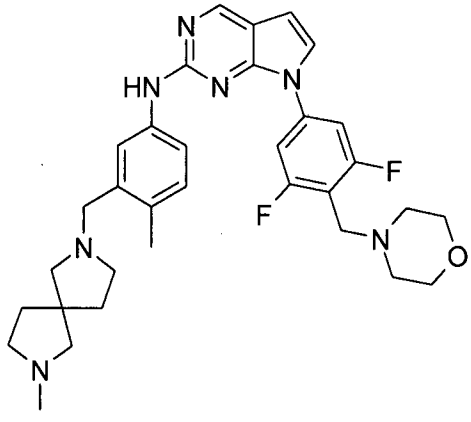
HPLC: $t_R$ = 4.25 minutos (Método F); MS-ES: $(M+H)^+$ = 455

**Ejemplo 449: {7-[4-(1-metoxi-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina (racémica)**



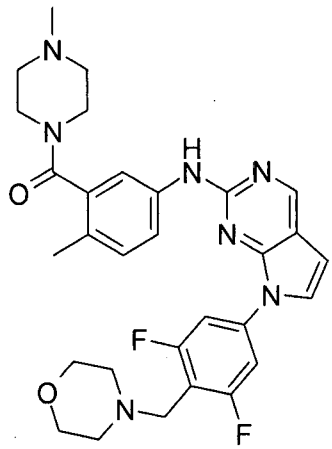
El compuesto se prepara de una manera análoga al Ejemplo 3. El bromuro de arilo correspondiente se obtiene a partir de la reacción del 1-(4-bromo-fenil)-etanol sobre yodo-metano bajo argón, en la presencia de hidruro de sodio en tetrahidrofurano. HPLC: $t_R$ = 4.54 minutos (Método F); MS-ES: $(M+H)^+$ = 444

**Ejemplo 450: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(7-metil-2,7-diaza-espiro-[4.4]-non-2-il-metil)-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 6.71 minutos (Método B); MS-ES: $(M+H)^+$ = 588; TLC (53 por ciento de cloroformo, 36 por ciento de metanol, 10 por ciento de agua, 0.5 por ciento de ácido acético): $R_f$ = 0.25

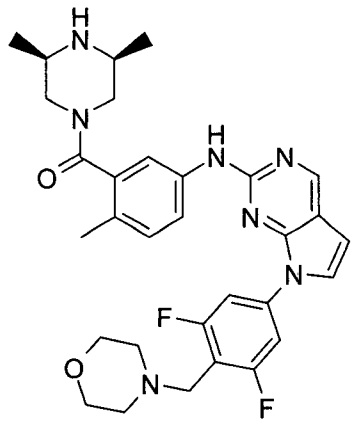
**Ejemplo 451: {5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 3.94 minutos (Método C); MS-ES: $(M+H)^+$ = 562

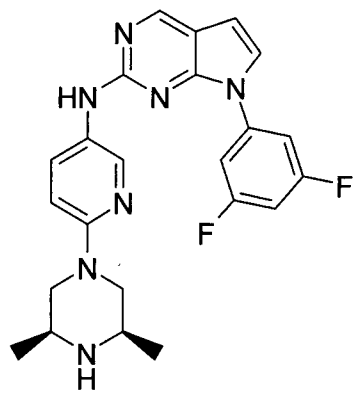
**Ejemplo 452: {5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(cis-3,5-dimetil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

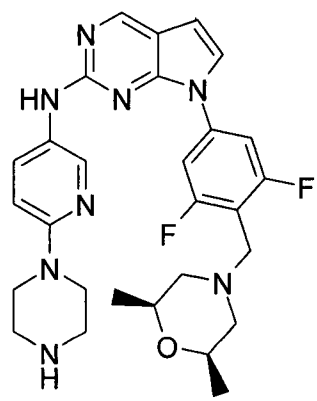
HPLC: $t_R$ = 4.00 minutos (Método C); MS-ES: $(M+H)^+$ = 576

Ejemplo 453: [7-(3,5-difluoro-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-amina



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.74 minutos (Método E1); MS-ES: $(M+H)^+$ = 436

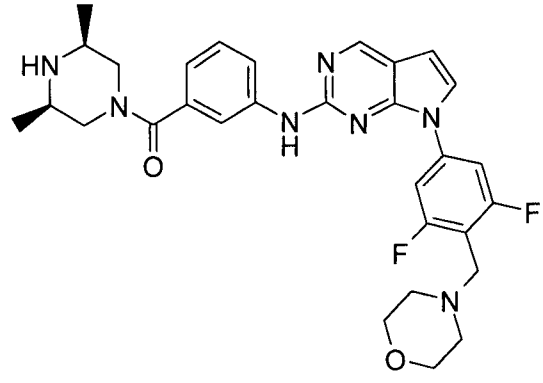
Ejemplo 454: {7-[4-(cis-2,6-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(6-piperazin-1-il-piridin-3-il)-amina



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 1.14 minutos (Método E2); MS-ES: $(M+H)^+$ = 535

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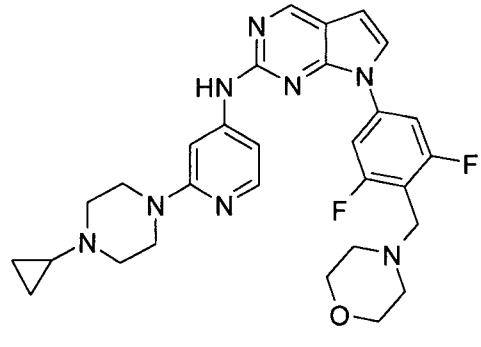
**Ejemplo 455: {3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(cis-3,5-dimetil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 3.97 minutos (Método C); MS-ES: $(M+H)^+$ = 562

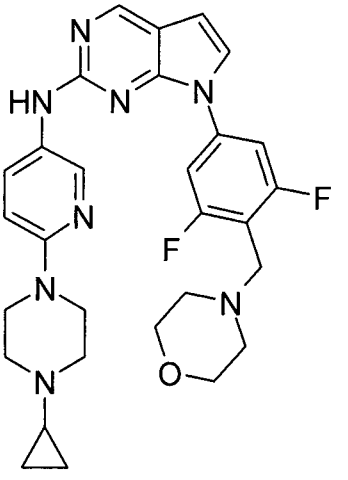
**Ejemplo 456: [2-(4-ciclopropil-piperazin-1-il)-piridin-4-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

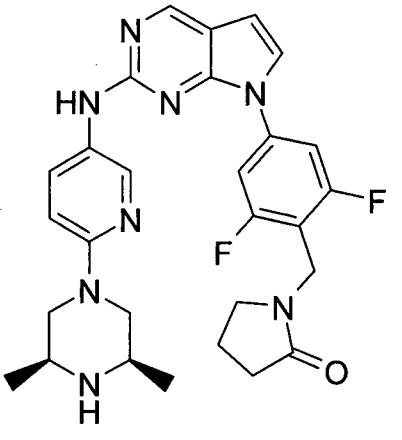
HPLC: $t_R$ = 3.96 minutos (Método C); MS-ES: $(M+H)^+$ = 547

**Ejemplo 457: [6-(4-ciclopropil-piperazin-1-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.89 minutos (Método C); MS-ES: $(M+H)^+$ = 547

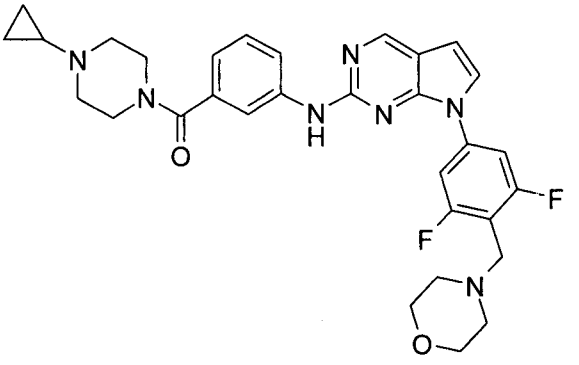
**Ejemplo 458: 1-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-pirrolidin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 0.81 minutos (Método E1); MS-ES: $(M+H)^+$ = 533

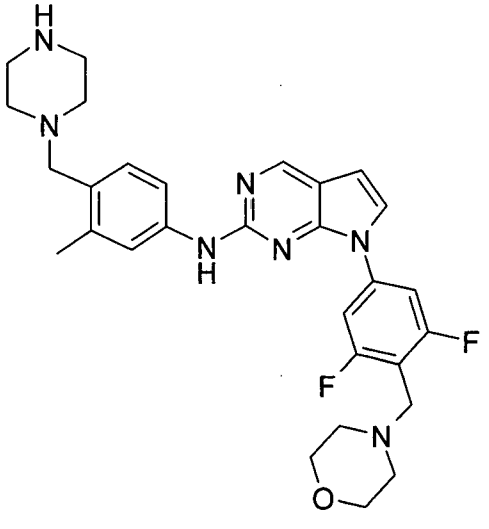
**Ejemplo 459: (4-ciclopropil-piperazin-1-il)-{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

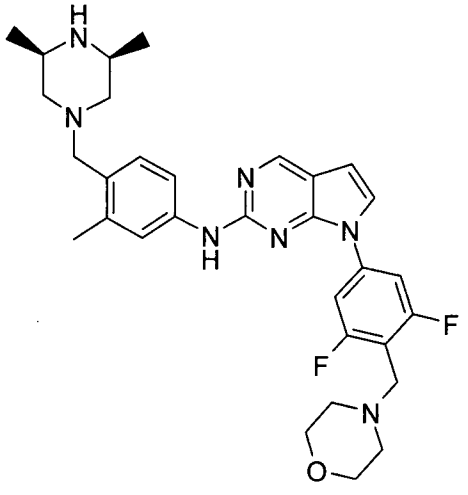
HPLC: $t_R$ = 4.02 minutos (Método C); MS-ES: $(M+H)^+$ = 574

**Ejemplo 460: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metil-4-piperazin-1-il-metil-fenil)-amina**



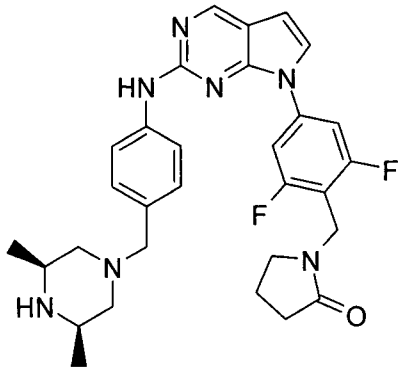
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.96 minutos (Método C); MS-ES: $(M+H)^+$ = 534

**Ejemplo 461: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-3-metil-fenil]-amina**



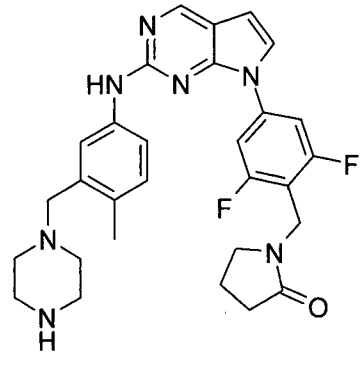
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.01 minutos (Método C); MS-ES: $(M+H)^+$ = 562

**Ejemplo 462: 1-(4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-pirrolidin-2-ona**



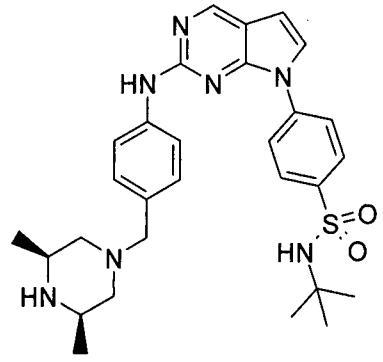
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.70 minutos (Método E1); MS-ES: $(M+H)^+$ = 546

**Ejemplo 463: 1-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-pirrolidin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 0.72 minutos (Método E1); MS-ES: $(M+H)^+$ = 532

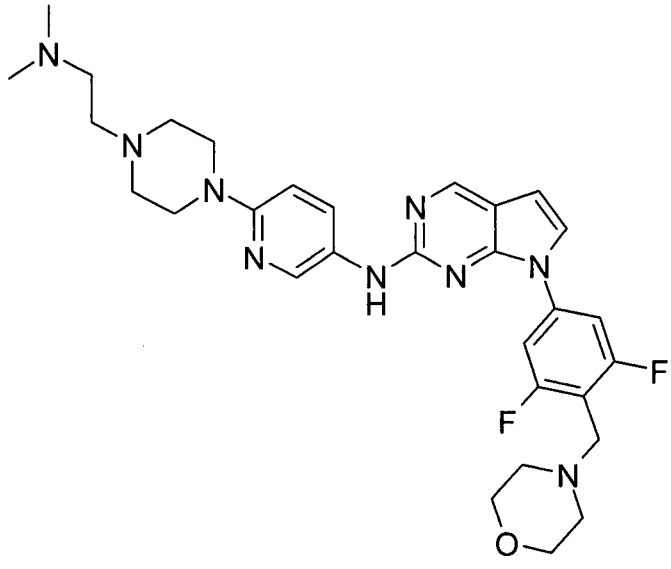
**Ejemplo 464: N-terbutil-4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 0.76 minutos (Método E1); MS-ES: $(M+H)^+$ = 548

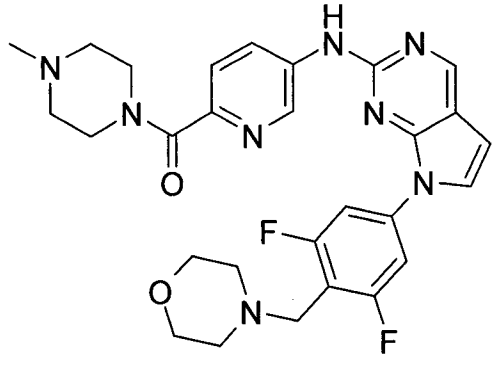
**Ejemplo 465: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{6-[4-(2-dimetil-amino-etil)-piperazin-1-il]-piridin-3-il}-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 3.84 minutos (Método C); MS-ES: $(M+H)^+$ = 578

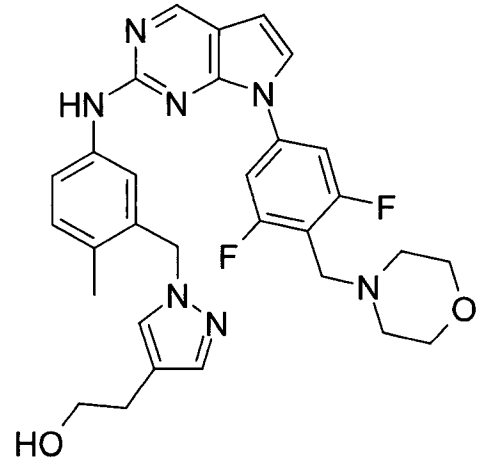
**Ejemplo 466: {5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(4-metil-piperazin-1-il)-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 3.99 minutos (Método F); MS-ES: $(M+H)^+$ = 549

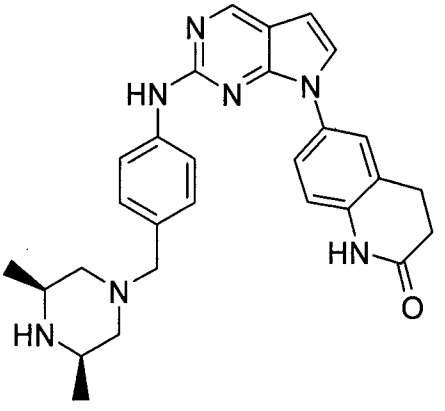
**Ejemplo 467: 2-(1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1H-pirazol-4-il)-etanol**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 7.34 minutos (Método B); MS-ES: $(M+H)^+$ = 560; TLC*: $R_f$ = 0.36

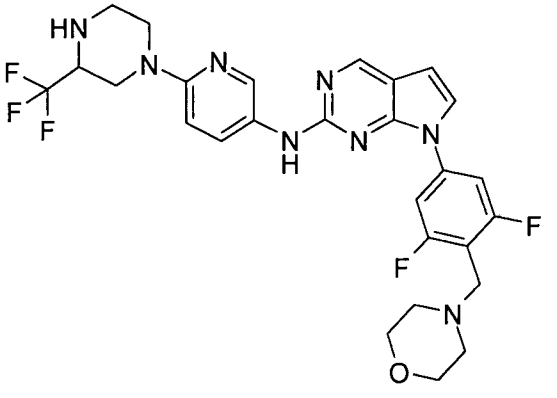
**Ejemplo 468: 6-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-3,4-dihidro-1H-quinolin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

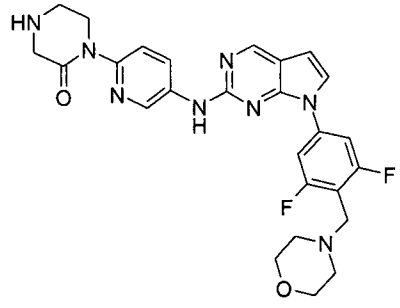
HPLC: $t_R$ = 0.49 minutos (Método E1); MS-ES: $(M+H)^+$ = 482

**Ejemplo 469: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(3-trifluoro-metil-piperazin-1-il)-piridin-3-il]-amina (racémica)**



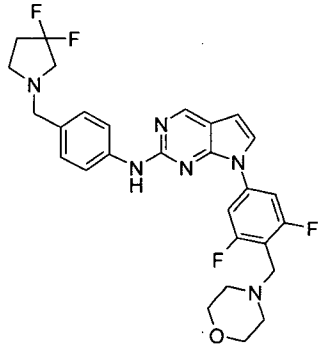
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.06 minutos (Método C); MS-ES: $(M+H)^+$ = 575

**Ejemplo 470: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona**



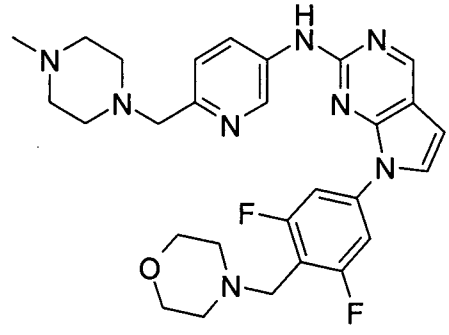
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.91 minutos (Método C); MS-ES: $(M+H)^+$ = 521

**Ejemplo 471: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3,3-difluoro-pirrolidin-1-il-metil)-fenil]-amina**



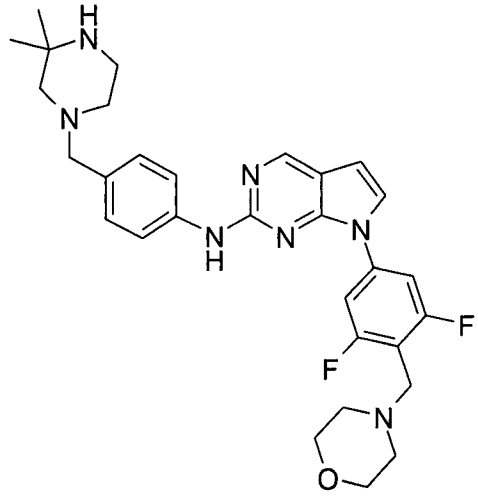
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.19 minutos (Método F); MS-ES: $(M+H)^+$ = 541

**Ejemplo 472: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il-metil)-piridin-3-il]-amina**



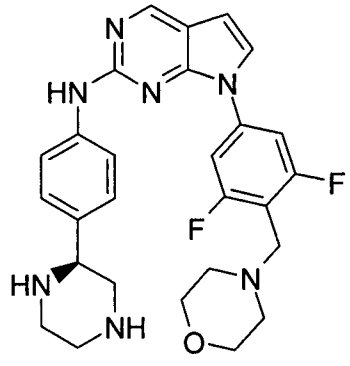
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.12 minutos (Método E2); MS-ES: $(M+H)^+$ = 535

**Ejemplo 473: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3,3-dimetil-piperazin-1-il-metil)-fenil]-amina**



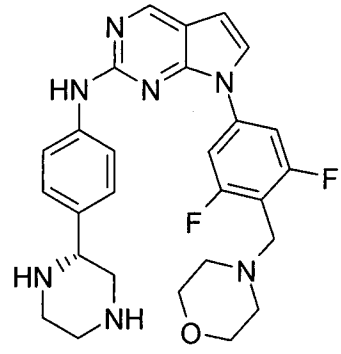
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = .01 minutos (Método C); MS-ES: $(M+H)^+$ = 548

**Ejemplo 474: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-piperazin-2-il-fenil)-amina**



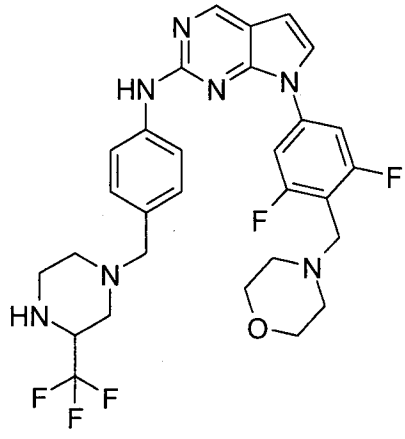
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. La anilina utilizada para esta síntesis se prepara a partir de la 2-(4-nitro-fenil)-piperazina (racémica) mediante protección con Boc, reducción de nitro, y separación quiral (otro enantiómero utilizado para el Ejemplo 475). HPLC: $t_R$ = 0.68 minutos (Método E2); MS-ES: $(M+H)^+$ = 506

**Ejemplo 475: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((R)-4-piperazin-2-il-fenil)-amina**



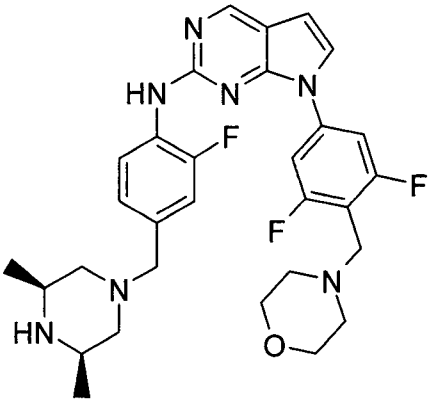
El compuesto se prepara de una manera análoga al Ejemplo 2 y representa el enantiómero del Ejemplo 474. HPLC: $t_R$ = 0.68 minutos (Método E2); MS-ES: $(M+H)^+$ = 506

**Ejemplo 476: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3-trifluoro-metil-piperazin-1-il-metil)-fenil]-amina (racémica)**



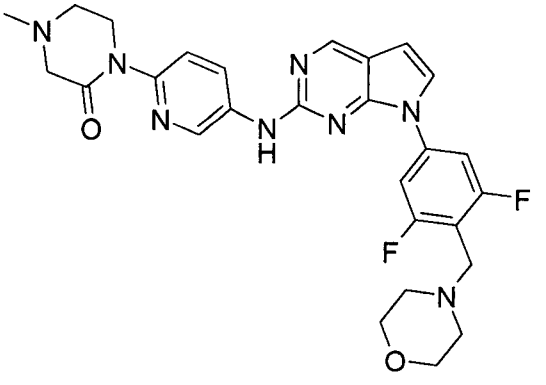
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.24 minutos (Método C); MS-ES: $(M+H)^+$ = 588

**Ejemplo 477: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-2-fluoro-fenil]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.06 minutos (Método C); MS-ES: $(M+H)^+$ = 566

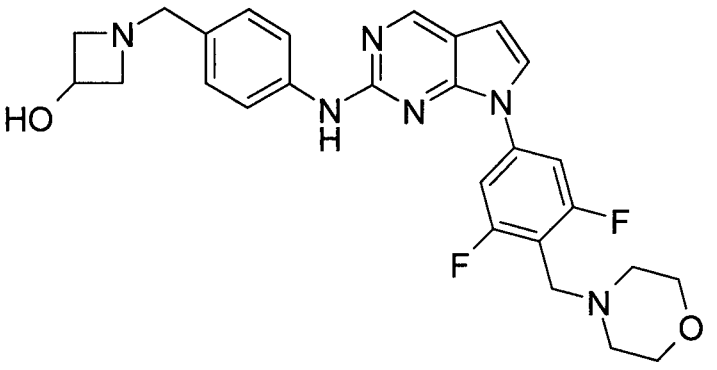
**Ejemplo 478: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-4-metil-piperazin-2-ona**



El compuesto se obtiene a partir de la reacción de la 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona (Ejemplo 470) con formaldehído

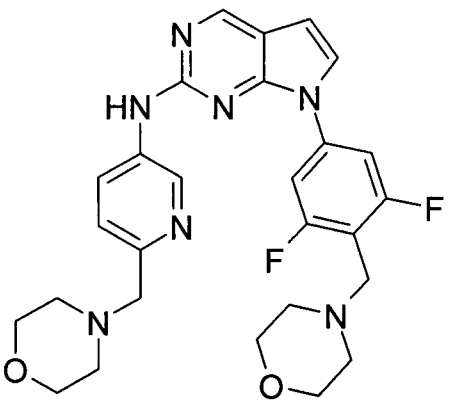
y ciano-borohidruro de sodio en metanol y dicloro-metano, 2:1, a temperatura ambiente. HPLC: $t_R$ = 3.94 minutos (Método C); MS-ES: $(M+H)^+$ = 535

**Ejemplo 479: 1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-azetidin-3-ol**



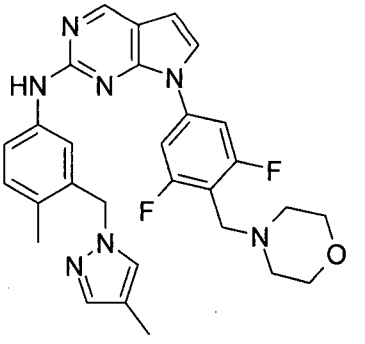
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.97 minutos (Método C); MS-ES: $(M+H)^+$ = 507

**Ejemplo 480: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-morfolin-4-il-metil-piridin-3-il)-amina**



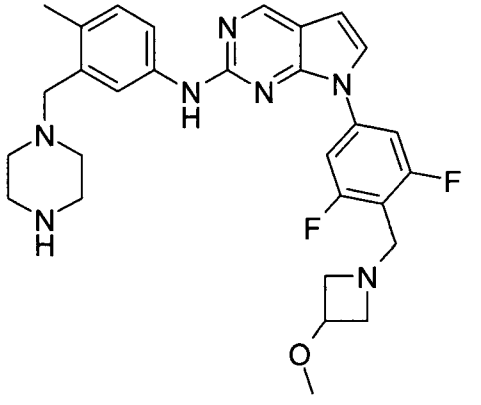
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.20 minutos (Método E2); MS-ES: $(M+H)^+$ = 522

**Ejemplo 481: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(4-metil-pirazol-1-il-metil)-fenil]-amina**



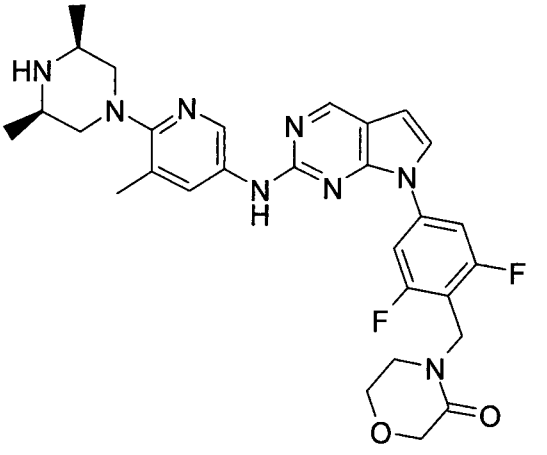
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 8.11 minutos (Método B); MS-ES: $(M+H)^+$ = 530; TLC*: $R_f$ = 0.67

**Ejemplo 482: {7-[3,5-difluoro-4-(3-metoxi-azetidin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-metil-3-piperazin-1-il-metil-fenil)-amina**



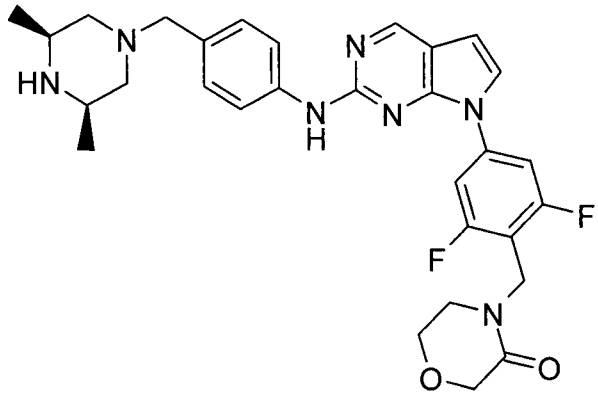
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 4.05 minutos (Método F); MS-ES: $(M+H)^+$ = 534

**Ejemplo 483: 4-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-morfolin-3-ona**



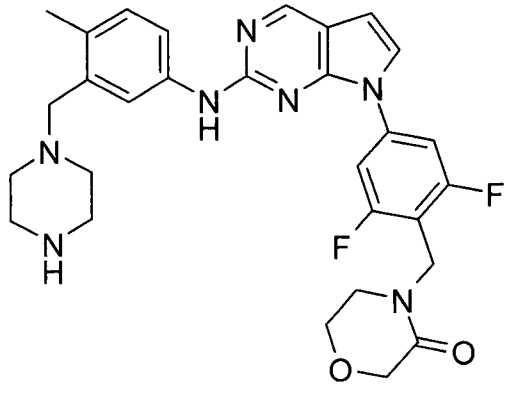
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.58 minutos (Método F); MS-ES: $(M+H)^+$ = 563

**Ejemplo 484: 4-(4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-morfolin-3-ona**



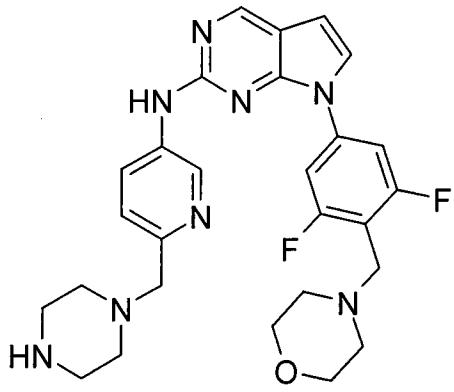
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.40 minutos (Método F); MS-ES: $(M+H)^+$ = 562

**Ejemplo 485: 4-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-morfolin-3-ona**



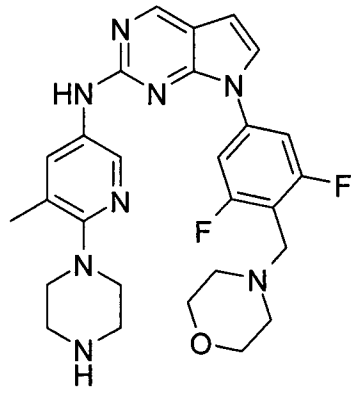
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 4.44 minutos (Método F); MS-ES: $(M+H)^+$ = 548

**Ejemplo 486: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-metil-piridin-3-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 1.12 minutos (Método E); MS-ES: $(M+H)^+$ = 521

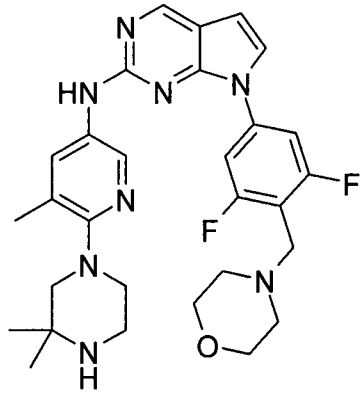
**Ejemplo 487: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(5-metil-6-piperazin-1-il-piridin-3-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en

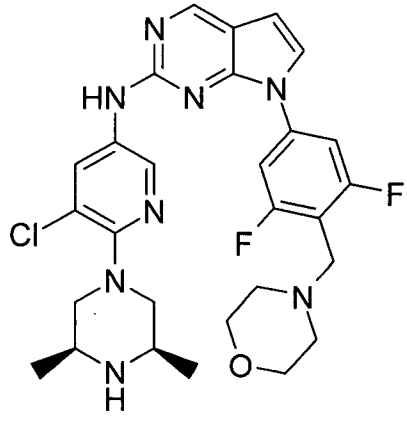
$CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.99 minutos (Método C); MS-ES: $(M+H)^+$ = 521

**Ejemplo 488: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(dimetil-piperazin-1-il)-5-metil-piridin-3-il]-amina**



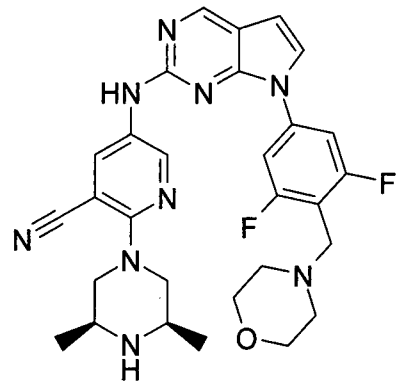
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.16 minutos (Método C); MS-ES: $(M+H)^+$ = 549

**Ejemplo 489: [5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



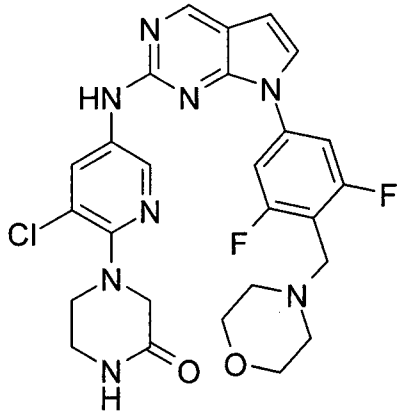
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.42 minutos (Método F); MS-ES: $(M+H)^+$ = 569

**Ejemplo 490: 5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-(cis-3,5-dimetil-piperazin-1-il)-nicotinonitrilo**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.34 minutos (Método C); MS-ES: $(M+H)^+$ = 560

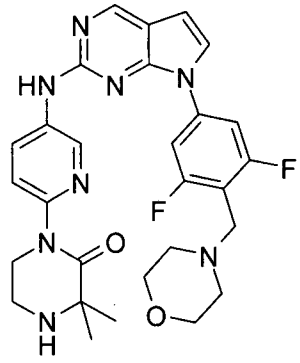
**Ejemplo 491: 4-{3-cloro-5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.56 minutos (Método C); MS-ES: $(M+H)^+$ = 555

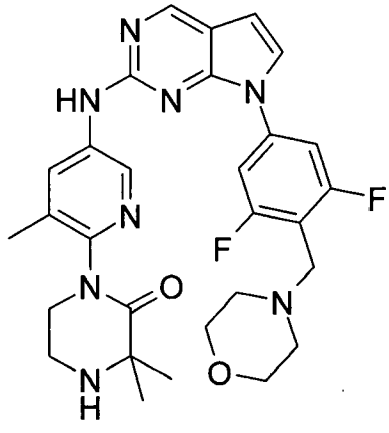
**Ejemplo 492: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-3,3-dimetil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

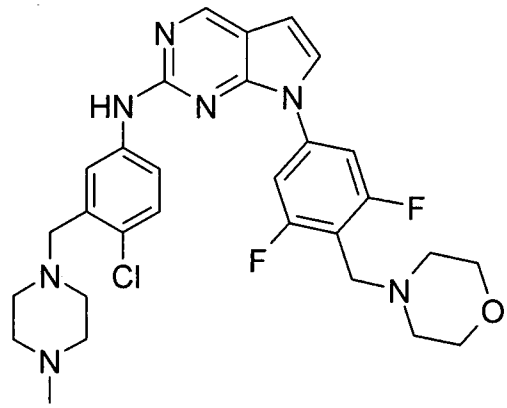
HPLC: $t_R$ = 4.04 minutos (Método C); MS-ES: $(M+H)^+$ = 549

**Ejemplo 493: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-3-metil-piridin-2-il}-3,3-dimetil-piperazin-2-ona**



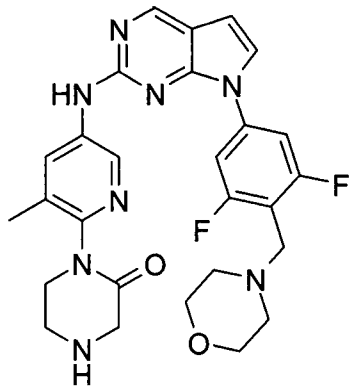
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 3.54 minutos (Método C); MS-ES: $(M+H)^+$ = 563

**Ejemplo 494: [4-cloro-3-(4-metil-piperazin-1-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



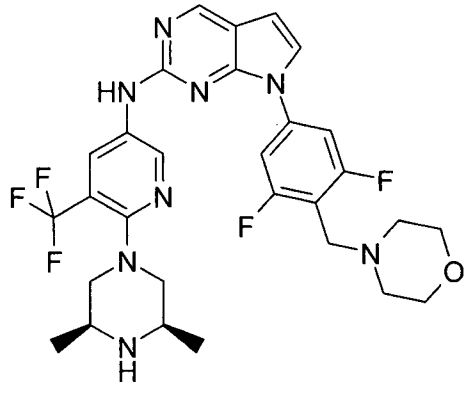
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 7.25 minutos (Método B); MS-ES: $(M+H)^+$ = 568

**Ejemplo 495: 1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-3-metil-piridin-2-il}-piperazin-2-ona**



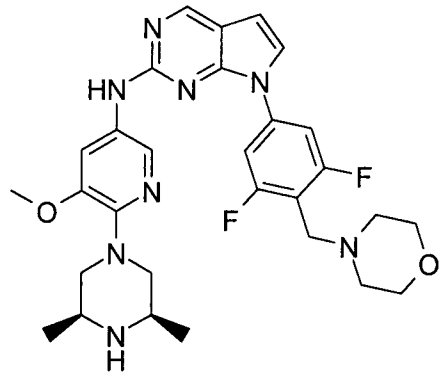
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.98 minutos (Método C); MS-ES: $(M+H)^+$ = 535

**Ejemplo 496: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-trifluoro-metil-piridin-3-il]-amina**



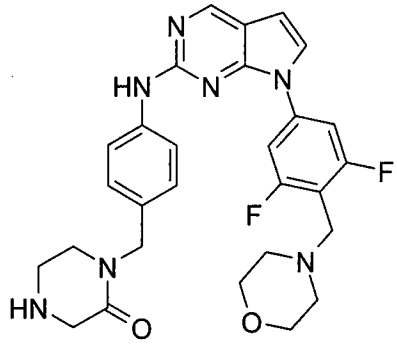
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.67 minutos (Método C); MS-ES: $(M+H)^+$ = 603

Ejemplo 497: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metoxi-piridin-3-il]-amina



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.07 minutos (Método C); MS-ES: $(M+H)^+$ = 565

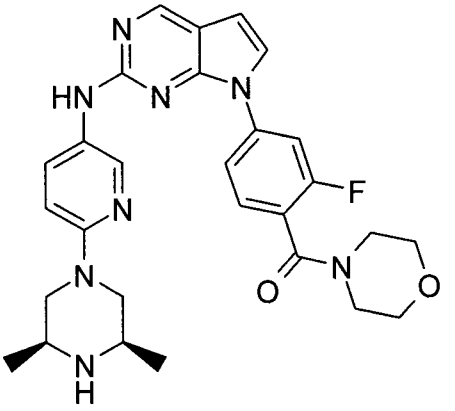
**Ejemplo 498: 1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.96 minutos (Método C); MS-ES: $(M+H)^+$ = 534

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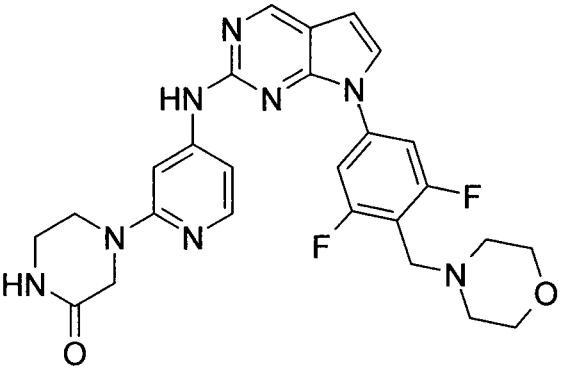
**Ejemplo 499: (4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.27 minutos (Método C); MS-ES: $(M+H)^+$ = 531

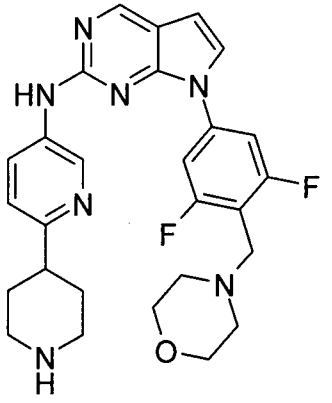
**Ejemplo 500: 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

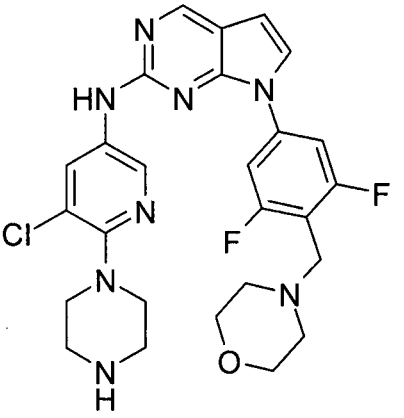
HPLC: $t_R$ = 4.20 minutos (Método C); MS-ES: $(M+H)^+$ = 521

**Ejemplo 501: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1',2',3',4',5',6'-hexahidro-[2,4']-bipiridinil-5-il)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 3.92 minutos (Método C); MS-ES: $(M+H)^+$ = 506

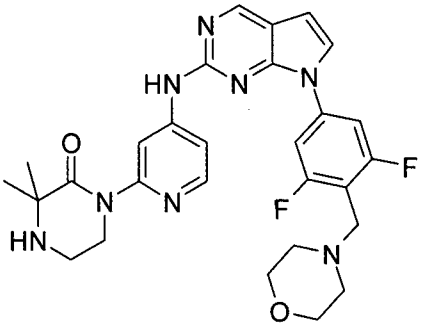
**Ejemplo 502: (5-cloro-6-piperazin-1-il-piridin-3-il)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



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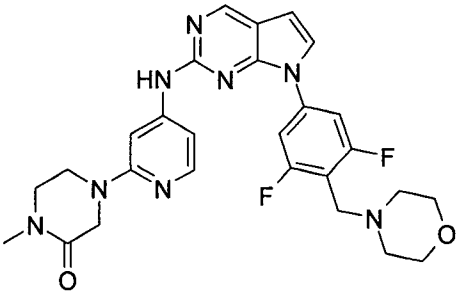
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de piperazina protegido por Boc en el paso 2.2. La desprotección final se logra con ácido trifluoro-acético en $CH_2Cl_2$ a temperatura ambiente. HPLC: $t_R$ = 4.27 minutos (Método C); MS-ES: $(M+H)^+$ = 541

**Ejemplo 503: 1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-3,3-dimetil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.00 minutos (Método C); MS-ES: $(M+H)^+$ = 549

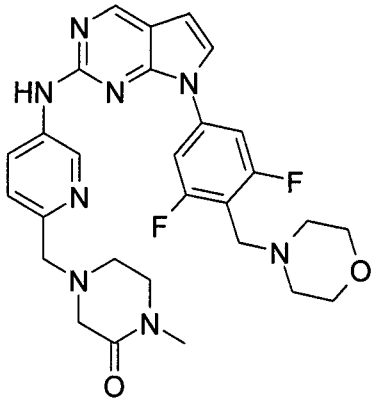
**Ejemplo 504: 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-1-metil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.23 minutos (Método C); MS-ES: $(M+H)^+$ = 535

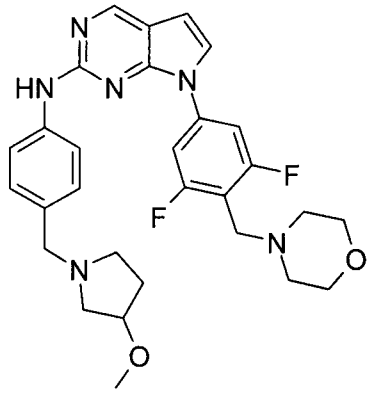
**Ejemplo 505: 4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-1-metil-piperazin-2-ona**



El compuesto se prepara de una manera análoga al Ejemplo 2.

HPLC: $t_R$ = 4.06 minutos (Método C); MS-ES: $(M+H)^+$ = 549

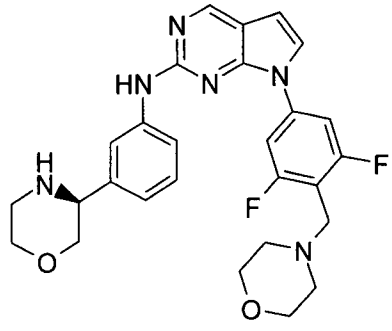
**Ejemplo 506: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3-metoxi-pirrolidin-1-il-metil)-fenil]-amina (racémica)**



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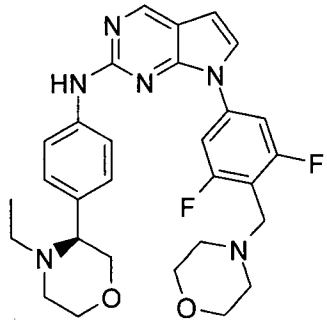
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 4.17 minutos (Método C); MS-ES: $(M+H)^+$ = 535

**Ejemplo 507: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-3-morfolin-3-il-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de morfolina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl en EtOH a 60°C. HPLC: $t_R$ = 0.60 minutos (Método G); MS-ES: $(M+H)^+$ = 507

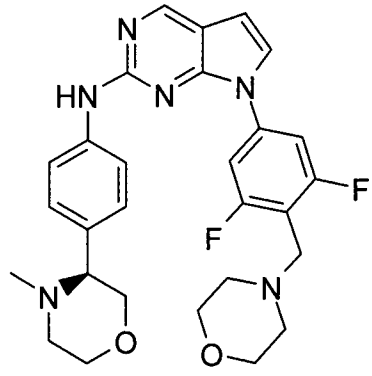
**Ejemplo 508: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-((S)-4-etil-morfolin-3-il)-fenil]-amina**



El compuesto se obtiene mediante el tratamiento de la [7-(3,5-

difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-3-morfolin-3-il-fenil)-amina (Ejemplo 507) con acetaldehído en metanol y ciano-borohidruro de sodio desde la temperatura ambiente hasta 60°C. HPLC: $t_R$ = 0.63 minutos (Método G); MS-ES: $(M+H)^+$ = 535

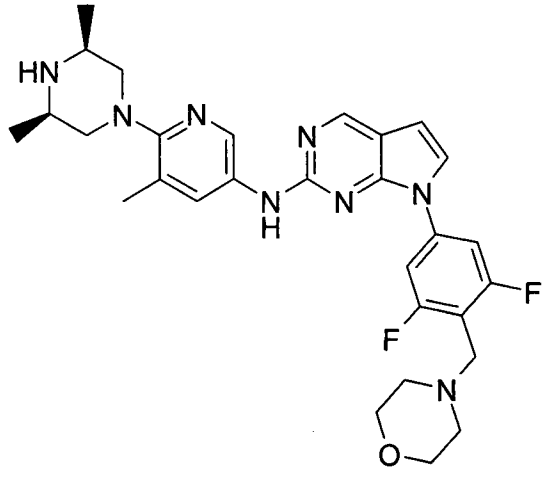
**Ejemplo 509: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-((S)-4-metil-morfolin-3-il)-fenil]-amina**



El compuesto se obtiene mediante el tratamiento de [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-3-morfolin-3-il-fenil)-amina (Ejemplo 507) con formaldehído en metanol y ciano-borohidruro de sodio desde la temperatura ambiente hasta 60°C. HPLC: $t_R$ = 0.61 minutos (Método G); MS-ES: $(M+H)^+$ = 521

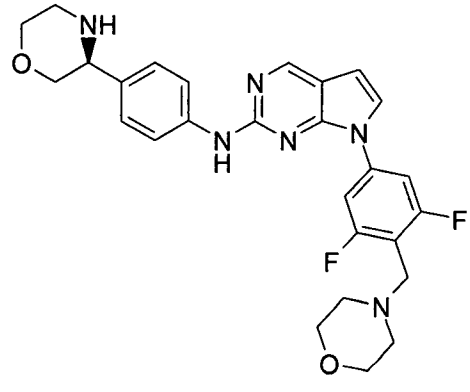
366

**Ejemplo 510: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il]-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.61 minutos (Método G); MS-ES: $(M+H)^+$ = 549; TLC (10 por ciento de metanol / 90 por ciento de cloruro de metileno / 1 por ciento de amoníaco): $R_f$ = 0.18

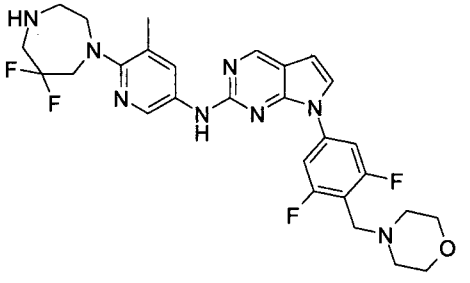
**Ejemplo 511: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-morfolin-3-il-fenil)-amina**



El compuesto se prepara de una manera análoga al Ejemplo 2,

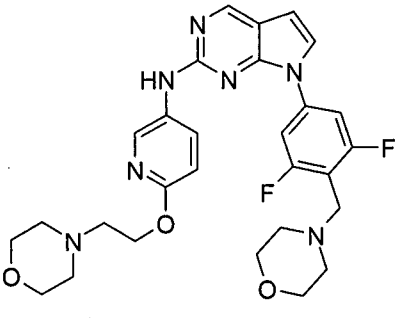
utilizando un derivado de morfolina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 1.25 M en EtOH a 60°C. HPLC: $t_R$ = 0.61 minutos (Método G); MS-ES: $(M+H)^+$ = 507; TLC (10 por ciento de metanol / 90 por ciento de cloruro de metileno / 1 por ciento de amoníaco): $R_f$ = 0.50

**Ejemplo 512: [6-(6,6-difluoro-[1,4]-diazepan-1-il)-5-metil-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



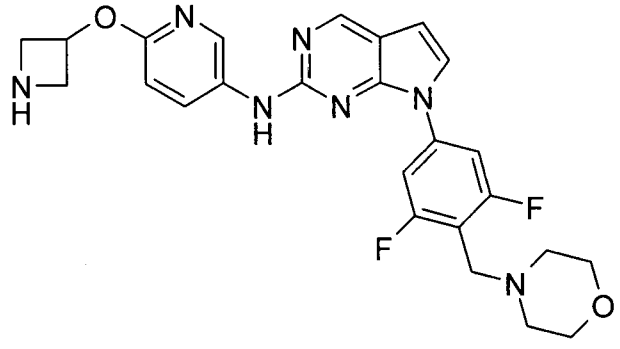
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.65 minutos (Método G); MS-ES: $(M+H)^+$ = 571

**Ejemplo 513: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(2-morfolin-4-il-etoxi)-piridin-3-il]-amina**



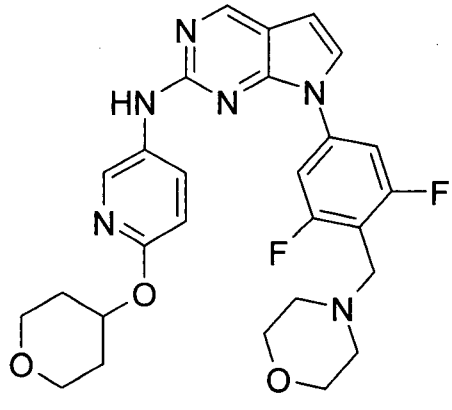
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.59 minutos (Método G); MS-ES: $(M+H)^+$ = 552

**Ejemplo 514: [6-(Azetidin-3-iloxi)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



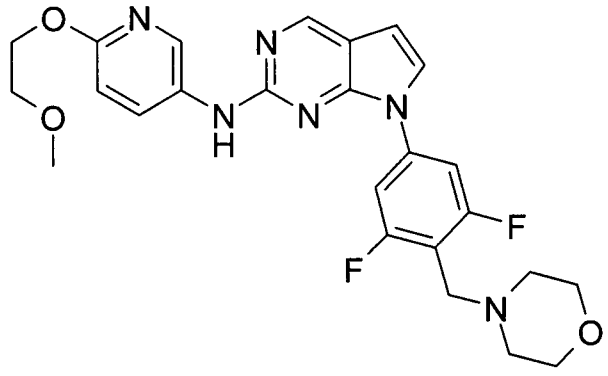
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de azetidina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 1.25 M en EtOH a 60°C. HPLC: $t_R$ = 0.55 minutos (Método G); MS-ES: $(M+H)^+$ = 538

**Ejemplo 515: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(tetrahidro-piran-4-iloxi)-piridin-3-il]-amina**



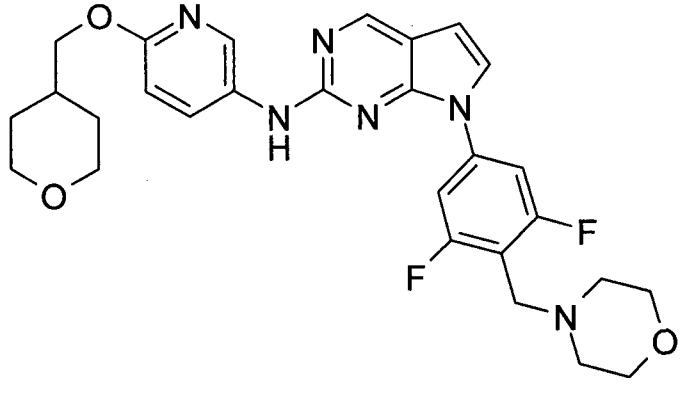
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.71 minutos (Método G); MS-ES: $(M+H)^+$ = 523

**Ejemplo 516: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(2-metoxi-etoxi)-piridin-3-il]-amina**



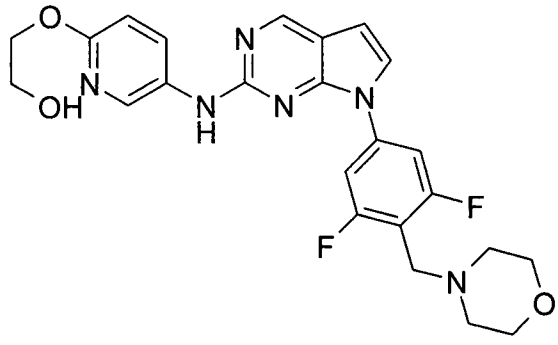
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.67 minutos (Método G); MS-ES: $(M+H)^+$ = 497

**Ejemplo 517: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(tetrahidro-piran-4-il-metoxi)-piridin-3-il]-amina**



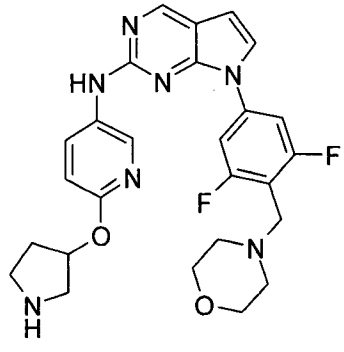
El compuesto se prepara de una manera análoga al Ejemplo 2. HPLC: $t_R$ = 0.74 minutos (Método G); MS-ES: $(M+H)^+$ = 537

**Ejemplo 518: 2-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-iloxi}-etanol**



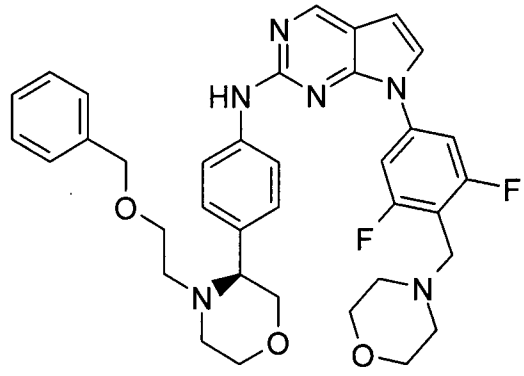
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de alcohol protegido por TBDPS en el paso 2.2. La desprotección final se logra con TBAF 1 M en tetrahidrofurano a temperatura ambiente. HPLC: $t_R$ = 0.60 minutos (Método G) y MS-ES: $(M+H)^+$ = 483.

**Ejemplo 519: [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(pirrolidin-3-iloxi)-piridin-3-il]-amina (racémica)**



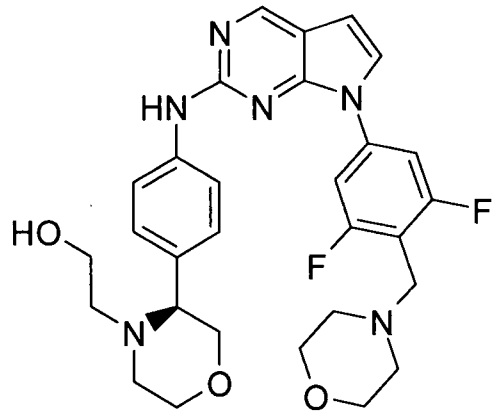
El compuesto se prepara de una manera análoga al Ejemplo 2, utilizando un derivado de pirrolidina protegido por Boc en el paso 2.2. La desprotección final se logra con HCl 1.25 M en EtOH a 50°C. HPLC: $t_R$ = 0.58 minutos (Método G); MS-ES: $(M+H)^+$ = 508

**Ejemplo 520: {4-[(S)-4-(2-benciloxi-etil)-morfolin-3-il]-fenil}-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina**



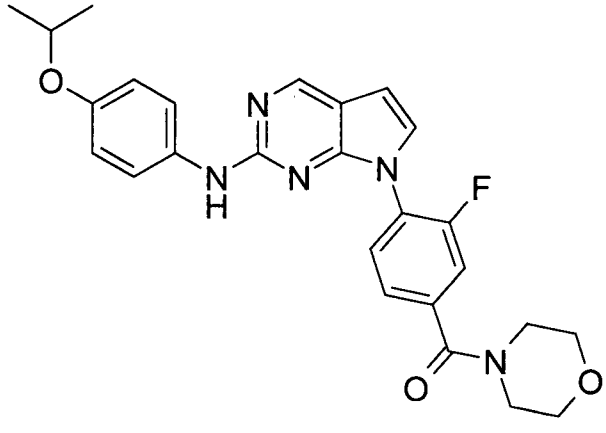
El compuesto se obtiene mediante el tratamiento de la [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-morfolin-3-il-fenil)-amina (Ejemplo 511) con benciloxi-acetaldehído en metanol y ciano-borohidruro de sodio a 60°C. HPLC: $t_R$ = 0.78 minutos (Método G); MS-ES: $(M+H)^+$ = 641

**Ejemplo 521: 2-((S)-3-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il)-etanol**



El compuesto se obtiene mediante el tratamiento de la [7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-morfolin-3-il-fenil)-amina (Ejemplo 511) con (terbutil-dimetil-sililoxi)-acetaldehído en metanol y ciano-borohidruro de sodio a 60°C, seguido por una desprotección con TBAF en tetrahidrofurano. HPLC: $t_R$ = 0.60 minutos (Método G); MS-ES: $(M+H)^+$ = 551

**Ejemplo 522: {3-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona**



El compuesto se prepara de una manera análoga al Ejemplo 3. HPLC: $t_R$ = 1.60 minutos (Método A); MS-ES: $(M+H)^+$ = 476.

**Ejemplo 523: Cápsulas Blandas**

Se preparan 5000 cápsulas de gelatina blanda, cada una comprendiendo, como ingrediente activo, 0.05 gramos de uno de los compuestos de la fórmula I mencionados en los Ejemplos anteriores, como sigue:

250 gramos del ingrediente activo pulverizado se suspenden en 2L Lauroglykol® (laurato de propilenglicol, Gattefossé S.A., Saint Priest, Francia), y se muelen en un pulverizador húmedo. Entonces se introducen porciones de 0.419 gramos de la mezcla en cápsulas de gelatina blanda, utilizando una máquina llenadora de cápsulas.

**Ensayos**

Los compuestos de la presente invención se ensayan con el objeto de medir su capacidad para inhibir JAK2 y la senda de translocalización ya sea de STAT1 o de STAT5, como se describe anteriormente. Los resultados se proporcionan en el Cuadro 2:

**Cuadro 2**

**Inhibición de JAK2 y de la senda de translocalización de STAT1 / STAT5**

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 1 | <0.003 | 0.0435 | n.d. |
| 2 | 0.0032 | 0.19 | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 3 | 0.0094 | 0.0985 | n.d. |
| 4 | 0.0022 | 0.0367 | n.d. |
| 5 | < 0.003 | n.d. | n.d. |
| 6 | < 0.003 | n.d. | n.d. |
| 7 | 0.0062 | 0.2545 | n.d. |
| 8 | < 0.003 | 0.032 | n.d. |
| 9 | < 0.003 | n.d. | n.d. |
| 10 | < 0.003 | n.d. | n.d. |
| 11 | 0.19 | n.d. | n.d. |
| 12 | < 0.003 | n.d. | n.d. |
| 13 | 0.0038 | 0.032 | n.d. |
| 14 | 2.1 | n.d. | n.d. |
| 15 | 0.0085 | n.d. | n.d. |
| 16 | < 0.003 | 0.025 | n.d. |
| 17 | < 0.003 | 0.0205 | n.d. |
| 18 | < 0.003 | n.d. | n.d. |
| 19 | 0.0069 | n.d. | n.d. |
| 20 | 0.0039 | n.d. | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 21 | 0.023 | n.d. | n.d. |
| 22 | 0.17 | n.d. | n.d. |
| 23 | 0.0036 | n.d. | n.d. |
| 24 | 0.0035 | n.d. | n.d. |
| 25 | < 0.003 | n.d. | n.d. |
| 26 | < 0.003 | n.d. | n.d. |
| 27 | < 0.003 | 0.085 | n.d. |
| 28 | 0.004 | n.d. | n.d. |
| 29 | < 0.003 | 0.091 | n.d. |
| 30 | < 0.003 | 0.2045 | n.d. |
| 31 | < 0.003 | 0.046 | n.d. |
| 32 | 0.0054 | n.d. | n.d. |
| 33 | < 0.003 | n.d. | n.d. |
| 34 | < 0.003 | 0.0695 | n.d. |
| 35 | 0.0049 | n.d. | n.d. |
| 36 | < 0.003 | 0.0109 | n.d. |
| 37 | < 0.003 | n.d. | n.d. |
| 38 | 0.0045 | n.d. | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 39 | 0.014 | 1.3695 | n.d. |
| 40 | < 0.003 | 0.155 | n.d. |
| 41 | < 0.003 | 0.075 | n.d. |
| 42 | 0.0031 | 0.17 | n.d. |
| 43 | < 0.003 | 0.35 | n.d. |
| 44 | < 0.003 | 0.1425 | n.d. |
| 45 | 0.0061 | n.d. | n.d. |
| 46 | 0.038 | n.d. | n.d. |
| 47 | < 0.003 | 0.073 | n.d. |
| 48 | 0.027 | 4.213 | n.d. |
| 49 | 0.014 | 0.878 | n.d. |
| 50 | < 0.003 | 0.184 | n.d. |
| 51 | < 0.003 | n.d. | n.d. |
| 52 | < 0.003 | n.d. | n.d. |
| 53 | < 0.003 | 0.0905 | n.d. |
| 54 | 0.0044 | 3.1085 | n.d. |
| 55 | 0.02 | n.d. | n.d. |
| 56 | 0.032 | 4.675 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 57 | < 0.003 | 0.7725 | n.d. |
| 58 | 0.012 | 5.295 | n.d. |
| 59 | 0.0065 | 0.92 | n.d. |
| 60 | 0.0081 | 4.0785 | n.d. |
| 61 | 0.0071 | 0.835 | n.d. |
| 62 | 0.18 | 5.39 | n.d. |
| 63 | 0.073 | n.d. | n.d. |
| 64 | < 0.003 | 0.04 | n.d. |
| 65 | 0.0054 | 0.0995 | n.d. |
| 66 | 0.0035 | 0.0755 | n.d. |
| 67 | < 0.003 | 0.039 | n.d. |
| 68 | < 0.003 | 0.105 | n.d. |
| 69 | 0.0048 | n.d. | n.d. |
| 70 | 0.0056 | 0.275 | n.d. |
| 71 | 0.0068 | 0.362 | n.d. |
| 72 | 0.0037 | 0.75 | n.d. |
| 73 | < 0.003 | 0.0805 | n.d. |
| 74 | < 0.003 | 0.0755 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 75 | < 0.003 | 0.0825 | n.d. |
| 76 | 0.038 | 0.9345 | n.d. |
| 77 | 0.038 | 2.62 | n.d. |
| 78 | 0.029 | 0.545 | n.d. |
| 79 | 0.0048 | 0.257 | n.d. |
| 80 | 0.43 | 10 | n.d. |
| 81 | 0.018 | 2.7 | n.d. |
| 82 | 0.0041 | 0.86 | n.d. |
| 83 | < 0.003 | 0.46 | n.d. |
| 84 | < 0.003 | 0.275 | n.d. |
| 85 | 0.0038 | 3.505 | n.d. |
| 86 | 0.008 | 12.975 | n.d. |
| 87 | 0.0038 | 18.3 | n.d. |
| 88 | 0.0089 | 3.27 | n.d. |
| 89 | < 0.003 | 0.41 | n.d. |
| 90 | 0.0034 | 0.715 | n.d. |
| 91 | < 0.003 | 0.435 | n.d. |
| 92 | 0.0042 | 0.26 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 93 | < 0.003 | 0.191 | n.d. |
| 94 | 0.0038 | 0.259 | n.d. |
| 95 | 0.0165 | 2.365 | n.d. |
| 96 | 0.0485 | 26.2 | n.d. |
| 97 | 0.0094 | 1.455 | n.d. |
| 98 | 0.0056 | 0.575 | n.d. |
| 99 | 0.0039 | 0.555 | n.d. |
| 100 | < 0.003 | 0.51 | n.d. |
| 101 | < 0.003 | 0.18 | n.d. |
| 102 | < 0.003 | 0.275 | n.d. |
| 103 | < 0.003 | 0.22 | n.d. |
| 104 | 0.0036 | 0.865 | n.d. |
| 105 | 0.0115 | 5.845 | n.d. |
| 106 | 0.033 | 8.385 | n.d. |
| 107 | 0.0081 | 1.835 | n.d. |
| 108 | 0.0066 | 1.685 | n.d. |
| 109 | 0.0083 | 0.3105 | n.d. |
| 110 | 0.0135 | 1.1125 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 111 | 0.0145 | 0.8465 | n.d. |
| 112 | < 0.003 | 0.073 | n.d. |
| 113 | 0.0042 | 0.108 | n.d. |
| 114 | 0.0059 | 0.2015 | n.d. |
| 115 | 0.016 | 0.7145 | n.d. |
| 116 | 0.0125 | 0.563 | n.d. |
| 117 | 0.0094 | 0.384 | n.d. |
| 118 | 0.075 | 1.515 | n.d. |
| 119 | 0.088 | 1.757 | n.d. |
| 120 | 0.155 | 7.851 | n.d. |
| 121 | 0.0155 | 0.152 | n.d. |
| 122 | 0.0033 | 0.1645 | n.d. |
| 123 | 0.028 | 0.8025 | n.d. |
| 124 | 0.085 | 2.155 | n.d. |
| 125 | < 0.003 | 0.12 | n.d. |
| 126 | 0.011 | 1.6225 | n.d. |
| 127 | 0.0105 | 0.7205 | n.d. |
| 128 | 0.12 | 3.6775 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 129 | 0.009 | 0.471 | n.d. |
| 130 | 0.115 | 8.412 | n.d. |
| 131 | 0.016 | 1.502 | n.d. |
| 132 | 0.0405 | 6.2805 | n.d. |
| 133 | 0.0071 | 0.573 | n.d. |
| 134 | 0.0205 | 1.875 | n.d. |
| 135 | 0.0049 | 0.42 | n.d. |
| 136 | 0.011 | 0.775 | n.d. |
| 137 | 0.0033 | 0.15 | n.d. |
| 138 | < 0.003 | 0.165 | n.d. |
| 139 | 0.011 | 0.63 | n.d. |
| 140 | 0.0045 | 0.31 | n.d. |
| 141 | < 0.003 | 0.13 | n.d. |
| 142 | < 0.003 | 0.101 | n.d. |
| 143 | < 0.003 | 0.195 | n.d. |
| 144 | 0.0047 | 0.475 | n.d. |
| 145 | 0.007 | 0.365 | n.d. |
| 146 | 0.03 | 2.51 | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 147 | < 0.003 | 0.033 | n.d. |
| 148 | 0.0079 | 0.047 | n.d. |
| 149 | 0.13 | 1.509 | n.d. |
| 150 | 0.0045 | 0.0645 | n.d. |
| 151 | 0.0057 | 0.2285 | n.d. |
| 152 | 0.0035 | 0.168 | n.d. |
| 153 | < 0.003 | 0.0175 | n.d. |
| 154 | 0.25 | 6.435 | n.d. |
| 155 | 0.2 | 3.275 | n.d. |
| 156 | 0.013 | 0.06 | n.d. |
| 157 | 0.0061 | 0.13 | n.d. |
| 158 | 0.0094 | 0.265 | n.d. |
| 159 | 0.0465 | 1.123 | n.d. |
| 160 | 0.0418 | 0.973 | n.d. |
| 161 | 0.87 | 9.348 | n.d. |
| 162 | 0.305 | 9.695 | n.d. |
| 163 | 0.295 | 23.495 | n.d. |
| 164 | 0.23 | 10.725 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 165 | < 0.003 | 0.125 | n.d. |
| 166 | 0.0034 | 0.145 | n.d. |
| 167 | 0.039 | 2.07 | n.d. |
| 168 | 0.0305 | 3.905 | n.d. |
| 169 | 0.0043 | 0.093 | n.d. |
| 170 | 0.017 | 0.3745 | n.d. |
| 171 | < 0.003 | 0.26 | n.d. |
| 172 | < 0.003 | 0.22 | n.d. |
| 173 | 0.0055 | 0.235 | n.d. |
| 174 | < 0.003 | 0.15 | n.d. |
| 175 | < 0.003 | 0.275 | n.d. |
| 176 | 0.0073 | 1.55 | n.d. |
| 177 | 0.0053 | 1.035 | n.d. |
| 178 | 0.0091 | 0.79 | n.d. |
| 179 | 0.0104 | 1.515 | n.d. |
| 180 | < 0.003 | 0.12 | n.d. |
| 181 | 0.0155 | 16.6 | n.d. |
| 182 | < 0.003 | 0.125 | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 183 | 0.0033 | 0.095 | n.d. |
| 184 | < 0.003 | 0.035 | n.d. |
| 185 | < 0.003 | 0.29 | n.d. |
| 186 | < 0.003 | 0.095 | n.d. |
| 187 | < 0.003 | 0.055 | n.d. |
| 188 | < 0.003 | 0.06 | n.d. |
| 189 | 0.0095 | 0.846 | n.d. |
| 190 | 0.0052 | 0.439 | n.d. |
| 191 | 0.0285 | 3.9175 | n.d. |
| 192 | 0.0115 | 1.488 | n.d. |
| 193 | 0.0084 | 0.351 | n.d. |
| 194 | < 0.003 | 0.2015 | n.d. |
| 195 | 0.0053 | 0.3525 | n.d. |
| 196 | < 0.003 | 0.176 | n.d. |
| 197 | < 0.003 | 0.09 | n.d. |
| 198 | < 0.003 | n.d. | n.d. |
| 199 | < 0.003 | 0.222 | n.d. |
| 200 | 0.0037 | n.d. | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 201 | < 0.003 | 0.199 | n.d. |
| 202 | 0.0045 | 0.198 | n.d. |
| 203 | 0.0074 | 0.4125 | n.d. |
| 204 | < 0.003 | n.d. | n.d. |
| 205 | 0.005 | n.d. | n.d. |
| 206 | < 0.003 | n.d. | n.d. |
| 207 | < 0.003 | n.d. | n.d. |
| 208 | 0.0048 | 0.442 | n.d. |
| 209 | 0.125 | n.d. | n.d. |
| 210 | 0.0058 | 0.634 | n.d. |
| 211 | 0.0059 | n.d. | n.d. |
| 212 | < 0.003 | 0.1055 | n.d. |
| 213 | 0.0059 | 0.7275 | n.d. |
| 214 | 0.0051 | 0.643 | n.d. |
| 215 | 0.42 | 10 | n.d. |
| 216 | 0.0033 | 0.579 | n.d. |
| 217 | 0.0073 | 0.993 | n.d. |
| 218 | 1.05 | 10 | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 219 | 0.0077 | 0.518 | n.d. |
| 220 | 0.011 | 0.88 | n.d. |
| 221 | 0.0047 | 0.36 | n.d. |
| 222 | 0.29 | n.d. | n.d. |
| 223 | 0.0092 | 0.455 | n.d. |
| 224 | 0.0085 | 1.075 | n.d. |
| 225 | 0.0074 | 0.4335 | n.d. |
| 226 | 0.0105 | 0.666 | n.d. |
| 227 | 0.0415 | n.d. | n.d. |
| 228 | 0.0565 | n.d. | n.d. |
| 229 | 0.021 | 1.5765 | n.d. |
| 230 | 0.0205 | 2.475 | n.d. |
| 231 | 0.0032 | 0.2575 | n.d. |
| 232 | 0.019 | 1.16 | n.d. |
| 233 | 0.0064 | 1.182 | n.d. |
| 234 | 0.0081 | 0.91 | n.d. |
| 235 | 0.056 | n.d. | n.d. |
| 236 | 0.046 | n.d. | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 237 | 0.007 | 2.555 | n.d. |
| 238 | 0.0111 | 0.785 | n.d. |
| 239 | 0.0039 | 0.66 | n.d. |
| 240 | 0.0052 | 0.73 | n.d. |
| 241 | 0.0054 | 0.37 | n.d. |
| 242 | 0.0043 | 0.355 | n.d. |
| 243 | < 0.003 | 0.225 | n.d. |
| 244 | < 0.003 | 0.43 | n.d. |
| 245 | < 0.003 | 0.43 | n.d. |
| 246 | 0.028 | 3.995 | n.d. |
| 247 | 0.0037 | 0.255 | n.d. |
| 248 | 0.024 | 4.27 | n.d. |
| 249 | 0.0043 | 0.815 | n.d. |
| 250 | 0.0091 | 0.94 | n.d. |
| 251 | 0.0061 | 0.45 | n.d. |
| 252 | 0.0033 | 0.34 | n.d. |
| 253 | 0.0071 | 0.13 | n.d. |
| 254 | < 0.003 | n.d. | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 255 | 0.0069 | 0.115 | n.d. |
| 256 | < 0.003 | 0.115 | n.d. |
| 257 | 0.01 | 0.15 | n.d. |
| 258 | < 0.003 | 0.08 | n.d. |
| 259 | < 0.003 | 0.08 | n.d. |
| 260 | 0.005 | 0.28 | n.d. |
| 261 | 0.012 | 0.18 | n.d. |
| 262 | 0.0042 | 0.285 | n.d. |
| 263 | < 0.003 | 0.055 | n.d. |
| 264 | < 0.003 | 0.165 | n.d. |
| 265 | < 0.003 | 0.04 | n.d. |
| 266 | 0.0084 | 0.15 | n.d. |
| 267 | < 0.003 | 0.05 | n.d. |
| 268 | 0.0078 | 0.21 | n.d. |
| 269 | 0.01 | 0.465 | n.d. |
| 270 | 0.0043 | 0.035 | n.d. |
| 271 | 0.0031 | 0.065 | n.d. |
| 272 | 0.011 | 0.175 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 273 | 0.006 | 0.19 | n.d. |
| 274 | 0.0072 | 0.52 | n.d. |
| 275 | 0.007 | n.d. | n.d. |
| 276 | 0.12 | n.d. | n.d. |
| 277 | 0.0083 | n.d. | n.d. |
| 278 | 0.011 | n.d. | n.d. |
| 279 | 0.004 | n.d. | n.d. |
| 280 | 0.0035 | n.d. | n.d. |
| 281 | 0.024 | n.d. | n.d. |
| 282 | 0.082 | n.d. | n.d. |
| 283 | 0.023 | n.d. | n.d. |
| 284 | 0.0037 | n.d. | n.d. |
| 285 | < 0.003 | n.d. | n.d. |
| 286 | 0.0106 | 0.285 | n.d. |
| 287 | 0.0465 | 0.441 | n.d. |
| 288 | < 0.003 | 0.0675 | n.d. |
| 289 | < 0.017 | 0.2315 | n.d. |
| 290 | < 0.003 | 0.037 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 291 | < 0.003 | 0.054 | n.d. |
| 292 | < 0.003 | 0.0125 | n.d. |
| 293 | < 0.003 | 0.008 | n.d. |
| 294 | < 0.003 | 0.415 | n.d. |
| 295 | 0.0145 | 0.795 | n.d. |
| 296 | < 0.003 | 1.105 | n.d. |
| 297 | 0.03 | 2.145 | n.d. |
| 298 | 0.023 | 2.21 | n.d. |
| 299 | 0.0185 | 0.145 | n.d. |
| 300 | 0.0175 | 2.03 | n.d. |
| 301 | < 0.003 | 0.05 | n.d. |
| 302 | 0.0061 | 0.085 | n.d. |
| 303 | 0.0049 | 0.295 | n.d. |
| 304 | 0.0135 | 1.485 | n.d. |
| 305 | 0.026 | 2.675 | n.d. |
| 306 | 0.0395 | 0.55 | n.d. |
| 307 | 0.014 | 0.12 | n.d. |
| 308 | < 0.003 | 0.015 | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 309 | 0.78 | 4.155 | n.d. |
| 310 | 0.0064 | 0.57 | n.d. |
| 311 | 0.031 | 1.4 | n.d. |
| 312 | 0.013 | 0.565 | n.d. |
| 313 | 0.0037 | n.d. | n.d. |
| 314 | < 0.003 | n.d. | n.d. |
| 315 | < 0.003 | n.d. | n.d. |
| 316 | 0.073 | n.d. | n.d. |
| 317 | 0.94 | n.d. | n.d. |
| 318 | < 0.003 | n.d. | n.d. |
| 319 | < 0.003 | n.d. | n.d. |
| 320 | 0.0095 | n.d. | n.d. |
| 321 | < 0.003 | n.d. | n.d. |
| 322 | < 0.003 | n.d. | n.d. |
| 323 | 0.0032 | n.d. | n.d. |
| 324 | 0.026 | n.d. | n.d. |
| 325 | 0.025 | n.d. | n.d. |
| 326 | < 0.003 | n.d. | n.d. |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 327 | < 0.003 | n.d. | n.d. |
| 328 | 0.016 | n.d. | n.d. |
| 329 | 0.004 | n.d. | n.d. |
| 330 | 0.014 | n.d. | n.d. |
| 331 | 0.003 | n.d. | 0.0028 |
| 332 | 0.003 | 0.375 | 0.073 |
| 333 | 0.0039 | 0.53 | n.d. |
| 334 | 0.003 | 0.26 | n.d. |
| 335 | 0.0093 | 0.36 | n.d. |
| 336 | 0.0036 | 0.205 | n.d. |
| 337 | 0.0061 | 0.185 | n.d. |
| 338 | 0.0039 | 0.135 | n.d. |
| 339 | 0.0037 | 0.285 | n.d. |
| 340 | 0.0072 | 0.27 | n.d. |
| 341 | 0.003 | n.d. | n.d. |
| 342 | 0.003 | 0.4788 | n.d. |
| 343 | 0.003 | 0.1512 | n.d. |
| 344 | 0.003 | n.d. | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 345 | 0.0033 | n.d. | n.d. |
| 346 | 0.003 | n.d. | 0.0028 |
| 347 | 0.003 | n.d. | 0.0133 |
| 348 | 0.0062 | n.d. | n.d. |
| 349 | 0.016 | n.d. | n.d. |
| 350 | 0.003 | n.d. | 0.0218 |
| 351 | 0.0043 | n.d. | 0.0013 |
| 352 | 0.003 | n.d. | 0.0221 |
| 353 | 0.0049 | n.d. | 0.017 |
| 354 | 0.003 | n.d. | 0.0013 |
| 355 | 0.0037 | n.d. | 0.0053 |
| 356 | 0.0032 | n.d. | 0.0059 |
| 357 | 0.0069 | n.d. | n.d. |
| 358 | 0.0072 | n.d. | 0.059 |
| 359 | 0.0074 | n.d. | 0.135 |
| 360 | 0.0033 | n.d. | 0.0072 |
| 361 | 0.023 | n.d. | 0.2595 |
| 362 | 0.024 | n.d. | 0.152 |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 363 | 0.0032 | n.d. | 0.011 |
| 364 | 0.003 | n.d. | 0.0028 |
| 365 | 0.0046 | n.d. | 0.043 |
| 366 | 0.0086 | n.d. | 0.065 |
| 367 | 0.0084 | n.d. | 0.144 |
| 368 | 0.0032 | n.d. | n.d. |
| 369 | 0.003 | n.d. | 0.057 |
| 370 | 0.003 | n.d. | 0.0313 |
| 371 | 0.013 | n.d. | 0.135 |
| 372 | 0.0047 | n.d. | 0.057 |
| 373 | 0.0043 | n.d. | n.d. |
| 374 | 0.0099 | n.d. | n.d. |
| 375 | 0.0065 | n.d. | 0.0077 |
| 376 | 0.003 | n.d. | 0.067 |
| 377 | 0.049 | n.d. | >2.6 |
| 378 | 0.013 | n.d. | 0.045 |
| 379 | 0.011 | n.d. | n.d. |
| 380 | 0.0032 | n.d. | 0.046 |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 381 | 0.003 | n.d. | 0.043 |
| 382 | 0.0035 | n.d. | 0.121 |
| 383 | 0.0051 | n.d. | 0.0061 |
| 384 | 0.003 | n.d. | 0.012 |
| 385 | 0.003 | n.d. | 0.0655 |
| 386 | 0.11 | n.d. | 0.101 |
| 387 | 0.0096 | n.d. | 0.0455 |
| 388 | 0.003 | n.d. | n.d. |
| 389 | 0.003 | n.d. | n.d. |
| 390 | 0.015 | n.d. | 0.104 |
| 391 | 0.0049 | n.d. | 0.15 |
| 392 | 0.003 | n.d. | 0.068 |
| 393 | 0.013 | n.d. | 0.052 |
| 394 | 0.003 | n.d. | 0.0016 |
| 395 | 0.003 | n.d. | 0.017 |
| 396 | 0.003 | n.d. | 0.147 |
| 397 | 0.003 | n.d. | 0.013 |
| 398 | 0.003 | n.d. | 0.245 |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 399 | 0.003 | n.d. | 0.0066 |
| 400 | 0.007 | n.d. | 0.0017 |
| 401 | 0.007 | n.d. | 0.1385 |
| 402 | 0.003 | n.d. | 1.372 |
| 403 | 0.003 | n.d. | 0.0225 |
| 404 | 0.0056 | n.d. | 0.141 |
| 405 | 0.003 | n.d. | 0.0032 |
| 406 | 0.004 | n.d. | >4 |
| 407 | 0.003 | n.d. | 0.305 |
| 408 | 0.003 | n.d. | 0.0092 |
| 409 | 0.003 | n.d. | 0.0816 |
| 410 | 0.003 | n.d. | 0.0083 |
| 411 | 0.003 | n.d. | 0.0026 |
| 412 | 0.003 | n.d. | 0.0265 |
| 413 | 0.003 | n.d. | 0.0285 |
| 414 | 0.003 | n.d. | 0.0042 |
| 415 | 0.003 | n.d. | 0.0069 |
| 416 | 0.003 | n.d. | n.d. |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 417 | 0.003 | n.d. | 0.005 |
| 418 | 0.0046 | n.d. | 0.016 |
| 419 | 0.0043 | n.d. | 0.0385 |
| 420 | 0.003 | n.d. | n.d. |
| 421 | 0.003 | n.d. | 0.0027 |
| 422 | 0.003 | n.d. | 0.0057 |
| 423 | 0.003 | n.d. | 0.0059 |
| 424 | 0.003 | n.d. | 0.009 |
| 425 | 0.003 | n.d. | 0.0036 |
| 426 | 0.003 | n.d. | 0.0183 |
| 427 | 0.003 | n.d. | 0.0332 |
| 428 | 0.003 | n.d. | 0.0107 |
| 429 | 0.003 | n.d. | 0.041 |
| 430 | 0.003 | n.d. | 0.0036 |
| 431 | 0.0032 | n.d. | 0.0235 |
| 432 | 0.003 | n.d. | 0.0004 |
| 433 | 0.003 | n.d. | 0.0063 |
| 434 | 0.003 | n.d. | 0.0315 |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 435 | 0.003 | n.d. | 0.0034 |
| 436 | 0.003 | n.d. | 0.0061 |
| 437 | 0.0033 | n.d. | n.d. |
| 438 | 0.003 | n.d. | n.d. |
| 439 | 0.019 | n.d. | n.d. |
| 440 | 0.0032 | n.d. | 0.061 |
| 441 | 0.003 | 0.045 | n.d. |
| 442 | 0.003 | n.d. | n.d. |
| 443 | 0.003 | 0.0095 | n.d. |
| 444 | 0.003 | 0.09 | n.d. |
| 445 | 0.043 | n.d. | n.d. |
| 446 | 0.0043 | 0.05 | 0.0013 |
| 447 | 0.0096 | 0.105 | 0.0118 |
| 448 | 0.005 | n.d. | 0.0074 |
| 449 | 0.003 | n.d. | n.d. |
| 450 | 0.003 | n.d. | n.d. |
| 451 | 0.0038 | n.d. | 0.024 |
| 452 | 0.0062 | n.d. | 0.0795 |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 453 | 0.0041 | n.d. | 0.036 |
| 454 | 0.0045 | n.d. | 0.0535 |
| 455 | 0.0043 | n.d. | 0.038 |
| 456 | 0.003 | n.d. | 0.0019 |
| 457 | 0.003 | n.d. | 0.021 |
| 458 | 0.003 | n.d. | 0.0014 |
| 459 | 0.0051 | n.d. | 0.1045 |
| 460 | 0.003 | n.d. | n.d. |
| 461 | 0.003 | n.d. | n.d. |
| 462 | 0.003 | n.d. | 0.051 |
| 463 | 0.003 | n.d. | 0.048 |
| 464 | 0.003 | n.d. | 0.059 |
| 465 | 0.003 | n.d. | 0.0032 |
| 466 | 0.0079 | n.d. | 0.056 |
| 467 | 0.0046 | n.d. | n.d. |
| 468 | 0.003 | n.d. | 0.014 |
| 469 | 0.003 | n.d. | 0.025 |
| 470 | 0.061 | n.d. | 0.017 |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 471 | 0.0035 | n.d. | 0.0315 |
| 472 | 0.0036 | n.d. | 0.092 |
| 473 | 0.003 | n.d. | 0.0123 |
| 474 | 0.003 | n.d. | 0.0086 |
| 475 | 0.003 | n.d. | 0.0053 |
| 476 | 0.003 | n.d. | 0.0345 |
| 477 | 0.017 | n.d. | 0.718 |
| 478 | 0.0055 | n.d. | 0.051 |
| 479 | 0.0035 | n.d. | 0.015 |
| 480 | 0.003 | n.d. | 0.071 |
| 481 | 0.0051 | n.d. | n.d. |
| 482 | 0.003 | n.d. | 0.15 |
| 483 | 0.003 | n.d. | 0.0123 |
| 484 | 0.003 | n.d. | 0.067 |
| 485 | 0.003 | n.d. | 0.11 |
| 486 | 0.003 | n.d. | 0.487 |
| 487 | 0.003 | n.d. | 0.0058 |
| 488 | 0.003 | n.d. | 0.0405 |

| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 489 | 0.0007 | n.d. | 0.012 |
| 490 | 0.0034 | n.d. | 0.014 |
| 491 | 0.003 | n.d. | 0.015 |
| 492 | 0.0022 | n.d. | 0.0555 |
| 493 | 0.003 | n.d. | 0.1045 |
| 494 | 0.003 | n.d. | 0.394 |
| 495 | 0.003 | n.d. | 0.051 |
| 496 | 0.003 | n.d. | 0.0972 |
| 497 | 0.003 | n.d. | 0.0077 |
| 498 | 0.003 | n.d. | 0.083 |
| 499 | 0.0048 | n.d. | 0.22 |
| 500 | 0.003 | n.d. | 0.016 |
| 501 | 0.003 | n.d. | 0.038 |
| 502 | 0.003 | n.d. | 0.017 |
| 503 | 0.003 | n.d. | 0.0275 |
| 504 | 0.003 | n.d. | 0.0815 |
| 505 | 0.0041 | n.d. | 0.06 |
| 506 | 0.003 | n.d. | 0.038 |

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| Ej.# | JAK2/IC50 [µmol $l^{-1}$] | STAT1/IC50 [µmol $l^{-1}$] | STAT5/IC50 [µmol $l^{-1}$] |
|---|---|---|---|
| 507 | <0.003 | n.d. | 0.0002 |
| 508 | 0.0041 | n.d. | 0.0148 |
| 509 | <0.003 | n.d. | 0.0431 |
| 510 | 0.003 | n.d. | 0.001 |
| 511 | 0.003 | n.d. | 0.0039 |
| 512 | 0.003 | n.d. | 0.014 |
| 513 | 0.0046 | n.d. | 0.116 |
| 514 | 0.025 | n.d. | 1.323 |
| 515 | 0.003 | n.d. | 0.054 |
| 516 | 0.0064 | n.d. | 0.119 |
| 517 | 0.003 | n.d. | 0.0695 |
| 518 | 0.003 | n.d. | 0.0395 |
| 519 | 0.0036 | n.d. | 0.0605 |
| 520 | 0.057 | n.d. | 0.543 |
| 521 | 0.003 | n.d. | n.d. |
| 522 | 0.008 | 2.89 | n.d. |

n.d. = no determinado

Como se muestra en el Cuadro 2, los compuestos de los Ejemplos 1 a 522 muestran valores $IC_{50}$ de inhibición de JAK2 en el intervalo de < 0.003 a 2.1 micromoles/litro$^{-1}$, en particular en el intervalo de < 0.003 a 0.05 micromoles/litro$^{-1}$.

Los compuestos de la invención inhiben selectivamente JAK2 cuando se comparan con otras cinasas, por ejemplo cMet, cKit, ALK y PDGFRa, como se muestra por los resultados del Cuadro 3.

Los compuestos se ensayan en un ensayo de fosforilación de cinasa basado en anticuerpos, utilizando los dominios recombinantes de las cinasas cMet, cKit, ALK y PDGFRalfa, y un sustrato peptídico genérico de fosfotirosina. LanthaScreen$^{MR}$ es la detección de la Transferencia de Energía de Resonancia de Fluorescencia Resuelta en el Tiempo (TR-FRET) utilizando quelatos de lantánido para medir las interacciones entre diferentes componentes de enlace. En un ensayo de cinasa TR-FRET, se conjuga una especie donadora de lantánido de largo tiempo de vida, con un anticuerpo que se enlaza específicamente a un producto fosforilado de una reacción de cinasa, que se marca con un fluoróforo aceptor adecuado. Esta interacción mediada por anticuerpos pone al donador de lantánido y al aceptor en proximidad, de tal manera que puede tener lugar la transferencia de energía de resonancia, dando como resultado un aumento detectable en FRET. El LanthaScreen se ejecuta a temperatura ambiente, y se termina mediante la adición de una solución de paro, seguida por el anticuerpo P-20 marcado con Tb. Después de incubar en la oscuridad, las placas se transfieren a un lector de

fluorescencia para el conteo. En todos los ensayos, se obtiene el efecto del compuesto sobre la actividad enzimática, a partir de las curvas lineales de progreso, y se determina a partir de una lectura (medición de punto final).

**Cuadro 3**

| Ej. # | JAK2/IC50 [µmol $l^{-1}$] | cMet/IC50 [µmol $l^{-1}$] | cKit/IC50 [µmol $l^{-1}$] | ALK/IC50 [µmol $l^{-1}$] | PDGFRa/IC50 [µmol $l^{-1}$] |
|---|---|---|---|---|---|
| 96 | 0.0485 | > 10 | > 10 | > 10 | > 10 |
| 151 | 0.0057 | > 10 | > 10 | > 10 | > 10 |
| 184 | < 0.003 | > 10 | > 10 | > 10 | > 10 |
| 203 | 0.0064 | 6.9 | 4.7 | > 10 | > 10 |
| 235 | 0.056 | > 10 | > 10 | > 10 | > 10 |
| 238 | 0.0111 | 8.2 | > 10 | > 10 | 6.6 |
| 278 | 0.011 | 1.4 | 1.35 | > 10 | 2.65 |
| 300 | 0.0175 | > 10 | 3.4 | > 10 | 7.7 |
| 301 | < 0.003 | 3.6 | 4.75 | > 10 | 5.6 |
| 311 | 0.031 | > 10 | > 10 | > 10 | > 10 |
| 332 | 0.001 | 7.567 | 1.552 | 9.05 | 6.7 |
| 372 | 0.0047 | > 10 | 5.7 | > 10 | > 10 |
| 380 | 0.0032 | 5.4 | 1.7 | > 10 | 5.3 |
| 382 | 0.0035 | 2.4 | 1.1 | > 10 | 7.7 |
| 440 | 0.0032 | > 10 | > 10 | > 10 | > 10 |

| Ej. # | JAK2/IC50 [µmol $l^{-1}$] | cMet/IC50 [µmol $l^{-1}$] | cKit/IC50 [µmol $l^{-1}$] | ALK/IC50 [µmol $l^{-1}$] | PDGFRa/IC50 [µmol $l^{-1}$] |
|---|---|---|---|---|---|
| 446 | 0.0043 | 6 | 2.65 | > 10 | 7.45 |
| 503 | < 0.003 | 6.1 | 9.5 | > 10 | > 10 |
| 521 | < 0.003 | 3.5 | 2.9 | > 10 | 2.8 |

Los compuestos de la presente invención se ensayan adicionalmente para medir su capacidad para inhibir JAK1, como se describe anteriormente. Los compuestos de los Ejemplos 1 a 522 muestran en este ensayo valores $IC_{50}$ en el intervalo de < 0.003 a > 10 micromoles/litro$^{-1}$.

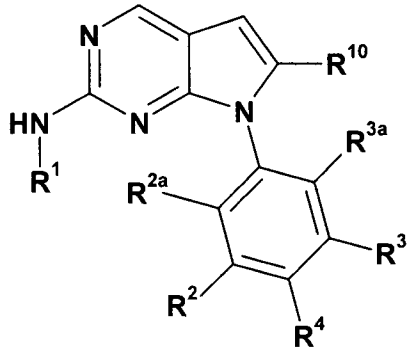
Los compuestos de la presente invención se ensayan adicionalmente para medir su capacidad para inhibir JAK3 como se describe anteriormente. Los compuestos de los Ejemplos 1 a 522 muestran en este ensayo valores $IC_{50}$ en el intervalo de < 0.003 a > 10 micromoles/litro$^{-1}$.

Los compuestos de la presente invención se ensayan adicionalmente para medir su capacidad para inhibir TYK2 como se describe anteriormente. Los compuestos de los Ejemplos 1 a 522 muestran en este ensayo valores $IC_{50}$ en el intervalo de < 0.003 a > 10 micromoles/litro$^{-1}$.

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## REIVINDICACIONES

1. Un compuesto de la fórmula I:



(I)

en donde:

$R^1$ representa heterociclilo insustituido o sustituido, arilo insustituido o sustituido, cicloalquilo insustituido o sustituido;

$R^2$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^3$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

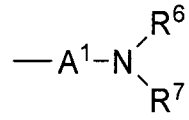
o $R^2$ y/o $R^3$ se conectan con $R^5$ o $R^7$ para formar una fracción cíclica fusionada con el anillo de fenilo con el que $R^2/R^3$ están unidos;

$R^{2a}$ representa hidrógeno, halógeno, alquilo inferior, alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

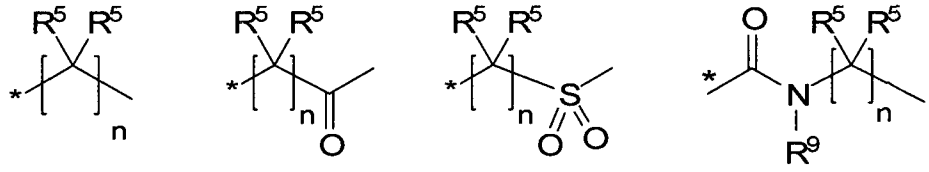
$R^{3a}$ representa hidrógeno, halógeno, alquilo inferior,

alquiloxilo inferior, halo-alquilo inferior, cicloalquilo, cicloalquiloxilo, halo-cicloalquilo, cicloalquiloxilo, halo-cicloalquiloxilo;

$R^4$ representa un grupo:



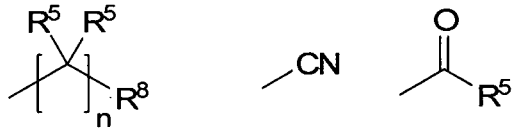
en donde $A^1$ representa uno de los siguientes grupos:



en donde el átomo marcado con * es un enlace con el anillo de fenilo;

o

$R^4$ representa uno de los siguientes grupos:



$R^5$ representa, independientemente de cada otro hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo o forma, junto con el átomo de carbono con el que está unido, un cicloalquilo;

$R^6$ y $R^7$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido;

o

$R^6$ representa hidrógeno o alquilo opcionalmente sustituido; y

$R^7$ representa alquilo opcionalmente sustituido;

$R^8$ representa hidroxilo, alquiloxilo inferior, halo-alquiloxilo inferior, cicloalquiloxilo, halo-cicloalquiloxilo, alquilo inferior-sulfonilo, halo-alquilo inferior-sulfonilo, cicloalquil-sulfonilo, halo-cicloalquil-sulfonilo, alquilo inferior-sulfinilo, halo-alquilo inferior-sulfinilo, cicloalquil-sulfinilo, halo-cicloalquil-sulfinilo;

$R^9$ representa H o alquilo inferior;

$R^{10}$ representa hidrógeno, alquilo inferior, halo-alquilo inferior, cicloalquilo, halo-cicloalquilo;

n representa 0, 1 ó 2;

o sales de los mismos.

2. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

$R^1$ representa heterociclilo insustituido o sustituido, o arilo insustituido o sustituido

en donde este heterociclilo se selecciona a partir de heterociclos insaturados, saturados o parcialmente saturados, los cales son monocíclicos, bicíclicos, tricíclicos o espirocíclicos, y tienen de 4 a 16 átomos del anillo, en donde están presentes de uno a cuatro átomo heterogéneos;

en donde el arilo mencionado se selecciona a partir de fracciones aromáticas con 6 a 14 átomos de carbono del anillo;

en donde los sustituyentes mencionados se seleccionan independientemente a partir de una o más, de preferencia una a cuatro de las siguientes fracciones: alquilo de 1 a 7 átomos de

carbono, amino-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, N-alcano de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, pirrolidino-alquilo de 1 a 7 átomos de carbono, oxo-pirrolidino-alquilo de 1 a 7 átomos de carbono, piperidino-alquilo de 1 a 7 átomos de carbono, piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-il-alquilo de 1 a 7 átomos de carbono, morfolino-alquilo de 1 a 7 átomos de carbono, tiomorfolino-alquilo de 1 a 7 átomos de carbono, S-mono- o S,S-dioxo-tiomorfolino-alquilo de 1 a 7 átomos de carbono, carbamoil-alquilo de 1 a 7 átomos de carbono, [N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil]-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfinil-alquilo de 1 a 7 átomos de carbono, alcano de 1 a 7 átomos de carbono-sulfonil-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, pirrolidino, oxo-pirrolidino, piperidino, piperazin-1-ilo, 4-

(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 10 átomos de carbono)-piperazin-1-ilo, 4-(amino-alquilo de 1 a 7 átomos de carbono)-piperazin-1-ilo, 4-[N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alquilo de 1 a 7 átomos de carbono]-piperazin-1-ilo, morfolino, tiomorfolino, S-oxo- o S,S-dioxo-tiomorfolino, alcano de 1 a 7 átomos de carbono-sulfonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono y/o (N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono)-carbamoílo, pirrolidin-1-carbonilo, piperidin-1-carbonilo, piperazin-1-carbonilo, 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-carbonilo, morfolin-1-carbonilo, tiomorfolin-1-carbonilo, S-oxo- o S,S-dioxo-tiomorfolin-1-carbonilo, sulfo, alcano de 1 a 7 átomos de carbono-sulfonilo, alcano de 1 a 7 átomos de carbono-sulfinilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-sulfamoílo, morfolino-sulfonilo, tiomorfolino-sulfonilo, ciano y nitro;

$R^2$ representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono;

$R^{2a}$ representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono;

$R^{3}$ representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono;

$R^{3a}$ representa hidrógeno, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono;

$R^{5}$ representa hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, o forma, junto con el átomo de carbono con el que está unido, un cicloalquilo;

$R^{6}$ y $R^{7}$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido por uno o

más sustituyentes,

en donde este heterociclo está saturado, contiene 5 ó 6 átomos del anillo y 1, 2 ó 3 átomo heterogéneos seleccionados a partir del grupo de N, O y S, y

en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), hidroxilo, halógeno, alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-amino, di-alquilo de 1 a 7 átomos de carbono-amino;

$R^8$ representa hidroxilo, alquiloxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, cicloalquiloxilo de 3 a 6 átomos de carbono, halo-cicloalquiloxilo de 3 a 6 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, cicloalquilo de 3 a 6 átomos de carbono-sulfonilo, halo-cicloalquilo de 3 a 6 átomos de carbono-sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, halo-alquilo de 1 a 7 átomos de carbono-sulfinilo, cicloalquilo de 3 a 6 átomos de carbono-sulfinilo, halo-cicloalquilo de 3 a 6 átomos de carbono-sulfinilo;

$R^{10}$ representa hidrógeno, alquilo de 1 a 7 átomos de carbono,

halo-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, halo-cicloalquilo de 3 a 6 átomos de carbono;

o una sal del mismo.

3. Un compuesto de la fórmula I de acuerdo con la reivindicación 1 ó 2, en donde:

$R^2$ representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro;

$R^{2a}$ representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro;

$R^3$ representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro;

$R^{3a}$ representa hidrógeno, flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopentilo, ciclopropiloxilo o ciclopentiloxilo, en cada caso opcionalmente sustituido por uno o más sustituyentes seleccionados a partir del grupo que consiste en flúor y cloro;

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$R^5$ representa hidrógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 2 átomos de carbono, o forma, junto con el átomo de carbono con el que está unido, un ciclopropilo;

$R^6$ y $R^7$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido por uno a tres sustituyentes,

en donde este heterociclo se selecciona a partir del grupo de morfolinilo, piperazinilo, tiazidinilo, pirrolidinilo; y

en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopropiloxilo, hidroxi-alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-amino, di-alquilo de 1 a 4 átomos de carbono-amino;

$R^8$ representa hidroxilo, metoxilo, etoxilo, isopropoxilo, halo-metoxilo, metil-sulfonilo, ciclopropil-sulfonilo, metil-sulfinilo;

$R^{10}$ representa hidrógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 2 átomos de carbono, ciclopropilo;

o una sal del mismo.

4. Un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde:

$R^2$ representa hidrógeno, flúor, cloro, metilo;

$R^{2a}$ representa hidrógeno;

$R^3$ representa hidrógeno, flúor, cloro, metilo;

$R^{3a}$ representa hidrógeno;

$R^5$ representa hidrógeno, metilo, o forma, junto con el átomo de carbono con el que está unido, un ciclopropilo;

$R^8$ representa hidroxilo o metil-sulfonilo;

$R^{10}$ representa hidrógeno o metilo;

o una sal del mismo.

5. Un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde:

$R^2$ representa hidrógeno, flúor, cloro, metilo;

$R^{2a}$ representa hidrógeno;

$R^3$ representa hidrógeno, flúor, cloro, metilo;

$R^{3a}$ representa hidrógeno;

$R^5$ representa hidrógeno, metilo, o forma, junto con el átomo de carbono con el que está unido, un ciclopropilo;

$R^6$ y $R^7$ representan, junto con el átomo de nitrógeno con el que están unidos, un heterociclo opcionalmente sustituido por uno a tres sustituyentes,

en donde este heterociclo se selecciona a partir del grupo de morfolinilo, piperazinilo, tiazidinilo, pirrolidinilo; y

en donde los sustituyentes mencionados se seleccionan a partir del grupo que consiste en oxo (por ejemplo, en C=O o $SO_2$), flúor, cloro, alquilo de 1 a 4 átomos de carbono, alquiloxilo de 1 a 4 átomos de carbono, ciclopropilo, ciclopropiloxilo, hidroxi-alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-amino, di-alquilo de 1 a 4 átomos de carbono-amino;

$R^8$ representa hidroxilo o metil-sulfonilo;

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$R^{10}$ representa hidrógeno o metilo;

o una sal del mismo.

6. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde cuando menos uno de $R^2$ y $R^3$ no representa hidrógeno.

7. Un compuesto seleccionado a partir del grupo que consiste en:

(3,4-dietoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

(4-isopropoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4,5-trimetoxi-fenil)-amina;

(3,4-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

N-terbutil-4-[2-(3,4-dimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida;

N-terbutil-4-[2-(3,4-dimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida;

N-terbutil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida;

N-terbutil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida;

N,N-dimetil-4-[2-(3,4,5-trimetoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida;

(4,5-dimetoxi-2-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metil-1,2,3,4,4a,5-hexahidro-7H-6-oxa-3,11b-diaza-dibenzo-[a,c]-ciclohepten-9-il)-amina;

dietil-amida del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-piperazin-1-carboxílico;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2,2,3,3-tetrafluoro-2,3-dihidro-benzo-[1,4]-dioxin-6-il)-amina;

benzo-[1,3]-dioxol-5-il-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(1-metil-piperidin-4-il)-fenil]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il)-fenil]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il)-fenil]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-fenil-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-fenil)-amina;

N-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-N',N'-dimetil-bencen-1,4-diamina;

(2,4-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(3,5-dimetoxi-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metoxi-fenol;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(4-metil-piperazin-1-il)-fenil]-amina;

[3-(2-dimetil-amino-etoxi)-4-metoxi-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[3-(3-dimetil-amino-propoxi)-4-metoxi-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(2-morfolin-4-il-etoxi)-fenil]-amina;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metoxi-3-(2-pirrolidin-1-il-etoxi)-fenil]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{3-[2-(4-metil-piperazin-1-il)-etoxi]-fenil}-amina;

[4-(2-dietil-amino-etoxi)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-

(2-morfolin-4-il-etoxi)-fenil]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(2-morfolin-4-il-etoxi)-fenil]-amina;

[3-(2-dietil-amino-etoxi)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-fenil)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina;

{3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

N-(2-dimetil-amino-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-piperidin-1-il-metil-fenil)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperidin-1-il-metil-fenil)-amina;

(4-imidazol-1-il-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-4-il-metil-fenil)-amina;

terbutil-éster del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-carboxílico;

terbutil-éster del ácido 2-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-pirrolidin-1-carboxílico;

(3-imidazol-1-il-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

N-(2-dimetil-amino-etil)-3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-fenil-benzamida;

{3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

N-(2-dimetil-amino-etil)-3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida;

N-(2-hidroxi-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-metil-fenil)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-pirrolidin-2-il-fenil)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina;

(4-fluoro-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-pirrolidin-1-il-metanona;

{2-fluoro-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

{2-fluoro-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-

il]-fenil}-morfolin-4-il-metanona;

1-{4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona;

{4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-N-(2-morfolin-4-il-etil)-benzamida;

N-(1-etil-pirrolidin-2-il-metil)-4-[2-(4-fluoro-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzamida;

[4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

N-(2-dimetil-amino-etil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-metil-benzamida;

(4-dimetil-amino-piperidin-1-il)-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-metanona;

4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-N-(2-morfolin-4-il-etil)-benzamida;

N-(1-etil-pirrolidin-2-il-metil)-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida;

terbutil-éster del ácido 4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzoil}-piperazin-1-carboxílico;

2-{3-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

{2-fluoro-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-trifluoro-metil-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-morfolin-4-il-metanona;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-pirrolidin-1-il-metanona;

{2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

{2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

N-(1-etil-pirrolidin-2-il-metil)-2-fluoro-5-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzamida;

1-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-etanona;

(4-fluoro-3-trifluoro-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-fluoro-3-metil-fenil)-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{2,6-difluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-2-metil-1-morfolin-4-il-propan-1-ona;

(1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-

fenil}-ciclopropil)-morfolin-4-il-metanona;

{2-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

1,1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona;

{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-piperazin-1-il-metanona;

{2-fluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-cloro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il-metil)-fenil]-amina;

{2-cloro-4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzonitrilo;

4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-benzonitrilo;

[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina;

{2-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-cloro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona;

2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

2-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona;

(1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona;

1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-piperazin-2-ona;

1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-pirrolidin-2-ona;

{7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina;

(4-isopropoxi-fenil)-[7-(4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

7-(4-[1,4]-diazepan-1-il-metil-3-fluoro-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina;

(4-isopropoxi-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-

[2,3-d]-pirimidin-2-il]-amina;

[7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina;

(4-isopropoxi-fenil)-[7-(3-metil-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina;

{7-[3-cloro-4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina;

1-{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanol;

(4-isopropoxi-fenil)-{7-[4-(2-morfolin-4-il-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

{4-[2-(3-cloro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-fenil}-morfolin-4-il-metanona;

(1-{4-[2-(3-cloro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona;

(3-cloro-4-metil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(3-cloro-4-metil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(3-cloro-4-metil-fenil)-{7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

(3-cloro-4-metil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

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(1-{4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-ciclopropil)-(4-metil-piperazin-1-il)-metanona;

(4-fluoro-3-metil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{7-[4-(4-etil-piperazin-1-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3-fluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-isopropoxi-fenil)-amina;

(4-fluoro-3-metil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(3-cloro-4-metil-fenil)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(3-cloro-4-metil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

(3-cloro-4-metil-fenil)-{7-[4-(4-etil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-fluoro-3-metil-fenil)-amina;

{7-[4-(4-etil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina;

1-(4-{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-1-il)-etanona;

4-{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-

d]-pirimidin-7-il]-bencil}-1-etil-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina;

4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-benzonitrilo;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-fluoro-3-metil-fenil)-amina;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

[7-(4-metan-sulfinil-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina;

[7-(4-metan-sulfonil-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina;

1-morfolin-4-il-2-[4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona;

2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona;

1-morfolin-4-il-2-[4-(2-fenil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona;

1-morfolin-4-il-2-{4-[2-(4-trifluoro-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona;

1-(4-metil-piperazin-1-il)-2-{4-[2-(4-trifluoro-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-etanona;

[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-p-tolil-amina;

(3,4-dietoxi-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

1-(4-metil-piperazin-1-il)-2-[4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-etanona;

2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

{2-fluoro-4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona;

(4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-fenil)-morfolin-4-il-metanona;

{2-fluoro-4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-(4-metil-piperazin-1-il)-metanona;

2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-1-(1,1-dióxido-1-tiomorfolin-4-il)-etanona;

{4-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

(1-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-

fenil}-ciclopropil)-(4-etil-piperazin-1-il)-metanona;

(3,4-dimetil-fenil)-[7-(4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

2-{4-[2-(3,4-dimetil-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

2-{4-[2-(4-fluoro-3-metoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

(3,4-dimetil-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-fluoro-3-metoxi-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

2-{4-[2-(3,4-dietoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-etil-piperazin-1-il)-etanona;

2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona;

2-{4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-(4-metil-piperazin-1-il)-etanona;

(3,4-dietoxi-fenil)-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-6-metil-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-etil-piperazin-1-il)-metanona;

2-{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-1-(4-etil-piperazin-1-il)-etanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il)-fenil]-amina;

{4-[7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

[7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina;

[7-(3-cloro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4-dietoxi-fenil)-amina;

{4-[7-(3,5-difluoro-4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-pirrolidin-1-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metoxi-metil-fenil)-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-fenil-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-2-il-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-3-il-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-piridin-4-il-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-

pirrolo-[2,3-d]-pirimidin-2-il}-(4-metoxi-metil-fenil)-amina;

4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-benzonitrilo;

(4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-trifluoro-metil-fenil)-(4-metil-piperazin-1-il)-metanona;

(4-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-fenil)-morfolin-4-il-metanona;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[4-(4-etil-piperazin-1-il-metil)-fenil]-amina;

{2,6-difluoro-4-[2-(4-metoxi-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

(4-{2-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-(4-metil-piperazin-1-il)-metanona;

(4-{2-[4-(4-etil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-(4-metil-piperazin-1-il)-metanona;

{2,6-difluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-(4-metil-piperazin-1-il)-metanona;

(4-isopropoxi-fenil)-{7-[4-(1-morfolin-4-il-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina (racémica);

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-isopropoxi-fenil)-amina;

{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-

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pirimidin-2-il-amino]-piridin-2-il}-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-etil-piperazin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-4-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-morfolin-4-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-metil-piperazin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-3-trifluoro-metil-fenil]-amina;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-trifluoro-metil-fenil}-(4-metil-piperazin-1-il)-metanona;

{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il-metanona;

{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(4-metil-piperazin-1-il)-metanona;

(2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il-metil)-3-trifluoro-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

(2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-

d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

(2,6-difluoro-4-{2-[3-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-fenil-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-2-il-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-3-il-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-piridin-4-il-amina;

2-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-[4-(2-hidroxi-etil)-piperazin-1-il]-etanona;

{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

[2,6-difluoro-4-(2-fenil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(piridin-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(piridin-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(pirimidin-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(5,6-dimetil-piridin-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(4-fluoro-3-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(6-isopropoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(6-trifluoro-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

5-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-piridin-2-carbonitrilo;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-metil-piridin-3-il)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-metoxi-piridin-3-il)-amina;

{4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-

fenil}-morfolin-4-il-metanona;

{4-[2-(6-isopropoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(3-fluoro-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

5-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-piridin-2-carbonitrilo;

Morfolin-4-il-{4-[2-(6-trifluoro-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona;

4-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-benzonitrilo;

{4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(4-metoxi-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{4-[2-(3-metoxi-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(5-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

(2,6-difluoro-4-{2-[2-(4-metil-piperazin-1-il)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

[7-(3-fluoro-4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(4-metil-piperazin-1-il-metil)-fenil]-amina;

(2,6-difluoro-4-{2-[3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(tiazol-2-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1-metil-1H-pirazol-4-il)-amina;

{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-3-il}-morfolin-4-il-metanona;

(1,1-dióxido-tiomorfolin-4-il)-{4-[2-(6-metil-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona;

(1,1-dióxido-tiomorfolin-4-il)-{4-[2-(6-metoxi-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-metanona;

(2,6-difluoro-4-{2-[1-(2-metoxi-etil)-1H-pirazol-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[1-(2-metoxi-etil)-1H-pirazol-4-il]-amina;

{4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil]-amina;

(4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona;

4-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

4-{2-[4-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona;

4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-2-ona;

4-(4-{7-[3,5-difluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-((2S,5R)-2,5-dimetil-piperazin-1-il-metil)-fenil]-amina (racémica);

(4-{2-[4-((2S,5R)-2,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona (racémica);

{2,6-difluoro-4-[2-(6-piperazin-1-il-piridin-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-piridin-3-il)-amina;

[2,6-difluoro-4-(2-{6-[4-(2-hidroxi-etil)-piperazin-1-il]-piridin-3-il-amino}-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona;

2-(4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-1-il)-etanol;

(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-

metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-amina;

(4-{2-[6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona;

(4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona (racémica);

Ejemplo 270: [6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il]-amina (racémica);

[6-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina (racémica);

[2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(4-metil-piperazin-1-il)-pirimidin-5-il]-amina;

Ciclopropil-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanol;

4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo;

1-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-etanol;

(2,6-difluoro-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanol;

(4-{2-[2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-fenil)-morfolin-4-il-metanona;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-piridin-3-il)-amina;

1-(4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-pirrolidin-2-ona;

2-(4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-1-(4-metil-piperazin-1-il)-etanona;

[4-(4-etil-piperazin-1-il)-3-metil-fenil]-[7-(3-fluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

2-{4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-1-(1,1-dióxido-tiomorfolin-4-il)-etanona;

{4-[2-(3,4-dietoxi-fenil-amino)-6-metil-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(4-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

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[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3,4-dimetil-fenil)-amina;

(3,4-dimetil-fenil)-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-(1,1-dióxido-tiomorfolin-4-il)-metanona;

1-(1,1-dióxido-tiomorfolin-4-il)-2-(4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-etanona;

(4-{2-[4-(4-etil-piperazin-1-il)-3-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona;

{4-[2-(4-cloro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona;

{4-[2-(4-fluoro-3-metoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-metil-fenil}-morfolin-4-il-metanona;

4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-N-(2-morfolin-4-il-etil)-benzamida;

4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-N-[2-(4-metil-piperazin-1-il)-etil]-benzamida;

(4-dimetil-amino-piperidin-1-il)-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-metanona;

{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-[4-(2-hidroxi-etil)-piperazin-1-il]-metanona;

2-{4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-1-morfolin-4-il-etanona;

{2-fluoro-4-[2-(1-metil-1H-pirazol-4-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2-fluoro-4-[2-(3-metoxi-4-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{7-[3,5-difluoro-4-(4-metil-piperazin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina;

{7-[3,5-difluoro-4-(4-isopropil-piperazin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina;

{7-[4-(4-ciclopropil-piperazin-1-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metoxi-4-metil-fenil)-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3-metoxi-4-metil-fenil)-amina;

{7-[4-(3,3-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(3,4-dimetil-fenil)-amina;

4-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-bencil}-1-metil-piperazin-2-ona;

{4-[2-(1,5-dimetil-1H-pirazol-3-il-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2-fluoro-fenil}-morfolin-4-il-metanona;

4-{4-[2-(3,4-dimetil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-2,6-difluoro-bencil}-piperazin-2-ona;

{2-fluoro-4-[2-(4-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-

pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

{2,6-difluoro-4-[2-(4-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperazin-1-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[5-(4-etil-piperazin-1-il-metil)-piridin-2-il]-amina;

[5-(4-etil-piperazin-1-il-metil)-piridin-2-il]-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

1-(4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-il)-etanona;

1-(4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-1-il)-etanona;

terbutil-éster del ácido 4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-pirazol-1-il}-piperidin-1-carboxílico;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1-piperidin-4-il-1H-pirazol-4-il)-amina;

1-[4-(4-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona;

1-[4-(4-{7-[3,5-difluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona;

[2-fluoro-4-(2-p-tolil-amino-pirrolo-[2,3-d]-pirimidin-7-il)-fenil]-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-

pirimidin-2-il]-p-tolil-amina;

(2-fluoro-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

{2-fluoro-4-[2-(4-metil-3-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-morfolin-4-il-metil-fenil)-amina;

[4-(4-ciclopropil-piperazin-1-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-piperazin-1-il-metil-fenil)-amina;

[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-piperazin-1-il-metil-fenil)-amina;

4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-2-ona;

4-{4-[7-(4-metan-sulfonil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-1-metil-piperazin-2-ona;

{2-fluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

4-(4-{7-[3-fluoro-4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-1-metil-piperazin-2-ona;

1-[4-(4-{7-[4-(morfolin-4-carbonil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-bencil)-piperazin-1-il]-etanona;

4-(4-{2-[4-(4-acetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona;

4-(4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona;

4-(2,6-difluoro-4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencil)-piperazin-2-ona;

4-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-piperazin-2-ona;

4-(2,6-difluoro-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencil)-piperazin-2-ona;

4-{2,6-difluoro-4-[2-(4-metil-3-morfolin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-2-ona;

N-terbutil-4-{2-[4-(4-ciclopropil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((R)-3-metil-4-pirrolidin-2-il-fenil)-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-pirrolidin-3-ol (racémico);

N-terbutil-4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

4-{2-[4-(4-metil-piperazin-1-il)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-

pirimidin-2-il]-[2-(tetrahidro-piran-4-iloxi)-piridin-4-il]-amina;

N-terbutil-4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(2-morfolin-4-il-etoxi)-piridin-4-il]-amina;

N-terbutil-4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-morfolin-2-il-fenil)-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina;

N-terbutil-4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida (racémica);

4-{2-[6-((2R,5S)-2,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-4-metil-fenil]-amina;

(4-{2-[3-(2,5-Dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-

pirimidin-2-il}-amina;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(4-metil-piperazin-1-il)-metanona;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(2,5-dioxa-8-aza-espiro-[3.5]-non-8-il)-metanona;

N-terbutil-4-{2-[4-(2-pirrolidin-1-il-etoxi)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-trifluoro-metil-piperazin-1-il)-piridin-4-il]-amina (racémica);

[3-(4-ciclopropil-piperazin-1-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-{2-[3-(4-ciclopropil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

(4-{2-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-1-carbaldehído;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(cis-3,5-dimetil-piperazin-1-il)-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2-piperazin-1-il-metil-piridin-4-il)-amina;

[3-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-{2-[3-(4,7-diaza-espiro-[2.5]-oct-7-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-amida del ácido propan-2-sulfónico;

N-terbutil-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[5-(4-metil-piperazin-1-il)-piridin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina (racémica);

(4-{2-[3-((2R,5S)-2,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona (racémica);

N-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-

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pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metan-sulfonamida;

{2-fluoro-4-[2-(4-piperidin-4-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona;

4-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-piperidin-4-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(4-metil-piperazin-1-il-metil)-piridin-4-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3,3-dimetil-piperazin-1-il-metil)-4-metil-fenil]-amina;

(4-{2-[3-(3,3-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

N-terbutil-4-{2-[3-(cis-3,5-dimetil-piperazin-1-il-metil)-4-metil-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-pirrolidin-3-ol (racémico);

3-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-hexahidro-pirido-[1,2-a]-pirazin-1-ona;

{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-1-il-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(cis-3,5-dimetil-piperazin-1-il-metil)-piridin-4-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(piperidin-4-il-metoxi)-piridin-4-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3,3-difluoro-pirrolidin-1-il-metil)-4-metil-fenil]-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-azetidin-3-ol;

4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1-metil-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{2-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-piridin-4-il}-amina;

4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-1-metil-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{3-[4-(2-dimetil-amino-etil)-piperazin-1-il-metil]-4-metil-fenil}-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-piperazin-2-ona;

1-{2-cloro-5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-azetidin-3-ol;

(4-cloro-3-piperazin-1-il-metil-fenil)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3,3-difluoro-pirrolidin-1-il-metil)-piridin-4-il]-amina;

(1,1-dióxido-tiomorfolin-4-il)-(2-fluoro-4-{2-[4-metil-3-(3-trifluoro-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanona (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(3-trifluoro-metil-piperazin-1-il-metil)-fenil]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3-metoxi-azetidin-1-il-metil)-4-metil-fenil]-amina;

(1,1-dióxido-tiomorfolin-4-il)-(2-fluoro-4-{2-[2-(4-metil-piperazin-1-il-metil)-piridin-4-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-metanona;

[2-(4-ciclopropil-piperazin-1-il-metil)-piridin-4-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-trifluoro-metil-piperazin-1-il-metil)-piridin-4-il]-amina (racémica);

1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-piperazin-2-ona;

4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1-(2-dimetil-amino-etil)-piperazin-2-ona;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-pirrolidin-3-ol (racémico);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-

pirimidin-2-il]-(3-imidazol-1-il-metil-4-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-pirazol-1-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(4-metil-3-[1,2,4]-triazol-4-il-metil-fenil)-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-4-metil-piperazin-2-ona;

1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-pirrolidin-3-ol (racémico);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-l]-[3-(3-metoxi-pirrolidin-1-il-metil)-4-metil-fenil]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(4-dimetil-amino-metil-[1,2,3]-triazol-1-il-metil)-4-metil-fenil]-amina;

(1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1H-[1,2,3]-triazol-4-il)-metanol;

[3-(Azetidin-3-iloxi-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil]-amina;

4-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-1-metil-

piperazin-2-ona;

1-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-azetidin-3-ol;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1,2,3,4-tetrahidro-1,4-epiazano-naftalen-6-il)-amina;

1-(5-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino}-2-metil-bencil)-pirrolidin-3-ol (racémico);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-metoxi-pirrolidin-1-il-metil)-piridin-4-il]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[2-(3-dimetil-amino-pirrolidin-1-il-metil)-piridin-4-il]-amina (racémica);

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-metil-3-piperazin-1-il-metil-fenil)-amina;

[6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

[5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(2,3-dihidro-1H-indol-6-il)-amina;

[3,5-dimetil-4-(2-morfolin-4-il-etoxi)-fenil]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3,5-dimetil-4-(2-morfolin-4-il-etoxi)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[3-(3-dimetil-amino-pirrolidin-1-il-metil)-4-metil-fenil]-amina (racémica);

[3-(3-dimetil-amino-pirrolidin-1-il-metil)-4-metil-fenil]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina (racémica);

[3-(7-Aza-biciclo-[2.2.1]-hept-7-il-metil)-4-metil-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

(4-{2-[4-metil-3-(4-metil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-fenil)-morfolin-4-il-metanona;

[7-(4-etil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina;

3-metil-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[5-(4-metil-piperazin-1-il)-piridin-2-il]-amina;

[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-

2-il}-amina;

[2-(4,7-diaza-espiro-[2.5]-oct-7-il)-piridin-4-il]-{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina;

{7-[4-(1,1-dióxido-tiomorfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(6-piperazin-1-il-piridin-3-il)-amina;

2,6-difluoro-4-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-benzonitrilo;

[7-(3,5-difluoro-4-metoxi-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina;

{7-[4-(cis-2,6-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina;

1-metil-5-{2-[6-(4-metil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-1,3-dihidro-indol-2-ona;

{7-[4-(1-metoxi-etil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-[6-(4-metil-piperazin-1-il)-piridin-3-il]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(7-metil-2,7-diaza-espiro-[4.4]-non-2-il-metil)-fenil]-amina;

{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(4-metil-piperazin-1-il)-metanona;

{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-fenil}-(cis-3,5-dimetil-piperazin-1-il)-metanona;

[7-(3,5-difluoro-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-amina;

{7-[4-(cis-2,6-dimetil-morfolin-4-il-metil)-3,5-difluoro-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(6-piperazin-1-il-piridin-3-il)-amina;

{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-(cis-3,5-dimetil-piperazin-1-il)-metanona;

[2-(4-ciclopropil-piperazin-1-il)-piridin-4-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[6-(4-ciclopropil-piperazin-1-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

1-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-pirrolidin-2-ona;

(4-ciclopropil-piperazin-1-il)-{3-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-metanona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(3-metil-4-piperazin-1-il-metil-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-3-metil-fenil]-amina;

1-(4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-pirrolidin-2-ona;

1-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-

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pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-pirrolidin-2-ona;

N-terbutil-4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-bencen-sulfonamida;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-{6-[4-(2-dimetil-amino-etil)-piperazin-1-il]-piridin-3-il}-amina;

{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-(4-metil-piperazin-1-il)-metanona;

2-(1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-metil-bencil}-1H-pirazol-4-il)-etanol;

6-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-3,4-dihidro-1H-quinolin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(3-trifluoro-metil-piperazin-1-il)-piridin-3-il]-amina (racémica);

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3,3-difluoro-pirrolidin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(4-metil-piperazin-1-il-metil)-piridin-3-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3,3-dimetil-piperazin-1-il-metil)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-piperazin-2-il-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((R)-4-piperazin-2-il-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3-trifluoro-metil-piperazin-1-il-metil)-fenil]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-2-fluoro-fenil]-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-4-metil-piperazin-2-ona;

1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-azetidin-3-ol;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-morfolin-4-il-metil-piridin-3-il)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-metil-3-(4-metil-pirazol-1-il-metil)-fenil]-amina;

{7-[3,5-difluoro-4-(3-metoxi-azetidin-1-il-metil)-fenil]-7H-pirrolo-[2,3-d]-pirimidin-2-il}-(4-metil-3-piperazin-1-il-metil-fenil)-amina;

4-(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-morfolin-3-ona;

4-(4-{2-[4-(cis-3,5-dimetil-piperazin-1-il-metil)-fenil-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2,6-difluoro-bencil)-morfolin-3-ona;

4-{2,6-difluoro-4-[2-(4-metil-3-piperazin-1-il-metil-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-bencil}-morfolin-3-ona;

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[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(6-piperazin-1-il-metil-piridin-3-il)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(5-metil-6-piperazin-1-il-piridin-3-il)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(dimetil-piperazin-1-il)-5-metil-piridin-3-il]-amina;

[5-cloro-6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-2-(cis-3,5-dimetil-piperazin-1-il)-nicotinonitrilo;

4-{3-cloro-5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-3,3-dimetil-piperazin-2-ona;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-3-metil-piridin-2-il}-3,3-dimetil-piperazin-2-ona;

[4-cloro-3-(4-metil-piperazin-1-il-metil)-fenil]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

1-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-3-metil-piridin-2-il}-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-trifluoro-metil-piridin-3-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metoxi-piridin-3-il]-amina;

1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-bencil}-piperazin-2-ona;

(4-{2-[6-(cis-3,5-dimetil-piperazin-1-il)-piridin-3-il-amino]-pirrolo-[2,3-d]-pirimidin-7-il}-2-fluoro-fenil)-morfolin-4-il-metanona;

4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-(1',2',3',4',5',6'-hexahidro-[2,4']-bipiridinil-5-il)-amina;

(5-cloro-6-piperazin-1-il-piridin-3-il)-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

1-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-3,3-dimetil-piperazin-2-ona;

4-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il}-1-metil-piperazin-2-ona;

4-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-il-metil}-1-metil-piperazin-2-ona;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-(3-metoxi-pirrolidin-1-il-metil)-fenil]-amina (racémica);

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-3-morfolin-3-il-fenil)-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-

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pirimidin-2-il]-[4-((S)-4-etil-morfolin-3-il)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[4-((S)-4-metil-morfolin-3-il)-fenil]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(cis-3,5-dimetil-piperazin-1-il)-5-metil-piridin-3-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-((S)-4-morfolin-3-il-fenil)-amina;

[6-(6,6-difluoro-[1,4]-diazepan-1-il)-5-metil-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(2-morfolin-4-il-etoxi)-piridin-3-il]-amina;

[6-(Azetidin-3-iloxi)-piridin-3-il]-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(tetrahidro-piran-4-iloxi)-piridin-3-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(2-metoxi-etoxi)-piridin-3-il]-amina;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(tetrahidro-piran-4-il-metoxi)-piridin-3-il]-amina;

2-{5-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-piridin-2-iloxi}-etanol;

[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-[6-(pirrolidin-3-iloxi)-piridin-3-il]-amina (racémica);

{4-[(S)-4-(2-benciloxi-etil)-morfolin-3-il]-fenil}-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il]-amina;

2-((S)-3-{4-[7-(3,5-difluoro-4-morfolin-4-il-metil-fenil)-7H-pirrolo-[2,3-d]-pirimidin-2-il-amino]-fenil}-morfolin-4-il)-etanol;

{3-fluoro-4-[2-(4-isopropoxi-fenil-amino)-pirrolo-[2,3-d]-pirimidin-7-il]-fenil}-morfolin-4-il-metanona.

8. Un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable como un producto farmacéutico.

9. Un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable, para utilizarse como un producto farmacéutico, en particular para el uso en una o más enfermedades mediadas por la cinasa de proteína tirosina.

10. El uso de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable, para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

11. El uso de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable, para la fabricación de un medicamento para el tratamiento de una o más enfermedades mediadas por la cinasa de proteína tirosina.

12. Un método para el tratamiento de una enfermedad mediada por la cinasa de proteína tirosina, el cual comprende el

paso de administrar a un sujeto que lo necesite, una cantidad terapéuticamente efectiva de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable.

13. Una composición farmacéutica, la cual comprende una cantidad terapéuticamente efectiva de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable, como ingrediente activo; y uno o más materiales portadores y/o diluyentes farmacéuticamente aceptables.

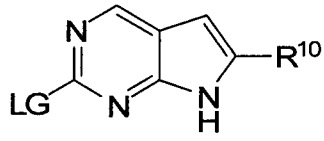
14. Una composición farmacéutica combinada, adaptada para su administración simultánea o en secuencia, la cual comprende una cantidad terapéuticamente efectiva de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, en forma libre o en forma de sal farmacéuticamente aceptable; y una cantidad terapéuticamente efectiva de uno o más componentes de combinación; y uno o más materiales portadores y/o diluyentes farmacéuticamente aceptables.

15. Una composición farmacéutica de acuerdo con la reivindicación 13, o una composición farmacéutica combinada de acuerdo con la reivindicación 14, para utilizarse en el tratamiento de una enfermedad mediada por la cinasa de proteína tirosina, en particular una enfermedad mediada por cinasa JAK2 y/o JAK3.

16. Un proceso para la fabricación de un compuesto de la fórmula I de acuerdo con cualquiera de las reivindicaciones 1 a 7, el

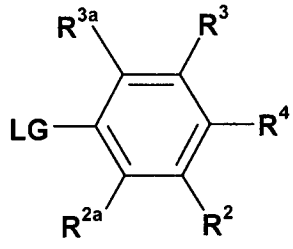
cual comprende cualquiera de:

método a) hacer reaccionar, en un primer paso, un compuesto de la fórmula II:



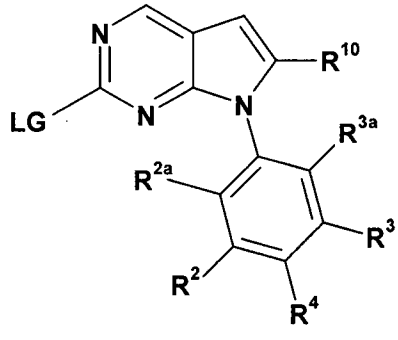
(II)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente, con un compuesto de la fórmula IV:



(IV)

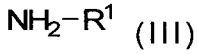
en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente, en una reacción de Buchwald catalizada por Cu, para obtener un compuesto de la fórmula VI:



(VI)

en donde los sustituyentes son como se definen anteriormente, y hacer reaccionar, en un segundo paso, el compuesto obtenido de la

fórmula VI con un compuesto de la fórmula (III):

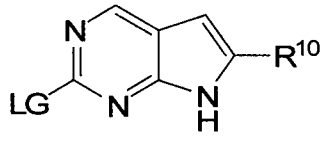


(III)

en donde $R^1$ es como se define en la fórmula I, para obtener un compuesto de la fórmula I;

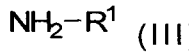
o

método B) hacer reaccionar, en un primer paso, un compuesto de la fórmula II:



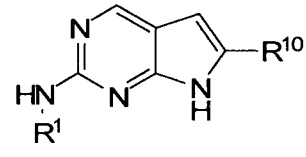
(II)

en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente, con un compuesto de la fórmula III:



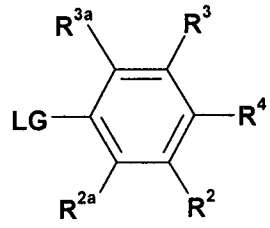
(III)

en donde $R^1$ es como se define en la fórmula I, ya sea en una reacción de Buchwald catalizada por Pd, o bien bajo condiciones ácidas, para obtener un compuesto de la fórmula (V):



(V)

en donde los sustituyentes son como se definen anteriormente, y hacer reaccionar, en un segundo paso, el compuesto obtenido de la fórmula (V) con un compuesto de la fórmula IV:




(IV)

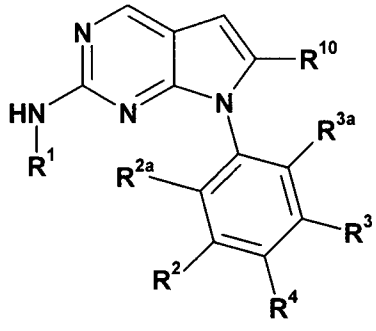
en donde los sustituyentes son como se definen para un compuesto de la fórmula I, y LG representa un grupo saliente, para obtener un compuesto de la fórmula I;

y, opcionalmente, convertir un compuesto de la fórmula I que se pueda obtener de acuerdo con el método A) o con el método B) en un compuesto diferente de la fórmula I, y/o convertir una sal que se pueda obtener de un compuesto de la fórmula I en una sal diferente del mismo, y/o convertir un compuesto libre que se pueda obtener de la fórmula I en una sal del mismo, y/o separar un isómero que se pueda obtener de un compuesto de la fórmula I, de uno o más isómeros diferentes que se puedan obtener de la fórmula I.

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## RESUMEN

La invención se refiere a los compuestos de la fórmula I, y sales de los mismos, en donde los sustituyentes son como se definen en la memoria descriptiva, a procesos para la preparación de los mismos; a productos farmacéuticos que contienen tales compuestos, en particular para el uso en una o más enfermedades mediadas por la cinasa de proteína tirosina.



# LISTA DE SECUENCIAS

<110> Novartis AG

<120> PIRROLO[2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA

<130> 52213A

<150> EP 08151137.0

<151> 2008-02-06

<160> 2

<170> PatentIn versión 3.3

<210> 1

<211> 14

<212> PRT

<213> Artificial

<220>

<223> FITC-labeled Insulin Receptor Kinase Substrate IRS-1 derivative (mammalian) [Derivado de sustrato IRS-

1 de cinasa receptora de insulina marcado con FITC (mamífero)], véase J. Biol. Chem. 268(33), 125146-51 (1993)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> X en el término C es el ácido amino-caproico marcado con FITC

<220>

<221> MOD_RES

<222> (14)..(14)

<223> X en el término N es glicil-amida (Gly-$NH_2$)

<400> 1

Xaa Lys Lys Ser Arg Gly Asp Tyr Met Thr Met Gln Ile Xaa

1 5 10

<210> 2

<211> 15

<212> PRT

<213> Artificial

<220>

<223> FITC-labeled peptide substrate for JAK2 and JAK3 [Sustrato peptídico marcado con FITC para JAK2 y JAK3], Caliper Sciences, Mountain View, California, EUA

<220>

<221> MOD_RES

<222> (1)..(1)

<223> X en el término C es glicina marcada con FITC

<220>

<221> MOD_RES

<222> (15)..(15)

<223> X en el término N es lisil-amida (Lys-$NH_2$)

<400> 2

Xaa Gly Glu Glu Glu Glu Tyr Phe Glu Leu Val Lys Lys Lys Xaa
1 5 10 15

JDY
418

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOVARTIS PHARMA AG
Patent Department
Postfach
4002 Basel
SUISSE

MAR 04 2010

Processed by M/D
04. März 2010 PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 02.03.2010 |
| Applicant's or agent's file reference<br>PAT052213-WO-PCT | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP2009/051281 | 04.02.2009 | 06.02.2008 |

Applicant
Novartis AG

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

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

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

4. **REMINDER**

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

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

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

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

| Name and mailing address of the international preliminary examining authority: | Authorized Officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Hutterer, Georg<br>Tel. +49 89 2399-8066 |

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>PAT052213-WO-PCT | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2009/051281 | International filing date *(day/month/year)*<br>04.02.2009 | Priority date *(day/month/year)*<br>06.02.2008 |
| International Patent Classification (IPC) or national classification and IPC<br>INV. C07D487/04 | | |
| Applicant<br>Novartis AG | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

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

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 2009-12-04 | 02.03.2010 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Rudolf, Manfred<br>Telephone No. +49 89 2399-8604 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2009/051281

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ 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 (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

| | |
|---|---|
| 1-271 | as originally filed |

**Claims, Numbers**

| | |
|---|---|
| 1(part), 2(part), 3-16 | as originally filed |
| 1(part), 2(part) | received on 07.12.2009 with letter of 03.12.2009 |

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/EP2009/051281

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-9,11,13-16 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/EP2009/051281

**Supplemental Box relating to Sequence Listing**

**Continuation of Box I, item 2:**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

**Re Item V.**

1 Reference is made to the following documents:

D1 : WO 2005/107760 A (IRM LLC [US]; HONG JIYONG [US]; GRAY NATHANAEL S [US]; SCHULTZ PETER [) 17 November 2005 (2005-11-17)

D2 : WO 2005/080393 A (IRM LLC [US]; CHOI HA-SOON [US]; WANG ZHICHENG [US]; GRAY NATHANAEL SC) 1 September 2005 (2005-09-01)

D3: WO 2006/045828 A (TIBOTEC PHARM LTD [IE]; ARTS FRANK XAVIER JOZEF HERWIG [BE]; GUILLEMON) 4 May 2006 (2006-05-04)

D4: WO 02/076985 A (SMITHKLINE BEECHAM CORP [US]; BONDINELL WILLIAM E [US]; HOLT DENNIS A) 3 October 2002 (2002-10-03)

D5: WO 2006/096270 A (VERTEX PHARMA [US]; LEDEBOER MARK W [US]; PIERCE ALBERT C [US]; BEMIS) 14 September 2006 (2006-09-14)

D6: HA-SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL.: "Design and synthesis of 7H-pyrrolo[2,3-d]pyrimidines as focal adhesion kinase inhibitors. Part 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, pages 2689-2692, XP002496172

2. The present application relates to compounds of formula I as depicted in claim 1, its preparation and the use thereof for preparation of medicaments for the treatment of cancer.

3. The claimed subject matter is novel. The prior art discloses structurally related anticancer compounds (e.g. D1, compounds 118, 124, 172) which do not fall within claim 1.

4. The compounds defined in claims 1-7 fall within the scope of the antitumour compounds suggested in documents D1 and D2 and therefore are considered as a selection from the compounds suggested in D1 and D2. It is apparent from the present application (table 3) that compounds of the present invention exhibit a pronounced selectivity towards JAK2. Such feature is not derivable from the cited

prior art. Insofar the claimed compounds exhibit such non-obvious effect, the claimed compoundsand their use and production may be considered non-obvious.

5. Claims 10,12: The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

**Re Item VIII.**

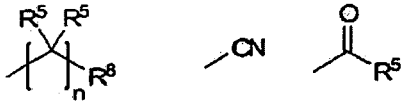
The claims contain open-ended definitions such as substituted heterocyclyl, substituted aryl, etc. which embrace virtually any imaginable substituents on said heterocyclyl, aryl etc. groups.

The IPEA's opinion is that it is inherently unlikely that substantially all compounds falling under a claim comprising an open-ended definition of a structural feature (here: substituted with any substituent) would exhibit a particular desired biological activity.

Therefore, it appears that, as certain claims comprise various open-ended structural definitions, the claims are likely to embrace subject matter which will not represent any solution to the relevant problem underlying the present application. Merely as a solution to the problem of providing new compounds, the subject matter of such claims would seem obvious to the person skilled in the art.

The scope and limits of the terms "lower" in connection with chain lengths should be clarified as found in the description (Art. 6 PCT).

Claims 10, 12: The scope and limits of "Protein tyrosine kinase mediated disease" are not clear, and it should be clarified as found in the description which diseases fall within such definition (Art. 6 PCT).



$R^5$ represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle

or

$R^6$ represents hydrogen or optionally substituted alkyl and

$R^7$ represents optionally substituted alkyl;

$R^8$ represents hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;

$R^9$ represents H or lower alkyl;

$R^{10}$ represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;

n represens 0, 1 or 2;

or salts thereof.

2. A compound of the formula I according to claim 1, wherein

$R^1$ represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl

wherein said heterocyclyl is selected from unsaturated, saturated or partially saturated heterocycles which are monocyclic bicyclic, tricyclic or spirocyclic and have 4 to 16, ring atoms wherein one to four heteroatoms are present;

wherein said aryl is selected from aromatic moieties with 6 to 14 ring carbon atoms;

wherein said substiutents are independently selected from one or more, preferably one to four of the following moieties: $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-

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# 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. |
|---|---|---|
| 52213-WO-PCT | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/EP2009/051281 | 04/02/2009 | 06/02/2008 |
| Applicant | | |
| NOVARTIS AG | | |

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 7 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. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application, see Box No. I.

2. [X] **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,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

PYRROLO[2,3-D]PYRIDINES AND USE THEREOF AS TYROSINE KINASE INHIBITORS

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. [X] none of the figures is to be published with the abstract

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/051281

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)**

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

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [X] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/051281

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2005/107760 A (IRM LLC [US]; HONG JIYONG [US]; GRAY NATHANAEL S [US]; SCHULTZ PETER [])<br>17 November 2005 (2005-11-17)<br>Formula I;<br>paragraphs [0029] - [0047]; claims 2,6,7;<br>compounds 118,124,172 | 1-15 |
| X | example 1; sequence 1 | 16 |
| X | WO 2005/080393 A (IRM LLC [US]; CHOI HA-SOON [US]; WANG ZHICHENG [US]; GRAY NATHANAEL SC)<br>1 September 2005 (2005-09-01)<br>Formula I; Ig; examples<br>paragraphs [0027], [0032] - [0034];<br>claims 6,8-10; sequences 1,2 | 1-16 |

-/--

[X] 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 |
|---|---|
| 24 June 2009 | 03/07/2009 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Rudolf, Manfred |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/051281

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2006/045828 A (TIBOTEC PHARM LTD [IE]; ARTS FRANK XAVIER JOZEF HERWIG [BE]; GUILLEMON) 4 May 2006 (2006-05-04) Formula I;claims 1,17 | 1-16 |
| A | WO 02/076985 A (SMITHKLINE BEECHAM CORP [US]; BONDINELL WILLIAM E [US]; HOLT DENNIS A) 3 October 2002 (2002-10-03) Formula I; page 14, lines 9-32; claims 1,7 | 1-16 |
| A | WO 2006/096270 A (VERTEX PHARMA [US]; LEDEBOER MARK W [US]; PIERCE ALBERT C [US]; BEMIS) 14 September 2006 (2006-09-14) Formula I; paragraphs [0105], [0106]; claims 1,72,79 | 1-16 |
| A | HA-SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL.: "Design and synthesis of 7H-pyrrolo[2,3-d]pyrimidines as focal adhesion kinase inhibitors. Part 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, pages 2689-2692, XP002496172 compounds 13, 17, 28 | 1-16 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 8 and 10 are directed to a method of treatment of the human/animal body (Article 53(c) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box II.1

Claims Nos.: 10,12

Although claims 10 and 12 are directed to a method of treatment of the human/animal body (Article 53(c) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/051281

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10,12
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/051281

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2005107760 A | 17-11-2005 | NONE | |
| WO 2005080393 A | 01-09-2005 | AU 2005214352 A1 | 01-09-2005 |
| | | BR PI0507668 A | 17-07-2007 |
| | | CA 2553785 A1 | 01-09-2005 |
| | | CN 1918158 A | 21-02-2007 |
| | | EP 1713806 A1 | 25-10-2006 |
| | | JP 2007522241 T | 09-08-2007 |
| | | US 2007225306 A1 | 27-09-2007 |
| WO 2006045828 A | 04-05-2006 | AR 051410 A1 | 10-01-2007 |
| | | AU 2005298637 A1 | 04-05-2006 |
| | | BR PI0517272 A | 07-10-2008 |
| | | CA 2577588 A1 | 04-05-2006 |
| | | CN 101048410 A | 03-10-2007 |
| | | JP 2008517978 T | 29-05-2008 |
| | | KR 20070085286 A | 27-08-2007 |
| | | US 2008085907 A1 | 10-04-2008 |
| WO 02076985 A | 03-10-2002 | NONE | |
| WO 2006096270 A | 14-09-2006 | AT 420883 T | 15-01-2009 |
| | | AU 2006221065 A1 | 14-09-2006 |
| | | CA 2596830 A1 | 14-09-2006 |
| | | CN 101142218 A | 12-03-2008 |
| | | EP 1844050 A1 | 17-10-2007 |
| | | ES 2320487 T3 | 22-05-2009 |
| | | JP 2008528705 T | 31-07-2008 |
| | | JP 2009102361 A | 14-05-2009 |
| | | KR 20070104641 A | 26-10-2007 |

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Industria y Comercio
SUPERINTENDENCIA

No. 10-110021- -00000-0000
Fecha: 2010-09-06 17:06:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 432

**PATENTE DE INVENCIÓN** ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ 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

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 10 110021 |
| | Solicitud internacional | PCT/EP2009/051281 |
| | Fecha inicio fase nacional | 06/09/2010 |
| | Trámite | 11 |
| | Evento | 379 |
| | Actuación | 430 |
| | Oficio No. | 12036 |

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 traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 07 SET. 2010.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 10 110021 |
| | Solicitud internacional | PCT/EP2009/051281 |
| | Fecha inicio fase nacional | 06/09/2010 |
| | Trámite | 11 |
| | Evento | 379 |
| | Actuación | 430 |
| | Oficio No. | № 12037 |

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 titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 17 SET. 2010.
adpa11



Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

**OLARTERAISBECK**
OLARTE RAISBECK MOURE & CASTRO LTDA.

1

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIRECCIÓN DE NUEVAS CREACIONES

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-110021- -00003-0000
Fecha: 2010-11-08 16:56:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 12

**Ref.: Expediente N° 10-110.021**

**Solicitud de Patente de Invención Titulada: "PIRROLO [2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA"**

**Solicitante: NOVARTIS AG**

**Nuestra Ref.: P2010/000115**

**RESPUESTA AL OFICIO No. 12036 NOTIFICADO POR FIJACION EN LISTA No. 8322, DE FECHA 17 DE SEPTIEMBRE DE 2010 (EXAMEN DE FORMA)**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto proferido por ese Despacho, dentro del término legal previsto en el artículo 39 de la Decisión 486, en los siguientes términos:

1. En respuesta a la única observación del Examinador, me permito adjuntar la traducción del reporte del examen preliminar internacional.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Copia de la traducción del reporte de examen preliminar

**REPORTE PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD**
**Solicitud Internacional No.**
**PCT/EP2009/051281**

**Recuadro No. V**

1. Se hace referencia a los siguientes documentos:

D1: WO 2005/107760 A (IRM LLC (US) ; HONG JIYONG (US) ; GRAY NATHANAEL S (US) ; SCHULTZ PETER (17 de noviembre de 2005)
D2: WO 2005/080393 A (IRM LLC (US) ; CHOI HA- SOON (US) ; WANG ZHICHENG (US) ; GRAY NATHANAEL SC) 1 de septiembre de 2005
D3: WO 2006/045828 A (TIBOTEC PHARM LTD (IE) ; ARTS FRANK XAVIER JOZEF HERWIG (BE) ; GUILLEMON) 4 de mayo de 2006
D4: WO 02/076985 A (SMITHKLINE BEECHAM CORP (US) ; BONDINELL WILLIAM E (US) ; HOLT DENNIS A) 3 de octubre de 2002
D5: WO 2006/096270 A (VERTEX PHARMA (US) ; LEDEBOER MARK W (US) ; PIERCE ALBERT C (US) ; BEMIS) 14 de septiembre de 2006
D6: HA- SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL: "Diseño y síntesis de 7H- pirrolo[2,3- d]pirimidinas como inhibidores de quinasas de adhesión focal. Parte 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, páginas 2689- 2692, XP002496172

2. La presente solicitud se relaciona con compuestos de fórmula I según lo ilustrado en la reivindicación 1, su preparación y uso de los mismos para la preparación de medicamentos para el tratamiento de cáncer.

3. La materia reivindicada es novedosa. Los antecedentes divulgan compuestos anti-cancerígenos estructuralmente relacionados (por ejemplo D1, compuestos 118, 124, 172) los cuales no caben en la reivindicación 1.

4. Los compuestos definidos en las reivindicaciones 1- 7 están dentro del alcance de los compuestos anti- tumorales sugeridos en los documentos D1 y D2 y por lo tanto se consideran como una selección de los compuestos sugeridos en D1 y D2. Es aparente a partir de la solicitud presente (tabla 3) que los compuestos del presente invento exhiben una selectividad pronunciada a favor de JAK2. Tal característica no podría derivarse a partir de los antecedentes citados. Puesto que los compuestos reivindicados exhiben tal efecto no obvio, los compuestos reivindicados y su uso y fabricación pueden considerarse no obvios.

5. Reivindicaciones 10,12: La patentabilidad puede ser dependiente de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como patentable aquellas reivindicaciones sobre el uso de un compuesto en un tratamiento médico, pero podrá permitir reivindicaciones sobre un producto, particularmente sustancias o composiciones para uso en un primer o posterior tratamiento.

**Recuadro No. VIII.**

Las reivindicaciones contienen definiciones abiertas como por ejemplo heterociclilo sustituido, aril sustituido, etcétera, las cuales abarcan prácticamente cualquier sustitución imaginable sobre tales grupos de heterociclilo, arilo, etc.

El concepto de IPEA es que es poco probable de manera inherente que prácticamente todos los compuestos que estuvieran cobijados bajo una reivindicación que comprendiera una definición abierta acerca de una característica estructural (en este caso: sustituido con cualquier sustituto) exhibiera una deseada actividad biológica en particular.

Por lo tanto, parece ser que como ciertas reivindicaciones comprenden varias definiciones estructurales abiertas, las reivindicaciones posiblemente abarcarían materia que no representaría ninguna solución al problema relevante que formula la presente solicitud. Apenas como una solución al problema de proporcionar nuevos compuestos, la materia de tales reivindicaciones parecerían obvias para aquellas persona experta en el estado de la técnica.

El alcance y los límites de los términos "menor" en conexión con las longitudes de cadena deberían aclararse tal como se encuentran en la descripción (Artículo 6 del PCT) .

Las reivindicaciones 10, 12: El alcance y límites de "Enfermedad mediada por la proteína tirosinquinasa" no están claros, y deberían aclararse tal como se encuentra en la descripción, en cuanto a cuáles enfermedades están cobijadas en tal definición (Art. 6 del PCT) .

$R^5$ representa de manera independiente entre sí, hidrógeno, alquilo menor, haloalquilo menor, cicloalquilo, halocicloalquilo o forma junto al carbono al cual está unido, un cicloalquilo;

$R^6$ y $R^7$ representan junto con el nitrógeno al cual está unidos, un heterociclo opcionalmente sustituido

ó

$R^6$ representa hidrógeno o alquilo opcionalmente sustituido y

$R^7$ representa alquilo opcionalmente sustituido;

$R^8$ representa hidroxilo, alquiloxilo menor, haloalquiloxilo menor, cicloalquiloxilo, halocicloalquiloxilo, alquil- sulfonilo menor, haloalquil- sulfonil menor, cicloalquilo- sulfonilo, halocicloalquilo- sulfonilo, alquil- sulfinilo menor, haloalquil- sulfinil menor, cicloalquil- sulfinilo, halocicloalquil- sulfinilo;

$R^9$ representa H ó alquilo menor;

$R^{10}$ representa hidrógeno, alquilo menor, haloalquilo menor, cicloalquilo, halocicloalquilo;

n representa 0, 1 ó 2;

o sales de los mismos.

2. Un compuesto de fórmula I según la reivindicación 1, en donde

$R^1$ representa heterociclilo sustituido o no sustituido o aril sustituido o no sustituido

en donde dicho heterociclilo es seleccionado a partir de heterociclos no saturados, saturados o parcialmente saturados los cuales son monocíclicos, bicíclicos, tricíclicos, o espirocíclicos y contienen entre 4 y 16 átomos cíclicos en donde están presentes entre uno y cuatro heteroátomos;

en donde dicho arilo es seleccionado a partir de fracciones aromáticas con 6 a 14 átomos de carbono cíclicos;

en donde dichas sustituciones están seleccionadas de manera independiente a partir de una o más, preferiblemente entre una y cuatro de las siguientes fracciones: $C_{1-7}$- alquilo, amino- $C_{1-7}$- alquilo, halo- $C_{1-7}$- alquilo, N- $C_{1-7}$- alcanoilamino- $C_{1-7}$- alquilo, N- $C_{1-7}$- alcanosulfonil- amino- $C_{1-7}$- alquilo, pirrolidino- $C_{1-7}$- alquilo, oxo- pirrolidino- $C_{1-7}$- alquilo, piperidino- $C_{1-7}$- alquilo, piperazin- 1- il- $C_{1-7}$- alquilo, 4- ($C_{1-7}$- alquilo, $C_{1-7}$- alcoxilo- $C_{1-7}$- alquilo, halo- $C_{1-7}$- alquilo ó $C_{3-10}$- cicloalquilo) - piperazin- 1- il- $C_{1-7}$- alquilo, 4- (amino- $C_{1-7}$- alquil) - piperazin- 1- il- $C_{1-7}$- alquilo, 4- [N- mono- ó N,N- di- ($C_{1-7}$- alquilamino) - $C_{1-7}$- ...

# PATENT COOPERATION TREATY

JDY 5

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOVARTIS PHARMA AG
Patent Department
Postfach
4002 Basel
SUISSE

MAR 01 2010

Processed by M/D
04. März 2010 PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 02.03.2010 |
| Applicant's or agent's file reference<br>PAT052213-WO-PCT | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/EP2009/051281 | 04.02.2009 | 06.02.2008 |

Applicant
Novartis AG

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

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

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

4. **REMINDER**

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

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

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

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

| Name and mailing address of the international preliminary examining authority: | Authorized Officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Hutterer, Georg<br>Tel. +49 89 2399-8066 |



440

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>PAT052213-WO-PCT | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2009/051281 | International filing date *(day/month/year)*<br>04.02.2009 | Priority date *(day/month/year)*<br>06.02.2008 |
| International Patent Classification (IPC) or national classification and IPC<br>INV. C07D487/04 | | |
| Applicant<br>Novartis AG | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

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

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the report |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 2009-12-04 | 02.03.2010 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Rudolf, Manfred<br>Telephone No. +49 89 2399-8604 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2009/051281

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ 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 (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

| | |
|---|---|
| 1-271 | as originally filed |

**Claims, Numbers**

| | |
|---|---|
| 1(part), 2(part), 3-16 | as originally filed |
| 1(part), 2(part) | received on 07.12.2009 with letter of 03.12.2009 |

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

International application No.
PCT/EP2009/051281

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-9,11,13-16 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Supplemental Box relating to Sequence Listing**

**Continuation of Box I, item 2:**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

**Re Item V.**

1 Reference is made to the following documents:

D1 : WO 2005/107760 A (IRM LLC [US]; HONG JIYONG [US]; GRAY NATHANAEL S [US]; SCHULTZ PETER [) 17 November 2005 (2005-11-17)

D2 : WO 2005/080393 A (IRM LLC [US]; CHOI HA-SOON [US]; WANG ZHICHENG [US]; GRAY NATHANAEL SC) 1 September 2005 (2005-09-01)

D3: WO 2006/045828 A (TIBOTEC PHARM LTD [IE]; ARTS FRANK XAVIER JOZEF HERWIG [BE]; GUILLEMON) 4 May 2006 (2006-05-04)

D4: WO 02/076985 A (SMITHKLINE BEECHAM CORP [US]; BONDINELL WILLIAM E [US]; HOLT DENNIS A) 3 October 2002 (2002-10-03)

D5: WO 2006/096270 A (VERTEX PHARMA [US]; LEDEBOER MARK W [US]; PIERCE ALBERT C [US]; BEMIS) 14 September 2006 (2006-09-14)

D6: HA-SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL.: "Design and synthesis of 7H-pyrrolo[2,3-d]pyrimidines as focal adhesion kinase inhibitors. Part 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, pages 2689-2692, XP002496172

2. The present application relates to compounds of formula I as depicted in claim 1, its preparation and the use thereof for preparation of medicaments for the treatment of cancer.

3. The claimed subject matter is novel. The prior art discloses structurally related anticancer compounds (e.g. D1, compounds 118, 124, 172) which do not fall within claim 1.

4. The compounds defined in claims 1-7 fall within the scope of the antitumour compounds suggested in documents D1 and D2 and therefore are considered as a selection from the compounds suggested in D1 and D2. It is apparent from the present application (table 3) that compounds of the present invention exhibit a pronounced selectivity towards JAK2. Such feature is not derivable from the cited

prior art. Insofar the claimed compounds exhibit such non-obvious effect, the claimed compoundsand their use and production may be considered non-obvious.

5. Claims 10,12: The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

**Re Item VIII.**

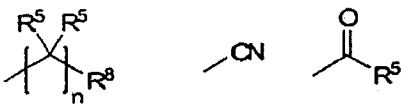
The claims contain open-ended definitions such as substituted heterocyclyl, substituted aryl, etc. which embrace virtually any imaginable substituents on said heterocyclyl, aryl etc. groups.

The IPEA's opinion is that it is inherently unlikely that substantially all compounds falling under a claim comprising an open-ended definition of a structural feature (here: substituted with any substituent) would exhibit a particular desired biological activity.

Therefore, it appears that, as certain claims comprise various open-ended structural definitions, the claims are likely to embrace subject matter which will not represent any solution to the relevant problem underlying the present application. Merely as a solution to the problem of providing new compounds, the subject matter of such claims would seem obvious to the person skilled in the art.

The scope and limits of the terms "lower" in connection with chain lengths should be clarified as found in the description (Art. 6 PCT).

Claims 10, 12: The scope and limits of "Protein tyrosine kinase mediated disease" are not clear, and it should be clarified as found in the description which diseases fall within such definition (Art. 6 PCT).



$R^5$ represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;

$R^6$ and $R^7$ represent together with the nitrogen to which they are attached an optionally substituted heterocycle

or

$R^6$ represents hydrogen or optionally substituted alkyl and

$R^7$ represents optionally substituted alkyl;

$R^8$ represents hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;

$R^9$ represents H or lower alkyl;

$R^{10}$ represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;

n represens 0, 1 or 2;

or salts thereof.

2. A compound of the formula I according to claim 1, wherein

$R^1$ represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl

wherein said heterocyclyl is selected from unsaturated, saturated or partially saturated heterocycles which are monocyclic bicyclic, tricyclic or spirocyclic and have 4 to 16, ring atoms wherein one to four heteroatoms are present;

wherein said aryl is selected from aromatic moieties with 6 to 14 ring carbon atoms;

wherein said substiutents are independently selected from one or more, preferably one to four of the following moieties: $C_1$-$C_7$-alkyl, amino-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanoylamino-$C_1$-$C_7$-alkyl, N-$C_1$-$C_7$-alkanesulfonyl-amino-$C_1$-$C_7$-alkyl, pyrrolidino-$C_1$-$C_7$-alkyl, oxo- pyrrolidino-$C_1$-$C_7$-alkyl, piperidino-$C_1$-$C_7$-alkyl, piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-($C_1$-$C_7$-alkyl, $C_1$-$C_7$-alkoxy-$C_1$-$C_7$-alkyl, halo-$C_1$-$C_7$-alkyl or $C_3$-$C_{10}$-cycloalkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-(amino-$C_1$-$C_7$-alkyl)-piperazin-1-yl-$C_1$-$C_7$-alkyl, 4-[N-mono- or N,N-di-($C_1$-$C_7$-alkylamino)-$C_1$-$C_7$-

OLARTE RAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COM

DIRECCIÓN DE NUEVAS CREACIONES

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-110021- -00004-0000
Fecha: 2010-11-11 17:01:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 2

**Ref.: Expediente Nº 10-110.021**

**Solicitud de Patente de Invención Titulada: "PIRROLO [2,3-D]PIRIDINAS Y USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE TIROSINA"**

**Solicitante: NOVARTIS AG**

**Nuestra Ref.: P2010/000115**

**RESPUESTA AL OFICIO Nº 12037 NOTIFICADO**

**POR FIJACION EN LISTA No. 322, DE FECHA 17 DE SEPTIEMBRE DE 2010,**

**(EXAMEN DE FORMA ART 12)**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto emanado de ese Despacho dentro del término legal previsto en el artículo 12 del Código Contencioso Administrativo en los siguientes términos:

1. En respuesta a la única observación del Examinador me permito adjuntar un recibo de pago por valor de $156.000, que cubre la tasa por 6 reivindicaciones adicionales.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Adjunto: Recibo de pago por valor de $156.000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-110021- -00004-0000
Fecha: 2010-11-11 17:01:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 2

CERTIFICACION DE EXCEDENTE : 10 - 96,005
FECHA : NOVIEMBRE 11 DE 2010

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| OLARTE RAISBEK | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 396426795 | 11/11/2010 | 6,076,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-09 OTROS SERVICIOS DE PROPIEDAD I | 99 OTROS SERVCIOS ADMINISTRATIVOS | 156,000.00 |
| | | TOTAL : $ | 156,000.00 |

SON: CIENTO CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

459

Industria y Comercio
SUPERINTENDENCIA

Folio 450

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 10 110021 |
| | Solicitud internacional | PCT/EP2009/051281 |
| | Fecha inicio fase nacional | 06/09/2010 |
| | Trámite | 11 |
| | Evento | 379 |
| | Actuación | 416 |
| | Oficio No. | 13211 |
| | Folios | 1 |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 21 JUN. 2011

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

jfernand



Sede Centro: Carrera 13 No. 27-00 pisos 2, 5, 7 y 10 PBX: 5870000
Sede CAN: Av. Carrera 50 No. 26 - 55 int.2. Tel 5880070
Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. Colombia