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Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y C
INVENTAR

09-81255

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE 2-AMINO-5, 7-DIHIDRO-6H PIRROLO [3,4-D] PIRIMIDINA COMO INHIBIDORES DE HSP-90 PARA EL TRATAMIENTO DE CANCER.

SOLICITANTE: PFIZER INC

DIRECCIÓN: 235 East 42nd Street, New York, NY 10017, E. U. A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 03 de Agosto de 2009

Fv. 06-09-2009

P2009/0000138

# OLARTERAISBECK

OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Fecha: 2009-08-04 15:43:11 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 519

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** **P2009/000138**

**SOLICITUD DE:**

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2)

**SOLICITANTE (71)**

**Nombre:** PFIZER INC
**Dirección:** 235 East 42nd Street, New York, NY 10017 E.U.A
**Nacionalidad o Domicilio:** Estadounidense
**Lugar de Constitución:** Estados Unidos
**Teléfono:** _____ **Fax:** _____
**E-mail:** _____

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

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

**INVENTOR (ES) (72)**

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2008/000200 Fecha Enero 25, 2008

Publicación Internacional No. WO 2008/096218 Fecha Agosto 14, 2008

(6) **Título (54)** **DERIVADOS DE 2-AMINO-5, 7-DIHIDRO-6H PIRROLO [3,4-D] PIRIMIDINA COMO INHIBIDORES DE HSP-90 PARA EL TRATAMIENTO DE CANCER.**

**Clasificación Internacional (51)** C07D 487/04, A61K 31/519, A61P 35/00

**Prioridad**

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| | | |
| | | |

(9) **Comprobante de pago No.** 09-56.479 **Fecha** 31 de Julio de 2009

## ANEXOS

- [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. 08-018680
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 519

***** 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 | 105797215 | 30/07/2009 | 3,134,000.00 |

***** 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 | 540,000.00 |
| | | TOTAL : $ | 540,000.00 |

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
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# Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** 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, appeals, 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.

# Poder

El suscrito,

Pfizer Inc.

domiciliado en

235 East 42nd Street, New York, NY 10017 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** 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, apelaciones, 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: July 14, 2003

City,Country/Ciudad,País: New York, USA

[redacted]

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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# Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb

of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in
New York, New York, U.S.A.
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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

# Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Epsom in Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par: K Greenwood

3. Acting in the capacity of / agissant en qualité de: Notary Public

4. Bears the seal/stamp of / est revêtu du sceau/timbre de: The Said Notary Public

5. at London/à Londres

   Certified/Attesté

6. the/le 17 July 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G210434

9. Stamp: / timbre:

10. Signature: R. Bawden

FOREIGN AND COMMONWEALTH OFFICE LONDON

*For the Secretary of State / Pour le Secrétaire d'Etat*

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

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

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(71) Applicant *(for all designated States except US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

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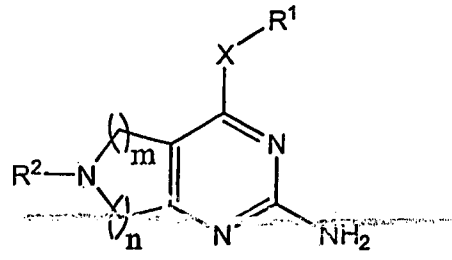
(74) Agents: **FULLER, Grover, Jr., F.** et al.; Pfizer Inc., 150 East 42nd Street, New York, NY 10017 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: 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, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: 2-AMIN0-5, 7-DIHYDR0-6H- PYRROLO [3, 4-D] PYRIMIDINE DERIVATIVES AS HSP-90 INHIBITORS FOR TREATING CANCER



(I)

(57) Abstract: The present invention is directed to compounds of formula (I), and pharmaceutically acceptable salts thereof, their synthesis, and their use as HSP-90 inhibitors.

WO 2008/096218 A1

# 2-AMINO-5,7-DIHYDRO-6H-PYRROLO[3,4-D]PYRIMIDINE DERIVATIVES AS HSP-90 INHIBITORS FOR TREATING CANCER

This application claims the benefit of United States Provisonal Patent Application No. 60/888,433 filed February 6, 2007 and 61/020,661 filed on January 11, 2008, the disclosure of which is hereby incorporated by reference in its entirety.

## Field of the Invention

The present invention is directed to compounds, and pharmaceutically acceptable salts and solvates thereof, their synthesis, and their use as modulators or inhibitors of HSP-90. The compounds of the present invention are useful for modulating (e.g. inhibiting) HSP-90 activity and for treating diseases or conditions mediated by HSP-90, such as for example, disease states associated with abnormal cell growth such as cancer.

## Background

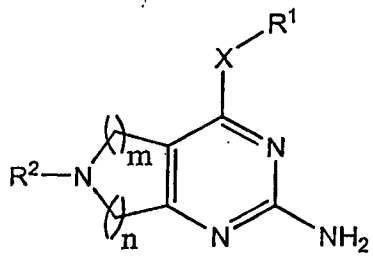
Molecular chaperones play important roles in cellular function by ensuring proper folding of proteins upon synthesis as well as their refolding under conditions of denaturing stress. By regulating the balance between protein synthesis and degradation, molecular chaperones are a significant part of the cellular response to stress. In addition, by regulating the proper folding of various cellular proteins, chaperones play an important role in regulating cellular functions such as cell proliferation and apoptosis. (See, e.g. Jolly, et al., *J. Natl. Cancer Inst.* 92: 1564-1572 (2000)). Heat shock proteins (HSPs) are a class of chaperones that accumulate in the cell in response to various environmental stresses, such as heat shock, oxidative stress, or the presence of alcohols or heavy metals. In addition to their role in protecting the cell from such environmental stresses, HSPs may also play a significant role as chaperones for a variety of cellular proteins under stress-free conditions. Members of the HSP family are classified according to their molecular weight (e.g. HSP-27, HSP-70, and HSP-90). Evidence of differential expression of HSPs in various stages of tumor progression suggests HSPs play a role in cancer. (See, e.g. Martin, et al., *Cancer Res.* 60:2232-2238 (2000)).

HSP-90 is a homodimer with ATPase activity and functions in a series of complex interactions with a variety of substrate proteins (Young, et al., *J. Cell Biol.* 154: 267-273 (2001)). HSP-90 is unique with regard to other chaperones, however, since most of its known substrate proteins are signal transduction proteins. Thus, HSP-90 plays an essential role in regulating cellular signal transduction networks. (See, e.g. Xu, et al., *Proc. Natl. Acad. Sci* 90:7074-7078 (1993)). In particular, substrate proteins of HSP-90

include many mutated or over-expressed proteins implicated in cancer such as p53, Bcr-Ab1 kinase, Raf-1 kinase, Akt kinase, Npm-Alk kinase $p185^{ErbB2}$ transmembrane kinase, Cdk4, Cdk6, Wee1 (a cell cycle-dependent kinase), HER2/Neu (ErbB2), and hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$). Thus inhibition of HSP-90 results in selective degradation of these important signaling proteins involved in apoptosis, cell proliferation, and cell cycle regulation (Holstein, et al., *Cancer Res.* 61:4003-4009 (2001)). Accordingly, HSP-90 is an attractive therapeutic target because of the important roles played by these signaling proteins in disease states involving abnormal cell growth, such as cancer. It is thus desirable to discover and develop new inhibitors of HSP-90 activity that can provide a therapeutic benefit to patients suffering from disease states related to abnormal cell growth such as cancer.

## Summary

In one embodiment, the present invention provides a compound of formula (I)



(I)

wherein:

m is 1 or 2; n is 1 or 2; when m is 2, n is 1;

X is a bond or a diradical selected from the group consisting of -O-, -S-, -($C_1$-$C_3$ alkylene)-, -O-($C_1$-$C_3$ alkylene)-, -NH-($C_1$-$C_3$ alkylene)-, –S-($C_1$-$C_3$ alkylene)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, –NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- and -$S(O)_2$-NH-, wherein each end of the diradical may be connected to $R^1$ or to the aminopyrimidine ring of formula I;

where permissible, each nitrogen or carbon atom of X is optionally further substituted by one group selected from -($C_1$-$C_3$ alkylene)$_t$-CN, -($C_1$-$C_3$ alkylene)$_t$-F, -($C_1$-$C_3$ alkylene)$_t$-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_3$ alkylene)$_t$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_3$ alkylene)$_t$-OH, -($C_1$-$C_3$ alkylene)$_t$-$NH_2$, -($C_1$-$C_3$ alkylene)$_t$-NH($C_1$-$C_3$ alkyl) and -($C_1$-$C_3$ alkylene)$_t$-N($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl), and t is 0 or 1;

$R^1$ is selected from the group consisting of $C_6$-$C_{12}$ aryl, 5 to 12 member heteroaryl, $C_3$-$C_{12}$ cycloalkyl, 3-12 member heterocyclyl and $C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl, and each $R^1$ is optionally further substituted with 1-5 R,

provided that when $R^1$ is phenyl, then $R^1$ is further substituted with at least two R and at least one of the R is not a halogen;

R is selected from the group consisting of $R^x$, -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_7$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(7-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(7-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl);

$R^2$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)$_p$-C(O)-$R^b$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-O-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-S(O)-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$-O-$R^a$, and $R^3$, wherein $R^3$ is selected from –($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-(5-12 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

each $R^a$ is independently selected from the group consisting of H, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-(5 to 12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

two $R^a$ attached to the same nitrogen atom, together with the nitrogen atom, may optionally form a 3-12 member heterocyclyl or a 5-12 member heteroaryl; the said 3-12 member heterocyclyl and the said 5-12 member heteroaryl is optionally further substituted by 1-5 $R^x$;

$R^b$ is selected from the group consisting of –$NR^aN(R^a)_2$, -$NR^aOR^a$, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_3$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-(5-12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

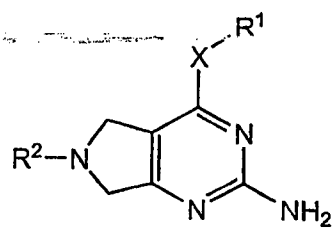
p is 0 or 1;

each R, $R^a$, $R^b$ and $R^3$ is optionally further substituted with 1-5 $R^x$;

each $R^x$ is independently selected from the group consisting of –oxo-, -($C_1$-$C_4$ alkylene)-, halogen, -CN, -OH, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_1$-$C_6$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)-OH, -($C_1$-$C_6$ alkylene)-CN, -($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkylene)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -($C_1$-$C_6$ alkylene)$_q$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$- NHC(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH($C_1$-$C_3$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl) and -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-N($C_1$-$C_3$ alkyl)$_2$; each q is independently 0 or 1; where permissible, each carbon atom of $R^x$ is optionally further substituted by 1-3 fluorine;

or a pharmaceutically acceptable salt thereof.

In a preferred aspect of this embodiment, and in combination of any other aspects not inconsistent, m is 1, n is 1, and the compound is of formula II,



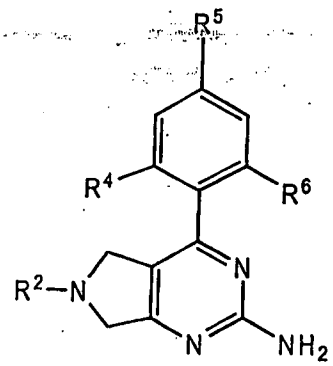
II

In another preferred aspect of this embodiment, and in combination of any other aspects not inconsistent, X is a bond or –O-, $R^1$ is $C_6$-$C_{12}$ aryl, 5 to 12 member

heteroaryl, or 3-12 member heterocyclyl, and $R^1$ is further substituted with 2-5 R. More preferably, X is a bond and $R^1$ is a $C_6$-$C_{12}$ aryl further substituted with 2-5 R. Even more preferably, $R^1$ is phenyl further substituted with 2-5 R and at least one of the R is not a halogen.

In another preferred aspect of this embodiment, and in combination of any other aspects not inconsistent, R is selected from the group consisting of F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); wherein each R is optionally further substituted by 1-5 $R^x$.

In another preferred aspect of this embodiment, and in combination with any other aspects not inconsistent, m is 1, n is 1 and the compound is of formula V,



V

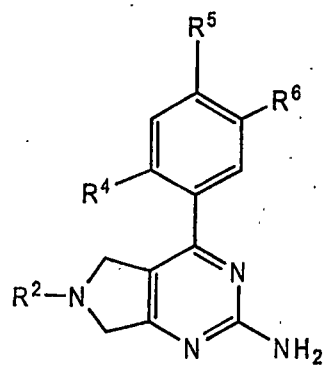
wherein

$R^4$ and $R^5$ are independently F, Cl, Br, -OH, -CN, unsubstituted $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, unsubstituted -($C_1$-$C_6$ alkylene)-OH or unsubstituted -O-($C_1$-$C_6$ alkyl);

$R^6$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-

($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); and $R^6$ is optionally further substituted with 1-5 $R^x$.

In another preferred aspect of this embodiment, and in combination with any other aspects not inconsistent, m is 1, n is 1 and the compound is of formul VI,



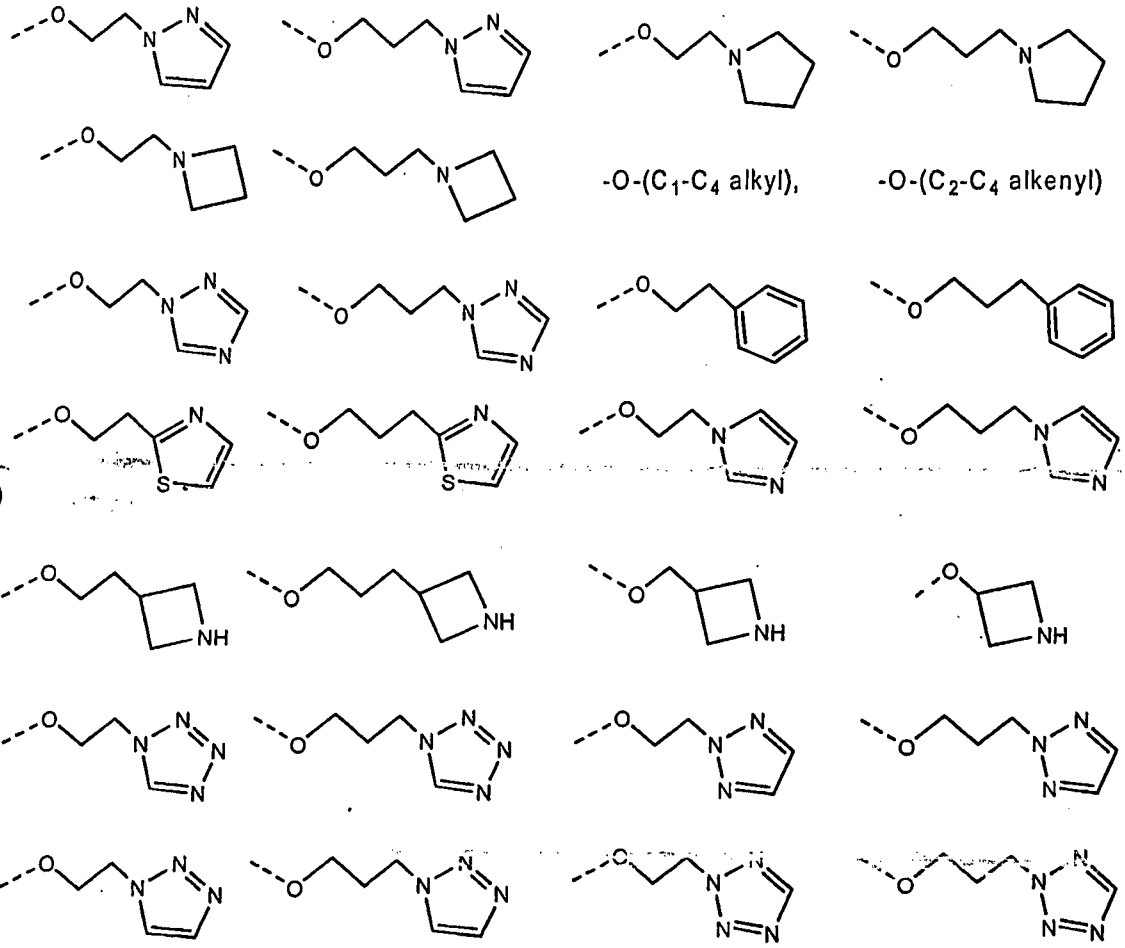
VI

wherein

$R^4$ and $R^5$ are independently F, Cl, Br, -OH, -CN, unsubstituted $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, unsubstituted -($C_1$-$C_6$ alkylene)-OH or unsubstituted -O-($C_1$-$C_6$ alkyl);

$R^6$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); and $R^6$ is optionally further substituted with 1-5 $R^x$.

In formula V and formula VI, preferably, $R^6$ is –O-($C_1$-$C_6$ alkylene)-(5-10 member heteroaryl), and $R^6$ is optionally further substituted with 1-5 $R^x$; more preferably, $R^6$ is –O-($C_1$-$C_6$ alkylene)-(5 member heteroaryl), and $R^6$ is optionally further substituted with 1-5 $R^x$; also preferably, $R^6$ is –O-($C_1$-$C_6$ alkylene)-(3-10 member heterocyclyl), and $R^6$ is optionally further substituted with 1-5 $R^x$; also preferably, $R^6$ is –O-($C_1$-$C_6$ alkylene)-phenyl, and $R^6$ is optionally further substituted with 1-5 $R^x$; also prefereably, $R^6$ is –O-($C_1$-$C_6$ alkyl) or –O-($C_2$-$C_6$ alkenyl), and $R^6$ is optionally further substutituted with 1-5 $R^x$. Preferrred substituent of $R^6$ is F, Cl, $C_1$-$C_3$ alkyl, -O-($C_1$-$C_3$ alkyl), -OH, -CN and -($C_1$-$C_3$ alkylene)-CN. Most preferred $R^6$ includes the following group, wherein each group is unsubstituted or substituted with 1-5 $R^x$; preferably, the following group is unsubstituted or substituted with 1-5 groups of F, Cl, $C_1$-$C_3$ alkyl, -O-($C_1$-$C_3$ alkyl), -OH, -CN or -($C_1$-$C_3$ alkylene)-CN:

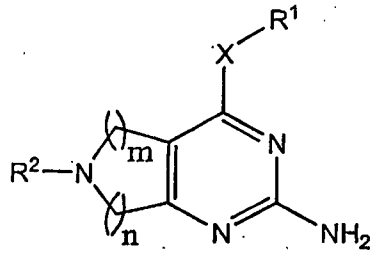



In another preferred aspect of this embodiment, and in combination with any other aspects not inconsistent, particularly in combination with the aspect wherein the compound is of formula V, also particularly in combination with the aspect wherein the compound is of formula VI, $R^2$ is $-C(O)-N(R^a)_2$. Preferably, a first $R^a$ is -H or

unsubstituted $C_1$-$C_3$ alkyl; and a second $R^a$ is selected from $C_1$-$C_6$ alkyl, cyclopropyl, cyclobutyl, bicyclo[1.1.1]pent-1-yl, (1S,5R)-3-aza-bicyclo[3.1.0]hex-6-yl, 5-6 membered heteroaryl, 3-7 member heterocyclyl and $C_2$-$C_6$ alkenyl, and the second $R^a$ is optionally further substituted by 1-5 groups selected from F, Cl, $C_1$-$C_3$ alkyl, -O-($C_1$-$C_3$ alkyl), -OH, -CN and –($C_1$-$C_3$ alkylene)-CN. More preferably, the first $R^a$ is H.

In another preferred aspect of this embodiment, and in combination with any other aspects not inconsistent, particularly in combination with the aspect wherein the compound is of formula V, also particularly in combination with the aspect wherein the compound is of formula VI, $R^2$ is –C(O)-$OR^a$. Preferably, $R^a$ is selected from $C_1$-$C_6$ alkyl, cyclopropyl, cyclobutyl, bicyclo[1.1.1] pent-1-yl, 5-6 membered heteroaryl, 3-7 member heterocyclyl and $C_2$-$C_6$ alkenyl, and $R^a$ is optionally further substituted by 1-5 groups selected from F, Cl, $C_1$-$C_3$ alkyl, -O-($C_1$-$C_3$ alkyl), -OH, -CN and –($C_1$-$C_3$ alkylene)-CN.

In another embodiment, the present invention provides a compound of formula (I)



(I)

wherein:

m is 1 or 2, n is 1 or 2, when m is 2, n is 1;

X is a bond or a diradical selected from the group consisting of -O-, -S-, -($C_1$-$C_3$ alkylene)-, -O-($C_1$-$C_3$ alkylene)-, -NH-($C_1$-$C_3$ alkylene)-, –S-($C_1$-$C_3$ alkylene)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, –NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- and -$S(O)_2$-NH-, wherein each end of the diradical may be connected to $R^1$ or to the aminopyrimidine ring of formula I;

where permissible, each nitrogen or carbon atom of X is optionally further substituted by one group selected from -($C_1$-$C_3$ alkylene)$_t$-CN, -($C_1$-$C_3$ alkylene)$_t$-F, -($C_1$-$C_3$ alkylene)$_t$-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_3$ alkylene)$_t$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_3$ alkylene)$_t$-OH, -($C_1$-$C_3$ alkylene)$_t$-$NH_2$, -($C_1$-$C_3$ alkylene)$_t$-NH($C_1$-$C_3$ alkyl) and -($C_1$-$C_3$ alkylene)$_t$-N($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl), and t is 0 or 1;

$R^1$ is selected from the group consisting of $C_5$-$C_{12}$ aryl, 5 to 12 member heteroaryl, $C_3$-$C_{12}$ cycloalkyl, 3-12 member heterocyclyl and $C_5$-$C_{12}$ unsaturated

nonaromatic carbocyclyl, and each $R^1$ is optionally further substituted with 1-5 $R^x$, provided that when $R^1$ is phenyl, $R^1$ is further substituted with at least two $R^x$ and one of the $R^x$ is not a halogen;

preferred substituents of $R^1$ are selected from F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -O-($C_1$-$C_6$ alkylene)-halogen, -O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -O-($C_1$-$C_6$ alkylene)-$NH_2$ and -O-($C_1$-$C_6$ alkylene)-NH($C_1$-$C_6$ alkyl);

$R^2$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)$_p$-C(O)-$R^b$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-O-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-S(O)-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-$S(O)_2$-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-$S(O)_2$-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-$S(O)_2$-O-$R^a$, and $R^3$, wherein $R^3$ is selected from –($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), $C_2$-$C_8$ alkynyl, -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-(5-12 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

each $R^a$ is independently selected from the group consisting of H, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-(5 to 12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

two $R^a$ attached to the same nitrogen atom, together with the nitrogen atom, may optionally form a 3-12 member heterocyclyl or a 5-12 member heteroaryl; the said 3-12 member heterocyclyl and the said 5-12 member heteroaryl is optionally further substituted by 1-5 $R^x$;

$R^b$ is selected from the group consisting of $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_3$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-(5-12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

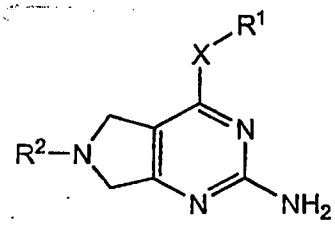
p is 0 or 1; each $R^a$, $R^b$ and $R^3$ is optionally further substituted with 1-5 $R^x$;

each $R^x$ is independently selected from the group consisting of –oxo-, -($C_1$-$C_4$ alkylene)-, halogen, -CN, -OH, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_1$-$C_6$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)-OH, -($C_1$-$C_6$ alkylene)-CN, -($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$

alkylene)$_q$-C(O)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkylene)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -($C_1$-$C_6$ alkylene)$_q$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$- NHC(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH($C_1$-$C_3$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl) and -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-N($C_1$-$C_3$ alkyl)$_2$; each q is independently 0 or 1; where permissible, each carbon atom of $R^x$ is optionally further substituted by 1-3 fluorine;

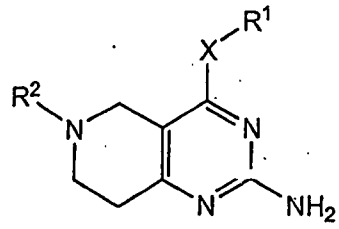
or a pharmaceutically acceptable salt thereof.

In the first particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 1 and n is 1, and the compound is of formula II,



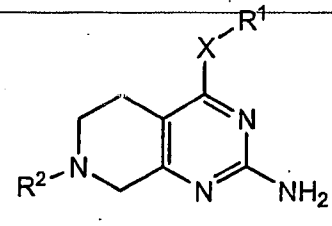
II

In the second particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 1 and n is 2, and the compound is of formula III,



III

In the third particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 2 and n is 1, and the compound is of formula IV,



IV

In the fourth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is a bond and $R^1$ is a $C_6$-$C_{12}$ aryl optionally substituted with 1-5 $R^x$. Preferably, $R^1$ is phenyl substituted with 2-5 $R^x$ and at least one of the $R^x$ is not a halogen. More preferably, $R^1$ is phenyl substituted with 2-3 groups selected from F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -O-($C_1$-$C_6$ alkylene)-halogen, -O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -O-($C_1$-$C_6$ alkylene)-$NH_2$ and -O-($C_1$-$C_6$ alkylene)-NH($C_1$-$C_6$ alkyl), provided that at least one of the said 2-3 groups is not a halogen.

In the fifth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is a bond, $R^1$ is 5-12 member heteroaryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the sixth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is a bond, $R^1$ is 3-12 member heterocyclyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the seventh particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect

one, two or three, X is a bond, $R^1$ is $C_3$-$C_{12}$ cycloalkyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the eighth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is –O- or unsubstituted -O-($C_1$-$C_3$ alkylene)-, $R^1$ is $C_6$-$C_{12}$ aryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the ninth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is –O- or unsubstituted -O-($C_1$-$C_3$ alkylene)-, $R^1$ is 5-12 member heteroaryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the tenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is –O- or unsubstituted -O-($C_1$-$C_3$ alkylene)-, $R^1$ is 3-12 member heterocyclyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the eleventh particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is –O- or unsubstituted -O-($C_1$-$C_3$ alkylene)-, $R^1$ is $C_3$-$C_{12}$ cycloalkyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the twelfth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted –NH-($C_1$-$C_3$ alkylene)-, $R^1$ is $C_6$-$C_{12}$ aryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the thirteenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted –NH-($C_1$-$C_3$ alkylene)-, $R^1$ is 5-12 member heteroaryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the fourteenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted –NH-($C_1$-$C_3$ alkylene)-, $R^1$ is 3-12 member heterocyclyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the fifteenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted –NH-($C_1$-$C_3$ alkylene)-, $R^1$ is $C_3$-$C_{12}$ cycloalkyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the sixteenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, wherein X is unsubstituted -($C_1$-$C_3$ alkylene)-, $R^1$ is $C_6$-$C_{12}$ aryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the nineteenth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted -($C_1$-$C_3$ alkylene)-, $R^1$ is 5-12 member heteroaryl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the twentieth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted -($C_1$-$C_3$ alkylene)-, $R^1$ is 3-12 member heterocyclyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

In the twenty-first particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, especially in combination with particular aspect one, two or three, X is unsubstituted -($C_1$-$C_3$ alkylene)-, $R^1$ is $C_3$-$C_{12}$ cycloalkyl, and $R^1$ is optionally further substituted with 1-5 $R^x$.

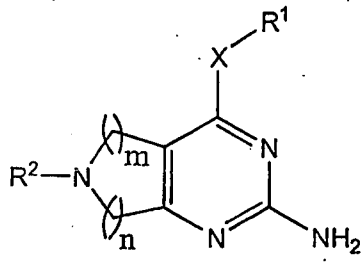
In the twenty-second particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, including any of the particular aspect one to twenty-one, $R^2$ is -C(O)-$OR^a$ or -($C_1$-$C_6$ alkylene)-C(O)-O-$R^a$.

In the twenty-third particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, including any of the particular aspect one to twenty-one, $R^2$ is –C(O)-$N(R^a)_2$ or -($C_1$-$C_6$ alkylene)-C(O)-$N(R^a)_2$.

In the twenty-fourth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, including any of the particular aspect one to twenty-one,$R^2$ is selected from -$S(O)_2$-$R^a$, -$S(O)_2$-$N(R^a)_2$, -$S(O)_2$-O-$R^a$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-$R^a$, -($C_1$-$C_6$ alkylene)-$S(O)_2$-O-$R^a$ and -($C_1$-$C_6$ alkylene)-$S(O)_2$-$N(R)_2$.

In the twenty-fifth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, including any of the particular aspect one to twenty-one,$R^2$ is –C(O)-$R^b$ or –($C_1$-$C_6$ alkylene)-C(O)-$R^b$.

In another embodiment, the present invention provides a compound of formula I,



I

wherein:

m is 1 or 2, n is 1 or 2 , when m is 2, n is 1;

X is a bond or a diradical selected from the group consisting of –O- and unsubstituted -O-($C_1$-$C_3$ alkylene)-, wherein each end of the diradical may be connected to $R^1$ or to the aminopyrimidine ring of formula I;

$R^1$ is phenyl, 5-12 member heteroaryl or 3-12 member heterocyclyl;

when $R^1$ is phenyl, $R^1$ is further substituted with 2-5 groups selected from F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -O-($C_1$-$C_6$ alkylene)-halogen, -O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -O-($C_1$-$C_6$ alkylene)-$NH_2$ and -O-($C_1$-$C_6$ alkylene)-NH($C_1$-$C_6$ alkyl); and at least one of the substituent of $R^1$ is not a halogen;

when $R^1$ is 5-12 member heteroaryl or 3-12 member heterocyclyl, $R^1$ is optionally further substituted with 1-5 groups selected from F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -O-($C_1$-$C_6$ alkylene)-halogen, -O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -O-($C_1$-$C_6$ alkylene)-$NH_2$ and -O-($C_1$-$C_6$ alkylene)-NH($C_1$-$C_6$ alkyl);

$R^2$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)$_p$-C(O)-O-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-$R^b$ and -($C_1$-$C_6$ alkylene)$_p$-$SO_2$-$R^a$;

$R^a$ is selected from the group consisting of H, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-(5 to 12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl) and -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

two $R^a$ attached to the same nitrogen atom, together with the nitrogen atom, may optionally form a 3-12 member heterocyclyl or a 5-12 member heteroaryl; the said 3-12 member heterocyclyl and the said 5-12 member heteroaryl is optionally further substituted by 1-5 groups selected from $C_1$-$C_3$ alkyl, -CN, -F, -Cl, -Br, -O-($C_1$-$C_3$ alkyl) and $C_1$-$C_3$ perfluoroalkyl;

$R^b$ is selected from the group consisting of $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_3$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-(5-12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl);

each $R^a$ and $R^b$ is independently optionally further substituted by 1-5 groups selected from $C_1$-$C_3$ alkyl, -CN, -F, -Cl, -Br, -O-($C_1$-$C_3$ alkyl), $C_1$-$C_3$ perfluoroalkyl, -$NH_2$, -NH-($C_1$-$C_3$ alkyl), -N($C_1$-$C_3$ alkyl)$_2$ and OH;

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In the first particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 1 and n is 1.

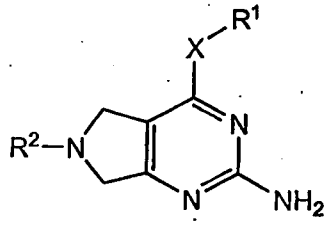
In the second particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 1 and n is 2.

In the third particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, m is 2 and n is 1.

In the fourth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, X is a bond.

In the fifth particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, X is diradical of -O- or unsubstituted -O-($C_1$-$C_3$ alkylene)-.

In another embodiment, the present invention provides a a compound of formula II,



II

wherein:

X is a bond or a diradical selected from the group consisting of -O-, -NH-, -S-, -($C_1$-$C_3$ alkylene)-, -O-($C_1$-$C_3$ alkylene)-, -NH-($C_1$-$C_3$ alkylene)-, –S-($C_1$-$C_3$ alkylene)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, –NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- and -$S(O)_2$-NH-, wherein each end of the diradical may be connected to $R^1$ or the aminopyrimidine ring of formula II;

where permissible, each nitrogen or carbon atom of X is optionally further substituted by a group selected from -($C_1$-$C_3$ alkylene)$_t$-CN, -($C_1$-$C_3$ alkylene)$_t$-F, -($C_1$-$C_3$ alkylene)$_t$-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_3$ alkylene)$_t$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_3$ alkylene)$_t$-OH, -($C_1$-$C_3$ alkylene)$_t$-$NH_2$, -($C_1$-$C_3$ alkylene)$_t$-NH($C_1$-$C_3$ alkyl), -($C_1$-$C_3$ alkylene)$_t$-N($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl), and t is 0 or 1;

$R^1$ is selected from the group consisting of $C_6$-$C_{12}$ aryl, 5 to 12 member heteroaryl, $C_3$-$C_{12}$ cycloalkyl, 3-12 member heterocyclyl and $C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl, and each $R^1$ is optionally further substituted with 1-5 $R^x$;

$R^2$ is selected from the group consisting of –($C_1$-$C_6$ alkylene)$_p$-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-O-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-C(O)-N($R^a$)$_2$, -($C_1$-$C_6$ alkylene)$_p$-S(O)-$R^a$, -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$$R^a$, -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$-N($R^a$)$_2$ and -($C_1$-$C_6$ alkylene)$_p$-S(O)$_2$-O-$R^a$;

each $R^a$ is independently selected from the group consisting of H, $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl, $C_2$-$C_8$ alkynyl, $C_1$-$C_8$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{12}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-(5 to 12 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{12}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-(3-12 member heterocyclyl), and -($C_1$-$C_6$ alkylene)$_p$-($C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl), $R^a$ is optionally further substituted with 1-5 $R^x$;

two $R^a$ attached to the same nitrogen atom, together with the nitrogen atom, may optionally form a 3-12 member heterocyclyl or a 5-12 member heteroaryl; the said 3-12 member heterocyclyl and the said 5-12 member heteroaryl is optionally further substituted by 1-5 $R^x$;

each p is independently 0 or 1;

each $R^x$ is independently selected from the group consisting of –oxo-, -($C_1$-$C_4$ alkylene)-, halogen, -CN, -OH, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_1$-$C_6$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)-OH, -($C_1$-$C_6$ alkylene)-CN, -($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-($C_1$-$C_6$ alkylene)-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-C(O)-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$

alkylene)-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -($C_1$-$C_6$ alkylene)$_q$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$- NHC(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH($C_1$-$C_3$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl) and -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-N($C_1$-$C_3$ alkyl)$_2$; q is independently 0 or 1; where permissible, each carbon atom of $R^x$ is optionally further substituted by 1-3 fluorine;

or a pharmaceutically acceptable salt thereof.

In the first particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, X is a bond or a diradical selected from the group consisting of -O- and unsubstituted -O-($C_1$-$C_3$ alkylene)-; $R^x$ is selected from the group consisting of F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -O-($C_1$-$C_6$ alkylene)-halogen, -O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -O-($C_1$-$C_6$ alkylene)-$NH_2$ and -O-($C_1$-$C_6$ alkylene)-NH($C_1$-$C_6$ alkyl. Preferably, X is a bond, $R^1$ is selected from the group consisting of phenyl, 5-12 member heteroaryl and 3-12 member heterocyclyl, $R^1$ is optionally further substituted by 1-5 $R^x$. More preferably, $R^1$ is phenyl optionally further substituted by 1-5 $R^x$.

In the second particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, X is a diradical –O-($C_1$-$C_3$ alkylene)-, $R^1$ is phenyl or 5-12 member heteroaryl, $R^1$ is optionally further substituted by 1-5 $R^x$.

In the third particular aspect of this embodiment, and in combination with any other particular aspects not inconsistent, X is a diradical -O-, $R^1$ is phenyl optionally further substituted by 1-5 $R^x$.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula I, II, III, IV, V or VI, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention provides a use of a compound of formula I, II, III, IV, V or VI, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cancer.

In another embodiment, the present invention provides a method of modulating the activity of HSP-90, comprising contacting a cell with a compound of formula I, II, III, IV, V or VI, or a pharmaceutically acceptable salt thereof.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the Formula I, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in treating abnormal cell growth.

In one embodiment of this method, the abnormal cell growth is cancer, including, but not limited to, mesothelioma, hepatobilliary (hepatic and billiary duct), a primary or secondary CNS tumor, a primary or secondary brain tumor, lung cancer (NSCLC and SCLC), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, non hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

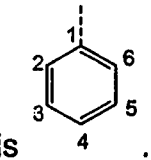
In a preferred embodiment of the present invention the cancer is selected from lung cancer (NSCLC and SCLC), cancer of the head or neck, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, breast cancer, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, non hodgkins's lymphoma, spinal axis tumors, or a combination of one or more of the foregoing cancers.

In another preferred embodiment of the present invention the cancer is selected from lung cancer (NSCLC and SCLC), ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, or a combination of one or more of the foregoing cancers.

In a more preferred embodiment of the present invention the cancer is selected from lung cancer (NSCLC and SCLC), ovarian cancer, colon cancer, rectal cancer, or a combination of one or more of the foregoing cancers.

In another embodiment of said method, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

This invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the Formula I, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier. In one embodiment of said composition, said abnormal cell growth is cancer, including, but not limited to, mesothelioma, hepatobilliary (hepatic and billiary duct), a primary or secondary CNS tumor, a primary or secondary brain tumor, lung cancer (NSCLC and SCLC), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, non hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers. In another embodiment of said pharmaceutical composition, said abnormal cell growth is a benign proliferative disease, including, but not limited to, psoriasis, benign prostatic hypertrophy or restinosis.

As used herein, the symbol [------] when incorporated into the chemical structure of a substituent means that the atom to which [------] is attached is the point of attachment of that substitutent to some position on another molecule. For example, X in the hypothetical molecule $CH_3CH_2$-X might be defined as X is 

. In which case, the placement of [------] attached to the arbitrarily numbered position C-1, means that C-1 of the phenyl ring is attached to the methylene carbon.

The symbols "wedge" and "hash", when used together in a single molecule without further indication otherwise, for example, chemical name or accompanying description, merely indicate relative stereochemistry of *trans* or *cis* where applicable. The symbol "wedge" and the symbol"hash", used together or separately, in combination with an indication of them representing the absolute stereochemistry, for example, an indication of "*S*" or "*R*" in the corresponding chemical structure or the accompanying chemical name, indicate the absolute stereochemistry of the corresponding chiral center.

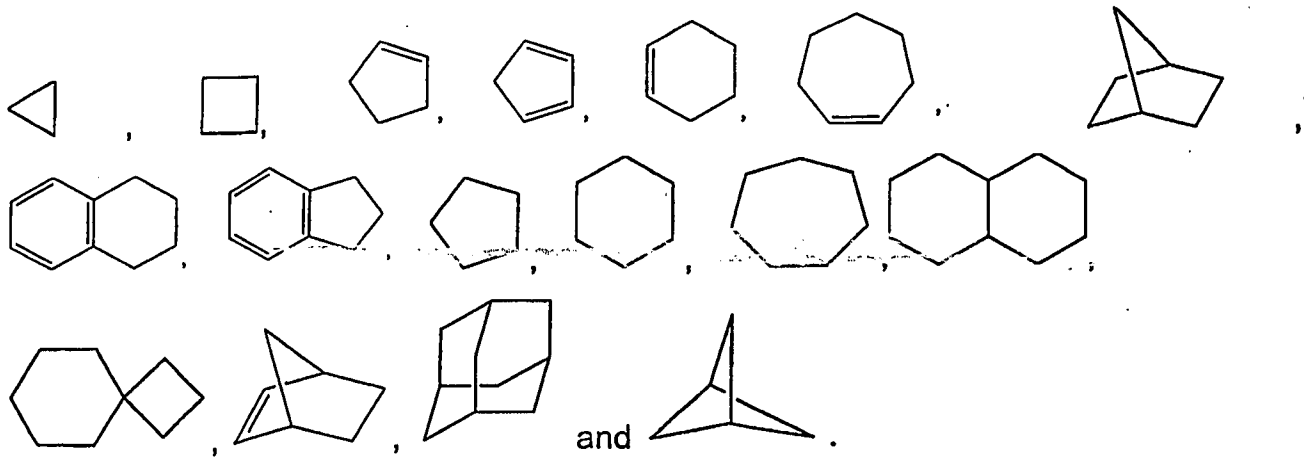
"Aliphatic" refers to straight-chain, branched or cyclic $C_1$-$C_{12}$ hydrocarbons which are completely saturated or which contains one or more units of unsaturation but which are not aromatic. Examples of aliphatic groups include linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, etc. An aliphatic group may be optionally substituted by 1-6 substituents. Suitable substituents on an aliphatic group include: 3-12 member heterocyclyl, $C_6$-$C_{10}$ aryl, 5-12 member heteroaryl, halogen, -$NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, -$CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, -$SO_2R$, -$SONR_2$, -$SO_2NR_2$, wherein R is H, $C_1$-$C_{10}$ alkyl, 3-10 member heterocyclyl, $C_6$-$C_{10}$ aryl, 5-12 member heteroaryl.

"$C_1$-$C_{12}$ alkyl" refers to a straight chain or branched saturated hydrocarbon radical having from 1 to 12 carbon atoms. A $C_1$-$C_{12}$ alkyl group may be optionally substituted by at least one substituent. Suitable substituents on a $C_1$-$C_{12}$ alkyl group include, but are not limited to, 3-12 member heterocyclyl, $C_6$-$C_{10}$ aryl, 5-12 member heteroaryl, halogen, -$NO_2$, -$NR_2$, -CN, -COR, -COOR, -$CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, -$SO_2R$, -$SONR_2$, -$SO_2NR_2$, wherein each R is independently -H, $C_1$-$C_{10}$ alkyl, 3-12 member heterocyclyl, $C_6$-$C_{10}$ aryl, 5-12 member heteroaryl. Examples of $C_1$-$C_{12}$ alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, neo-pentyl, sec-pentyl, hexyl, heptyl, octyl, and the like, including

substitutued forms thereof. Further, the term "alkyl" refers to a straight chain or branched saturated hydrocarbon radical of 1 to 20 carbon atoms, or 1 to 12 carbon atoms, or 1 to 8 carbon atoms, or 1 to 6 carbon atoms, or 1 to 4 carbon atoms. "Lower alkyl" refers specifically to an alkyl group having 1 to 4 carbon atoms. Alkyl may be substituted or unsubstituted. Suitable substituents on an alkyl group are the same as those described for a $C_1$-$C_{12}$ alkyl group.

"Cycloalkyl" refers to a cyclic saturated hydrocarbon radical having from 3 to 20 carbon atoms. A cycloalkyl group may be monocyclic and where permissible may be bicyclic or polycyclic. A cycloalkyl group may be optionally substituted by at least one substituent. Suitable substituents on a cycloalkyl group are the same as those described for an alkyl group. Examples of cycloalkyl groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, nobornyl, adamantyl, and the like, including substitutued forms thereof.

"Nonaromatic carbocyclyl" refers to a 3 to 12 member all-carbon monocyclic ring group, all-carbon bicyclic or multicyclic ring system group wherein one or more of the rings may contain one or more double bonds or an aromatic ring as part of the bicyclic or multicyclic ring system, but the monocyclic ring, the bicyclic or multicyclic ring system does not have a completely conjugated pi-electron system. Examples, without limitation, of nonaromatic carbocyclyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexadienyl, adamantanyl, cycloheptyl, cycloheptatrienyl and the like. A nonaromatic carbocyclyl may be substituted or unsubstituted. Typical substituent groups are the same with those of alkyl group, as defined herein. Illustrative examples of nonaromatic carbocyclyl are derived from, but not limited to, the following:



"Unsaturated nonaromatic carbocyclyl" or "nonaromatic unsaturated carbocyclyl" both refer to a nonaromatic carbocyclyl, as defined herein, that contains at least one

carbon carbon double bond or one carbon carbon triple bond, or an aromatic ring as part of the bicyclic or multicyclic ring system.

"$C_2$-$C_{12}$ alkenyl" refers to a straight chain or branched unsaturated hydrocarbon radical having from 2 to 12 carbon atoms. A $C_2$-$C_{12}$ alkenyl group may have one or more points of unsaturation (i.e.- one or more carbon-carbon double bonds). In the case where $C_2$-$C_{12}$ alkenyl has more than one carbon-carbon double bond, the carbon-carbon double bonds can be conjugated or unconjugated. A $C_2$-$C_{12}$ alkenyl group may be optionally substituted by at least one substituent. Suitable substituents on a $C_2$-$C_{12}$ alkenyl group are the same as those described for a $C_1$-$C_{12}$ alkyl group. Examples of $C_2$-$C_{12}$ alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, iso-butenyl, and the like, including substituted forms thereof. Further, the term "alkenyl" refers to a straight chain or branched unsaturated hydrocarbon radical having from 2 to 20 carbon atoms, or 2 to 12 carbon atoms, or 2 to 8 carbon atoms, or 2 to 6 carbon atoms, or 2 to 4 carbon atoms. An alkenyl group may have one or more points of unsaturation (i.e.- one or more carbon-carbon double bonds). In the case where an alkenyl group has more than one carbon-carbon double bond, the carbon-carbon double bonds can be conjugated or unconjugated. An alkenyl group may be substituted or unsubstituted. Suitable substituents on an alkenyl group are the same as those described for a $C_1$-$C_{12}$ alkyl group.

"Alkoxy" or "alkoxyl" refers to $-OR^c$ wherein $R^c$ is $C_1$-$C_{12}$ alkyl, $C_2$-$C_{12}$ alkenyl, $C_2$-$C_{12}$ alkynyl, $C_3$-$C_{12}$ cycloalkyl or ($C_1$-$C_6$ alkylene)-($C_3$-$C_{12}$ cycloalkyl). A "$C_1$-$C_{12}$ alkoxy" or "$C_1$-$C_{12}$ alkoxyl" refers to an alkoxy group, as defined herein, wherein $R^c$ has 1 to 12 total carbon atoms.

"Alkoxyalkyl" refers to an alkyl, as defined herein, that is substituted by at least one alkoxy group as defined herein. A "$C_2$-$C_6$ alkylalkoxy" refers an alkylalkoxy wherein the total carbon number of the alkyl and its alkoxy substituents are from 2 to 6.

"Alkylamino" refers to $-NR^pR^q$ wherein each $R^p$ and $R^q$ is independently H, $C_1$-$C_{12}$ alkyl, $C_2$-$C_{12}$ alkenyl, $C_2$-$C_{12}$ alkynyl, $C_3$-$C_{12}$ cycloalkyl, ($C_1$-$C_6$ alkylene)-($C_3$-$C_{12}$ cycloalkyl) provided $R^p$ and $R^q$ are not both H. A "monoalkylamino" refers to an alkylamino group, as defined herein, wherein one of $R^p$ and $R^q$ is H. A "dialkylamino" refers to an alkylamino group, as defined herein, wherein none of $R^p$ and $R^q$ is H. A "$C_1$-$_{12}$ alkylamino" refers to an alkylamino group that contains 1 to 10 carbon atoms.

"$C_2$-$C_{12}$ alkynyl" refers to a straight chain or branched hydrocarbon radical having from 2-12 carbon atoms and at least one carbon-carbon triple bond. In the case where

$C_2$-$C_{12}$ alkynyl has more than one carbon-carbon double bond, the carbon-carbon double bonds can be conjugated or unconjugated. A $C_2$-$C_{12}$ alkynyl group may be optionally substituted by at least one substituent. Suitable substituents on a $C_2$-$C_{12}$ alkynyl group are the same as those described for a $C_1$-$C_{12}$ alkyl group. Examples of $C_2$-$C_{12}$ alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and the like, including substituted forms thereof. Further, the term "alkynyl" refers to a straight chain or branched hydrocarbon radical of 2 to 20 carbon atoms, or 2 to 12 carbon atoms, or 2 to 8 carbon atoms, or 2 to 6 carbon atoms, or 2 to 4 carbon atoms, and having at least one carbon-carbon triple bond. Alkynyl may be substituted or unsubstituted. Suitable substituents on an alkynyl group are the same as those described for a $C_1$-$C_{12}$ alkyl group.

"Amino" refers to $-NH_2$.

"$C_6$-$C_{10}$ aryl" refers to an all-carbon monocyclic ring or polycyclic ring of 6 to 10 carbon atoms having a completely conjugated pi-electron system. A $C_6$-$C_{10}$ aryl group may be optionally substituted by at least one substituent. Suitable substituents on a $C_6$-$C_{10}$ aryl group are the same as those described for a $C_1$-$C_{12}$ alkyl group. Examples of $C_6$-$C_{10}$ aryl include, but are not limited to, phenyl and naphthyl. Further, the term "aryl" refers to an all-carbon monocyclic ring or polycyclic ring of 6 to 20 carbon atoms having a completely conjugated pi-electron system. The aryl group may be substituted or unsubstituted. Examples of aryl include, but are not limited to, anthracenyl, phenanthreneyl and peryleny!.

"Aralkyl" refers to alkyl, as defined herein, that is substituted with an $C_{6\text{-}10}$ aryl group as defined above; e.g., $-CH_2$phenyl, $-(CH_2)_2$phenyl, $-(CH_2)_3$phenyl, $CH_3CH(CH_3)CH_2$phenyl,and the like and derivatives thereof. A $C_1$-$C_6$ aralkyl refers to a $C_1$-$C_6$ alkyl that is substituted with a $C_6$-$C_{10}$ aryl group.

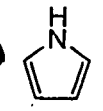
"Heteroaralkyl" group means alkyl, as defined herein, that is substituted with a 5-12 member heteroaryl group; e.g., $-CH_2$pyridinyl, $-(CH_2)_2$pyrimidinyl, $-(CH_2)_3$imidazolyl, and the like, and derivatives thereof. A $C_1$-$C_6$ heteroaralkyl refers to a $C_1$-$C_6$ alkyl that is substituted with an 5-12 member heteroaryl group.

"Heteroaryl" refers to a monocyclic or fused ring group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, and S; the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of unsubstituted heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine,

quinoline, isoquinoline, purine, tetrazole, triazine, and carbazole. The heteroaryl group may be substituted or unsubstituted. Typical substituents include $C_{1-12}$ aliphatic, 3-10 member heterocyclyl, 6-10 member aryl, halogen, $-NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, $-CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, $-SO_2R$, $-SONR_2$, $-SO_2NR_2$, wherein R is a $C_{1-10}$ aliphatic, 3-10 member heterocyclyl, $C_{6-10}$ aryl, 5-10 member heteroaryl.

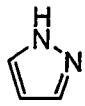
A "pharmaceutically acceptable heteroaryl" is one that is sufficiently stable to be attached to a compound of the invention, formulated into a pharmaceutical composition and subsequently administered to a patient in need thereof.

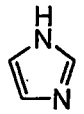
Examples of typical monocyclic heteroaryl groups include, but are not limited to:


pyrrole (pyrrolyl)


furan (furanyl)


thiophene (thiophenyl)


pyrazole (pyrazolyl)

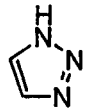

imidazole (imidazolyl)

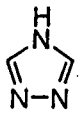

isoxazole (isoxazolyl)


oxazole (oxazolyl)


isothiazole (isothiazolyl)


thiazolyl (thiazolyl)


1,2,3-triazole (1,2,3-triazolyl)


1,3,4-triazole (1,3,4-triazolyl)


1-oxa-2,3-diazole (1-oxa-2,3-diazolyl)


1-oxa-2,4-diazole (1-oxa-2,4-diazolyl)


1-oxa-2,5-diazole (1-oxa-2,5-diazolyl)

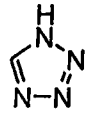

1-oxa-3,4-diazole (1-oxa-3,4-diazolyl)


1-thia-2,3-diazole (1-thia-2,3-diazolyl)


1-thia-2,4-diazole (1-thia-2,4-diazolyl)


1-thia-2,5-diazole (1-thia-2,5-diazolyl)

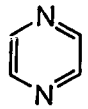

1-thia-3,4-diazole (1-thia-3,4-diazolyl)

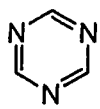

tetrazole (tetrazolyl)


pyridine (pyridinyl)

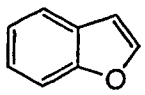

pyridazine (pyridazinyl)


pyrimidine (pyrimidinyl)

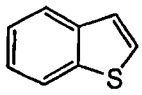

pyrazine (pyrazinyl)


1,3,5-triazine triazinyl

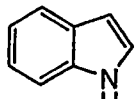
Examples of bicyclic heteroaryl groups include, but are not limited to:



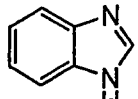
benzofuran (benzofuranyl)



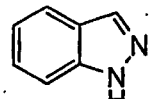
benzothiophene (benzothiophenyl)



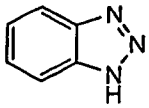
indole (indolyl)



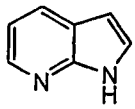
benzimidazole (benzimidazolyl)



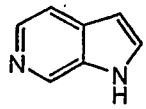
indazole (indazolyl)



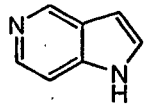
benzotriazole (benzotriazolyl)



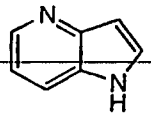
pyrrolo[2,3-b]pyridine (pyrrolo[2,3-b]pyridinyl)



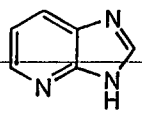
pyrrolo[2,3-c]pyridine (pyrrolo[2,3-c]pyridinyl)



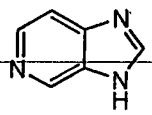
pyrrolo[3,2-c]pyridine (pyrrolo[3,2-c]pyridinyl)



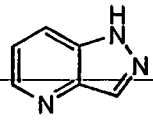
pyrrolo[3,2-b]pyridine (pyrrolo[3,2-b]pyridinyl)



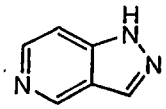
imidazo[4,5-b]pyridine (imidazo[4,5-b]pyridinyl)



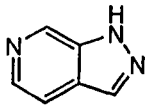
imidazo[4,5-c]pyridine (imidazo[4,5-c]pyridinyl)



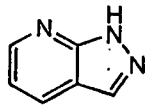
pyrazolo[4,3-d]pyridine (pyrazolo[4,3-d]pyidinyl)



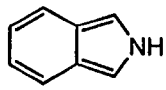
pyrazolo[4,3-c]pyridine (pyrazolo[4,3-c]pyidinyl)



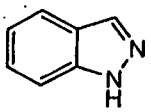
pyrazolo[3,4-c]pyridine (pyrazolo[3,4-c]pyidinyl)



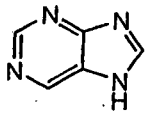
pyrazolo[3,4-b]pyridine (pyrazolo[3,4-b]pyidinyl)



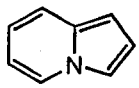
isoindole (isoindolyl)



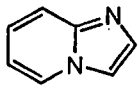
indazole (indazolyl)



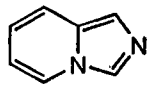
purine (purinyl)



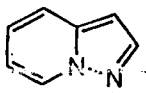
indolizine (indolininyl)



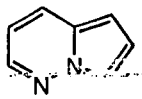
imidazo[1,2-a]pyridine (imidazo[1,2-a]pyridinyl)



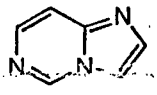
imidazo[1,5-a]pyridine (imidazo[1,5-a]pyridinyl)



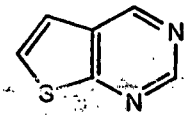
pyrazolo[1,5-a]pyridine (pyrazolo[1,5-a]pyridinyl)



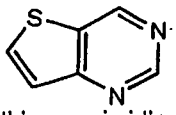
pyrrolo[1,2-b]pyridazine (pyrrolo[1-2,b]pyridazinyl)



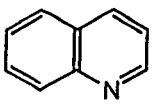
imidazo[1,2-c]pyrimidine (imidazo[1,2-c]pyrimidinyl)



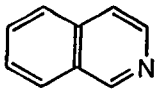
thienopyrimidine (thienopyrimidinyl)



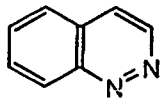
thienopyrimidine (thienopyrimidinyl)



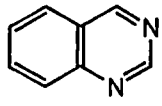
quinoline (quinolinyl)



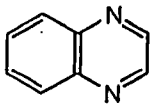
isoquinoline (isoquinolinyl)



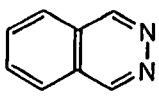
cinnoline (cinnolinyl)



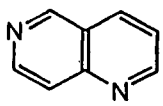
quinazoline (azaquinazoline)



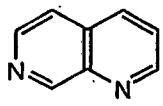
quinoxaline (quinoxalinyl)



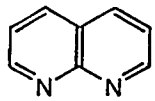
phthalazine (phthalazinyl)



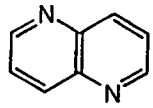
1,6-naphthyridine (1,6-naphthyridinyl)



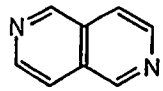
1,7-naphthyridine (1,7-naphthyridinyl)



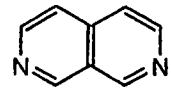
1,8-naphthyridine
(1,8-naphthyridinyl)



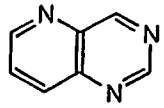
1,5-naphthyridine
(1,5-naphthyridinyl)



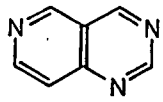
2,6-naphthyridine
(2,6-naphthyridinyl)



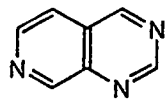
2,7-naphthyridine
(2,7-naphthyridinyl)



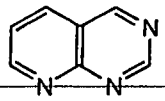
pyrido[3,2-d]pyrimidine
(pyrido[3,2-d]pyrimidinyl)



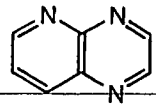
pyrido[4,3-d]pyrimidine
(pyrido[4,3-d]pyrimidinyl)



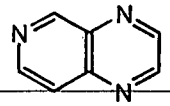
pyrido[3,4-d]pyrimidine
(pyrido[3,4-d]pyrimidinyl)



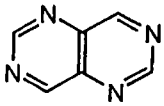
pyrido[2,3-d]pyrimidine
(pyrido[2,3-d]pyrimidinyl)



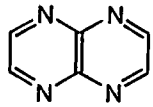
pyrido[2,3-b]pyrazine
(pyrido[2,3-b]pyrazinyl)



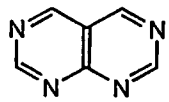
pyrido[3,4-b]pyrazine
(pyrido[3,4-b]pyrazinyl)



pyrimido[5,4-d]pyrimidine
(pyrimido[5,4-d]pyrimidinyl)



pyrazino[2,3-b]pyrazine
(pyrazino[2,3-b]pyrazinyl)



pyrimido[4,5-d]pyrimidine
(pyrimido[4,5-d]pyrimidinyl)

"Heteroalicyclic" or "heterocyclyl" refers to a monocyclic or polycyclic group having from 3 to 12 ring atoms, wherein from 1 to 4 ring atoms are heteroatoms selected from N, O, and S. "Heteroalicyclic" or "heterocyclyl" may also have one or more double bonds. However, "Heteroalicyclic" or "heterocyclyl" do not have a completely conjugated pi-electron system. "Heteroalicyclic" or "heterocyclyl" can be substituted or unsubstituted. Typical substituents include, but are not limited to, $C_1$-$C_{12}$ aliphatic, 6-10 member aryl, 6-10 member aryl, halogen, $-NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, $-CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, $-SO_2R$, wherein R is a $C_1$-$C_{10}$ alkyl, 3-10 member heterocyclyl, $C_6$-$C_{10}$ aryl, 5-10 member heteroaryl.

Examples of saturated heterocyclyl groups include, but are not limited to:



oxirane
(oxiranyl)



thiarane
(thiaranyl)



aziridine
(aziridinyl)



oxetane
(oxetanyl)



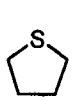
thiatane
(thiatanyl)



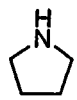
azetidine
(azetidinyl)



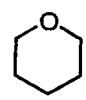
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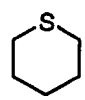
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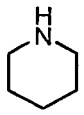
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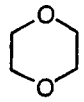


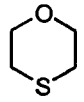
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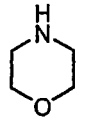


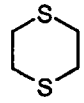
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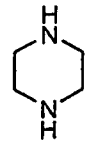

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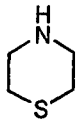

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1,4-oxathiane (1,4-oxathianyl)

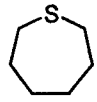

morpholine (morpholinyl)

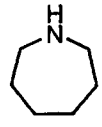

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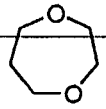

piperazine (piperazinyl)

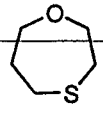

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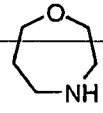

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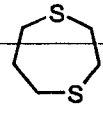

thiepane (thiepanyl)

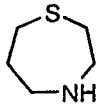

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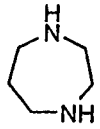

1,4-dioxepane (1,4-dioxepanyl)

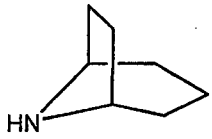

1,4-oxathiepane (1,4-oxathiepanyl)

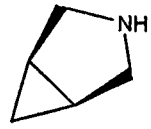

1,4-oxaazepane (1,4-oxaazepanyl)


1,4-dithiepane (1,4-dithiepanyl)

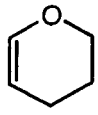

1,4-thieazepane (1,4-thieazepanyl)

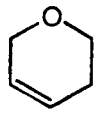

1,4-diazepane (1,4-diazepanyl)

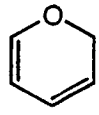

tropane (tropanyl)

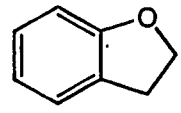

(1*S*,5*R*)-3-aza-bicyclo[3.1.0]hexane (1*S*,5*R*)-3-aza-bicyclo[3.1.0]hexyl

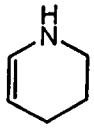
Examples of partially unsaturated heterocyclyl groups include, but are not limited to:

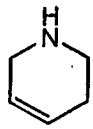

3,4-dihydro-2H-pyran (3,4-dihydro-2H-pyranyl)

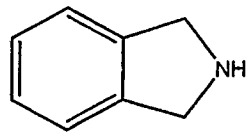

5,6-dihydro-2H-pyran (5,6-dihydro-2H-pyranyl)

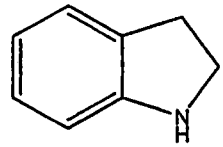

2H-pyran (2H-pyranyl)


2,3-dihydrobenzofuranyl


1,2,3,4-tetrahydropyridine (1,2,3,4-tetrahydropyridinyl)


1,2,5,6-tetrahydropyridine (1,2,5,6-tetrahydropyridinyl)


isoindoline isoindolinyl


indoline indolinyl

A "diradical" refers to a group that has two open valences and is further connected to two other groups, or forms a double bond with the same atom of one group, or forms two single bonds with the same atom of one group. Examples of diradicals are, but are not limited to $-CH_2-$, -O-, $-O-CH_2-$, -($C_1$-$C_3$ alkylene)-NH- and $-CH_2-CH_2-$. When a diradical is referred to as, for example, $-O-CH_2-$ or -($C_1$-$C_3$ alkylene)-NH-, it is understood that each end of the diradical can equally connect to another moiety. For example, if K is defined as A-L-B, and L is a diradical selected from $-O-CH_2-$ and -($C_1$-$C_3$ alkylene)-, it is understood that K is therefore selected from $A-O-CH_2-$

B, A-$CH_2$-O-B, and A-($C_1$-$C_3$ alkylene)-B. A and B herein are referred to as different organic moieties.

When "ene" is added after the "yl" at the end of any of the previously defined terms to form a new term, the new term refers to a diradical formed by removing one hydrogen atom from the original term of which the new term derived from. For example, an alkylene refers to a diradical group formed by removing one hydrogen atom from an alkyl group and that a "methylene" refers to a divalent radical -$CH_2$- derived from removing one hydrogen atom from methyl. More examples of such diradicals include, but are not limited to: alkenylene, alkynylene, cycloalkylene, phenylene, heterocyclylene, heteroarylene and (nonaromatic unsaturated carbocyclylene), which are derived from alkenyl, alkynyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl and (nonaromatic unsaturated carbocyclyl), respectively. For example, "cyclopropylene" refers to both  , and  . For example, "$C_1$-$C_2$ alkylene" refers to all of the following: –$CH_2$-, -$CH(CH_3)$- and -$CH_2$-$CH_2$-.

"oxo" or "-oxo-" refers to an oxygen double bond "=O" substitution.

"Hydroxy" or "hydroxyl" both refer to –OH.

"Perfluoroalkyl" refers to an alkyl group in which all of its hydrogen atoms are replaced by fluorine atoms.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heterocyclyl group optionally substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the heterocyclyl group is substituted with an alkyl group and situations where the heterocyclyl group is not substituted with the alkyl group.

When a group is "optionally substituted" or "optionally further substituted" by some substituents, it means a carbon or a nitrogen atom of this group wherein one or more hydrogen atoms are attached to the carbon or nitrogen atom, such carbon or nitrogen atom is optionally substituted by some other substituents. For example, "R is H, $C_1$-$C_3$ alkyl or phenyl, and R is optionally further substituted by 1-3 groups selected from –F, oxo and $C_1$-$C_3$ perfluoroalkyl", means that R is 1) H (when R is H, R cannot be further substituted); 2) $C_1$-$C_3$ alkyl optionally further substituted by 1-3 groups selected from –F, oxo and $C_1$-$C_3$ perfluoroalkyl; and 3) phenyl optionally further substituted by 1-3

groups selected from –F and $C_1$-$C_3$ perfluoroalkyl. Optional substitution of oxo does not apply when R is phenyl because no single atom of the phenyl group possess two hydrogen atoms to be substituted by oxo, i.e. =O bond. When a group is further substituted by a "-($C_1$-$C_4$ alkylene)-", it means the "-($C_1$-$C_4$ alkylene)-", together with the nitrogen atom or the carbon atom of the group to which "$C_1$-$C_4$ alkylene" is attached to, form a carbo or hetero spiro cycle.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically/pharmaceutically acceptable salts, solvates, hydrates or prodrugs thereof, with other chemical components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

As used herein, a "physiologically/pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

A "pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts that retain the biological effectiveness and properties of the parent compound. Such salts include:

(1) acid addition salts, which can be obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perchloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

"PK" refers to receptor protein tyrosine kinase (RTKs), non-receptor or "cellular" tyrosine kinase (CTKs) and serine-threonine kinases (STKs).

"Modulation" or "modulating" refers to the alteration of the catalytic activity of RTKs, CTKs and STKs. In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and STKs, depending on the concentration of the compound or salt to which the RTK, CTK or STK is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

"Catalytic activity" refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

"Contacting" refers to bringing a compound of the present teachings and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly, i.e., by interacting with the kinase itself, or indirectly, i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished "*in vitro*," i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a PK related disorder, i.e., the $IC_{50}$ of the compound, can be determined before use of compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the art, to get the PKs in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

"*In vitro*" refers to procedures performed in an artificial environment such as, e.g., without limitation, in a test tube or culture medium.

"*In vivo*" refers to procedures performed within a living organism such as, without limitation, a mouse, rat or rabbit.

"PK related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate, i.e., under or, more commonly, over, PK catalytic activity, where the particular PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs, (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth, or, (3) decreased PK expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of

a PK refers to either amplification of the gene encoding a particular PK or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more of the symptoms of the cellular disorder increases). Under-activity is, of course, the converse, wherein the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases.

"Treat", "treating" and "treatment" refer to a method of alleviating or abrogating a PK mediated cellular disorder and/or its attendant symptoms. With regard particularly to cancer, these terms simply mean that the life expectancy of an individual affected with a cancer will be increased or that one or more of the symptoms of the disease will be reduced.

"Organism" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukariotic cell or as complex as a mammal, including a human being.

"Therapeutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has at least one of the following effects:

(1) reducing the size of the tumor;

(2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis;

(3) inhibiting to some extent (that is, slowing to some extent, preferably stopping) tumor growth, and

(4) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the cancer.

"Monitoring" means observing or detecting the effect of contacting a compound with a cell expressing a particular PK. The observed or detected effect can be a change in cell phenotype, in the catalytic activity of a PK or a change in the interaction of a PK with a natural binding partner. Techniques for observing or detecting such effects are well-known in the art. The effect is selected from a change or an absence of change in a cell phenotype, a change or absence of change in the catalytic activity of said protein kinase or a change or absence of change in the interaction of said protein kinase with a natural binding partner in a final aspect of this invention.

"Cell phenotype" refers to the outward appearance of a cell or tissue or the biological function of the cell or tissue. Examples, without limitation, of a cell phenotype are cell size, cell growth, cell proliferation, cell differentiation, cell survival, apoptosis, and nutrient uptake and use. Such phenotypic characteristics are measurable by techniques well-known in the art.

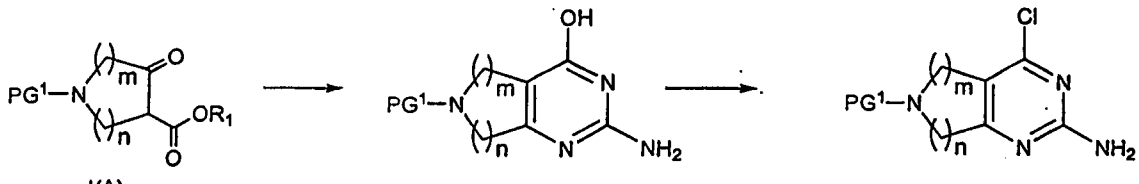
"Natural binding partner" refers to a polypeptide that binds to a particular PK in a cell. Natural binding partners can play a role in propagating a signal in a PK-mediated signal transduction process. A change in the interaction of the natural binding partner with the PK can manifest itself as an increased or decreased concentration of the PK/natural binding partner complex and, as a result, in an observable change in the ability of the PK to mediate signal transduction.

The term "stereoisomers" refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. In particular, the term "enantiomers" refers to two stereoisomers of a compound that are non-superimposable mirror images of one another. The terms "racemic" or "racemic mixture," as used herein, refer to a 1:1 mixture of enantiomers of a particular compound. The term "diastereomers", on the other hand, refers to the relationship between a pair of stereoisomers that comprise two or more asymmetric centers and are not mirror images of one another.

## Detailed Description

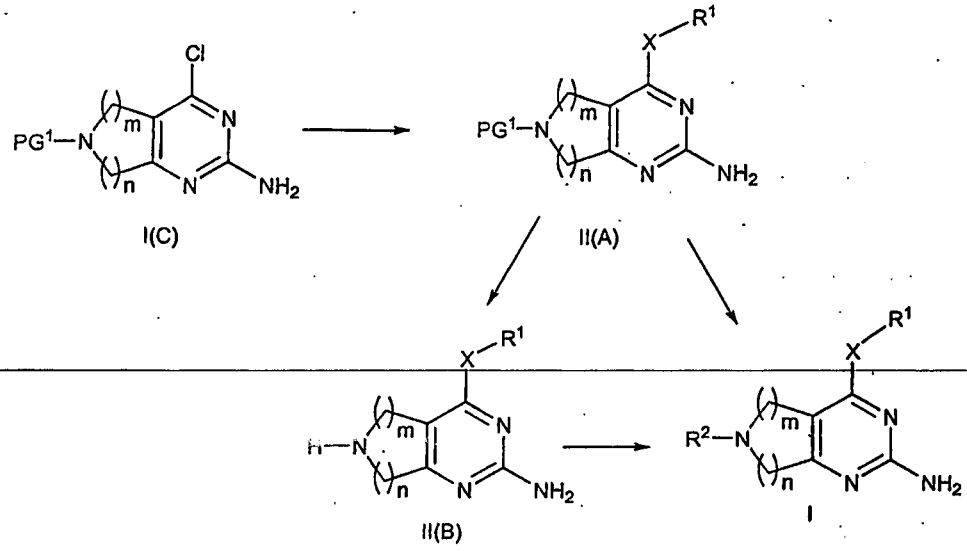
The compounds of the current invention, i.e., the compounds of formula I, as well as compounds of formula II, III and IV, can be made following reaction Scheme 1, 2 and 3.

**Scheme 1**

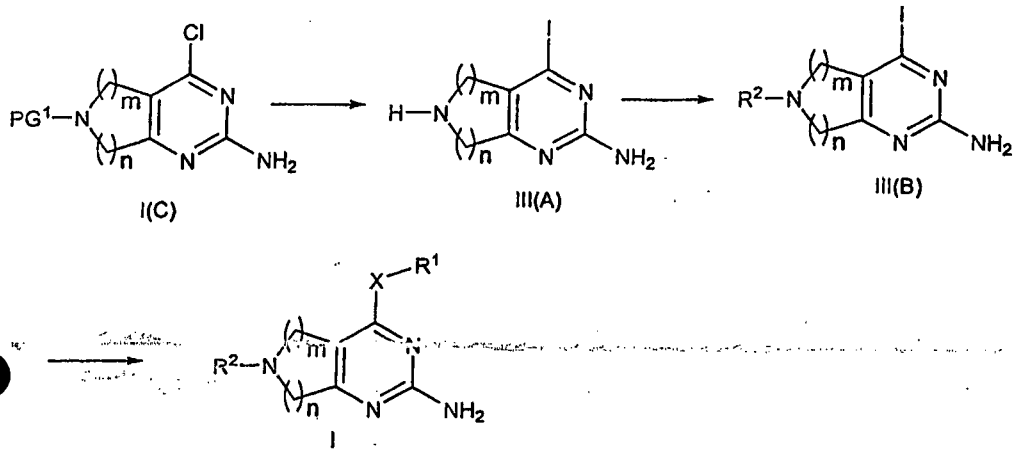


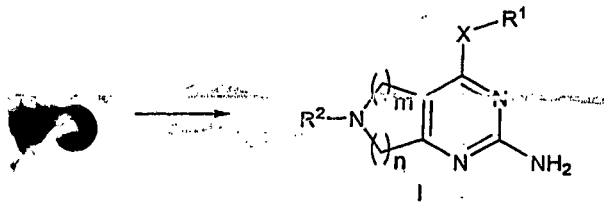

I(A) I(B) I(C)

**Scheme 2**




**Scheme 3**




Scheme 1 illustrates the synthesis of intermediate **I(C)** used to make compounds of formula **I**. The beta keto ester **I(A)** can be prepared based on a known procedures (see, e.g. Viscontini and Buhler *Helvetica Chimica Acta*, 50(5): 1289-93; (1967), Rosowsky et. al. *J. Heterocyclic Chem.*, 26: 509-16 (1989)). $PG^1$, the nitrogen protecting group, can be selected for compatability with subsequent chemistry. Protecting groups and general considerations for their use are described in T. Greene and P. Wuts, "Protective Groups in Organic Synthesis", 3rd Edition 1999, John Wiley & Sons and are well known to those skilled in the art. Compound **I(A)** is condensed with guanidine to give compound **I(B)**. This can typically be done by heating compound **I(A)** with guanidine or guanidine equivalent a protic solvent. A typical reaction condition would be to reflux compound **I(A)** with guandidine carbonate in *tert*-butanol as a solvent.

Conversion of the hydroxyl group of compound **I(B)** to chloro gives **I(C)**. This can typically be done by heating compound **I(B)** with $POCl_3$ in an aprotic solvent. A typical reaction condition would be to reflux compound **I(B)** together with excess $POCl_3$ either neat or in dry acetonitrile as solvent.

Scheme 2 illustrates the route through which compounds of formula **I** can be made from intermediate **I(C)**. In Scheme 2, the chloro leaving group of compound **I(C)** is replaced by a $R^1$-X- group to give compound **II(A)**. This reaction can typically be carried out by displacement of the chloro leaving group using a variety of nucleophiles such as carbon, oxygen, nitrogen, sulfur, or other nucleophiles. A typical nucleophilic displacement reaction for the transformation of compound **I(C)** to compound **II(A)** would be to treat compound **I(C)** with a nucleophile in the presence of base such as cesium carbonate using DMF or DMSO as solvent to give compound **II(A)**. Alternatively, the displacement of the chloro leaving group of compound **I(C)** by $R^1$-X- to give compound **II(A)** can also be carried out using cross coupling methodology utilizing Suzuki, Stille, Negishi or similar conditions. A typical cross coupling reaction for the transformation of compound **I(C)** to compound **II(A)** would be to treat compound **I(C)** with a boronic acid or ester in the presence of a base such as sodium carbonate and Pd(0) catalyst in a solvent mixture such as water and 1,4-dioxane to give compound **II(A)**. The nitrogen protecting group, $PG^1$, of compound **II(A)** is then removed to give compound **II(B)**. This can typically be done, when $PG^1$ forms an ethyl carbamate protecting group, by refluxing compound **II(A)** with trimethylsilyliodide in a solvent such as $CH_3CN$. Alternatively HBr in acetic acid or KOH in isopropanol can also be used. A typical condition for the transformation of compound **II(A)** to compound **II(B)** would be to treat compound **II(A)** with TMSI (5 equivalents) in refluxing $CH_3CN$ to give compound **II(B)**. The dihydropyrrolo amino moiety of compound **II(B)** then acts as a nucleophile in reactions with an electrophilic $R^2$ moiety to give compound **I**. This nucleophilic reaction can be alkylation, acylation, sulfonylation, and other reactions applicable to secondary alkyl amines. An alkylation reaction of compound **II(B)** can be carried out by reacting compound **II(B)** with an alkylating $R^2$ moiety. A typical alkylation reaction condition is to react compound **II(B)** with an $R^2$ alkyl bromide moiety in the presence of TEA at room temperature to give compound **I** as an N-alkyl. An acylation reaction of compound **II(B)** can be carried out by reacting compound **II(B)** with an acylating $R^2$ moiety. A typical acylation reaction condition is to react compound **II(B)** with an $R^2$ activated ester moiety or $R^2$ acyl halide in the presence of TEA to give compound **I** as an amide. Another

typical acylation reaction condition is to react compound **II(B)** with an $R^2$ isocyanate or isocyanate equivalent moiety in the presence of TEA to give compound **I** as a urea. A sulfonylation reaction of compound **II(B)** can be carried out by reacting compound **II(B)** with an sulfonylating $R^2$ moiety. A typical sulfonylation reaction condition is to react compound **II(B)** with an $R^2$ sulfonyl chloride moiety in the presence of TEA to give compound **I** as a sulfonamide.

Another method for the preparation of compound **I** as a urea takes compound **II(A)**, when $PG^1$ forms an ethyl carbamate protecting group, and directly converts compound **II(A)** into compound **I**. This reaction can typically be carried out using a nucleophilic amine in the presence of trimethylaluminum in a solvent such as toluene. A typical condition is to treat a nucleophilic amine in toluene at 0°C with a solution of trimethylaluminum in hexanes. After warming to room temperature, compound **II(A)** is added and the mixture is heated under microwave radiation to prepare compound **I**.

Scheme 3 illustrates another route through which compounds of formula **I** can be made from intermediate **I(C)**. In Scheme 3 when $PG^1$ forms an ethyl carbamate protecting group, the protecting group, $PG^1$, of compound **I(C)** is removed with concurrent conversion of chloro to iodo in one step. This can typically be carried out by heating compound **I(C)** with TMSI in an aprotic solvent. A typical reaction condition is to reflux compound **I(C)** in $CH_3CN$ with five equivalents of TMSI. Following a methanol quench, compound **III(A)** is obtained as an HI salt. The dihydropyrrolo amino moiety of compound **III(A)** then acts as a nucleophile in reactions with an electrophilic $R^2$ moiety to give compound **III(B)**. This nucleophilic reaction can be alkylation, acylation, sulfonylation, and other reactions applicable to secondary alkyl amines. An alkylation reaction of compound **III(A)** can be carried out by reacting compound **III(A)** with an alkylating $R^2$ moiety. A typical alkylation reaction condition is to react compound **III(A)** with an $R^2$ alkyl bromide moiety in the presence of TEA at room temperature to give compound **III(B)** as an N-alkyl. An acylation reaction of compound **III(A)** can be carried out by reacting compound **III(A)** with an acylating $R^2$ moiety. A typical acylation reaction condition is to react compound **III(A)** with an $R^2$ activated ester moiety or $R^2$ acyl halide in the presence of TEA to give compound **III(B)** as an amide. Another typical acylation reaction condition is to react compound **III(A)** with an $R^2$ isocyanate or isocyanate equivalent moiety in the presence of TEA to give compound **III(B)** as a urea. A sulfonylation reaction of compound **III(A)** can be carried out by reacting compound **III(A)** with an sulfonylating $R^2$ moiety. A typical sulfonylation reaction condition is to react **III(A)**

with an $R^2$ sulfonyl chloride moiety in the presence of TEA at 0°C to give compound **III(B)** as a sulfonamide. The iodo group of compound **III(B)** is then displaced by $R^1$-X- using cross coupling methodology to give compound **I**. This reaction can typically be carried out using Suzuki, Stille, Negishi or similar conditions. A typical cross coupling reaction for the transformation of compound **III(B)** to compound **I** would be to treat compound **III(B)** with a boronic acid or ester in the presence of a base such as sodium carbonate and Pd(0) catalyst in a solvent mixture such as water and 1,4-dioxane to give compound **I**.

The compounds of the present invention may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the present invention may be depicted herein using a solid line (——), a solid wedge (▬), or a dotted wedge (┈┈┈). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of the present invention can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of the invention (and chiral precursors thereof) may be

obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art. See, e.g. "Stereochemistry of Organic Compounds" by E. L. Eliel (Wiley, New York, 1994), the disclosure of which is incorporated herein by reference in its entirety.

Where a compound of the invention contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of the present invention containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism. Included within the scope of the invention are all stereoisomers, geometric isomers and tautomeric forms of the inventive compounds, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

Salts of the present invention can be prepared according to methods known to those of skill in the art. Examples of salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edislyate, estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate,

phthalate, phospate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium. These salts can also be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically

acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

In the case of compounds that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystalline or polymorphic forms, or in an amorphous form, all of which are intended to be within the scope of the present invention.

The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as $^{2}H$ and $^{3}H$, carbon, such as $^{11}C$, $^{13}C$ and $^{14}C$, chlorine, such as $^{36}Cl$, fluorine, such as $^{18}F$, iodine, such as $^{123}I$ and $^{125}I$, nitrogen, such as $^{13}N$ and $^{15}N$, oxygen, such as $^{15}O$, $^{17}O$ and $^{18}O$, phosphorus, such as $^{32}P$, and sulfur, such as $^{35}S$. Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, $^{3}H$, and carbon-14, $^{14}C$, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, $^{2}H$, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be

preferred in some circumstances. Substitution with positron emitting isotopes, such as $^{11}C$, $^{18}F$, $^{15}O$ and $^{13}N$, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term 'hydrate' is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of the invention in association with water, isopropanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate.

Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate. Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-hydrate form of the compounds.

Prodrugs of the compounds described herein are also within the scope of the invention. Thus certain derivatives of the compounds of the present invention, which derivatives may have little or no pharmacological activity themselves, when administered into or onto the body may be converted into compounds of the present invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compounds of the present invention contain a carboxylic acid functionality (-COOH), a prodrug compound wherein the hydrogen of the carboxylic acid functionality of the compound is replaced by ($C_1$-$C_8$)alkyl to form the corresponding ester;

(ii) where the compounds of the present invention contain an alcohol functionality (-OH), a prodrug compound wherein the hydrogen of the alcohol functionality of the compound is replaced by ($C_1$-$C_6$) alkanoyloxymethyl to form the corresponding ether; and

(iii) where the compounds of the present invention contain a primary or secondary amino functionality (-$NH_2$ or -NHR where R $\neq$ H), a prodrug compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound I is/are replaced by ($C_1$-$C_{10}$) alkanoyl to form the corresponding amide.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references. Moreover, certain compounds of the present invention may themselves act as prodrugs of other compounds of the present invention.

Also included within the scope of the invention are metabolites of compounds of the present invention, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include:

(i) where the compounds of the present invention contain a methyl group, a hydroxymethyl derivative thereof (e.g. -$CH_3$ -> -$CH_2OH$);

(ii) where the compounds of the present invention contain an alkoxy group, a hydroxy derivative thereof (e.g. -OR -> -OH);

(iii) where the compounds of the present invention contain a tertiary amino group, a secondary amino derivative thereof (e.g. -$NR^1R^2$ -> -$NHR^1$ or -$NHR^2$);

(iv) where the compounds of the present invention contain a secondary amino group, a primary derivative thereof (e.g. -$NHR^1$ -> -$NH_2$);

(v) where the compounds of the present invention contain a phenyl moiety, a phenol derivative thereof (e.g. -Ph -> -PhOH); and

(vi) where the compounds of the present invention contain an amide group, a carboxylic acid derivative thereof (e.g. -$CONH_2$ -> COOH).

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds can be administered alone or in combination with one or more other compounds of the invention, or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its entirety.

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending

agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001), the disclosure of which is incorporated herein by reference in its entirety.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X), the disclosure of which is incorporated herein by reference in its entirety.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298. The disclosures of these references are incorporated herein by reference in their entireties.

Parenteral Administration

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Topical Administration

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection. The disclosures of these references are incorporated herein by reference in their entireties.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Inhaled/Intranasal Administration

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with

phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may include a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μL to 100μL. A typical formulation includes a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid

(PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing a desired mount of the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

Rectal/Intravaginal Administration

Compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Ocular Administration

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

Other Technologies

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking,

bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in PCT Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 0.01 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.07 to about 7000 mg/day, preferably about 0.7 to about 2500 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several smaller doses for administration throughout the day.

This invention also relates to a method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of the present invention, or a salt or solvate thereof, that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In one embodiment of the present invention the anti-tumor agent used in conjunction with a compound of the present invention and pharmaceutical compositions described herein is an anti-angiogenesis agent, kinase inhibitor, pan kinase inhibitor or growth factor inhibitor. Preferred pan kinase inhibitors include Sutent™ (sunitinib), described in U.S. Patent No. 6,573,293 (Pfizer, Inc, NY, USA). Anti-angiogenesis agents, include but are not limited to the following agents, such as EGF inhibitors,

EGFR inhibitors, VEGF inhibitors, VEGFR inhibitors, TIE2 inhibitors, IGF1R inhibitors, COX-II (cyclooxygenase II) inhibitors, MMP-2 (matrix-metalloprotienase 2) inhibitors, and MMP-9 (matrix-metalloprotienase 9) inhibitors.

Preferred VEGF inhibitors, include for example, Avastin (bevacizumab), an anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California. Additional VEGF inhibitors include CP-547,632 (Pfizer Inc., NY, USA), AG13736 (Pfizer Inc.), ZD-6474 (AstraZeneca), AEE788 (Novartis), AZD-2171, VEGF Trap (Regeneron/Aventis), Vatalanib (also known as PTK-787, ZK-222584: Novartis & Schering AG), Macugen (pegaptanib octasodium, NX-1838, EYE-001, Pfizer Inc./Gilead/Eyetech), IM862 (Cytran Inc. of Kirkland, Washington, USA); and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California) and combinations thereof.

VEGF inhibitors useful in the practice of the present invention are described in US Patent No. 6,534,524 and 6,235,764, both of which are incorporated in their entirety for all purposes. Additional VEGF inhibitors are described in, for example in WO 99/24440, in WO 95/21613, WO 99/61422, U.S. Patent 5,834,504, WO 98/50356, U.S. Patent 5,883,113 U.S. Patent 5,886,020, U.S. Patent 5,792,783, U.S. Patent 6,653,308, WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438, WO 99/16755, and WO 98/02437, all of which are herein incorporated by reference in their entirety.

Other anti-angiogenic compounds include acitretin, fenretinide, thalidomide, zoledronic acid, angiostatin, aplidine, cilengtide, combretastatin A-4, endostatin, halofuginone, rebimastat, removab, Revlimid, squalamine, ukrain, Vitaxin and combinations thereof.

Other antiproliferative agents that may be used in combination with the compounds of the present invention include inhibitors of the enzyme farnesyl protein transferase and inhibitors of the receptor tyrosine kinase PDGFr, including the compounds disclosed and claimed in the following: U.S. Patent 6,080,769; U.S. Patent 6,194,438; U.S. Patent 6,258,824; U.S. Patent 6,586447; U.S. Patent 6,071,935; U.S. Patent 6,495,564; and U.S. Patent 6,150,377; U.S. Patent 6,596,735; U.S. Patent 6,479,513; WO 01/40217; U.S. 2003-0166675. Each of the foregoing patents and patent applications is herein incorporated by reference in their entirety.

PDGRr inhibitors include but are not limited to those disclosed in international patent application publication numbers WO01/40217 and WO2004/020431, the contents

of which are incorporated in their entirety for all purposes. Preferred PDGFr inhibitors include Pfizer's CP-673,451 and CP-868,596 and its salts.

Preferred GARF inhibitors include Pfizer's AG-2037 (pelitrexol and its salts). GARF inhibitors useful in the practice of the present invention are disclosed in US Patent No. 5,608,082 which is incorporated in its entirety for all purposes.

Examples of useful COX-II inhibitors which can be used in conjunction with a compound of Formula (I) and pharmaceutical compositions disclosed herein include CELEBREX™ (celecoxib), parecoxib, deracoxib, ABT-963, MK-663 (etoricoxib), COX-189 (Lumiracoxib), BMS 347070, RS 57067, NS-398, Bextra (valdecoxib), paracoxib, Vioxx (rofecoxib), SD-8381, 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole, 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-1H-pyrrole, T-614, JTE-522, S-2474, SVT-2016, CT-3, SC-58125 and Arcoxia (etoricoxib). Additonally, COX-II inhibitors are disclosed in U.S. Patent Applications US 2005-0148627 and US 2005-0148777, the contents of which are incorporated in their entirety for all purposes.

In a particular embodiment the anti-tumor agent is celecoxib (U.S. Patent No. 5,466,823), valdecoxib (U.S. Patent No. 5,633,272), parecoxib (U.S. Patent No. 5,932,598), deracoxib (U.S. Patent No. 5,521,207), SD-8381 (U.S. Patent No. 6,034,256, Example 175), ABT-963 (WO 2002/24719), rofecoxib (CAS No. 162011-90-7), MK-663 (or etoricoxib) as disclosed in WO 1998/03484, COX-189 (Lumiracoxib) as disclosed in WO 1999/11605, BMS-347070 (U.S. Patent 6,180,651), NS-398 (CAS 123653-11-2), RS 57067 (CAS 17932-91-3), 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole, 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-1H-pyrrole, or meloxicam.

Other useful inhibitors as anti-tumor agents used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein include aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit the enzyme that makes prostaglandins (cyclooxygenase I and II), resulting in lower levels of prostaglandins, include but are not limited to the following, Salsalate (Amigesic), Diflunisal (Dolobid), Ibuprofen (Motrin), Ketoprofen (Orudis), Nabumetone (Relafen), Piroxicam (Feldene), Naproxen (Aleve, Naprosyn), Diclofenac (Voltaren), Indomethacin (Indocin), Sulindac (Clinoril), Tolmetin (Tolectin), Etodolac (Lodine), Ketorolac (Toradol), Oxaprozin (Daypro) and combinations thereof.

Preferred COX-I inhibitors include ibuprofen (Motrin), nuprin, naproxen (Aleve), indomethacin (Indocin), nabumetone (Relafen) and combinations thereof.

Targeted agents used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein include EGFr inhibitors such as Iressa (gefitinib, AstraZeneca), Tarceva (erlotinib or OSI-774, OSI Pharmaceuticals Inc.), Erbitux (cetuximab, Imclone Pharmaceuticals, Inc.), EMD-7200 (Merck AG), ABX-EGF (Amgen Inc. and Abgenix Inc.), HR3 (Cuban Government), IgA antibodies (University of Erlangen-Nuremberg), TP-38 (IVAX), EGFR fusion protein, EGF-vaccine, anti-EGFr immunoliposomes (Hermes Biosciences Inc.) and combinations thereof. Preferred EGFr inhibitors include Iressa, Erbitux, Tarceva and combinations thereof.

Other anti-tumor agents include those selected from pan-erb-receptor inhibitors or ErbB2 receptor inhibitors, such as CP-724,714 (Pfizer, Inc.), CI-1033 (canertinib, Pfizer, Inc.), Herceptin (trastuzumab, Genentech Inc.), Omitarg (2C4, pertuzumab, Genentech Inc.), TAK-165 (Takeda), GW-572016 (lonafarnib, GlaxoSmithKline), GW-282974 (GlaxoSmithKline), EKB-569 (Wyeth), PKI-166 (Novartis), dHER2 (HER2 Vaccine, Corixa and GlaxoSmithKline), APC8024 (HER2 Vaccine, Dendreon), anti-HER2/neu bispecific antibody (Decof Cancer Center), B7.her2.IgG3 (Agensys), AS HER2 (Research Institute for Rad Biology & Medicine), trifunctional bispecific antibodies (University of Munich) and mAB AR-209 (Aronex Pharmaceuticals Inc) and mAB 2B-1 (Chiron) and combinations thereof.

Preferred erb selective anti-tumor agents include Herceptin, TAK-165, CP-724,714, ABX-EGF, HER3 and combinations thereof. Preferred pan erbb receptor inhibitors include GW572016, CI-1033, EKB-569, and Omitarg and combinations thereof.

Additional erbB2 inhibitors include those disclosed in WO 98/02434, WO 99/35146, WO 99/35132, WO 98/02437, WO 97/13760, WO 95/19970, U.S. Patent 5,587,458, and U.S. Patent 5,877,305, each of which is herein incorporated by reference in its entirety. ErbB2 receptor inhibitors useful in the present invention are also disclosed in U.S. Patents 6,465,449, and 6,284,764, and in WO 2001/98277 each of which are herein incorporated by reference in their entirety.

Additionally, other anti-tumor agents may be selected from the following agents, BAY-43-9006 (Onyx Pharmaceuticals Inc.), Genasense (augmerosen, Genta), Panitumumab (Abgenix/Amgen), Zevalin (Schering), Bexxar (Corixa/GlaxoSmithKline), Abarelix, Alimta, EPO 906 (Novartis), discodermolide (XAA-296), ABT-510 (Abbott), Neovastat (Aeterna), enzastaurin (Eli Lilly), Combrestatin A4P (Oxigene), ZD-6126 (AstraZeneca), flavopiridol (Aventis), CYC-202 (Cyclacel), AVE-8062 (Aventis), DMXAA

(Roche/Antisoma), Thymitaq (Eximias), Temodar (temozolomide, Schering Plough) and Revilimd (Celegene) and combinations thereof.

Other anti-tumor agents may be selected from the following agents, CyPat (cyproterone acetate), Histerelin (histrelin acetate), Plenaixis (abarelix depot), Atrasentan (ABT-627), Satraplatin (JM-216), thalomid (Thalidomide), Theratope, Temilifene (DPPE), ABI-007 (paclitaxel), Evista (raloxifene), Atamestane (Biomed-777), Xyotax (polyglutamate paclitaxel), Targetin (bexarotine) and combinations thereof.

Additionally, other anti-tumor agents may be selected from the following agents, Trizaone (tirapazamine), Aposyn (exisulind), Nevastat (AE-941), Ceplene (histamine dihydrochloride), Orathecin (rubitecan), Virulizin, Gastrimmune (G17DT), DX-8951f (exatecan mesylate), Onconase (ranpirnase), BEC2 (mitumoab), Xcytrin (motexafin gadolinium) and combinations thereof.

Further anti-tumor agents may be selected from the following agents, CeaVac (CEA), NeuTrexin (trimetresate glucuronate) and combinations thereof. Additional anti-tumor agents may be selected from the following agents, OvaRex (oregovomab), Osidem (IDM-1), and combinations thereof. Additional anti-tumor agents may be selected from the following agents, Advexin (ING 201), Tirazone (tirapazamine), and combinations thereof. Additional anti-tumor agents may be selected from the following agents, RSR13 (efaproxiral), Cotara (131I chTNT 1/b), NBI-3001 (IL-4) and combinations thereof. Additional anti-tumor agents may be selected from the following agents, Canvaxin, GMK vaccine, PEG Interon A, Taxoprexin (DHA/paclitaxel), and combinations thereof.

Other anti-tumor agents include Pfizer's MEK1/2 inhibitor PD325901, Array Biopharm's MEK inhibitor ARRY-142886, Bristol Myers' CDK2 inhibitor BMS-387,032, Pfizer's CDK inhibitor PD0332991 and AstraZeneca's AXD-5438, and combinations thereof.

Additionally, mTOR inhibitors may also be utilized such as CCI-779 (Wyeth) and rapamycin derivatives RAD001 (Novartis) and AP-23573 (Ariad), HDAC inhibitors, SAHA (Merck Inc./Aton Pharmaceuticals) and combinations thereof. Additional anti-tumor agents include aurora 2 inhibitor VX-680 (Vertex), and Chk1/2 inhibitor XL844 (Exilixis).

The following cytotoxic agents, e.g., one or more selected from the group consisting of epirubicin (Ellence), docetaxel (Taxotere), paclitaxel, Zinecard (dexrazoxane), rituximab (Rituxan) imatinib mesylate (Gleevec), and combinations thereof, may be used in combination with a compound of the present invention and pharmaceutical compositions disclosed herein.

The invention also contemplates the use of the compounds of the present invention together with hormonal therapy, including but not limited to, exemestane (Aromasin, Pfizer Inc.), leuprorelin (Lupron or Leuplin, TAP/Abbott/Takeda), anastrozole (Arimidex, Astrazeneca), gosrelin (Zoladex, AstraZeneca), doxercalciterol, fadrozole, formestane, tamoxifen citrate (tamoxifen, Nolvadex, AstraZeneca), Casodex (AstraZeneca), Abarelix (Praecis), Trelstar, and combinations thereof.

The invention also relates to the use of the compounds of the present invention together with hormonal therapy agents such as anti-estrogens including, but not limited to fulvestrant, toremifene, raloxifene, lasofoxifene, letrozole (Femara, Novartis), anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex™(4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl) propionanilide, bicalutamide) and combinations thereof.

Further, the invention provides a compound of the present invention alone or in combination with one or more supportive care products, e.g., a product selected from the group consisting of Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi, Emend, or combinations thereof.

Particularly preferred cytotoxic agents include Camptosar, Erbitux, Iressa, Gleevec, Taxotere and combinations thereof.

The following topoisomerase I inhibitors may be utilized as anti-tumor agents: camptothecin; irinotecan HCl (Camptosar); edotecarin; orathecin (Supergen); exatecan (Daiichi); BN-80915 (Roche); and combinations thereof. Particularly preferred toposimerase II inhibitors include epirubicin (Ellence).

Alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, temozolomide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, mafosfamide, and mitolactol; platinum-coordinated alkylating compounds include but are not limited to, cisplatin, Paraplatin (carboplatin), eptaplatin, lobaplatin, nedaplatin, Eloxatin (oxaliplatin, Sanofi) or satrplatin and combinations thereof. Particularly preferred alkylating agents include Eloxatin (oxaliplatin).

Antimetabolites include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, Alimta (premetrexed disodium, LY231514, MTA), Gemzar (gemcitabine, Eli Lilly),

fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine; or for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid and combinations thereof.

Antibiotics include intercalating antibiotics and include, but are not limited to: aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, bleomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, galarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, zinostatin and combinations thereof.

Plant derived anti-tumor substances include for example those selected from mitotic inhibitors, for example vinblastine, docetaxel (Taxotere), paclitaxel and combinations thereof.

Cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of aclarubicn, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan, and combinations thereof.

Preferred cytotoxic topoisomerase inhibiting agents include one or more agents selected from the group consisting of camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, SN-38, topotecan, and combinations thereof.

Immunologicals include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b (Actimmune), or interferon gamma-n1 and combinations thereof. Other agents include filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin,

Z-100, epratuzumab, mitumomab, oregovomab, pemtumomab (Y-muHMFG1), Provenge (Dendreon) and combinations thereof.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include krestin, lentinan, sizofiran, picibanil, ubenimex and combinations thereof.

Other anticancer agents that can be used in combination with a compound of the present invention include alitretinoin, ampligen, atrasentan bexarotene, bortezomib. Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotne, Telcyta (TLK-286, Telik Inc.), Velcade (bortemazib, Millenium), tretinoin, and combinations thereof.

Platinum-coordinated compounds include but are not limited to, cisplatin, carboplatin, nedaplatin, oxaliplatin, and combinations thereof.

Camptothecin derivatives include but are not limited to camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, topotecan and combinations thereof.

Other antitumor agents include mitoxantrone, l-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, tretinoin and combinations thereof.

Anti-tumor agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4 may also be utilized, such as MDX-010 (Medarex) and CTLA4 compounds disclosed in U.S. Patent 6,682,736; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors. Additionally, specific CTLA4 antibodies that can be used in combination with compounds of the present invention include those disclosed in U.S. Patents 6,682,736 and 6,682,736 both of which are herein incorporated by reference in their entirety.

Specific IGF1R antibodies that can be used in the combination methods of the present invention include those disclosed in WO 2002/053596, which is herein incorporated by reference in its entirety.

Specific CD40 antibodies that can be used in the present invention include those disclosed in WO 2003/040170 which is herein incorporated by reference in its entirety.

Gene therapy agents may also be employed as anti-tumor agents such as TNFerade (GeneVec), which express TNFalpha in response to radiotherapy.

In one embodiment of the present invention statins may be used in combination with a compound of the present invention and pharmaceutical compositions thereof. Statins (HMG-CoA reducatase inhibitors) may be selected from the group consisting of Atorvastatin (Lipitor™, Pfizer Inc.), Provastatin (Pravachol™, Bristol-Myers Squibb), Lovastatin (Mevacor™, Merck Inc.), Simvastatin (Zocor™, Merck Inc.), Fluvastatin (Lescol™, Novartis), Cerivastatin (Baycol™, Bayer), Rosuvastatin (Crestor™, AstraZeneca), Lovostatin and Niacin (Advicor™, Kos Pharmaceuticals), derivatives and combinations thereof.

In a preferred embodiment the statin is selected from the group consisting of Atovorstatin and Lovastatin, derivatives and combinations thereof. Other agents useful as anti-tumor agents include Caduet.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

Examples

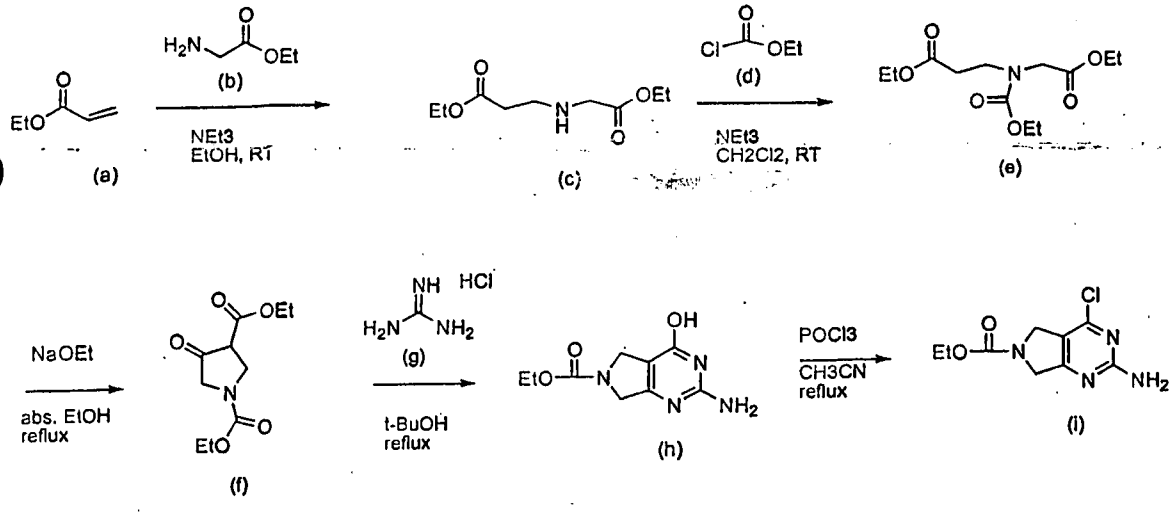
In the following examples molecules with a single chiral center, unless otherwise noted or indicated by the structural formula or chemical name, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted or indicated by the structural formula or chemical name, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

$^1$H-NMR spectra were recorded on a Bruker instrument operating either at 300 MHz, or 400 MHz and $^{13}$C-NMR spectra were recorded operating at 75 MHz.

The following abbreviations may be used herein: $Et_2O$ (diethyl ether); DMF (*N,N*-dimethylformamide); THF (tetrahydrofuran); DCM (dichloro-methane); DMA (dimethyl acetal); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); LiHMDS or LHMDS (lithium hexamethyldisilazide); TBME (*tert*-butyl methyl ether); LDA (lithium diisopropylamide); DMSO (dimethylsulfoxide); MeOH (methanol); EtOH (ethanol); BuOH (butanol); EtOAc (ethyl acetate); THF (tetrahydrofuran); Ac (acetyl); Me (methyl); Et (ethyl); Ph (phenyl); TMSI (trimethylsilyliodide); DSC (N,N'-disuccinimidyl carbonate); CDI (1,1'-carbonyldiimidazole); Boc (*tert*-butoxycarbonyl); nBuLi (n-butyl lithium); EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride); HOBt (N-hydroxybenzitriazole hydrate); DME (1,2-dimethoxyethane); $Pd(dba)_2$ (bis(dibenzylideneacetone)palladium(0)); and RT or rt (room temperature).

**Preparation of Compound (i): ethyl 2-amino-4-chloro-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate.**

Intermediate (**f**) was prepared in three steps using known procedures (see, e.g. Viscontini and Buhler *Helvetica Chimica Acta*, 50(5): 1289-93; (1967)) and then converted to compound (**i**) in two additional steps.




**Step 1. ethyl *N*-(ethoxycarbonyl)-*β*-alaninate (c)**

Ethyl acrylate (**a**) (50 mL, 460 mmol, 1.1eq), glycine ethyl ester hydrochloride (**b**) (58.4 g, 418 mmol, 1eq), and triethylamine (58.3 mL, 418 mmol, 1eq) in absolute EtOH (960 mL) was stirred at ambient temperature for approximately 72h. After reaction was complete, volatile components were removed under vacuum and the crude intermediate (**c**) was carried on directly.

**Step 2. ethyl *N*-(ethoxycarbonyl)-*N*-(2-ethoxy-2-oxoethyl)-β-alaninate (e)**

Crude intermediate (**c**) ( 418 mmol) was dissolved in $CH_2Cl_2$ (275 mL) and triethylamine (58.3 mL, 418 mmol) was added followed by ethyl chloroformate (**d**) (39.8 mL, 418 mmol). The reaction was stirred at ambient temperature for about 24 h. After the reaction was complete, the volatile components were removed under vacuum. The crude product was then distilled under vacuum (about 5mmHg) and dissolved in EtOAc which was washed with aqueous saturated $KHSO_4$ x3, with brine x1 and dried over $Na_2SO_4$. Following filtration, the volatile components were removed under vacuum to afford intermediate (**e**) as a clear oil (74.8g, 272 mmol) in 65% yield over two steps.

**Step 3. diethyl 4-oxopyrrolidine-1,3-dicarboxylate (f)**

Intermediate (**e**) (18.0g, 65.2 mmol) was added to an ice bath cooled solution of NaOEt (32.6 mL) (21% by weight in EtOH) in absolute EtOH (41.7 mL) under a nitrogen atmosphere.The ice bath was removed and the mixture was heated at 80°C for about 12h until the condensation was complete as observed by TLC. The mixture was poured onto ice/water and extracted into EtOAc. The solvent was dried with $Na_2SO_4$, filtered, and evaporated to afford crude intermediate (**f**) as an off white solid (14.05g) which was carried on without purification.

**Step 4. ethyl 2-amino-4-hydroxy-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (h)**

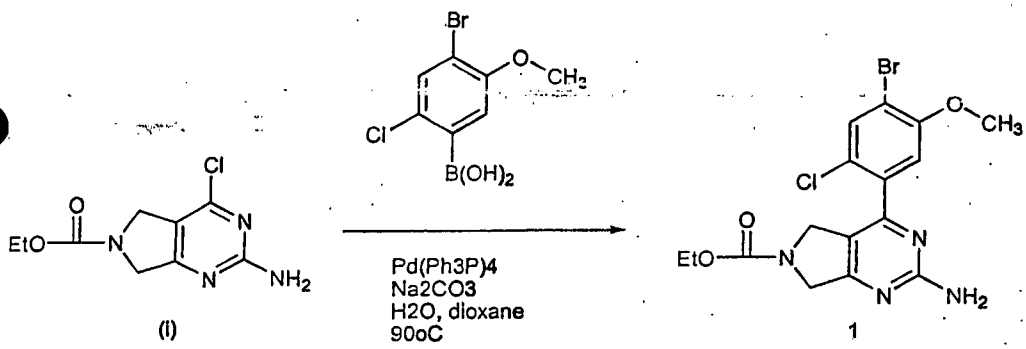
A suspension of intermediate (**f**) (14.05g) and guanidine carbonate (**g**) (16.6g, 91.9 mmol) was refluxed in t-butanol (147 mL) for about 6h. The mixture was allowed to cool to ambient temperature for about 2h. The volatile components were removed under vacuum and water was added. The pH was adjusted to about 6-7 using $KHSO_4$. The resulting slurry was filtered to collect the solids which were washed with water followed by EtOAc. The solids were dried under vacuum to afford intermediate (**h**) as cream solids (11.9g, 53.1 mmol) in 87% yield. 1H NMR (400 MHz, DMSO-D6) $\delta$ppm 11.01 (s, 1H), 6.97 (s, 0.5H, possible tautomer), 6.70 (s, 2H), 4.25 (s, 4H), 4.13-4.03 (m, 2H), 1.22 (t, 3H). LCMS $(M+H)^+$: 225.2.

**Step 5. ethyl 2-amino-4-chloro-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (i)**

Intermediate (**h**) (11g, 49 mmol) was azeotroped x2 with toluene on the rotovap to assure dryness. Anhydrous acetonitrile (250 mL) and $POCl_3$ (25 mL, 270 mmol) were added and the mixture was refluxed for about 2.5h. Additional $POCl_3$ (50 mL) was added and the mixture was refluxed for an additional 2h. The volatile components were concentrated under vacuum at 40 °C to give a red solution. A minimum amount of dry

acetonitrile was added until the solution was readily transferable whereupon it was poured onto ice in a large beaker. The flask was further rinsed with a small amount of acetonitrile which was added to the ice. Water (about 50 mL) was added to the ice mixture to help it with stirring. Concentrated $NH_4OH$ (25 mL) was added slowly with stirring until the ice slurry mixture was strongly basic, then 50% aqueous NaOH (25 mL) was also added to the still stirring slurry of ice. Additional ice was added. After about 5 minutes stirring as ice slurry, EtOAc was added. After stirring in the beaker for several more minutes, water was added to help melt the ice. The mixture was poured into a separatory funnel and the layers were allowed to partition. The aqueous layer was extracted with EtOAc x3. The combined EtOAc extracts were washed x2 with saturated aqueous $KHSO_4$, x2 with saturated aqueous $NaHCO_3$, x1 with brine, dried over $Na_2SO_4$, filtered and evaporated to afford a pale pink powder which was triturated with ethyl acetate to give compound (**i**) as pale pink solids (6.8g, 28 mmol) in 57% yield. HPLC/LCMS purity was greater than 90%. $^1H$ NMR (400 MHz, DMSO-D6) δ ppm 7.20 (s, 2H), 4.48 (s, 2H), 4.45 (s, 2H), 4.17-4.08 (m, 2H), 1.24 (t, 3H). LCMS $(M+H)^+$: 243.2, 245.2.

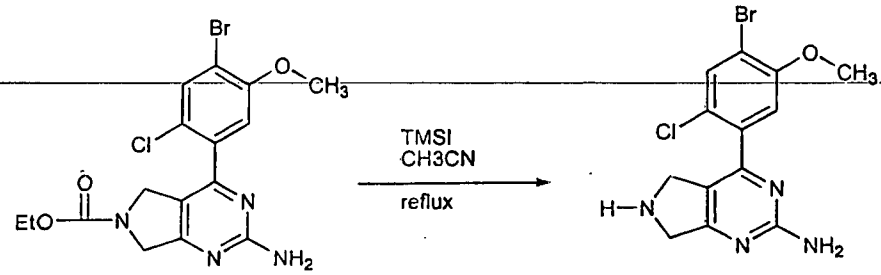
**Example 1: ethyl 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




To compound (**i**) (437 mg, 1.80 mmol), (4-bromo-2-chloro-5-methoxyphenyl)boronic acid (340 mg, 1.28 mmol), and sodium carbonate (382 mg, 3.60 mmol) in an Ar purged round bottom flask was added 1,4- dioxane (8.6 mL) and water (5.2 mL). Preceding the addition, Ar had been bubbled through both solvents to deoxygenate. Palladium tetrakis(triphenylphosphine) (220 mg, 0.19 mmol) was then added and Ar was bubbled through the mixture using a needle and septum for about 3 min. at which point the Ar needle was removed and the mixture was placed in a 90 °C oil bath and heated 2.5h. After cooling to ambient temperature, water was added and the resulting solid was

collected by filtration. The solid was washed with water x2, EtOAc x2 and dried at 35 °C for 72h to afford the title compound **1** (300 mg, 0.70 mmol) as a tan powder. $^1$H NMR (400 MHz, DMSO-D6) δ ppm 7.88 (s, 1H), 7.16 (s, 1H), 6.98 (br s, 2H), 4.55-4.47 (m, 2H), 4.39-4.32 (m, 2H), 4.17-4.03 (m, 2H), 3.87 (s, 3H), 1.27-1.15 (m, 3H). LCMS $(M+H)^+$: 429.0, 427.2.

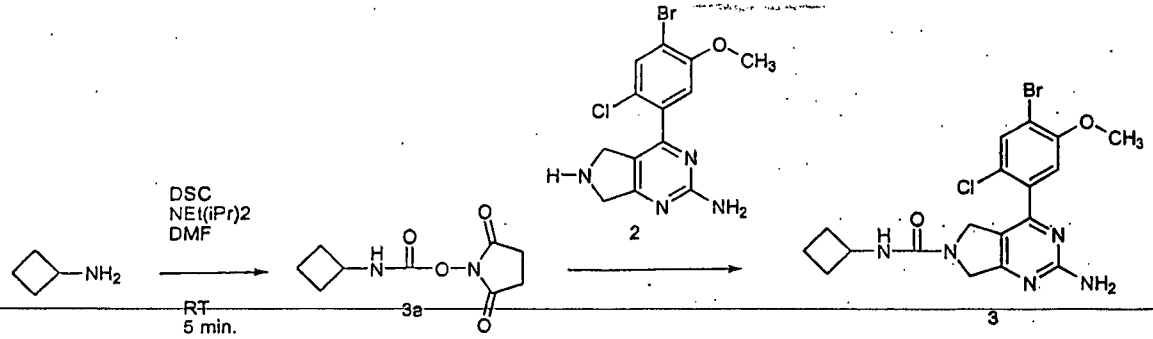
**Example 2: 4-(4-bromo-2-chloro-5-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine**




1 2

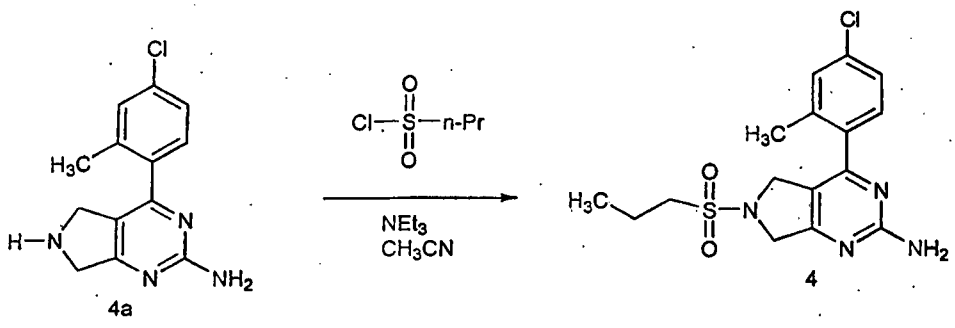
To compound **1** (300 mg, 0.70 mmol) was added anhydrous $CH_3CN$ (4 mL) followed by trimethylsilyliodide (0.5 mL, 4.0 mmol). The mixture was refluxed for about 1h and then cooled to ambient temperature whereupon a small amount of methanol was added to quench. The volatile components were then reduced under vacuum and a small amount of $CH_3CN$ was added followed by $Et_2O$ to precipitate yellow solids which gradually turned orange. The solids were washed with $Et_2O$ and then dried under vacuum at 30 °C overnight. Assuming a salt containing 2 HI, the title compound **2** (404 mg, 0.66 mmol) was obtained as orange solids in about 95% yield and was carried on without further purification. $^1$H NMR (400 MHz, DMSO-D6) δ ppm 3.81 - 3.90 (m, 3 H) 4.30 (s, 2 H) 4.39 (s, 2 H) 7.12 (s, 1 H) 7.16 (s, 2 H) 7.89 (s, 1 H) 9.40 (s, 1 H). LCMS $(M+H)^+$: 357.0, 355.0.

**Example 3: 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-cyclobutyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




At ambient temperature to stirring N,N'-disuccinimidyl carbonate (67 mg, 0.26 mmol) in DMF (1 mL) was added cyclobutylamine (0.022 mL, 0.26 mmol). Diisopropyl ethylamine (0.152 mL, 0.873 mmol) was then added and the mixture was allowed to stir for about 5 min. With continued stirring, compound **2** (177 mg, 0.289 mmol) in DMF (2 mL) was added. The mixture was allowed to stir overnight and then purified by preparative HPLC. Following lyophilization of the combined purified fractions, the title compound **3** was obtained (57 mg, 0.13 mmol) as a fluffy white solid in 48% yield. $^1$H NMR (400 MHz, DMSO-D6) δ ppm 7.80 (s, 1H), 7.09 (s, 1H), 6.83 (s, 2H), 6.46 (d, 1H), 4.35 (s, 2H), 4.20 (s, 2H), 4.06 (m, 1H), 3.79m (s, 3H), 2.07-1.97 (m, 2H), 1.92-1.79 (m, 2H), 1.53-1.41 (m, 2H). LCMS $(M+H)^+$: 454.2, 452.2.

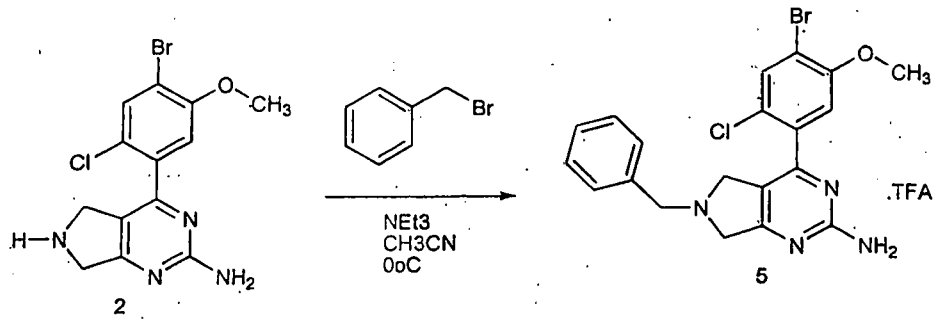
**Example 4: 4-(4-chloro-2-methylphenyl)-6-(propylsulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine**




The preparation of 4-(4-chloro-2-methylphenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine **4a** from compound (i) and 4-chloro-2methylphenylboronic acid was carried out in two steps in a manner analogous to that described for Examples 1 and 2. To a suspension of crude **4a** (100.7 mg, ~0.200 mmol) in acetonitrile (4.0 mL) at 0° C was added triethylamine (0.15 mL, 1.1 mmol) and 1-propanesulfonyl chloride (0.025 mL, 0.22 mmol). After 30 minutes at 0° C, the reaction mixture was concentrated under

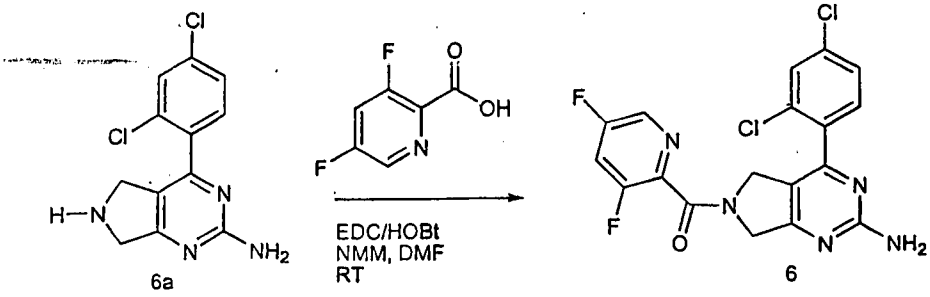
vacuum, redisolved in dichloromethane (10 mL), washed with water (10 mL), and concentrated. The residue was purified by preparative HPLC and following lyophilization of the combined purified fractions, the title compound was obtained (16 mg, 0.04 mmol) as a white solid in 22% yield. $^1$H NMR (300 MHz, DMSO-D6) δ ppm 7.43 (d, J = 1.9 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.33 (dd, J = 8.1 and 1.7 Hz, 1H), 6.86 (br s, 2H), 4.49 (s, 2H), 4.36 (s, 2H), 3.22-3.17 (m, 2H), 2.26 (s, 3H), 1.75-1.63 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). LCMS (M+H)$^+$: 367.2.

**Example 5: 6-benzyl-4-(4-bromo-2-chloro-5-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine trifluoroacetate**



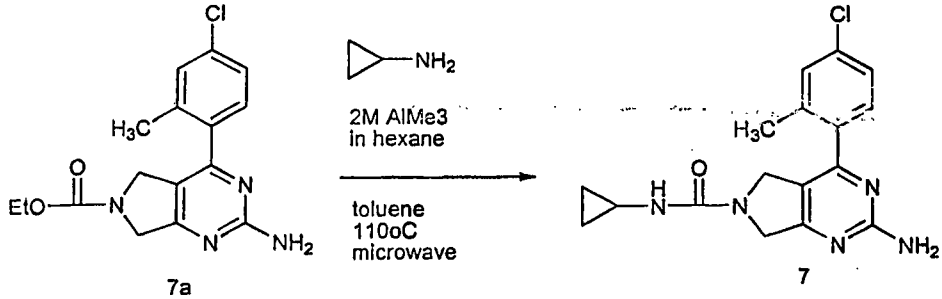

To compound **2** (91 mg, 0.15 mmol) in DMSO (1 mL), cooled in ice bath, was added N,N-diisopropylethylamine (0.078 mL, 0.45 mmol) followed by benzyl bromide (0.016 mL, 0.13 mmol). The frozen mixture was allowed to thaw and warmed to ambient temperature with stirring. After after about 20 min., the clear red solution was analyzed by LCMS. An approximately 3:2 mixture of the desired mono alkylated product and the quaternary salt was observed. The mixture was purified by preparative HPLC and following lyophilization of the combined purified fractions, the title compound **5** was obtained (29 mg, 0.05 mmol) as a white solid TFA salt in 32% yield. The bis-alkylated quaternary salt was also isolated as a by-product (15 mg). $^1$H NMR (400 MHz, DMSO-D6) δ ppm 7.90 (s, 1H), 7.58-7.39 (m, 5H), 7.29-7.14 (m, 2H), 7.08 (s, 1H), 4.68-4.25 (m, 6H), 3.89 (s, 3H). LCMS (M+H)$^+$: 447.2, 445.2.

**Example 6: 4-(2,4-dichlorophenyl)-6-[(35-difluoropyridin-2-yl)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine**




The preparation of 4-(2,4-dichlorophenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine **6a** from compound (i) and 2,4-dichlorophenylboronic acid was carried out in two steps in a manner analogous to that described for Examples 1 and 2. To a mixture of compound **6a** (54 mg, 0.1 mmol) and 3,5-difluoropyridine-2-carboxylic acid (24 mg, 0.15 mmol) in DMF (2.0 mL) was added 4-methylmorpholine (0.1 mL, 1.0 mmol), EDC (58 mg, 0.3 mmol) and HOBt (46 mg, 0.3 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was partitioned between EtOAc (200 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated under vacuum. The residue was purified by preparative HPLC and following lyophilization of the combined purified fractions, the title compound **6** was obtained (25 mg, 0.06 mmol) as a white solid (solvated with 0.4 equivalents of HOAc) in 56% yield. $^1H$ NMR (400 MHz, DMSO-d6) δ ppm 4.54 (d, J=32.08 Hz, 2 H) 4.70 (d, J=29.56 Hz, 2 H) 6.98 (d, J=16.93 Hz, 2 H) 7.38 - 7.62 (m, 2 H) 7.77 (dd, J=36.38, 2.02 Hz, 1 H) 8.02 - 8.21 (m, 1 H) 8.57 (dd, J=30.69, 2.15 Hz, 1 H). LCMS $(M+H)^+$: 424, 422.

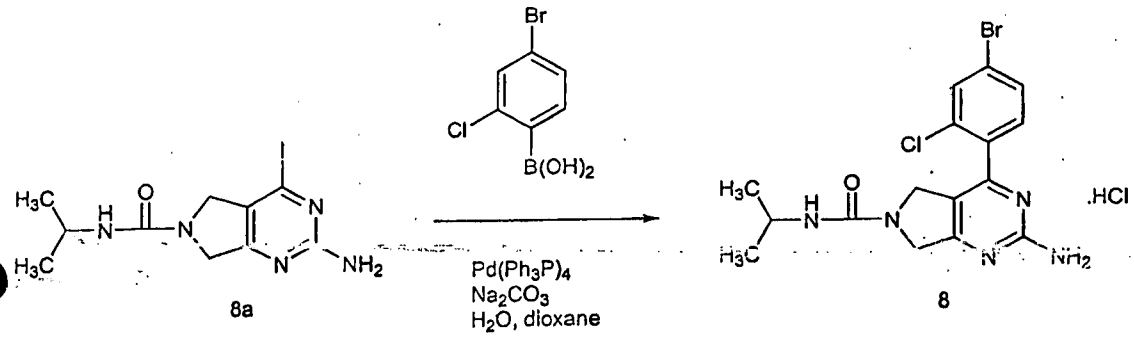
**Example 7: 2-amino-4-(4-chloro-2-methylphenyl)-N-cyclopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




The preparation of ethyl 2-amino-4-(4-chloro-2-methylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate **7a** from compound (i) and 4-chloro-2-

methylphenylboronic acid was carried out in a manner analogous to that described for Example 1. To a solution of cyclopropanamine (0.15 mL, 2.2 mmol) in toluene (2.5 mL) at 0° C was added trimethyl aluminum (2.0 M in hexanes, 0.60 mL, 1.2 mmol) dropwise and the reaction mixture was allowed to warm to room temperature. After 30 minutes, compound **7a** (75.0 mg, 0.225 mmol) was added in one portion, and the reaction was warmed to 110° C in the microwave for 30 minutes. The mixture was then cooled to room temperature, quenched with THF/water (2.5 mL/0.5 mL), and the precipitate was removed by filtration. The filtrate was concentrated under vacuum and purified by preparative HPLC. Following lyophilization of the combined purified fractions, the title compound **7** was obtained (55 mg, 0.16 mmol) as a white solid in 71% yield. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.3 and 1.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.77 (br s, 2H), 6.46 (d, J = 2.8 Hz, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 2.55-2.48 (m, 1H), 2.22 (s, 3H), 0.56-0.50 (m, 2H), 0.41-0.36 (m, 2H). LCMS $(M+H)^+$: 344.2.

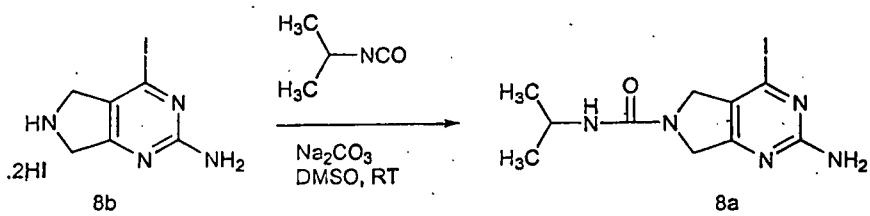
**Example 8: 2-amino-4-(4-bromo-2-chlorophenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide hydrochloride**




4-Bromo-2-chlorophenylboronic acid was prepared by treating 1-bromo-3-chloro-4-iodobenzene (1.339 g, 4.219 mmol) in THF (20.0 mL) at -78°C with nBuLi (2.30 mL, 4.60 mmol) dropwise. After 1h, trimethylborate (1.00 mL, 8.97 mmol) was added dropwise and the reaction was allowed to warm to rt. The reaction mixture was diluted with water (20 mL) and 3N NaOH (10 mL) and stirred for 30 minutes. The mixture was poured into $Et_2O$ (50 mL) and the layers were separated. The aqueous layer was then acidified with 1N aq. $KH_2PO_4$ (15 mL) and boronic acid extracted into EtOAc. Following isolation, the 4-bromo-2-chlorophenylboronic acid (26.3 mg, 0.112 mmol) was combined with compound **8a** (43.1 mg, 0.124 mmol), and aqueous sodium carbonate (2.0M, 0.125 mL, 3.4 mmol) in DME (2.0 mL). Nitrogen gas was bubbled into the mixture for ten minutes to deoxygenate. Tetrakis(triphenylphosphine)palladium(0) (12.1 mg, 0.0105

mmol) was added and the reaction was warmed to 85°C. After 4h the reaction mixture was cooled to ambient temperature, poured into EtOAc (50 mL), washed with water (50 mL), concentrated under vacuum and purified by preparative HPLC. The purified fractions were combined and 1N HCl (about 3 eq.) was added before lyophilization to prepare the hydrochloride. The title compound **8** was obtained (15 mg, 0.11 mmol) in 30% yield. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 7.92 (d, J = 1.6 Hz, 1H), 7.69 (dd, J = 8.0 and 1.9 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 4.41 (s, 2H), 4.24 (s, 2H), 3.82-3.74 (m, 1H), 1.05 (d, J = 6.6 Hz, 6H). LCMS $(M+H)^+$: 412.2, 410.2.

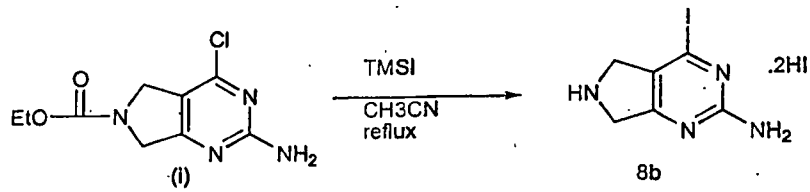
**Preparation of Compound 8a, 2-amino-4-iodo-*N*-isopropyl-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




8b 8a

To a solution of 4-iodo-6*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine **8b** (520 mg, 1.0 mmol) in DMSO at ambient temperature was added sodium carbonate (256 mg, 2.4 mmol) and isopropyl isocyanate (0.13 mL, 1.1 mmol). After 3h, the reaction was complete. The DMSO solution was filtered and the filtrate purified by preparative HPLC. Following lyophilization of the combined purified fractions, the title compound **8a** was obtained (204 mg, 0.59 mmol) in 59% yield. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 6.96 (br s, 2H), 6.08 (d, J = 7.7 Hz, 1H), 4.34 (s, 2H), 4.20 (s, 2H), 3.78-3.67 (m, 1H), 1.02 (d, J = 6.6 Hz, 6H). LCMS $(M+H)^+$: 348.2.

**Preparation of Compound 8b, 4-iodo-6*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine**

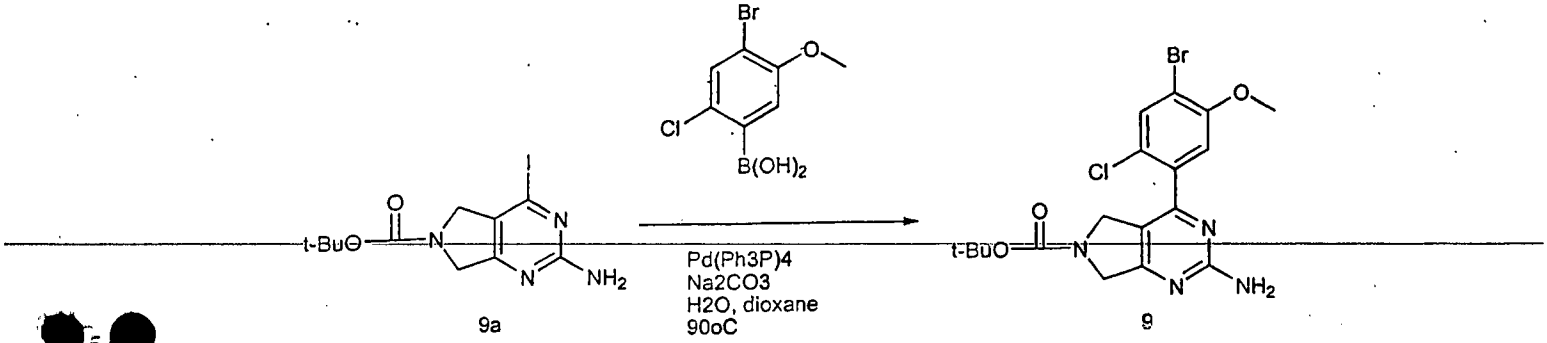



(i) 8b

To a suspension compound (i) (1.00 g, 4.12 mmol) in $CH_3CN$ (25.0 mL) was added iodotrimethylsilane TMSI (3.0 mL, 21.1 mmol). The mixture was refluxed 5 h and then cooled to ambient temperature. Methanol (5 mL) was added to quench the excess TMSI and the mixture was concentrated under vacuum to about 10 mL. Diethyl ether (40 mL) was added and the resulting precipitate was collected by filtration. The solids were then stirred in refluxing EtOAc (50 mL) for a few minutes at which point the mixture was cooled. The light tan solids (1.8g, 3.4 mmol) were collected by filtration to afford the title

compound **8b** in 83% yield (assuming · 2 HI salt). $^1$H NMR (300 MHz, DMSO-D6) δ ppm 9.47 (br s, 2H), 4.37 (s, 2H), 4.25 (s, 2H). LCMS $(M+H)^+$: 263.2.

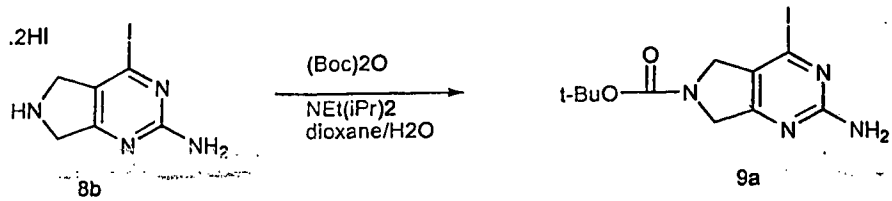
**Example 9: *tert*-butyl 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




9a 9

Impure compound **9a** (113 mg) in 1,4- dioxane (2 mL) and water (1.2 mL) was treated with (4-bromo-2-chloro-5-methoxyphenyl)boronic acid (385 mg, 0.32 mmol), sodium carbonate (89 mg, 0.84 mmol) and tetrakis(triphenylphosphino)palladium(0) (50 mg, 0.04 mmol) and heated under conditions similar to those described in Example 1. After cooling to ambient temperature, water and EtOAc was added. The water layer was extracted twice with EtOAc and the combined extracts were washed with brine, dried with $Na_2SO_4$, filtered, and volatile components removed under vacuum. The residue was purified by preparative HPLC. Following lyophylization of the combined purified fractions, the *tert*-butoxycarbonyl (Boc) protected title compound **9** was obtained (33 mg, 0.07 mmol) as a white solid in greater than 23% yield. $^1$H NMR (400 MHz, DMSO-D6) δ ppm 7.88 (s, 1H), 7.17 (s, 1H), 6.95 (s, 2H), 4.48-4.42 (m, 2H), 4.33-4.27 (m, 2H), 3.87 (s, 3H), 1.43 (d, 9H). LCMS $(M+H)^+$: 457.2, 455.2.

**Preparation of Compound 9a, *tert*-butyl 2-amino-4-iodo-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**

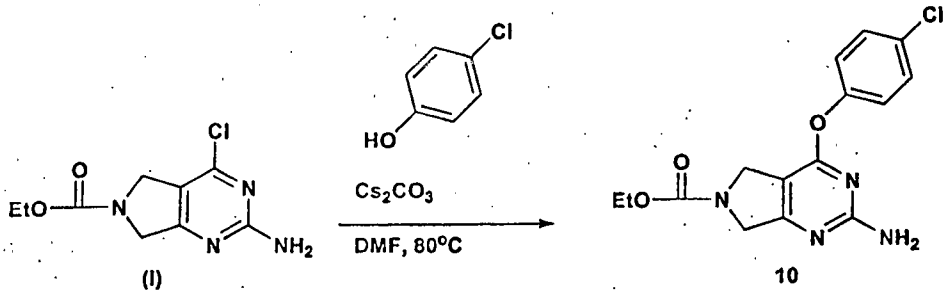



8b 9a

To a stirring mixture of impure compound **8b** (113 mg) in 1,4 dioxane (1 mL) and water (1 mL) was added di-*tert*-butyldicarbonate (0.16 mL, 0.70 mmol) and diisopropylethylamine (0.25 mL, 1.4 mmol). After stirring over night the volatile components were reduced under vacuum and EtOAC and aqueous saturated $KHSO_4$ were added. The resulting two phase mixture was extracted twice with EtOAC and the

combined extracts were washed with aqueous saturated $KHSO_4$ x1, with aqueous saturated $NaHCO_3$ x2, with brine x1, and dried over $Na_2SO_4$. Following filtration, the volatile components were removed under vacuum to afford the title compound **9a** as a tan solid (77 mg) which was combined with additional material **9a** (36 mg) from a previous reaction and carried on directy to the next step. $^1H$ NMR (400 MHz, DMSO-D6) δ ppm 1.44 (d, J=4.80 Hz, 9 H) 4.25 (d, J=13.14 Hz, 2 H) 4.42 (d, J=8.34 Hz, 2 H) 7.06 (s, 2 H). LCMS $(M+H)^+$: 348.2.

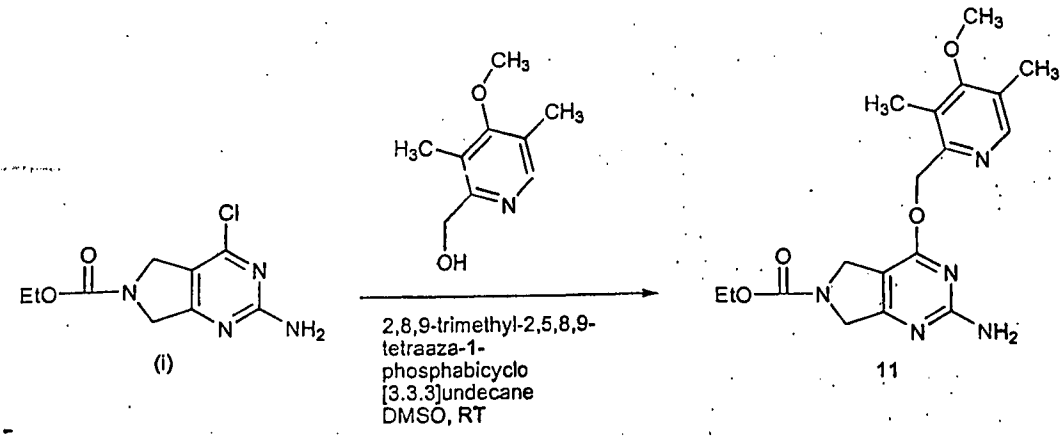
**Example 10: ethyl 2-amino-4-(4-chlorophenoxy)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




(I) 10

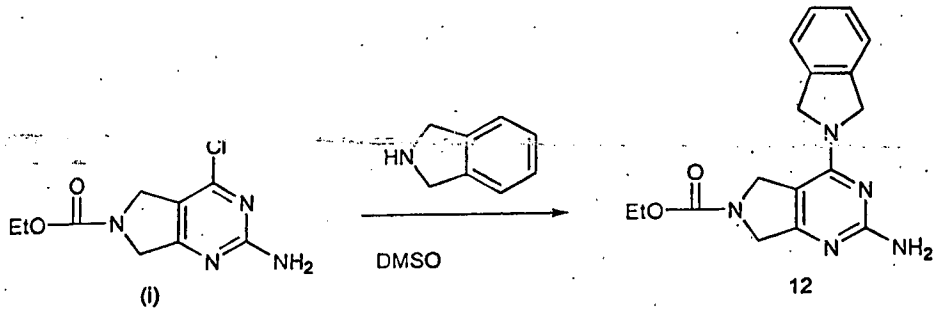
To compound (**i**) (99 mg, 0.41 mmol) and p-chlorophenol (52 mg, 0.41 mmol) in DMF (2 mL) was added cesium carbonate (266 mg, 0.82 mmol). The mixture was heated at 80 °C for 1.5 h and allowed to cool to ambient temperature. The mixture was filtered through a 0.45μM teflon syringe filter and the filtrate submitted for preparative RPHPLC. Following lyophilization of the combined purified fractions, the title compound was obtained (48 mg, 0.14 mmol) as a white solid in 34% yield. $^1H$ NMR (400 MHz, DMSO-D6) δ ppm 7.49 (d, 2H), 7.26 (d, 2H), 6.75 (s, 2H), 4.50 (s, 1H), 4.46-4.39 (m, 3H), 4.17-4.08 (m, 2H), 1.24 (t, 3H). LCMS $(M+H)^+$: 335.2.

**Example 11: ethyl 2-amino-4-[(4-methoxy-3,5-dimethylpyridin-2-yl)methoxy]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




Compound (i) (54 mg, 0.22 mmol), 3,5-dimethyl-4-methoxy-2-pyridinemethanol (45 mg, 0.268 mmol) and 2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane (58 mg, 0.27 mmol) were stirred in DMSO (1.5 mL) at ambient temperature for 2 h. The mixture was then purified by preparative HPLC, and following lyophilization of the combined purified fractions, the title compound **11** was obtained (37 mg, 0.10 mmol) as a white solid in 44% yield. $^1$H NMR (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 8.20 (s, 1H), 6.72 (br s, 2H), 5.39 (s, 1H), 5.38 (s, 1H), 4.36-4.29 (m, 4H), 4.11-4.03 (m, 2H), 3.75 (s, 3H), 2.22 (s, 6H), 1.23-1.17 (m, 3H). LCMS $(M+H)^+$: 374.2.

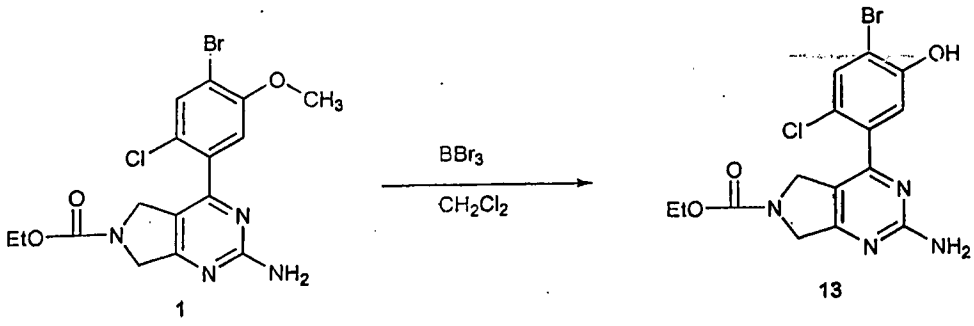
**Example 12: ethyl 2-amino-4-(1,3-dihydro-2H-isoindol-2-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




Compound (i) (74.8 mg, 0.308 mmol) and isoindoline (105 mg, 0.881 mmol) in DMSO (1 mL) were stirred and heated to 80°C for 20 minutes. After cooling, the mixture was poured into water and extracted into $CH_2Cl_2$. Following evaporation of the volatile components, the residue was dissolved in DMSO and submitted for preparative RPHPLC. Following lyophilization of the combined purified fractions, the title compound **12** was obtained (68 mg, 0.19 mmol) in 62% yield.

$^1$H NMR (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.42-7.39 (m, 2H), 7.32-7.29 (m, 2H), 6.13 (br s, 2H), 4.96-4.87 (br m, 4H), 4.28-4.23 (m, 2H), 4.16-4.10 (m, 2H), 3.31 (br s, partially obscured by H2O peak, 2H), 1.28-1.21 (m, 3H). LCMS $(M+H)^+$: 326.2.

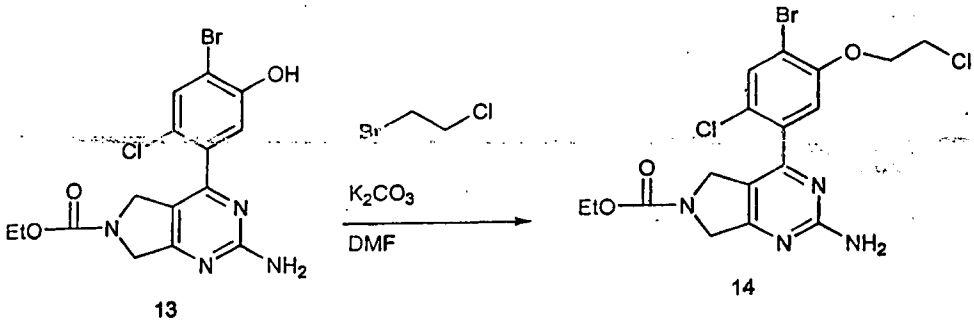
**Example 13: ethyl 2-amino-4-(4-bromo-2-chloro-5-hydroxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**




1 13

To a stirring suspension of compound **1** (428 mg, 1.0 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added $BBr_3$ (0.5 mL, 5.0 mmol). The mixture was stirred overnight and allowed to warm to ambient temperature whereupon ice and water (10 mL) were added and the resulting precipitate was collected by filtration. After washing with water and $CH_2Cl_2$, the solid was dried under vacuum to give the title compound **13** (375 mg, 0.91 mmol) as a yellow solid in 91% yield. $^1$H NMR (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 1.09 - 1.28 (m, 3 H) 3.99 - 4.16 (m, 2 H) 4.33 (d, J=8.34 Hz, 2 H) 4.47 (d, J=11.12 Hz, 2 H) 6.93 (d, J=1.77 Hz, 1 H) 7.74 (s, 1 H) 10.89 (s, 1 H). LCMS $(M+H)^+$: 417.0, 415.0.

**Example 14: ethyl 2-amino-4-[4-bromo-2-chloro-5-(2-chloroethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate**

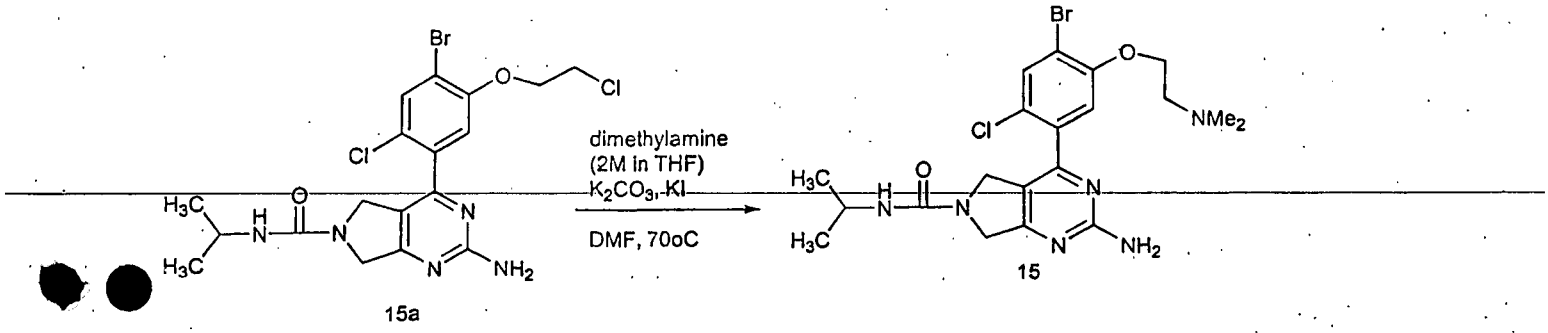



13 14

To a stirring mixture of compound **13** (360 mg, 0.87 mmol) and potassium carbonate (361 mg, 2.61 mmol) in anhydrous DMF (4 mL) was added 1-bromo-3-chloropropane (0.15 mL, 1.74 mmol). The mixture was heated at 50°C for 12 hours whereupon the mixture was cooled and filtered to remove suspended solids, and the solids were washed well with EtOAc. The washes and filtrate were combined and additional EtOAc (200 mL) was added. The combined organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and then dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The yellow residue was treated with $CH_2Cl_2$ (30 mL), and the resulting solids were collected by filtration. After washing with $CH_2Cl_2$ and hexane, the solids were dried under vacuum to give the title compound **14** (240 mg, 0.5 mmol)

as a white solid in 58% yield. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 1.11 - 1.27 (m, 3 H) 3.90 - 4.00 (m, 2 H) 4.08 (dd, J=14.53, 7.20 Hz, 2 H) 4.29 - 4.40 (m, 4 H) 4.48 (d, J=10.61 Hz, 2 H) 6.95 (s, 2 H) 7.20 (s, 1 H) 7.88 (s, 1 H). LCMS $(M+H)^+$: 477.0, 475.0.

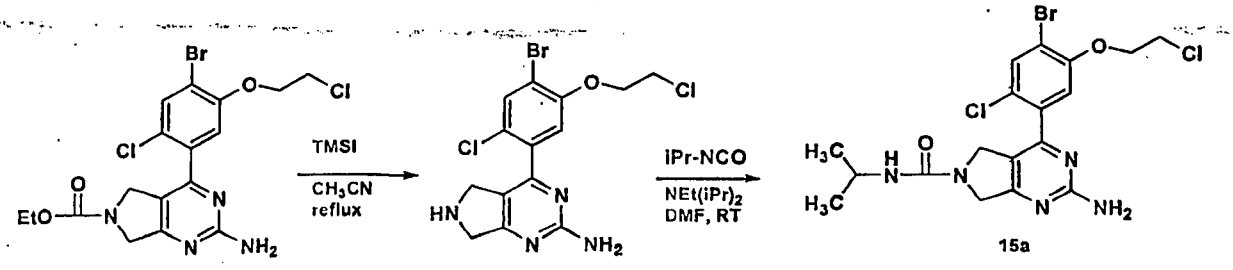
**Example 15: 2-amino-4-{4-bromo-2-chloro-5-[2-(dimethylamino)ethoxy]phenyl}-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6 carboxamide**




15a 15

To a mixture of compound 15a (90 mg, 0.18 mmol), $K_2CO_3$ (76 mg, 0.55 mmol), and KI (61 mg, 0.37 mmol) in DMF (2.0 mL) was added a 2M solution of dimethylamine in THF (0.3 mL, 0.55 mmol). After stirring at 70°C for 12 h, the mixture was cooled and filtered to remove suspended solids. The solids were washed with EtOAc. The washes and filtrate were combined and additional EtOAc (200 mL) was added. The combined organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and then dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was purified by preparative HPLC and following lyophilization of the combined purified fractions, the title compound 15 was obtained (16 mg, 0.03 mmol) as a yellow solid in 17% yield. $^1$H NMR (400 MHz, DMSO-d6) $\delta$ ppm 1.06 (t, J=7.07 Hz, 6 H) 2.22 (s, 6 H) 2.65 (t, J=5.68 Hz, 2 H) 3.78 (dd, J=13.89, 6.82 Hz, 1 H) 4.14 (t, J=5.56 Hz, 2 H) 4.25 (s, 2 H) 4.42 (s, 2 H) 6.08 (d, J=7.83 Hz, 1 H) 6.88 (s, 2 H) 7.19 (s, 1 H) 7.85 (s, 1 H). LCMS $(M+H)^+$: 501.2, 499.2.

**Preparation of compound 15a, 2-amino-4-[4-bromo-2-chloro-5-(2-chloroethoxy)phenyl]-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**

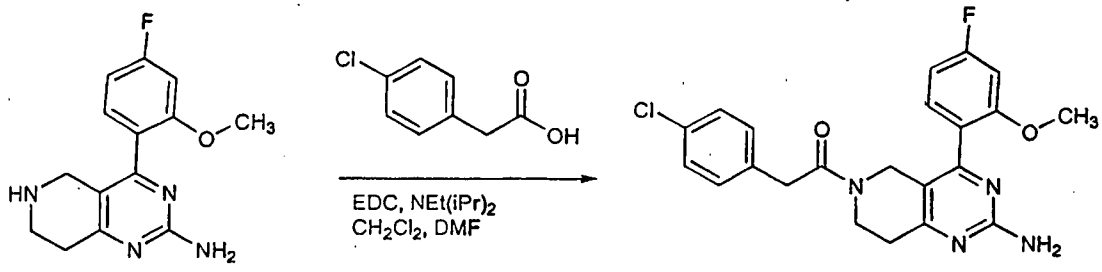



14 15b 15a

Compound 14 was deprotected in a manner similar to that described for Example 2. Extractive work up from EtOAc and saturated aqueous $NaHCO_3$ gave compound **15b**,

4-[4-bromo-2-chloro-5-(2-chloroethoxy)phenyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine, (191 mg, 0.473 mmol) which was dissolved in DMF (2.0 mL) and treated sequentially with diisopropylethylamine (0.4 mL, 2.36 mmol) and isopropylisocyanate (40 mg, 0.473 mmol) at ambient temperature. After 3 h, methanol was added and the mixture was concentrated under vacuum. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layers were dried over $Na_2SO_4$, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel eluting with 10% methanol in $CH_2Cl_2$. The purest fractions were combined and the volatile components removed under vacuum to give the title compound **15a** (180 mg, 0.37 mmol) as a brown foam in 78% yield. $^1H$ NMR (400 MHz, DMF-d7) $\delta$ ppm 1.04 - 1.11 (m, 6 H) 3.81 (s, 1 H) 3.92 - 4.04 (m, 2 H) 4.28 (s, 2 H) 4.39 (d, J=10.11 Hz, 2 H) 4.44 (s, 2 H) 6.09 (d, J=8.08 Hz, 1 H) 6.91 (s, 2 H) 7.24 (s, 1 H) 7.91 (s, 1 H). LCMS $(M+H)^+$: 488.0, 490.0.

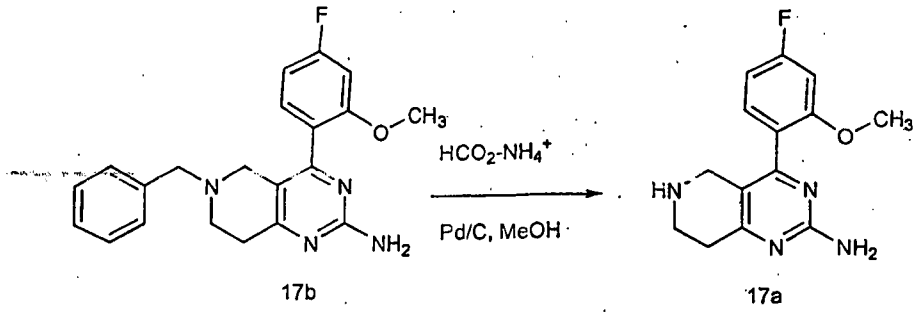
**Example 17: 6-[(4-chlorophenyl)acetyl]-4-(4-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine**




17a 17

Compound **17a** (32 mg, 0.19 mmol) was coupled to (4-chlorophenyl) acetic acid (32 mg, 0.19 mmol), using EDC (40 mg, 0.21 mmol) and $NEt(iPr)_2$ (0.051 mL, 0.29 mmol) in DMF (0.5 mL) and $CH_2Cl_2$ (0.5 mL) in a manner similar to that described for Example 6. Purification on silica gel (eluting with 10% MeOH in $CH_2Cl_2$) gave, after isolation, the title compound **17** (48 mg, 0.11 mmol) in 59% yield. 1H NMR (400 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.41-6.82 (m, 7H), 6.58-6.47 (m, 2H), 4.17 (s, 2H), 3.85-3.55 (m, 7H), 2.71 (br s, 2H). LCMS $(M+H)^+$: 429.2, 427.2.

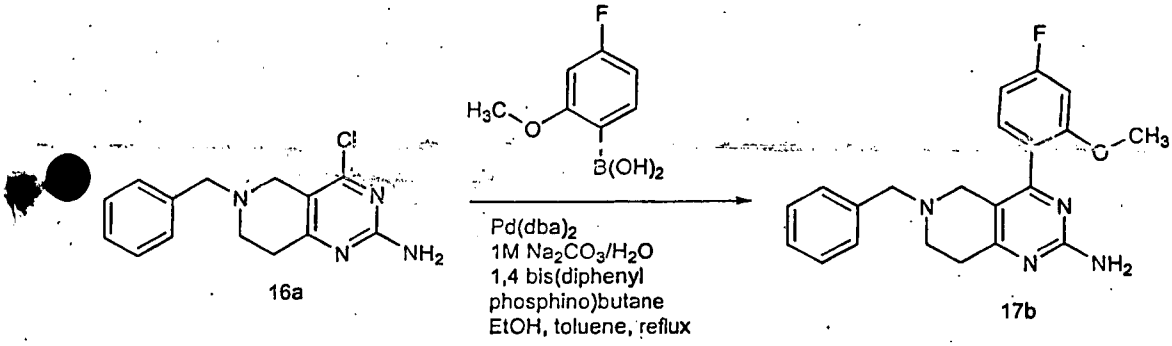
**Preparation of compound 17a, 4-(4-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine**




17b 17a

Compound **17b** (971 mg, 2.66 mmol) in methanol was treated with ammonium formate (1.9 g, 29.4 mmol) and 10% palladium on carbon (490 mg). After stirring for several days, the palladium on carbon was removed through two successive filtrations- first through filter paper and then through a 0.45 micron teflon syringe filter.The filtrate was reduced under vacuum and a small amount of water was added. The resulting precipitate was collected by filtration to afford the title compound **17a** (438 mg, 1.6 mmol) in 60% yield after drying under vacuum. $^1$H NMR (400 MHz, DMSO-D6) (conformers) δ ppm 8.26 (s, 1H), 7.19 (m, 1H), 7.03 (m, 1H), 6.87 (m, 1H), 6.41 (s, 2H), 3.78 (s, 3H), 3.53-3.39 (m, 2H, partially obscured), 3,12-3.02 (m, 2H), 2.71-2.62 (m, 2H). LCMS $(M+H)^+$: 275.0.

**Preparation of compound 17b, 6-benzyl-4-(4-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine**

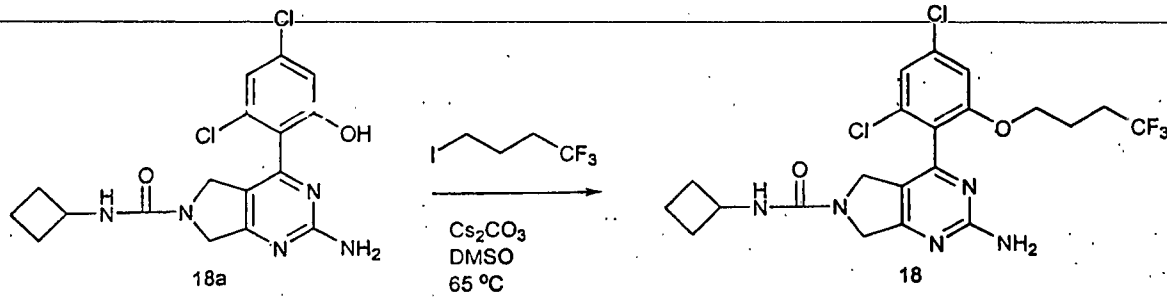



16a 17b

Argon was bubbled through a mixture of compound **16a** (286 mg, 1.04 mmol), 4-fluoro-2-methoxyphenyl)boronic acid (194 mg, 1.14 mmol), 1M aqueous $Na_2CO_3$ (1 mL) in toluene (2 mL) and ethanol (0.5 mL). $Pd(dba)_2$ (30 mg, 0.052 mmol) and 1,4 bis (diphenylphosphino)butane (44 mg, 0.104 mmol) were added and additional argon was bubbled through the mixture which was then refluxed for approximately 19h. After cooling to ambient temperature, water was added and the crude product was extracted into EtOAc, washed with brine, dried over $Na_2SO_4$ and filtered. The volatile components were removed under vacuum and the residue was purified on silica eluting with EtOAc followed by acetone. The purest fractions were combined and reduced to dryness

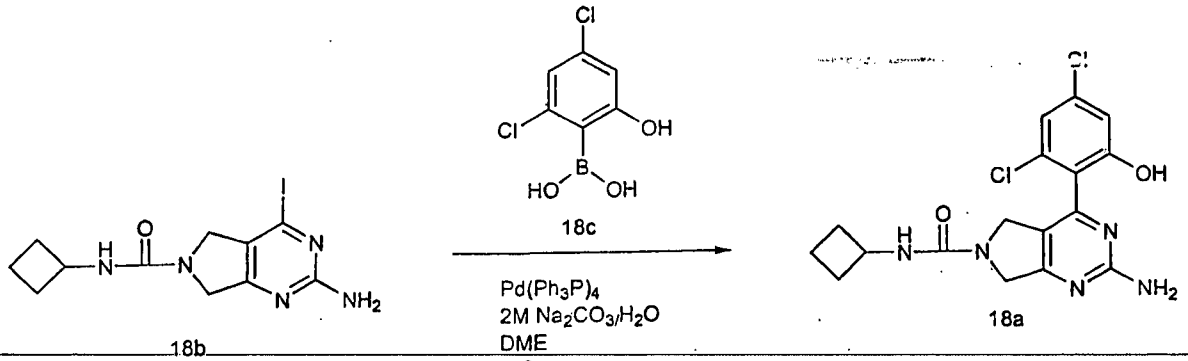
whereupon the solids were dissolved in THF and filtered through a 0.45 micron teflon filter. Again the volatile components were removed under vacuum to afford the title compound **17b** (228 mg, 0.62 mmol) in 60% yield. $^1$H NMR (400 MHz, DMSO-D6) (conformers) δ ppm 7.32-7.20 (m, 5H), 7.15 (m, 1H), 6.94 (d, 1H), 6.80 (m, 1H), 6.37 (s, 2H), 3.63-3.42 (m, 5H, (contains 3.63 (s, 3H)), 3.31-2.92 (m, 2H), 2.74-2.59 (m, 4H (contains 2.66 (s, 2H)). LCMS $(M+H)^+$: 365.0.

**Example 18: 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(4,4,4-trifluorobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




A solution of compound 18a 1 (91 mg, 0.231 mmol) in DMSO (1.5 mL) was treated with $Cs_2CO_3$ (174 mg, 0.533 mmol) and 1-iodo-4,4,4-trifluorobutane (89.2 mg, 0.375 mmol) and warmed to 65°C. After 30 minutes, the reaction mixture was filtered and the DMSO solution was subjected to preparative HPLC. The purified fractions were combined and lyophilized. The resulting white powder was then dissolved in a solution of $CH_3CN$, (2 mL), 1N HCl (0.45 mL) and water (5 mL). Following lyophilization, compound 18 (46 mg, 0.085 mmol) was obtained as a white powder in 37% yield. $^1$H NMR (300 MHz, DMSO-D6) δ ppm 7.32 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 4.40-4.30 (m, 2H), 4.11-4.02 (m, 5H), 2.12-1.99 (m, 4H), 1.91-1.81 (m, 2H), 1.74-1.67 (m, 2H), 1.52-1.43 (m,2H) . LCMS $(M+H)^+$: 504.0, 506.0. Anal. Calcd for $C_{21}H_{22}N_5Cl_2O_2F_3 \cdot 0.7$ HCl · 0.6 H2O: C, 46.65; H, 4.46; N12.95; Cl, 17.70. Found: C, 46.75; H, 4.26; N, 12.69; Cl, 17.43.

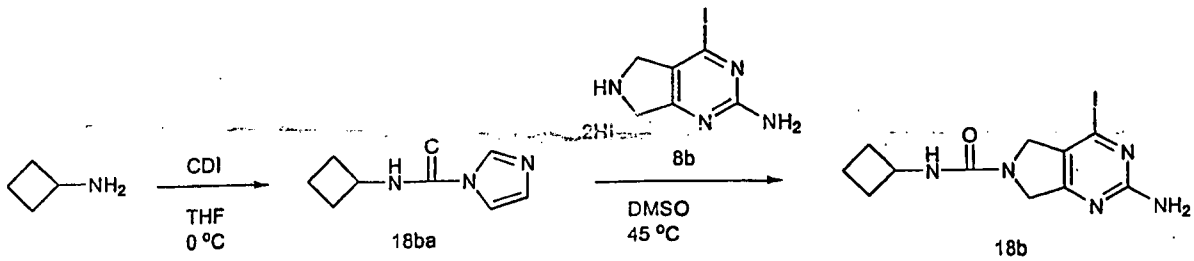
**Preparation of Compound 18a, 2-amino-*N*-cyclobutyl-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Nitroge

n was bubbled through a solution of compound 18b (1350 mg, 3.75 mmol), compound 18c ( 775 mg, 3.75 mmol) and 2.0M aqueous sodium carbonate (0.60 mL, 1.20 mmol) in 1,4-dioxane (7.0 mL) for 15 minutes. To this was added tetrakis(triphenylphosphino)palladium(0) (431 mg, 0.373 mmol) and the mixture was warmed to 85°C. After 5h, the mixture was cooled to ambient temperature and EtOAc (20 mL) and water (20 mL) were added. The aqueous layer was extracted with EtOAc and the EtOAc layer was discarded. The pH of the aqueous solution was adjusted to about 5 with 1N $KH_2PO_3$ and then extracted with a mixture of EtOAc and iPrOH. The volatile components were remove under vacuum to give compound 18a (869 mg, 2.2 mmol) in 59% yield which was carried on without further purification. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 10.64 (s, 1H), 7.16 (d, J = 1.7 Hz, 1H), 6.97 (d, J = 1.7 Hz, 1H), 6.79 (br, 2H), 6.52(d, J = 7.5 Hz, 1H), 4.40 (br s, 2H), 4.15 (br s, 2H), 4.08-3.99 (m, 1H), 2.15-2.03 (m, 2H), 1.97-1.86 (m, 2H), 1.60-1.47 (m, 2H). LCMS $(M+H)^+$: 394.2 and 396.2

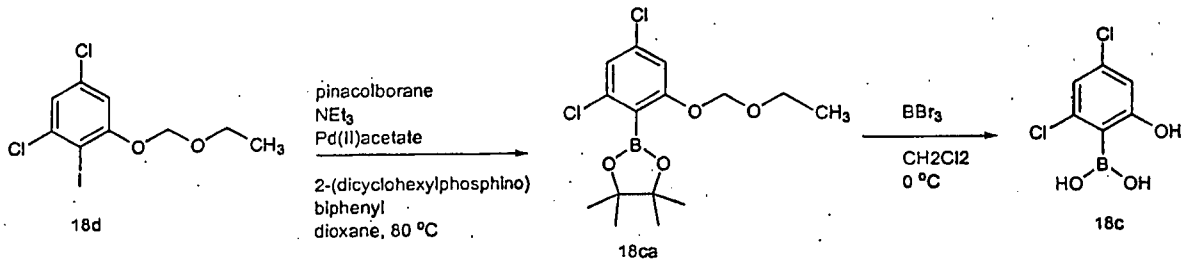
**Preparation of Compound 18b: 2-amino-*N*-cyclobutyl-4-iodo-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




To a solution of 1,1-carbonyldiimidazole (3.54 g, 21.8 mmol) in THF (100 mL) at 0 °C was added a solution of cyclobutylamine (1.00 g, 14.1 mmol) in THF (9.0 mL) dropwise over 10 minutes. The mixture was allowed to warm to ambient temperature and stirred

for 2h. The volatile components were removed under vacuum and the resulting oil was purified on silica gel, eluting with a gradient of 0-10% MeOH in $CH_2Cl_2$. The purest fractions were combined and the volatile components removed under vacuum to give compound 18ba, *N*-cyclobutyl-1*H*-imidazole-1-carboxamide, (2.2 g, 13.4 mmol) as clear oil. Compound 18ba (1.39 g, 8.41 mmol) and compound 8b (3.79 g, 7.32 mmol) were then dissolved in DMSO (20 mL) and $Cs_2CO_3$ (4.92 g, 15.1 mmol) was added. The mixture was stirred for 1h at ambient temperature and then heated at 45 °C for 4h whereupon the mixture was cooled to ambient temperature and water (150 mL) was added. The aqueous suspension was extracted with a mixture of EtOAc and EtOH (200 mL) and the volatile components were removed under vacuum to give the title compound 18b (2 g, 5.6 mmol) in 66% yield which was carried on without further purification. $^1$H NMR (300 MHz, DMSO-D6) $\delta$ ppm 7.02 (br s, 2H), 6.60 (d, J = 7.7 Hz, 1H), 4.41 (br s, 2H), 4.26 (br s, 2H), 4.19-4.07 (m, 1H), 2.18-2.07 (m, 2H), 2.04-1.91 (m, 2H), 1.64-1.50 (m, 2H). LCMS $(M+H)^+$ 360.2.

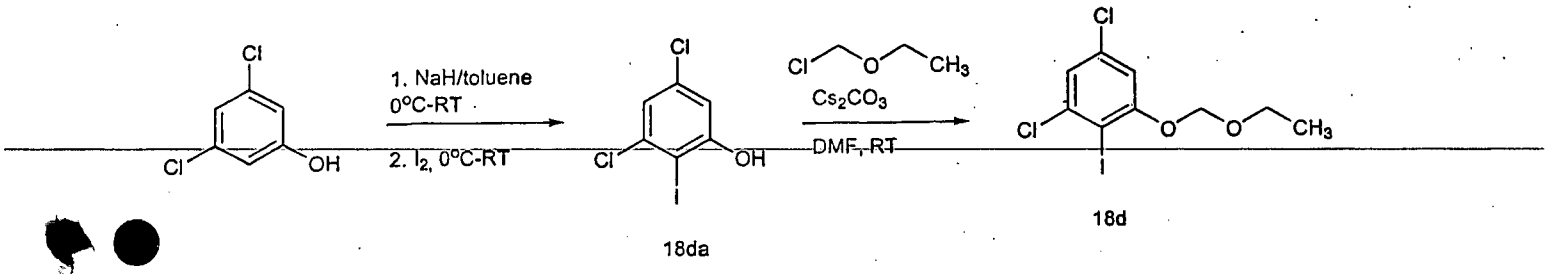
**Preparation of Compound 18c, 2,4-dichloro-6-hydroxyphenylboronic acid**




A solution of compound 18d (4.33 g, 12.5 mmol), pinacolborane (3.80 mL, 26.2 mmol), and triethylamine (5.2 mL, 37 mmol) in 1,4-dioxane (80 mL) was purged with $N_2$ for 15 minutes. Palladium (II) acetate (142 mg, 0.632 mmol) and 2-(dicyclohexylphosphino)biphenyl (439 mg, 1.25 mmol) were added and the mixture was warmed to 80 °C for 1.5h. After cooling to room temperature, the mixture was poured into EtOAc (200 mL), and washed with saturated aqueous NH4Cl (100 mL) and water (200 mL). Following concentation under vacuum, the residue was purified on silica gel, eluting with a gradient of 10-70% $CH_2Cl_2$ in hexane. The purest fractions were combined and the volatile components removed under vacuum to give the compound 18ca, 2,4-dichloro-6-(ethoxymethoxy)phenylboronic acid pinacol ester, (1.55 g, 4.47 mmol) which was then dissolved in dichloromethane (50.0 mL) and cooled to 0 °C. A 1.0 M solution of boron tribromide in $CH_2Cl_2$ (10.0 mL, 10.0 mmol) was added slowly over 5 minutes. After 15 minutes, the mixture was poured into ice water. The biphasic mixture was stirred vigorously and the pH of the aqueous phase was adjusted to about 10 with 3N

NaOH. The layers were separated and the dichloromethane phase discarded. The pH of the aqueous phase was then adjusted to about 3 with 1N HCl and extracted with a mixture of EtOAc and iPrOH. The organic layer was then concentrated to give the title compound 18c (778 mg, 3.8 mmol) as a tan powder that was carried on without further purification.

**Preparation of Compound 18d, 1,5-dichloro-3-(ethoxymethoxy)-2-iodobenzene**

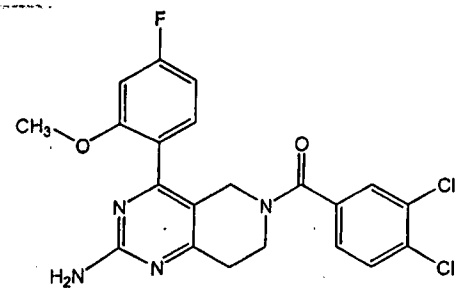
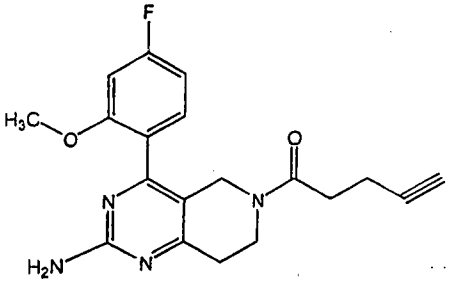
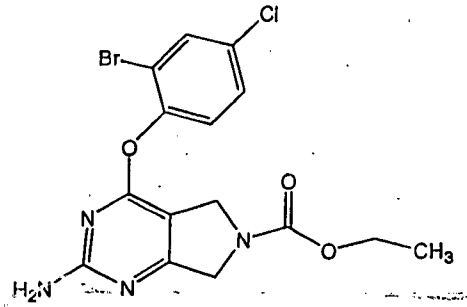
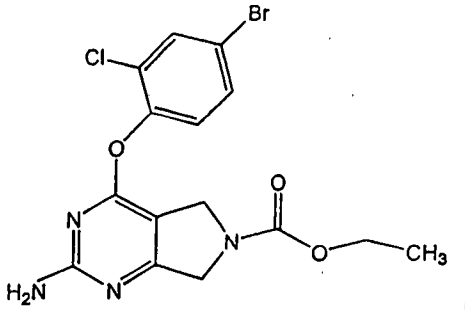


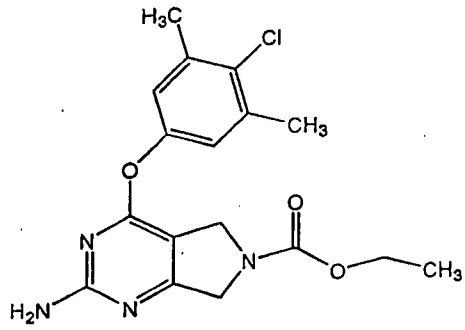
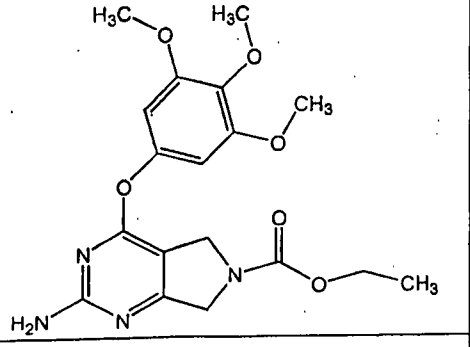
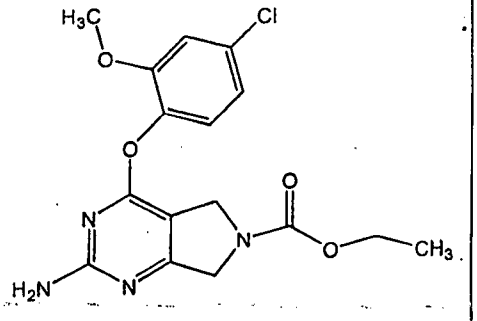
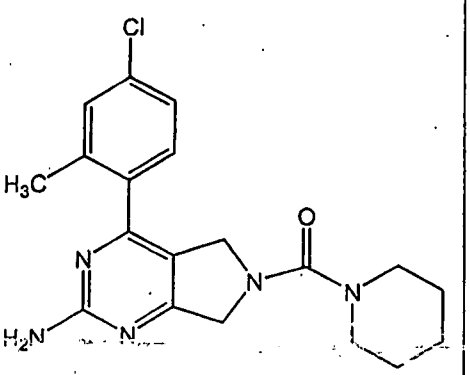

18da 18d

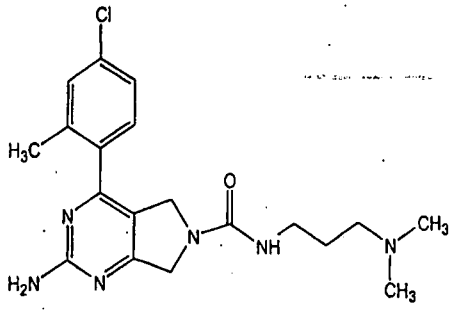
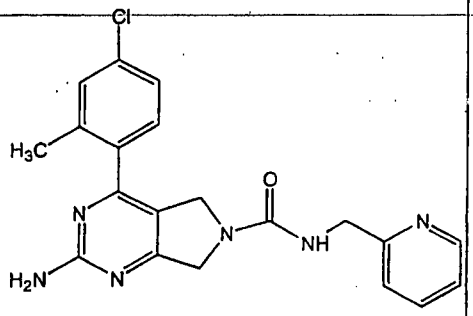
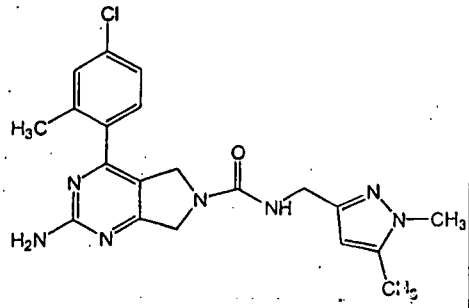
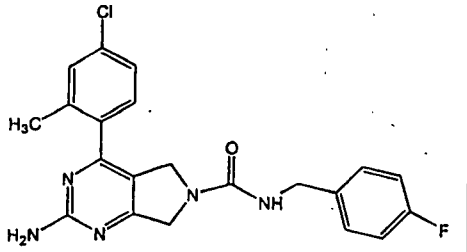
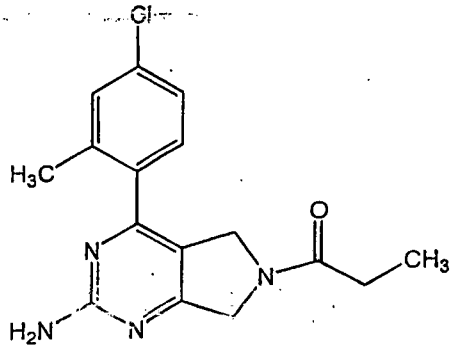
To a solution of 3,5-dichlorophenol (5.98 g, 36.7 mmol) in toluene (200 mL) at 0°C was added NaH (60% in oil, 4.50 g, 117 mmol) in portions. The reaction mixture was then allowed to warm to ambient temperature and stir for 20 minutes. The suspension was then cooled back to 0°C, and iodine (7.91 g, 31.2 mmol) was added slowly. The mixture was allowed to warm to ambient temperature and stirred overnight. Aqueous 1N HCl (200 mL) was added, and the mixture was exrtacted twice with $Et_2O$ (300 mL total). The combined organic extracts were concentrated under vacuum, and the residue was purified on silica gel, eluting with a gradient of 0-30% $CH_2Cl_2$ in hexane. The purest fractions were combined, and the volatile components removed under vacuum to give 3,5-dichloro-2-iodophenol, compound 18da, (6.53g, 22.7 mmol) in 62% yield. Compound 18da (3.726 g, 12.90 mmol) in DMF (50 mL) was then treated with $Cs_2CO_3$ (3.45 g, 10.6 mmol) and chloromethylethyl ether (1.50 mL, 16.2 mmol). After 3h at ambient temperature, $Et_2O$ (150 mL) was added, and the organic layer was washed with water (3 x 100 mL). The organic layer was concentrated under vacuum and the residue was purified on silica gel eluting with a gradient of 0-40% $CH_2Cl_2$ in hexane. The purest fractions were combined and the volatile components removed under vacuum to give the title compound 18d (4.3 g, 12.5 mmol) as a clear oil. Estimated purity (by NMR) was 86%. 1H NMR (300 MHz, $CDCl_3$) $\delta$ ppm 7.00 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 5.18 (s, 2H), 3.71 (q, J = 7.2 Hz, 2H), 1.39 (s, 12H), 1.22 (t, J = 7.2 Hz, 3H).

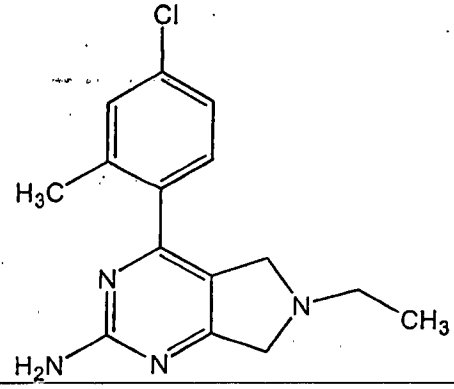
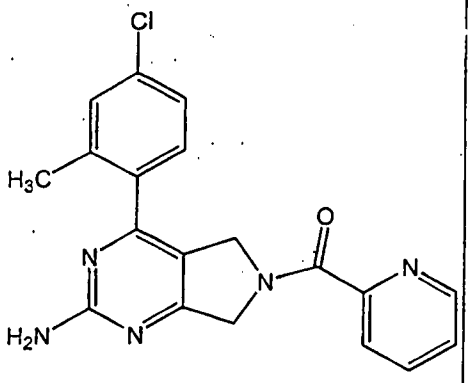
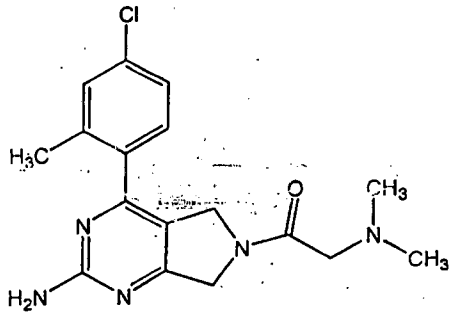
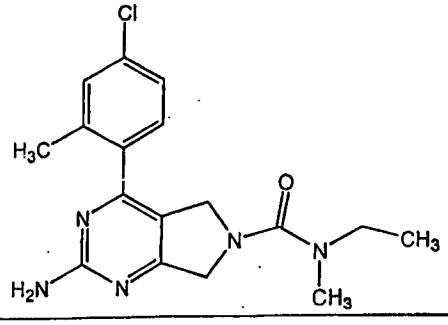
Compounds of Examples 20-98 were prepared followng the methods of Examples 1-18, as shown in the following Table 1.

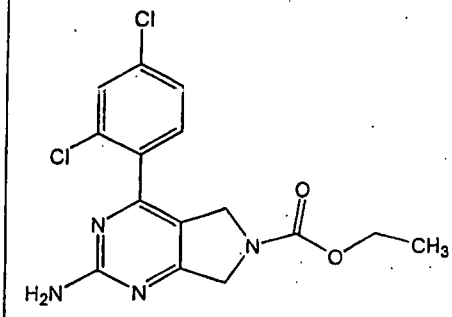
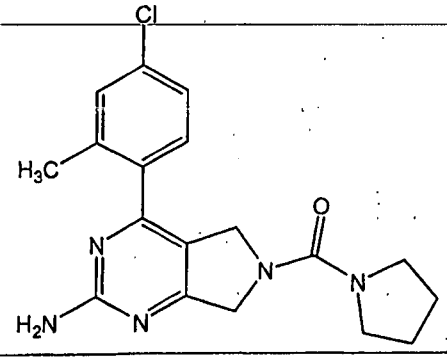
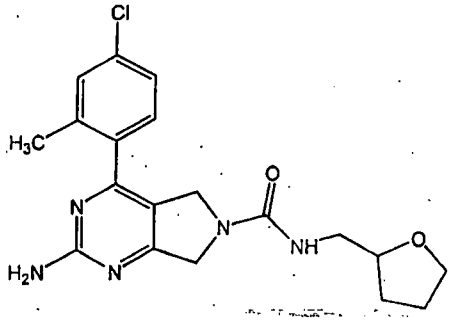
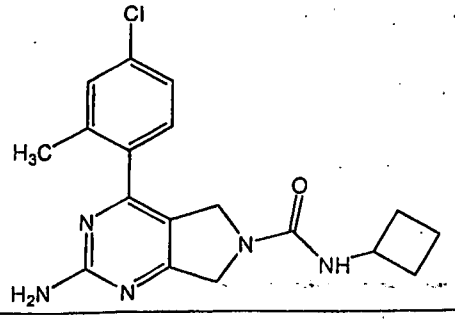
**Table 1**

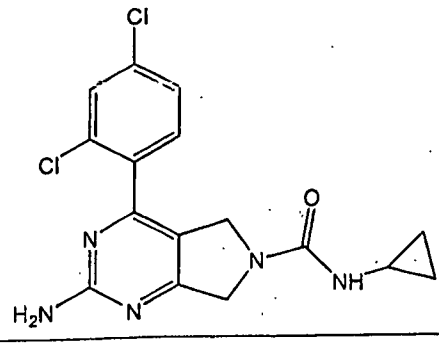
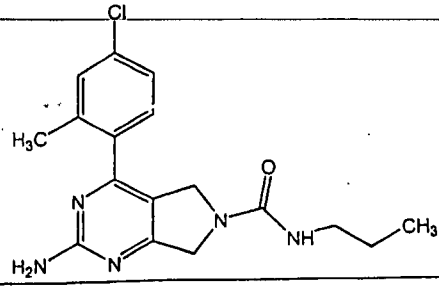
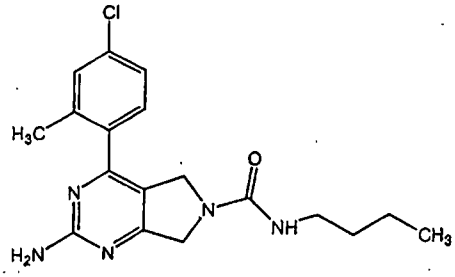
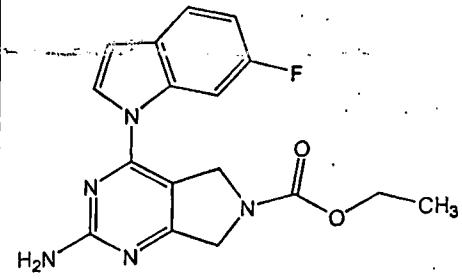
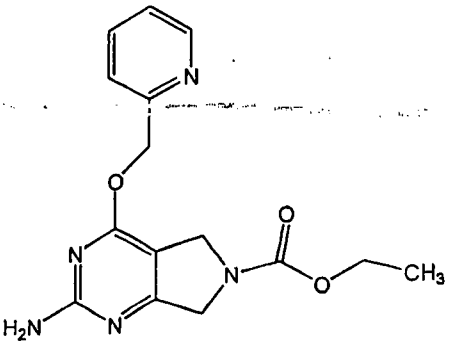
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 20 |  | 6-(3,4-dichlorobenzoyl)-4-(4-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine | Example 17 | (400 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.80-7.57 (m, 2H), 7.46 (m, 1H), 7.27 (m, 1H), 7.11 (m, 1H), 6.89 (m, 1H), 6.59 (s, 2H), 4.29 br s, 2H), 3.82, br s, 3H), 3.64-3.37 (m, 2H), 2.85-2.73 (m, 2H). | 449.2, 447.2 |
| 22 |  | 4-(4-fluoro-2-methoxyphenyl)-6-pent-4-ynoyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine | Example 17 | (400 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.22 (m, 1H), 7.08 (m, 1H), 6.90 (m, 1H), 6.52 (m, 2H), 4.15 (br s, 2H), 3.86-3.67 (m, 5H, contains 3.78 (s)), 2.84-2.49 (m, 5H, partially obscured), 2.45-2.27 (m, 2H). | 355.2 |
| 23 |  | ethyl 2-amino-4-(2-bromo-4-chlorophenoxy)-5,7-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxylate | Example 10 | (400 MHz, DMSO-D6) $\delta$ ppm 7.91 (s, 1H), 7.56 (m, 1H), 7.43 (m, 1H), 6.82 (br s, 2H), 4.55 (s, 1H), 4.52-4.42 (m, 3H), 4.19-4.09 (m, 2H), 1.24 (t, 3H). | 412.8, 414.8 |
| 24 |  | ethyl 2-amino-4-(4-bromo-2-chlorophenoxy)-5,7-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxylate | Example 10 | (400 MHz, DMSO-D6) $\delta$ ppm 7.92 (s, 1H), 7.66 (d, 1H), 7.39 (d, 1H), 6.82 (br s, 2H), 4.54 (s, 1H), 4.50 (s, 1H), 4.44 (d, 2H), 4.18-4.09 (m, 2H), 1.25 (t, 3H). | 412.8, 414.8 |

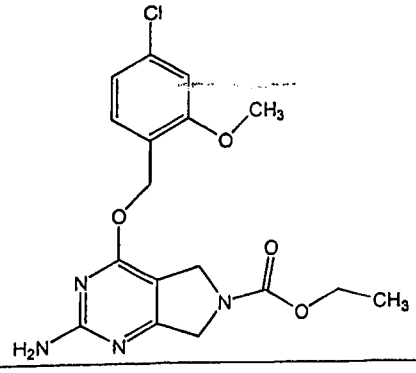
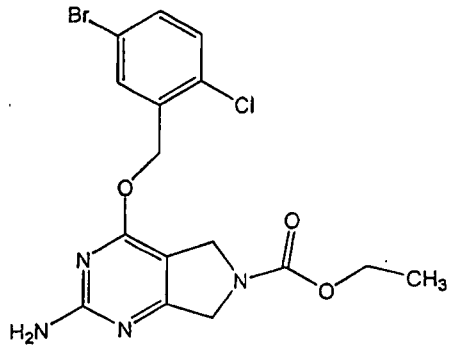
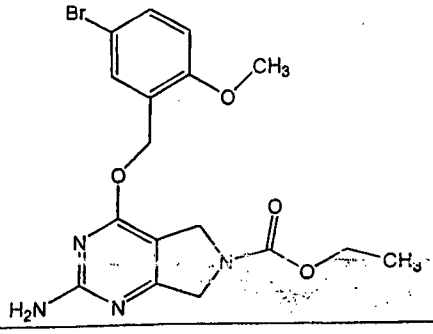
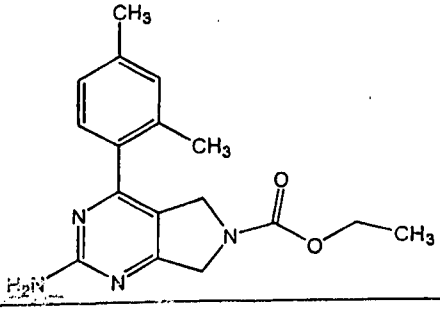
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 25 |  | ethyl 2-amino-4-(4-chloro-35-dimethylphenoxy)-5,7-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxylate hydrochloride | Example 10 | (400 MHz, DMSO-D6) $\delta$ ppm 7.09 (s, 2H), 4.50 (s, 1H), 4.46-4.42 (m, 3H), 4.17-4.10 (m, CH2, partially obscured), 2.35 (s, 6H), 1.25 (t, 3H). | 363.2 |
| 26 |  | ethyl 2-amino-4-(345-trimethoxyphenoxy)-5,7-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxylate | Example 10 | (400 MHz, DMSO-D6) $\delta$ ppm 6.59 (s, 2H), 4.49-4.40 (m, 4H), 4.17-4.09 (m, 2H, partially obscured), 3.78 (s, 6H), 3.67 (s, 3H), 1.28-1.21 (m, 3H). | 391.2 |
| 27 |  | ethyl 2-amino-4-(4-chloro-2-methoxyphenoxy)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 10 | (400 MHz, DMSO-D6) $\delta$ ppm 7.30-7.18 (m, 2H), 7.05 (m, 1H), 6.71 (s, 2H), 4.49 9s, 1H), 4.43-4.38 (m, 3H), 4.17-4.08 (m, 2H), 3.77 (s, 3H), 1.23 (t, 3H). | 365.0 |
| 29 |  | 4-(4-chloro-2-methylphenyl)-6-(piperidin-1-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (br s, 1H), 7.35-7.33 (m, 2H), 6.75 (br s, 2H), 4.52 (s, 2H), 4.39 (s, 2H), 3.18-3.15 (m, 4H), 2.24 (s, 3H), 1.56-1.39 (m, 6H). | 372.2 |

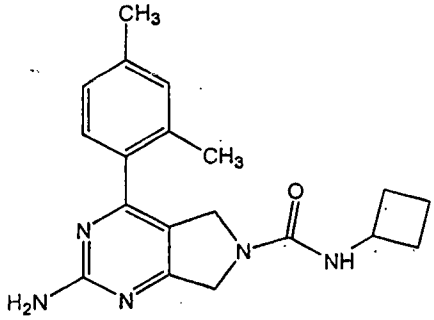
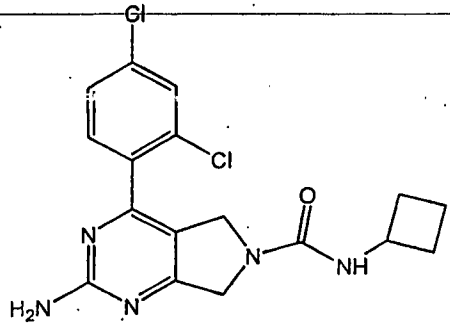
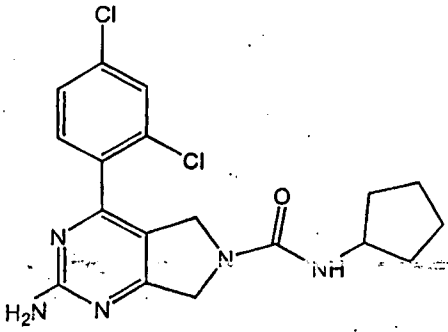
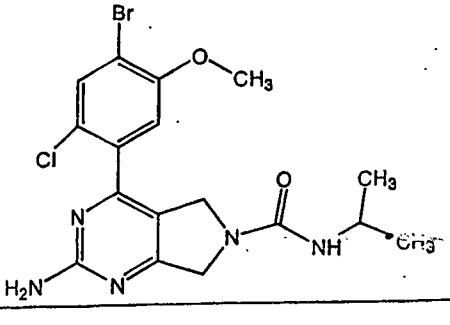
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 30 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-[3-(dimethylamino)propyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (br s, 1H), 7.35-7.32 (m, 2H), 6.77 (br s, 2H), 6.44 (t, J=5.5 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.07-3.00 (m, 2H), 2.23 (s, 3H), 2.18 (t, J = 7.1 Hz, 2H), 2.09 (s, 6H),1.57-1.48 (m, 2H). | 389.2 |
| 31 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-(pyridin-2-ylmethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 8.48-8.44 (m, 1H), 7.72 (dt, J = 7.7 and 1.9 Hz, 1H), 7.43 (br s, 1H), 7.36-7.33 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.25-7.18 (m, 1H), 7.07 (t, J = 5.9 Hz, 1H), 6.79 (br s, 2H), 4.48 (s, 2H), 4.36-4.31 (m, 4H), 2.24 (s, 3H). | 395.2 |
| 32 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-[(15-dimethyl-1H-pyrazol-3-yl)methyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (br s, 1H), 7.34-7.32 (m, 2H), 6.77 (br s, 2H), 6.73 (t, J = 5.8 Hz, 1H), 5.88 (s, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 4.08 (d, J = 5.7 Hz, 2H), 3.62 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H). | 412.2 |
| 33 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-(4-fluorobenzyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (br s, 1H), 7.34-7.27 (m, 4H), 7.14-7.06 (m, 2H), 6.99 (t, J = 5.8 Hz, 1H), 6.78 (br s, 2H), 4.45 (s, 2H), 4.30 (s, 2H), 4.22 (d, J = 5.7 Hz, 2H), 2.23 (s, 3H). | 412.2 |
| 34 |  | 4-(4-chloro-2-methylphenyl)-6-propionyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (br s, 1H), 7.35-7.32 (m, 2H), 6.79 (br s, 2H), 4.67 (s, 1H), 4.52 (s, 1H), 4.45 (s, 1H), 4.29 (s, 1H), 2.36-2.23 (m, 5H), 1.03-0.95 (m, 3H). | 317.2 |

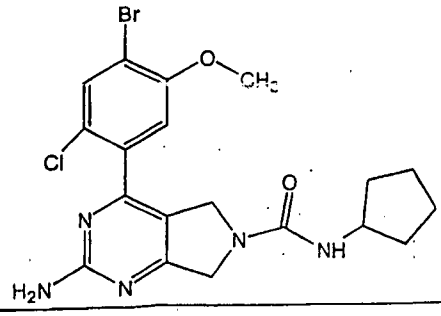
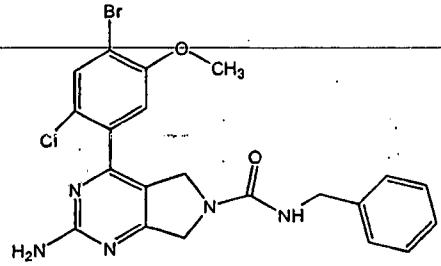
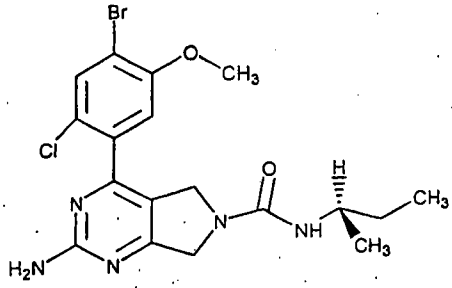
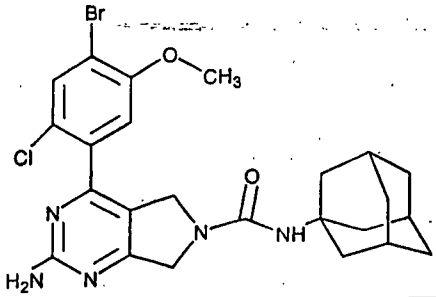
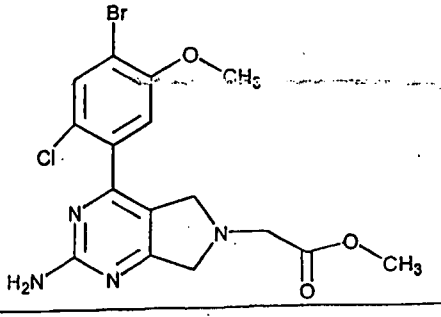
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 35 |  | 4-(4-chloro-2-methylphenyl)-6-ethyl-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 5 | (300 MHz, DMSO-D6) $\delta$ ppm 7.40 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.3 and 2.1 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.58 (br s, 2H), 3.70 (s, 2H), 3.58 (s, 2H), 2.65 (q, J = 7.2 Hz, 2H), 2.24 (s, 3H), 1.04 (t, J = 7.2 Hz, 3H). | 289.2 |
| 36 |  | 4-(4-chloro-2-methylphenyl)-6-(pyridin-2-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 8.68 (d, J = 4.3 Hz, 0.5H), 8.57 (d, J = 4.3 Hz, 0.5H), 8.01-7.91 (m, 1H), 7.88-7.78 (m, 1H), 7.58-7.37 (m, 3H), 7.29 (s, 1H), 6.82 (br s, 1H), 6.79 (br s, 1H), 4.99 (s, 1H), 4.80 (s, 1H), 4.74 (s, 1H), 4.60 (s, 1H), 2.27 (s, 1.5H), 2.22 (s, 1.5H). | 366.2 |
| 37 |  | 4-(4-chloro-2-methylphenyl)-6-[(dimethylamino)acetyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.43 (m,1H), 7.35-7.32 (m, 2H), 6.80 and 6.78 (2 overlapping br s, 2H), 4.75 (s, 1H), 4.58 (s, 1H), 4.46 (s, 1H), 4.32 (s, 1H), 3.12 (s, 1H), 3.08 (s, 1H), 2.25 (s, 1.5H), 2.24 (s, 1.5H), 2.23 (s, 3H), 2.18 (s, 3H). | 346.2 |
| 38 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-ethyl-N-methyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (s, 1H), 7.35-7.32 (m, 2H), 6.73 (br s, 2H), 4.51 (s, 2H), 4.38 (s, 2H), 3.15 (q, J = 7.0 Hz, 2H), 2.76 (s, 3H), 2.25 (s, 3H),1.05 (t, J = 7.0 Hz, 3H). | 346.2 |

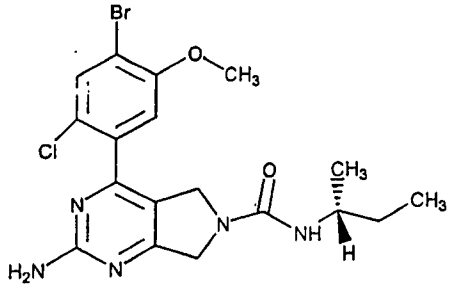
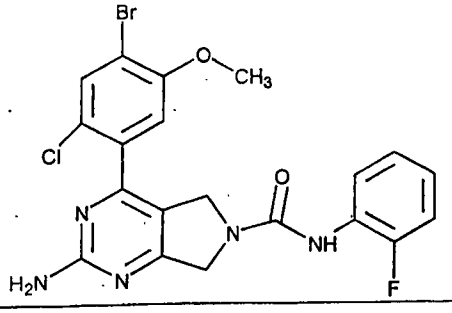
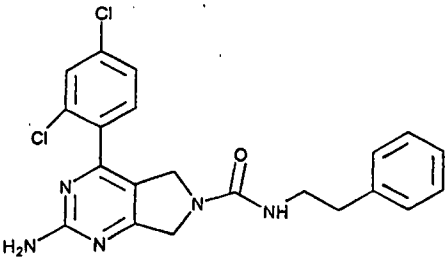
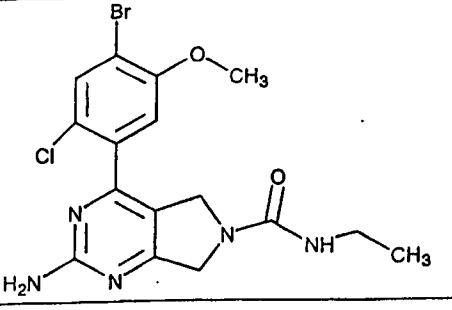
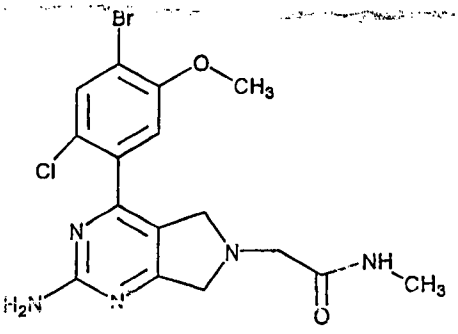
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 39 |  | ethyl 2-amino-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.78 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 8.3 and 1.9 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.92 (br s, 2H), 4.49 (s, 1H), 4.47 (s, 1H), 4.34 (s, 1H), 4.31 (s, 1H), 4.13-4.03 (m, 2H), 1.24-1.15 (m, 3H). | 355.2, 353.2 |
| 40 |  | 4-(4-chloro-2-methylphenyl)-6-(pyrrolidin-1-ylcarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (s, 1H), 7.35-7.32 (m, 2H), 6.73 (br s, 2H), 4.53 (s, 2H), 4.39 (s, 2H), 3.32-3.27 (m, 4H), 2.24 (s, 3H), 1.79-1.73 (m, 4H). | 358.2 |
| 41 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-(tetrahydrofuran-2-ylmethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (br s, 1H), 7.35-7.32 (m, 2H), 6.75 (br s, 2H), 6.41 (t, J = 5.8 Hz, 1H), 4.41 (s, 2H), 4.26 (s, 2H), 3.87-3.80 (m, 1H), 3.76-3.69 (m, 1H), 3.62-3.54 (m, 1H), 3.07 (dt, J = 5.8 and 2.3 Hz, 2H), 2.23 (s, 3H), 1.88-1.72 (m, 3H), 1.58-1.50 (m, 1H). | 388.2 |
| 42 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-cyclobutyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (br s, 1H), 7.35-7.32 (m, 2H), 6.75 (br s, 2H), 6.50 (d, J = 8.1 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 4.18-4.08 (m, 1H), 2.22 (s, 3H), 2.14-2.03 (m, 2H), 1.96-1.89 (m, 2H), 1.59-1.50 (m, 2H). | 358.2 |

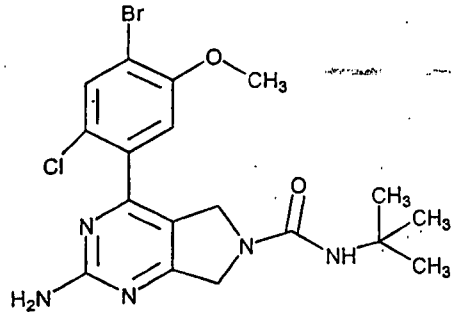
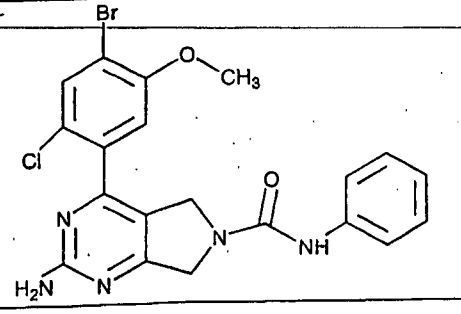
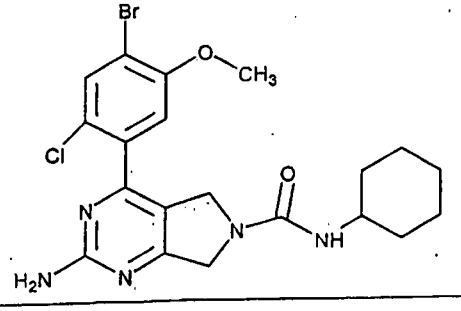
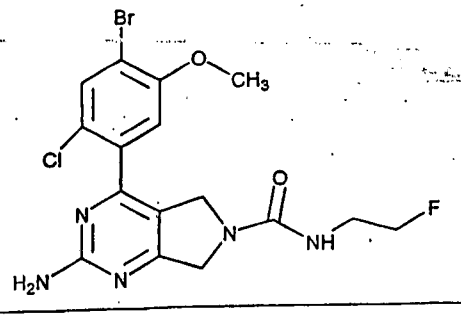
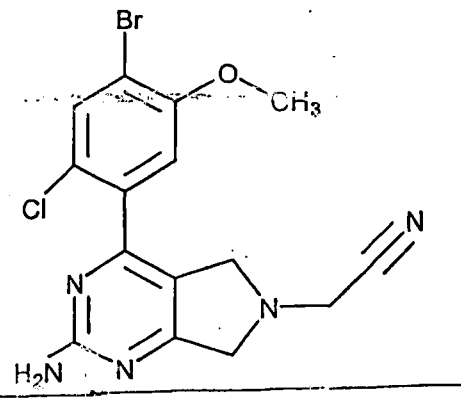
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 43 |  | 2-amino-N-cyclopropyl-4-(24-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.79 (d, J = 1.9 Hz, 1H), 7.55 (dd, J = 8.3 and 2.0 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 6.87 (br s, 2H), 6.46 (d, J = 2.6 Hz, 1H), 4.40 (s, 2H), 4.22 (s, 2H), 0.57-0.50 (m, 2H), 0.41-0.36 (m, 2H). | 364.2, 366.2 |
| 44 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-propyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.43 (br s, 1H), 7.34-7.32 (m, 2H), 6.77 (br s, 2H), 6.36 (t, J = 6.4 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 2.98 (m, 2H), 2.23 (s, 3H), 1.47-1.34 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). | 346.2 |
| 45 |  | 2-amino-N-butyl-4-(4-chloro-2-methylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.42 (br s, 1H), 7.34-7.32 (m, 2H), 6.77 (br s, 2H), 6.32 (t, J = 5.5 Hz, 1H), 4.39 (s, 2H), 4.23 (s, 2H), 3.01 (m, 2H), 2.22 (s, 3H), 1.45-1.36 (m, 2H), 1.33-1.24 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H | 360.2 |
| 46 |  | ethyl 2-amino-4-(6-fluoro-1H-indol-1-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 12 | (300 MHz, DMSO-D6) $\delta$ ppm 8.50-8.44 (m, 1H), 7.70-7.63 (m, 2H), 7.14-7.07 (m, 3H), 6.84 (d, J = 3.6 Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.47 (s, 1H), 4.44 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H) | 342.2 |
| 47 |  | ethyl 2-amino-4-(pyridin-2-ylmethoxy)-5,7-dihydro-6H-pyrroic[3,4-d]pyrimidine-6-carboxylate | Example 11 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 8.56 (m, 1H), 7.82 (dt, J = 7.7 and 1.7 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.36-7.32 (m, 1H), 6.72 (br s, 2H), 5.46 (s, 1H), 5.45 (s, 1H), 4.46-4.34 (m, 4H), 4.14-4.05 (m, 2H), 1.25-1.18 (m, 3H). | 316.2 |

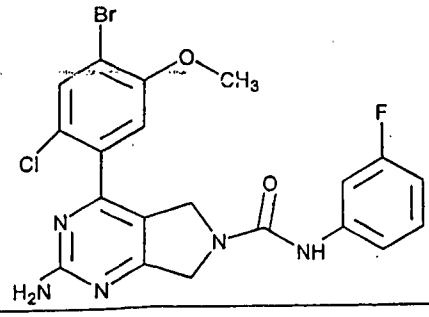
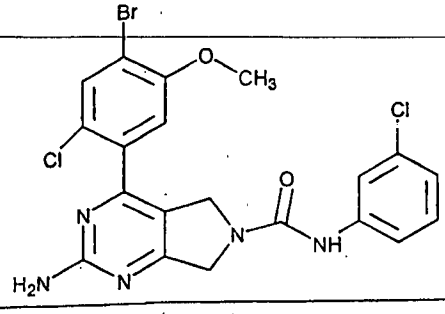
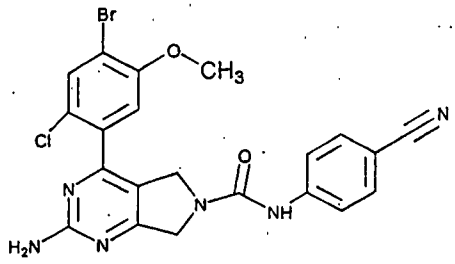
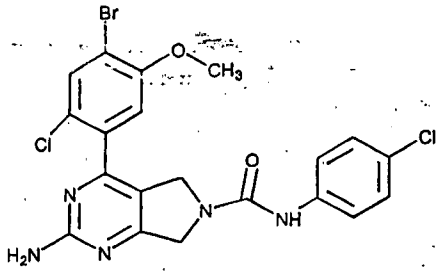
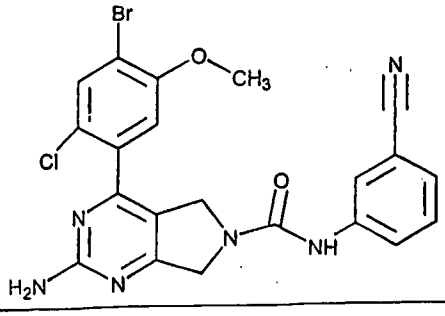
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 48 |  | ethyl 2-amino-4-[(4-chloro-2-methoxybenzyl)oxy]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 11 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.41 (d, J = 8.1 Hz, 1H), 7.13 (d, J =2.0 Hz, 1H), 7.03 (dd, J = 8.1 and 1.8 Hz, 1H), 6.73 (br s, 2H), 5.32 (s, 1H), 5.31 (s, 1H), 4.40-4.32 (m, 4H), 4.12-4.05 (m, 2H), 3.84 (s, 3H), 1.23-1.19 (m, 3H). | 379.2 |
| 49 |  | ethyl 2-amino-4-[(5-bromo-2-chlorobenzyl)oxy]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 11 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.78-7.76 (m, 1H), 7.62-7.59 (m, 1H), 7.49 (d, J = 8.6, 1H), 6.79 (br s, 2H), 5.42 (s, 1H), 5.41 (s, 1H), 4.42-4.33 (m, 4H), 4.12-4.06 (m, 2H), 1.23-1.19 (m, 3H). | 427.0, 429.0 |
| 50 |  | ethyl 2-amino-4-[(5-bromo-2-methoxybenzyl)oxy]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 11 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.53-7.48 (m, 2H), 7.05-7.00 (m, 1H), 6.75 (br s, 2H), 5.33 (s, 1H), 5.32 (s, 1H), 4.41-4.32 (m, 4H), 4.13-4.05 (m, 2H), 3.81 (s, 3H), 1.24-1.19 (m, 3H). | 423.2, 425.2 |
| 51 |  | ethyl 2-amino-4-(2,4-dimethylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.21-7.07 (m, 3H), 4.48 and 4.45 (2 overlapping br s, 2H), 4.32 and 4.29 (2 overlapping br s, 2H), 4.12-4.01 (m, 2H), 2.31 (s, 3H), 2.21 and 2.20 (2 overlapping s, 3H), 1.23-1.14 (m, 3H) | 313.2 |

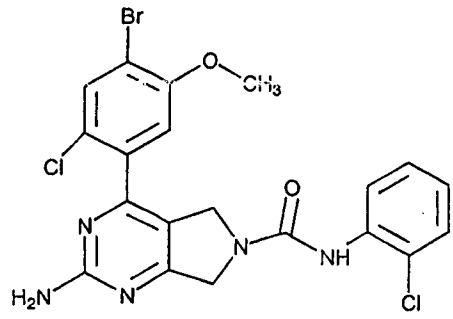
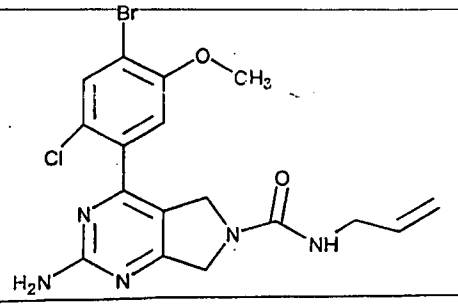
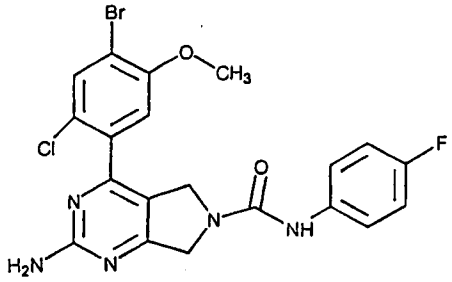
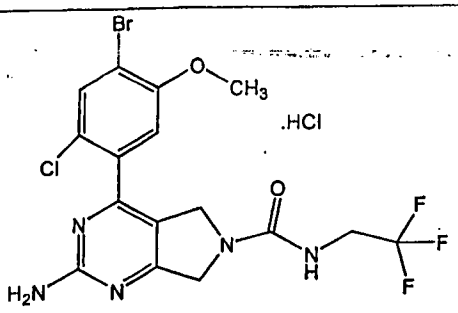
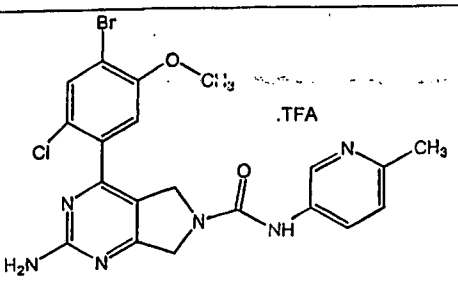
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 52 |  | 2-amino-N-cyclobutyl-4-(2,4-dimethylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) $\delta$ ppm 7.17-7.06 (m, 3H), 6.67 (br s, 2H), 6.50 (d, J = 7.5 Hz, 1H), 4.38 (br s, 2H), 4.24 (br s, 2H), 4.16-4.08 (m, 1H), 2.31 (s, 3H), 2.19 (s, 3H), 2.13-2.04 (m, 2H), 1.99-1.85 (m, 2H), 1.58-1.48 (m, 2H). | 338.2 |
| 53 |  | 2-amino-N-cyclobutyl-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 7.80 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.1 and 2.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.89 (br s, 2H), 6.53 (d, J = 7.8 Hz, 1H), 4.40 (br s, 2H), 4.24 (br s, 2H), 4.17-4.07 (m, 1H), 2.12-2.05 (m, 2H), 1.97-1.86 (m, 2H), 1.58-1.48 (m, 2H) | 378 |
| 54 |  | 2-amino-N-cyclopentyl-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.80 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.3 and 2.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.88 (br s, 2H), 6.13 (d, J = 7.3 Hz, 1H), 4.42 (br s, 2H), 4.25 (br s, 2H), 3.97-3.88 (m, 1H), 1.81-1.73 (m, 2H), 1.65-1.57 (m, 2H), 1.50-1.34 (m, 4H) | 378.2, 380.2 |
| 55 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s,1H), 7.16 (s, 1H), 6.89 (br s, 2H), 6.07 (d, J = 7.7 Hz, 1H), 4.42 (br s, 2H), 4.25 (br s, 2H), 3.86 (s, 3H), 3.82-3.75 (m, 1H), 1.05 (d, J = 6.4 Hz, 6H) | 440.2, 442.2 |

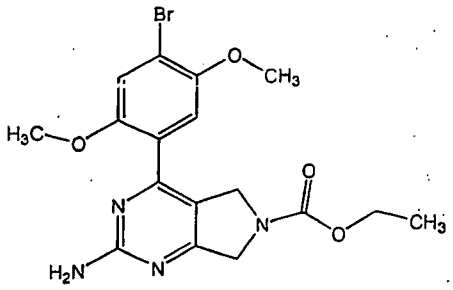
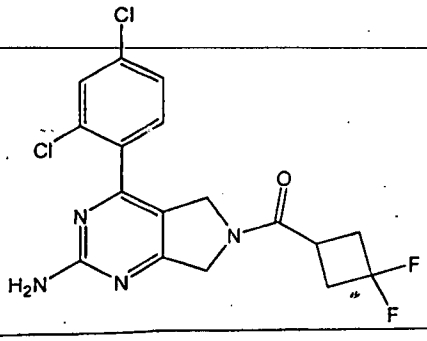
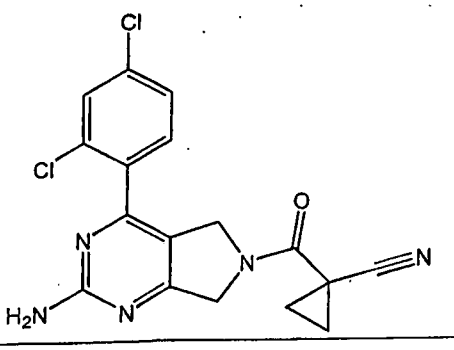
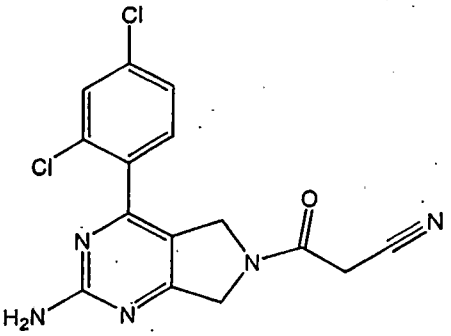
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 56 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-cyclopentyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.16 (s, 1H), 6.90 (br s, 2H), 6.13 (d, J = 7.5 Hz, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 3.97-3.87 (m, 1H), 3.86 (s, 3H), 1.84-1.71 (m, 2H), 1.67-1.56 (m, 2H), 1.52-1.32 (m, 4H) | 466.2, 468.2 |
| 57 |  | 2-amino-N-benzyl-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.31-7.24 (m, 4H), 7.22-7.17 (m, 1H), 7.17 (s, 1H), 7.00 (t, J = 5.7 Hz, 1H), 6.91 (br s, 2H), 4.47 (s, 2H), 4.33 (s, 2H), 4.25 (d, J = 5.7 Hz, 2H), 3.86 (s, 3H) | 488.2, 490.2 |
| 58 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-[(1R)-1-methylpropyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.17 (s, 1H), 6.90 (br s, 2H), 6.00 (d, J = 7.8 Hz, 1H), 4.43 (s, 2H), 4.27 (s, 2H), 3.86 (s, 3H), 3.62-3.49 (m, overlaps with H2O peak, 1H), 1.46-1.31 (m, 2H), 1.02 (d, J = 6.6 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H) | 454.2, 456.2 |
| 59 |  | N-1-adamantyl-2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.16 (s, 1H), 6.97 (br s, 2H), 5.45 (s, 1H), 4.41 (s, 2H), 4.26 (s, 2H), 3.86 (s, 3H), 1.99 (br s, 3 H), 1.94 (br s, 6H), 1.60 (br s, 6H) | 532.2, 534.2 |
| 60 |  | methyl [2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-57-dihydro-6H-pyrrolo[34-d]pyrimidin-6-yl]acetate | Example 5 | (300 MHz, CDCl3) $\delta$ ppm 7.66 (s, 1H), 6.98 (s, 1H), 5.76 (br s, 2H), 4.45 (br s, 2H), 4.38 (br s, 2H), 3.97 (s, 3H), 3.88 (s, 2H), 3.82 (s, 3 H) | 427.2, 429.2 |

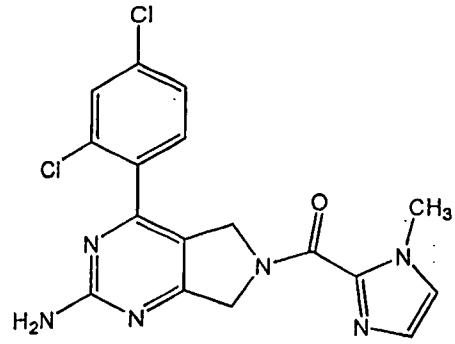
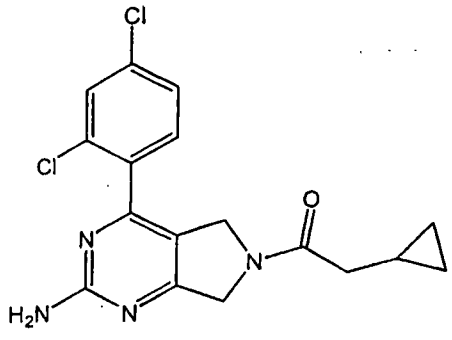
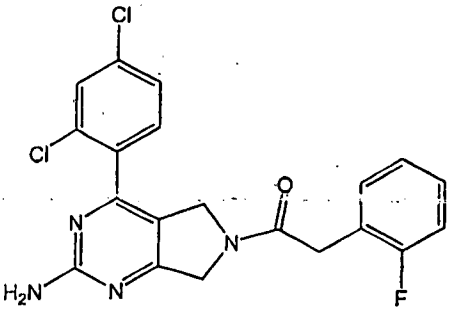
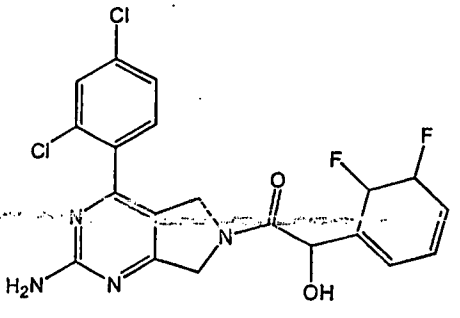
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 61 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-[(1S)-1-methylpropyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.17 (s, 1H), 6.89 (br s, 2H), 6.00 (d, J = 8.3 Hz, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 3.86 (s, 3H), 3.64-3.51 (m, overlaps with H2O peak, 1H), 1.47-1.30 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H). | 454.2, 456.2 |
| 62 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-fluorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.18 (s, 1H), 7.88 (s, 1H), 7.50-7.44 (m, 1H), 7.23-7.10 (m, 4H), 6.95 (br s, 2H), 4.61 (br s, 2H), 4.48 (br s, 2H), 3.88 (s, 3H). | 492.2, 494.2 |
| 63 |  | 2-amino-4-(2,4-dichlorophenyl)-N-(2-phenylethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.80 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.32-7.26 (m, 2H), 7.23-7.15 (m, 3H), 6.90 (br s, 2H), 6.52 (m, 1H), 4.42 (br s, 2H), 4.25 (br s, 2H), 3.32-3.19 (m, overlaps with H2O peak, 2H), 2.72 (t, J = 7.3 Hz, 2H). | 428.2, 430.2 |
| 64 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.17 (s, 1H), 6.90 (br s, 2H), 6.36 (t, J = 5.2 Hz, 1H), 4.42 (br s, 2H), 4.26 (br s, 2H), 3.86 (s, 3H), 3.10-3.01 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H). | 426.2, 428.2 |
| 65 |  | 2-[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[34-d]pyrimidin-6-yl]-N-methylacetamide | Example 5 | (300 MHz, DMSO-D6) $\delta$ ppm 7.82 (s, 1H), 7.81-7.75 (m, 1H), 7.07 (s, 1H), 6.76 (br s, 2H), 3.85 (s, 5H), 3.73 (s, 2H), 3.28 (s, 2H), 2.57 (d, J = 4.7 Hz, 3H). | 426.2, 428.2 |

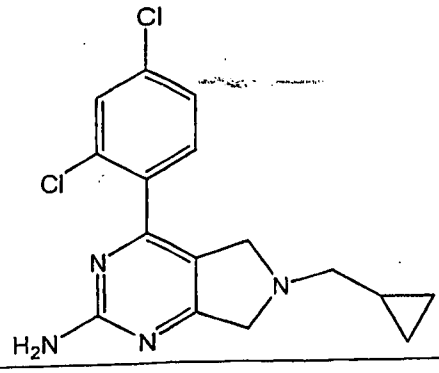
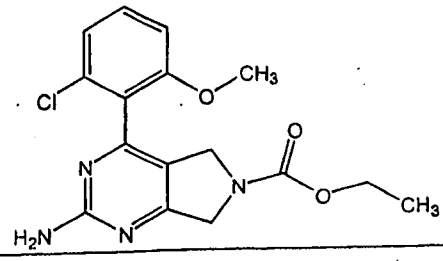
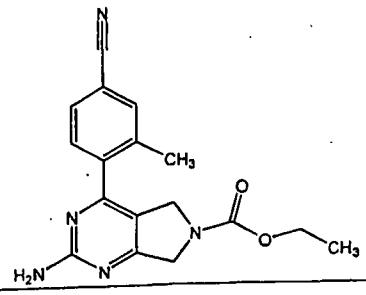
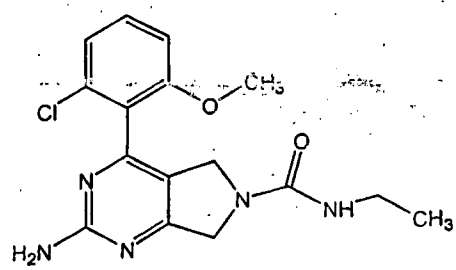
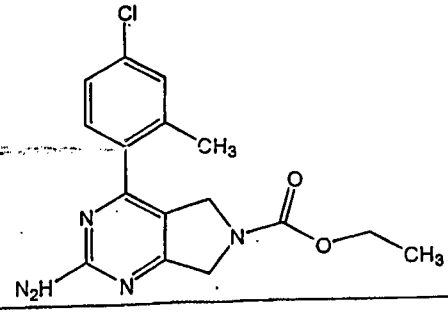
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 66 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(tert-butyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.16 (s, 1H), 6.88 (br s, 2H), 5.58 (s, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 3.86 (s, 3H), 1.26 (s, 9H). | 454.2, 456.2 |
| 67 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-phenyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.34 (s, 1H), 7.89 (s, 1H), 7.51 (d, J = 7.9 Hz, 2H), 7.26-7.19 (m, 3H), 6.98-6.91 (m, 3H), 4.60 (s, 2H), 4.48 (s, 2H), 3.88 (s, 3H). | 474.2, 476.2 |
| 68 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-cyclohexyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.16 (s, 1H), 6.89 (br s, 2H), 6.07 (d, J = 7.9 Hz, 1H), 4.42 (s, 2H), 4.25 (s, 2H), 3.49-3.44 (m, under H2O peak, 1H), 3.86 (s, 3H), 1.78-1.00 (M, 10H), | 480.2, 482.2 |
| 69 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-fluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 7.87 (s, 1H), 7.17 (s, 1H), 6.91 (br s, 2H), 6.65 (t, J = 5.4 Hz, 1H), 4.50-4.43 (m, 3H), 4.35-4.28 (m, 3H), 3.86 (s, 3H), 3.36-3.25 (m, under H2O peak, 2H). | 444.2, 446.2 |
| 70 |  | [2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]acetonitrile | Example 5 | (300 MHz, DMSO-D6) $\delta$ ppm 7.84 (s, 1H), 7.14 (s, 1H), 6.87 (br s, 2H), 3.96 (s, 2H), 3.86 (s, 3H), 3.85 (s, 2H), 3.74 (s, 2H). | 394.2, 396.2 |

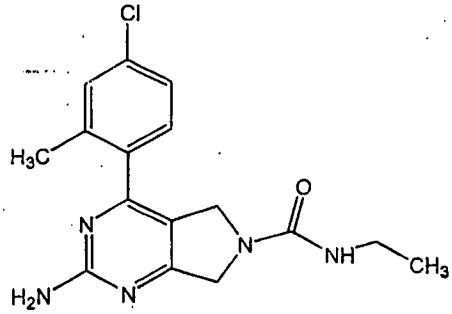
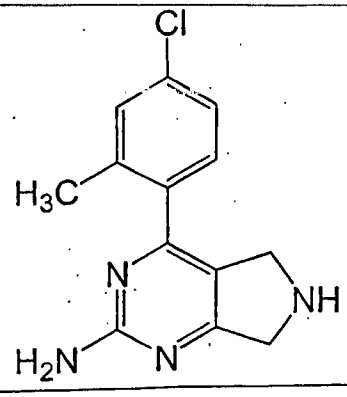
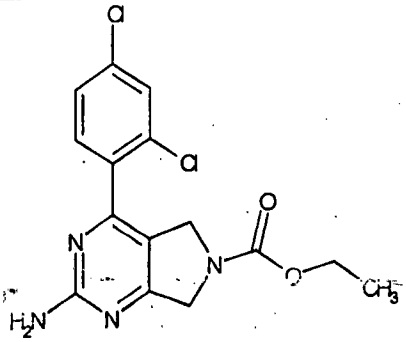
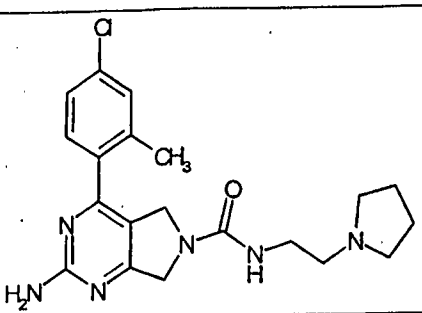
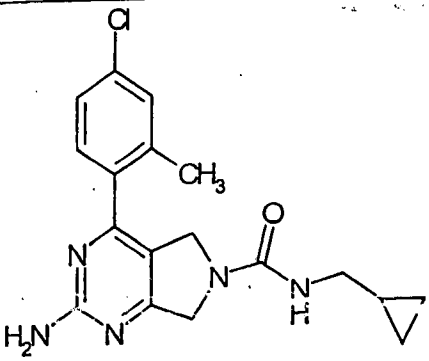
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 71 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(3-fluorophenyl)-57-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.54 (s, 1H), 7.88 (s, 1H), 7.50 (dt, J = 12.2 and 1.9 Hz, 1H), 7.33-7.21 (m, 2H), 7.19 (s, 1H), 6.95 (br s, 2H), 6.78-6.72 (m, 1H), 4.60 (s, 2H), 4.48 (s, 2H), 3.87 (s, 3H). | 492.2, 494.2 |
| 72 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(3-chlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.52 (s, 1H), 7.88 (s, 1H), 7.70 (t, J = 1.8 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.25 (t, J = 8.10 Hz, 1H), 7.19 (s, 1H), 7.01-6.94 (m, 3H), 4.60 (s, 2H), 4.47 (s, 2H), 3.87 (s, 3H). | 508.0, 510.2, 512.0 |
| 73 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(4-cyanophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.80 (s, 1H), 7.89 (s, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 6.97 (br s, 2H), 4.63 (s, 2H), 4.51 (s, 2H), 3.87 (s, 3H). | 499.2, 501.2 |
| 74 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(4-chlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.48 (s, 1H), 7.89 (s, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 6.95 (br s, 2H), 4.60 (s, 2H), 4.47 (s, 2H), 3.87 (s, 3H). | 508.0, 510.0, 512.0 |
| 75 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(3-cyanophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.69 (s, 1H), 8.01-7.99 (m, 1H), 7.89 (s, 1H), 7.85-7.80 (m, 1H), 7.49-7.38 (m, 2H), 7.20 (s, 1H), 6.97 (br s, 2H), 4.61 (s, 2H), 4.49 (s, 2H), 3.88 (s, 3H). | 499.2, 501.2 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 76 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-chlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.07 (s, 1H), 7.87 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.20 (s, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.95 (br s, 2H), 4.61 (s, 2H), 4.49 (s, 2H), 3.87 (s, 3H). | 508.0, 510.0, 512.0 |
| 77 |  | N-allyl-2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 7.86 (s, 1H), 7.17 (s, 1H), 6.92 (br s, 2H), 6.59 (t, J = 5.4 Hz, 1H), 5.87-5.74 (m, 1H), 5.12-4.97 (m, 2H), 4.45 (s, 2H), 4.30 (s, 2H), 3.86 (s, 3H), 3.67 (m, 2H). | 438.2, 440.2 |
| 78 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(4-fluorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (300 MHz, DMSO-D6) $\delta$ ppm 8.40 (s, 1H), 7.88 (s, 1H), 7.54-7.47 (M, 2H), 7.19 (s, 1H), 7.07 (t, J = 8.7 Hz, 2H), 6.95 (br s, 2H), 4.59 (s, 2H), 4.46 (s, 2H), 3.87 (s, 3H). | 492.2, 494.2 |
| 79 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2,2,2-trifluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide hydrochloride | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 7.66 (s, 1H), 7.17 (s, 1H), 7.09 (t, J = 6.0 Hz, 1H), 6.93 (br s, 2H), 4.47 (s, 2H), 4.32 (s, 2H), 3.86 (s, 3H), 3.86-3.76 (m, 2H). | 480.2, 482.2 |
| 80 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(6-methylpyridin-3-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide trifluoroacetate | Example 3 | (300 MHz, DMSO-D6) $\delta$ ppm 8.98 (s, 1H), 8.84 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.20 (s, 1H), 6.99 (br s, 2H), 4.63 (s, 2H), 4.51 (s, 2H), 3.88 (s, 3H), 2.55 (s, 3H). | 489.2, 491.2 |

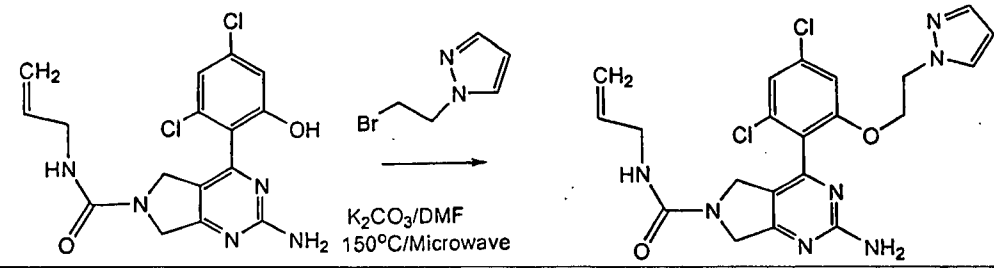
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 81 |  | ethyl 2-amino-4-(4-bromo-2,5-dimethoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (300 MHz, DMSO-D6) (conformers) $\delta$ ppm 7.39 (s, 1H), 7.05 (s, 1H), 6.82 (br s, 2H), 4.45 (br s, 1H), 4.43 (br s, 1H), 4.31 (br s, 1H), 4.29 (br s, 1H), 4.12-4.02 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 1.23-1.15 (m, 3H). | 423.2, 425.2 |
| 82 |  | 4-(2,4-dichlorophenyl)-6-[(3,3-difluorocyclobutyl)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 2.68 - 2.88 (m, 4 H) 3.14 - 3.28 (m, 1 H) 4.35 (s, 1 H) 4.52 (d, J=14.40 Hz, 2 H) 4.69 (s, 1 H) 6.95 (s, 2 H) 7.44 - 7.52 (m, 1 H) 7.53 - 7.61 (m, 1 H) 7.80 (d, J=1.77 Hz, 1 H). | 399, 401 |
| 83 |  | 1-{[2-amino-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]carbonyl}cyclopropanecarbonitrile | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 1.47 - 1.67 (m, 4 H) 4.49 (d, J=58.86 Hz, 2 H) 4.94 (d, J=43.96 Hz, 2 H) 7.00 (s, 2 H) 7.42 - 7.63 (m, 2 H) 7.81 (dd, J=17.94, 2.02 Hz, 1 H). | 374, 376 |
| 84 |  | 3-[2-amino-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]-3-oxopropanenitrile | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 4.03 (d, J=27.79 Hz, 2 H) 4.35 (s, 1 H) 4.51 (d, J=3.54 Hz, 2 H) 4.68 (s, 1 H) 6.99 (s, 2 H) 7.48 (dd, J=8.34, 6.32 Hz, 1 H) 7.52 - 7.61 (m, 1 H) 7.80 (dd, J=7.33, 2.02 Hz, 1 H). | 348, 350 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 85 |  | 4-(2,4-dichlorophenyl)-6-[(1-methyl-1H-imidazol-2-yl)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 3.86 (d, J=1.77 Hz, 3 H) 4.62 (d, J=61.38 Hz, 2 H) 5.04 (d, J=61.64 Hz, 2 H) 6.94 (s, 2 H) 7.03 (dd, J=34.61, 1.01 Hz, 1 H) 7.35 (d, J=14.91 Hz, 1 H) 7.44 - 7.52 (m, 1 H) 7.54 - 7.62 (m, 1 H) 7.80 (d, J=1.77 Hz, 1 H). | 389, 391 |
| 86 |  | 6-(cyclopropylacetyl)-4-(2,4-dichlorophenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 0.01 - 0.18 (m, 2 H) 0.36 - 0.52 (m, 2 H) 0.99 (dd, J=7.33, 4.80 Hz, 1 H) 2.25 (dd, J=30.06, 6.57 Hz, 2 H) 4.31 (s, 1 H) 4.48 (d, J=9.85 Hz, 2 H) 4.67 (s, 1 H) 6.93 (s, 2 H) 7.43 - 7.51 (m, 1 H) 7.52 - 7.61 (m, 1 H) 7.79 (d, J=1.26 Hz, 1 H). | 363, 365 |
| 87 |  | 4-(2,4-dichlorophenyl)-6-[(2-fluorophenyl)acetyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 3.77 (d, J=32.34 Hz, 2 H) 4.35 (s, 1 H) 4.51 (s, 1 H) 4.70 (s, 1 H) 4.86 (s, 1 H) 6.97 (s, 2 H) 7.08 - 7.21 (m, 2 H) 7.24 - 7.37 (m, 2 H) 7.46 - 7.63 (m, 2 H) 7.80 (dd, J=9.85, 1.77 Hz, 1 H). | 417, 419 |
| 88 |  | 2-[2-amino-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]-1-(2,3-difluorophenyl)-2-oxoethanol | Example 6 | (400 MHz, DMSO-d6) $\delta$ ppm 4.44 - 4.60 (m, 2 H) 4.75 - 5.02 (m, 2 H) 5.59 (dd, J=26.02, 7.07 Hz, 1 H) 6.18 (dd, J=6.82, 2.27 Hz, 1 H) 6.96 (d, J=8.59 Hz, 2 H) 7.16 - 7.33 (m, 2 H) 7.33 - 7.44 (m, 1 H) 7.44 - 7.54 (m, 1 H) 7.53 - 7.61 (m, 1 H) 7.79 (dd, J=3.03, 2.02 Hz, 1 H). | 451, 453 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 89 |  | 6-(cyclopropylmethyl)-4-(2,4-dichlorophenyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Example 5 | (400 MHz, MeOH-d4) $\delta$ ppm 0.29 (d, J=6.06 Hz, 2 H) 0.55 - 0.69 (m, 2 H) 0.93 - 1.10 (m, 1 H) 2.84 (d, J=7.07 Hz, 2 H) 4.04 (s, 2 H) 4.14 (s, 2 H) 7.35 - 7.54 (m, 2 H) 7.64 (d, J=1.77 Hz, 1 H). | 335, 337 |
| 90 |  | ethyl 2-amino-4-(2-chloro-6-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (400 MHz, DMSO-D6) $\delta$ ppm 7.45 (dd, 1H, J = 8.4, 8.3 Hz), 7.16-7.12 (m, 2H), 6.84 (br s, 2H), 4.55-4.45 (m, 2H), 4.20-3.98 (m, 4H), 3.74 (s, 3H), 1.27-1.12 (m, 3H) | 349.2 351.2 |
| 91 |  | ethyl 2-amino-4-(4-cyano-2-methylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (400 MHz, DMSO-D6) $\delta$ ppm 7.84 (s, 1H), 7.76 (d, 1H, J = 7.9 Hz), 7.68-7.48 (m, 1H), 6.89 (br s, 2H), 4.55-4.40 (m, 2H), 4.35-4.20 (m, 2H), 4.15-3.95 (m, 2H), 2.26 (s, 3H), 1.27-1.12 (m, 3H) | 324 |
| 92 |  | 2-amino-4-(2-chloro-6-methoxyphenyl)-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Example 15a | (400 MHz, DMSO-D6) $\delta$ ppm 7.44 (dd, 1H, J = 8.4, 8.3 Hz), 7.16-7.12 (m, 2H), 6.79 (br s, 2H), 6.36 (t, 1H), 4.42 (br s, 2H), 4.10 (br s, 2H), 3.74 (s, 3H), 3.08-2.95 (m, 2H), 1.00 (t, 3H) | 348.2, 350.2 |
| 93 |  | ethyl 2-amino-4-(4-chloro-2-methylphenyl)-57-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxylate | Example 1 | (400 MHz, DMSO-D6) $\delta$ ppm 7.43 (s, 1H), 7.34 (s, 2H), 6.82 (bs, 2H), 4.47 (d, 2H, J=8), 4.32 (d, 2H, J= 12 Hz), 4.07 (m, 2H), 2.24 (s, 3H), 1.22 (t, 3H, J= 7.1 Hz). | 333.2, 335.2 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 94 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-ethyl-57-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxamide | Example 15a | (400 MHz, CD3OD) δ ppm 7.27 (s, 1H), 7.20 (s, 2H), 4.44 (s, 2H), 4.27 (s, 2H), 3.11 (m, 2H), 2.17 (s, 3H), 1.01 (t, 3H, 8 Hz) | 332.4, 334.2 |
| 95 |  | 4-(4-chloro-2-methylphenyl)-67-dihydro-5H-pyrrolo[34-d]pyrimidin-2-amine | Example 2 | (400 MHz, DMSO-D6) δ ppm 7.41 (s, 1H), 7.32 (d, 1H, J= 8 Hz), 7.26 (d, 1H, J= 8hz), 6.56 (bs, 2H), 3.88 (s, 2H), 3.80 (s, 2H), 2.24 (s, 3H) | 261 |
| 96 |  | ethyl 2-amino-4-(2,4-dichlorophenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Example 1 | (300 MHz, DMSO-D6) (conformers) δ ppm 7.78 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 8.3 and 1.9 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 6.92 (br s, 2H), 4.49 (s, 1H), 4.47 (s, 1H), 4.34 (s, 1H), 4.31 (s, 1H), 4.13-4.03 (m, 2H), 1.24-1.15 (m, 3H). | 355.2, 353.2 |
| 97 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-(2-pyrrolidin-1-ylethyl)-57-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) δ ppm 7.43-7.42 (m, 1H), 7.36-7.30 (m, 2H), 6.77 (br s, 2H), 6.35 (t, J = 5.8 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.17-3.10 (m, 2H), 2.46-2.39 (m, 6H), 2.22 (s, 3H), 1.66-1.62 (m, 4H). | 401.2 |
| 98 |  | 2-amino-4-(4-chloro-2-methylphenyl)-N-(cyclopropylmethyl)-57-dihydro-6H-pyrrolo[34-d]pyrimidine-6-carboxamide | Example 7 | (300 MHz, DMSO-D6) δ ppm 7.43-7.42 (m, 1H), 7.35-7.33 (m, 2H), 6.77 (br s, 2H), 6.46 (t, J = 5.6 Hz, 1H), 4.41 (s, 2H), 4.25 (s, 2H), 2.90 (dd, J = 6.0 and 6.0 Hz, 2H), 2.23 (s, 3H), 0.97-0.87 (m, 1H), 0.38-0.32 (m, 2H), 0.16-0.11 (m, 2H) | 358.2 |

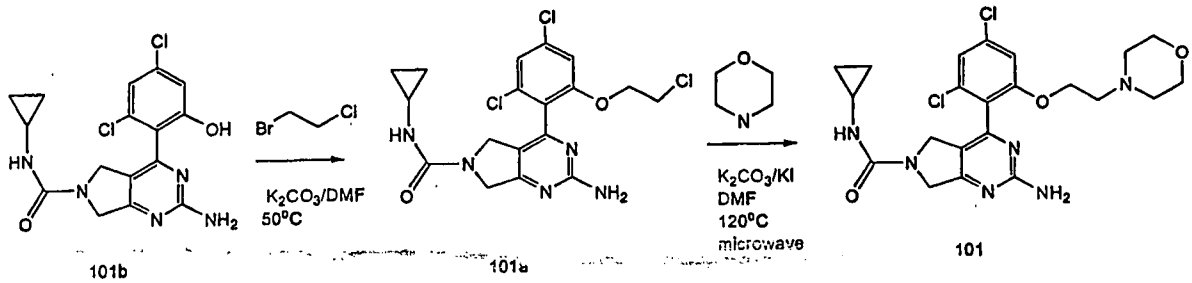
**Example 100: N-allyl-2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




100a 100

Compound **100a**, *N*-allyl-2-amino-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide, was prepared in a manner similar to Example **18a** except that allyl isocyanate was substituted for cyclobutylamine and CDI in Example **18b**. Compound **100a** (60mg, 0.16mmol), potassium carbonate (131mg, 0.95mmol.), 1-(2-bromoethyl)-1H-pyrazole (56mg, 0.316mmol) and DMF (2.0 mL) were microwaved at 120°C for 30 min. Isolation by preparative HPLC gave compound **100** (39 mg, 0.08 mmol) as a white solid in 52% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 3.60 (d, J=12.88 Hz, 2 H), 3.67 (t, J=5.05 Hz, 2 H), 3.94 (d, J=13.14 Hz, 2 H), 4.27 - 4.37 (m, 4 H), 4.41 (d, J=5.81 Hz, 2 H), 5.74 - 5.90 (m, 1 H), 6.00 (t, J=2.02 Hz, 1 H), 6.45 (br. s., 1 H), 6.78 (s, 2 H), 7.18 (d, J=2.02 Hz, 1 H), 7.25 (d, J=1.77 Hz, 1 H), 7.29 (d, J=1.52 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H). LCMS $(M+H)^+$ 474.0, 476.0.

**Example 101: 2-amino-N-cyclopropyl-4-[2,4-dichloro-6-(2-morpholin-4-ylethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**

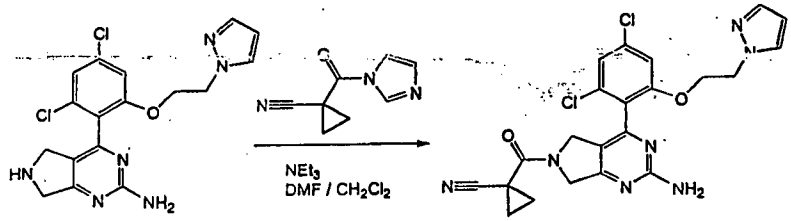



101b 101a 101

Compound **101b**, 2-amino-*N*-cyclopropyl-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide, was prepared in a manner similar to Example **18a** except that cyclopropylamine was substituted for cyclobutylamine in Example **18b**. Compound **101b** (800 mg, 2.1 mmol), potassium carbonate (872 mg, 6.31 mmol), 1-bromo-2-chloroethane (0.4 mL, 4.2 mmol) in DMF (8.0 mL) were heated

at 50°C for 12 h and the mixture was filtered. The collected insoluble material was washed with EtOAc. The combined filtrate/washings plus additional EtOAc (200 mL) were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50ml), dried ($Na_2SO_4$), filtered and concentrated. Isolation by silica gel chromatography (gradient of 0-10% MeOH in $CH_2Cl_2$) gave compound **101a**, 2-amino-N-cyclopropyl-4-[2,4-dichloro-6-(2-chloroethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide, (786 mg, 1.79 mmole) as brown grease in 85% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 0.32 - 0.43 (m, 2 H), 0.47 - 0.58 (m, 2 H), 3.69 - 3.86 (m, 1 H), 4.00 - 4.12 (m, 2 H), 4.19 (d, J=13.14 Hz, 2 H), 4.23 - 4.31 (m, 2 H), 4.32 - 4.45 (m, 2 H), 6.42 (d, J=2.78 Hz, 1 H), 6.80 (s, 2 H), 7.38 (d, J=1.77 Hz, 1 H), 7.96 (s, 1 H). LCMS $(M+H)^+$ 444.0, 446.0. Compound **101a** (50 mg, 0.11 mmol), $K_2CO_3$ (94mg, 0.68 mmol), KI (38mg, 0.23mmol), morpholine (30mg, 0.34mmol) and DMF (2.0 mL) were then microwaved at 130°C for 45min. Isolation by preparative HPLC gave compound **101** (32mg, 0.063mmole) as a white solid in 57% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 0.32 - 0.45 (m, 2 H), 0.48 - 0.58 (m, 2 H), 2.07 - 2.37 (m, 4 H), 2.52 - 2.58 (m, 1 H), 3.39 (br. s., 4 H), 4.02 - 4.22 (m, 5 H), 4.34 - 4.46 (m, 3 H), 6.46 (d, J=2.27 Hz, 1 H), 6.81 (br. s., 2 H), 7.32 (d, J=15.66 Hz, 2 H). LCMS $(M+H)^+$ 493.1, 495.1.

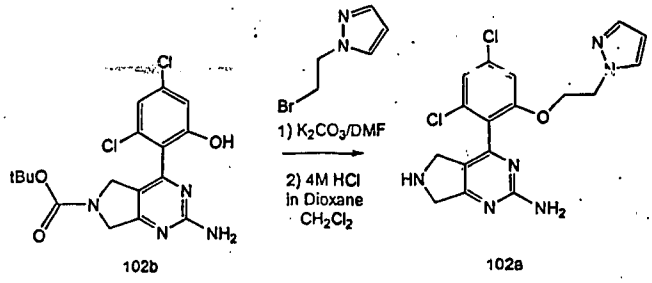
**Example 102: 2-amino-N-(1-cyanocyclopropyl)-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




102a 102

Compound **102a** ·HCl (45 mg, 0.12 mmol) was treated with the preformed adduct of 1-amino-cyclopropanecarbonitrile hydrochloride (59mg, 0.5 mmol) and CDI (126mg, 0.775 mmol) in a manner similar to that described for Example **18b**. Following extractive work up from EtOAc, washing with saturated aqueous $NaHCO_3$, the product was isolated by preparative HPLC to give compound **102** (38mg, 0.08mmole) as a white solid in 66%yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.12 (d, J=7.33 Hz, 2 H), 1.41 (br. s., 2 H), 3.57 (s, 2 H), 3.87 (d, J=12.63 Hz, 1 H), 4.33 (s, 4 H), 4.41 (d, J=7.33 Hz, 2 H), 6.02 (t, J=1.89 Hz, 1 H), 6.82 (s, 2 H), 7.21 (d, J=2.02 Hz, 1 H),7.26 (d, J=1.52 Hz, 1 H), 7.32 (dd,J=3.66,1.64 Hz,2H). LCMS $(M+H)^+$ 499.2.

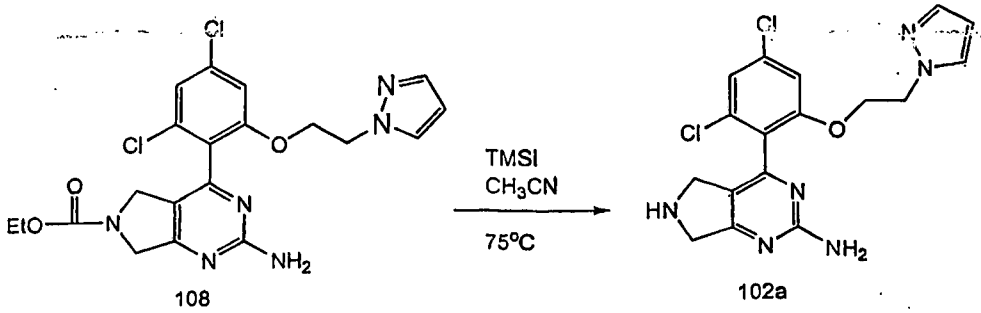
**Preparation of Compound 102a, 4-{2,4-dichloro-6-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine**




102b 102a

Compound **102b**, *tert*-butyl 2-amino-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, was prepared from compound **9a** (1090 mg, 3.0 mmol), compound **18c** (682mg, 3.3 mmol), $Pd(PPh_3)_4$ (347 mg, 0.3 mmol.), and 2M $Na_2CO_3$ (4.5 ml, 9.0 mmol) in 1,4-dioxane (25 mL) in a manner similar to that described for Example **1**. 1H NMR (400 MHz, DMSO-d6) d ppm 1.37 - 1.47 (m, J=12.88 Hz, 9 H) 4.07 - 4.24 (m, 2 H) 4.42 (d, J=7.58 Hz, 2 H) 6.82 (s, 2 H) 6.95 (d, J=1.77 Hz, 1 H) 7.08 - 7.21 (m, 1 H) 10.67 (s, 1 H). LCMS $(M+H)^+$ 397.1 399.1. Compound **102b** (1.627g, 4.1mmol) was O-alkylated using potassium carbonate (3.4 g, 24.6 mmol.), 1-(2-bromoethyl)-1H-pyrazole (1.43 g, 8.19 mmol) in DMF (10 mL) in a manner similar to that described for Example **100**. Boc deprotection was carried out using 4M HCl in 1,4-dioxane (10 mL) and MeOH (20mL)- stirring at ambient temperature for about 16h. Following extractive work up from EtOAc, washing with saturated aqueous $NaHCO_3$, the crude product was isolated by preparative HPLC to give compound **102a**, 4-{2,4-dichloro-6-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine, (405 mg, 0.95 mmol) as a white HCl salt in 26% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 3.51 (d, J=13.39 Hz, 2 H), 3.93 - 4.07 (m, 2 H), 4.24 - 4.44 (m, 4 H), 6.14 (br. s., 1 H), 6.65 (br. s., 2 H), 7.19 (br. s., 1 H), 7.24 (br. s., 1 H), 7.29 (br. s., 1 H), 7.40 (s, 1 H), 8.24 (s, 1 H). LCMS $(M+H)^+$ 391.2, 393.2.

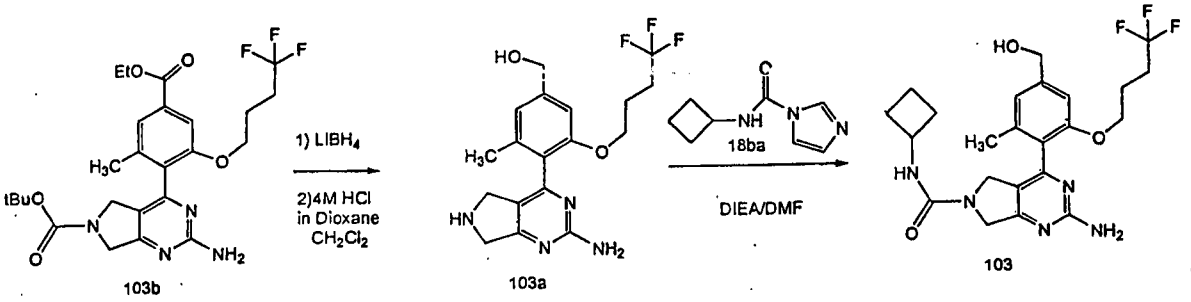
**Alternate Preparation of Compound 102a, 4-{2,4-dichloro-6-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine**




108 102a

Deprotection of the ethyl carbamate of compound **108** (5.06 g, 10.3 mmol) using iodotrimethylsilane (8.0 mL, 56 mmol) in $CH_3CN$ (80.0 mL) was carried out in a similar manner to Example **2**. Compound **102a** (8.46 g) was obtained as a crude HI salt. LCMS $(M+H)^+$: 393.2, 391.3.

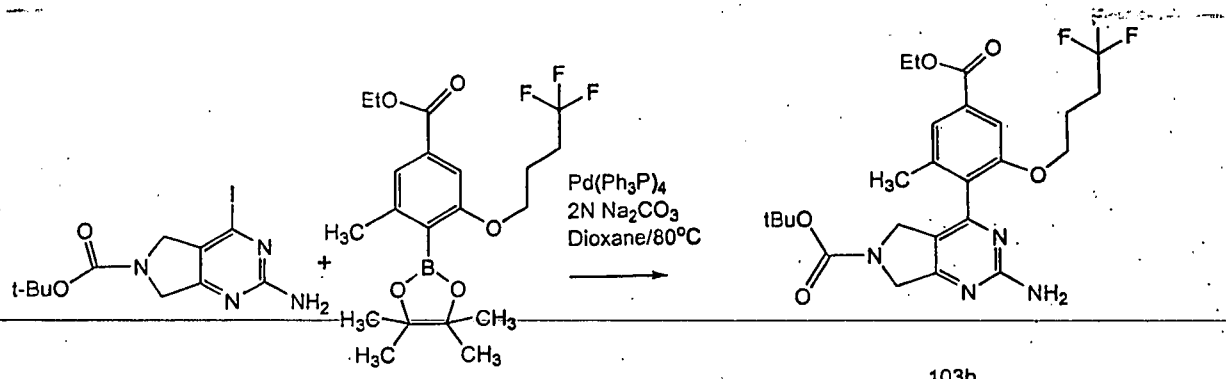
**Example 103: 2-amino-*N*-cyclobutyl-4-[4-(hydroxymethyl)-2-methyl-6-(4,4,4-trifluorobutoxy) phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




103b 103a 103

To compound **103b** (205 mg, 0.39 mmol) in THF (4 mL) at 0°C was added 2M $LiBH_4$ in THF (0.6 mL, 1.17 mmol) and MeOH (0.5 mL). The mixture was stirred at 0°C and allowed to warm to ambient temperature overnight. Following extractive work up from EtOAc (300 ml), washing with saturated aqueous $NaHCO_3$ (50ml) then brine (50ml), the EtOAc solution was dried ($Na_2SO_4$), filtered, and the volatile components removed to give the alcohol (185mg) as a clear grease which was carried on directly. LCMS $(M+H)^+$ 483.2, 484.2. For Boc deprotection, $CH_2Cl_2$ (5 mL) was added followed by 4M HCl in dioxane (1.0ml, 3.83mmol). After stirring 12 h, the mixture was concentrated and ether and hexane were added. The volatile components were removed to give compound **103a**, 4-(2-amino-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-yl)-3-methyl-5-(4,4,4-trifluorobutoxy)benzoic acid, (189 mg) as a yellow hydrochloride which was carried on without purification. LCMS $(M+H)^+$ 383.2, 384.2. Compound **103a** in DMF (2.0 mL) was reacted with compound **18ba** (76 mg, 0.46 mmol) and DIEA (0.4ml, 6.0mmol) in a manner similar to Example **18b**. Isolation by preparative HPLC gave compound **103** (33 mg, 0.083mmole) as a white solid in 21% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.44 - 1.61 (m, 2 H), 1.69 - 1.81 (m, 2 H), 1.84 - 1.98 (m, 2 H), 2.00 - 2.16 (m, 7 H), 3.92 - 4.05 (m, 3 H), 4.06 - 4.20 (m, 2 H), 4.37 (d, J=5.31 Hz, 2 H), 4.49 (d, J=5.56 Hz, 2 H), 5.25 (t, J=5.68 Hz, 1 H), 6.51 (d, J=7.83 Hz, 1 H), 6.65 (s, 2 H), 6.85 (s, 1 H), 6.89 (s, 1 H). LCMS $(M+H)^+$ 480.4, 481.4.

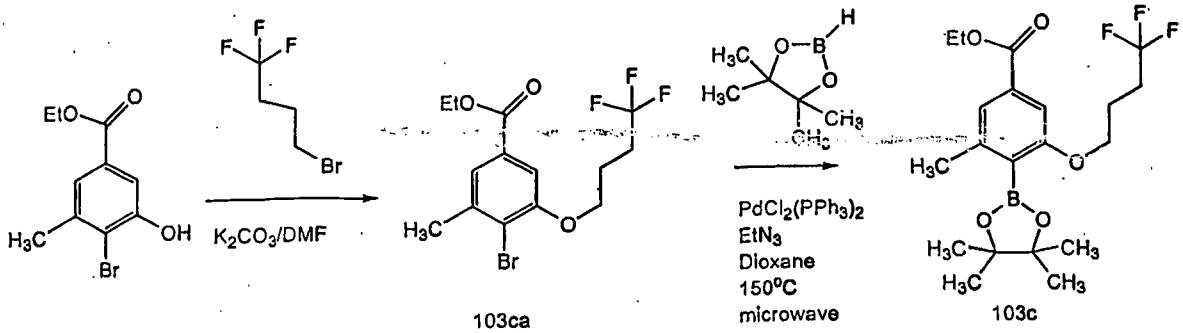
**Preparation of Compound 103b, 2-amino-N-cyclobutyl-4-[4-(hydroxymethyl)-2-methyl-6-(4,4,4-trifluorobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




9a 103c 103b

Compound **9a** (200 mg, 0.552 mmol) and compound **103c** (253mg, 0.61 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) and 2M $Na_2CO_3$ solution (0.8 ml, 1.66 mmol) in1,4-dioxane (6mL) were reacted for 48 h in a manner similar to Example **1**. Monitoring (LCMS) indicated that the reaction was incomplete so the mixture was microwaved at 160 °C for 1 h whereupon the suspension was filtered and the solids washed with MeOH. The combined filtrate/washings were concentrated and subjected to EtOAc (300 ml) extractive work up washing with saturated aqueous $NaHCO_3$ (50ml) and brine (50ml). Isolation by silica gel chromatography (gradient of 0-60% EtOAc in $CH_2Cl_2$) gave compound **103b** (205mg, 0.433mmole) as a clear grease in 71% yield. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.21 - 1.28 (m, 9 H), 1.38 - 1.54 (m, 4 H), 1.85 - 1.98 (m, 2 H), 1.98 - 2.12 (m, 2 H), 2.26 (d, J=4.55 Hz, 3 H), 3.98 - 4.13 (m, 2 H), 4.41 (q, J=7.07 Hz, 2 H), 4.60 (d, J=22.48 Hz, 2 H), 7.39 - 7.52 (m, 2 H), 7.59 - 7.73 (m, 1 H). LCMS $(M+H)^+$ 524.2, 526.2.

**Preparation of Compound 103c, ethyl 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4,4,4-trifluorobutoxy)benzoate**

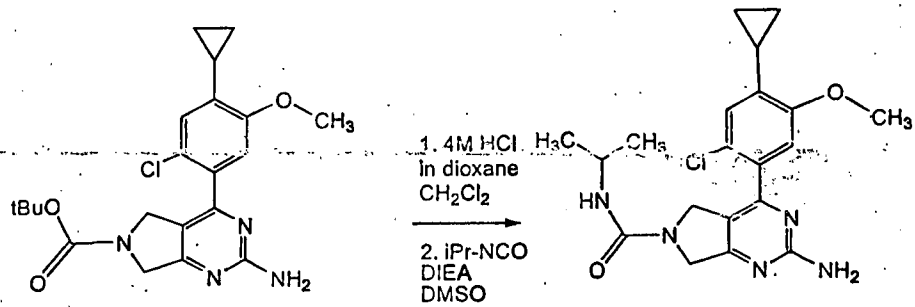



103ca 103c

Ethyl 4-bromo-3-hydroxy-5-methylbenzoate (650mg, 2.5mmol) was O-alkylated with 4-bromo-1,1,1-trifluorobutane (950mg, 5.0mmol) using potassium carbonate (1040mg,

7.5mmol) in DMF (5.0 mL) in a manner similar to that described for Example **100**. Isolation using silica gel chromatography (0-20% gradient of EtOAc in hexane) gave compound **103ca**, ethyl 4-bromo-3-methyl-5-(4,4,4-trifluorobutoxy)benzoate, (858 mg, 2.33mmole) as a white solid in 93% yield. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.41 (t, *J*=7.20 Hz, 3 H), 2.04 - 2.21 (m, 2 H), 2.32 - 2.44 (m, 2 H), 2.44 - 2.50 (m, 3 H), 4.15 (t, *J*=5.94 Hz, 2 H), 4.38 (q, *J*=7.07 Hz, 2 H), 7.35 (d, *J*=1.77 Hz, 1 H), 7.57 (d, *J*=1.01 Hz, 1 H). Compound **103ca** (561mg, 1.52mmol), pinacolborane (0.7ml, 4.6 mmol), $Et_3N$ (0.9ml, 6.1mmol) in 1,4-dioxane (6.0 mL) were purged with $N_2$ for 15 min, then $Pd(II)Cl_2(PPh_3)_2$ (107mg, 0.1 mmol) was added. The mixture was microwaved at 150°C for 1 h, cooled and filtered through celite washing with EtOAc. The combined filtrate/washings were washed with water (50ml), brine (50ml), dried ($Na_2SO_4$), filtered and concentrated. Isolation using silica gel chromatography (0-20% gradient of EtOAc in hexane) gave compound **103c** (252mg, 0.61mmole) in 40% yield. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.37 - 1.41 (m, 15 H), 2.05 (dd, J=10.74, 5.68 Hz, 2 H), 2.31 - 2.39 (m, 2 H), 2.39 - 2.41 (m, 3 H), 4.06 (t, J=5.81 Hz, 2 H), 4.36 (q, J=7.24 Hz, 2 H), 7.25 (s, 1 H), 7.46 (s, 1 H).

**Example 104: 2-amino-4-(2-chloro-4-cyclopropyl-5-methoxyphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**

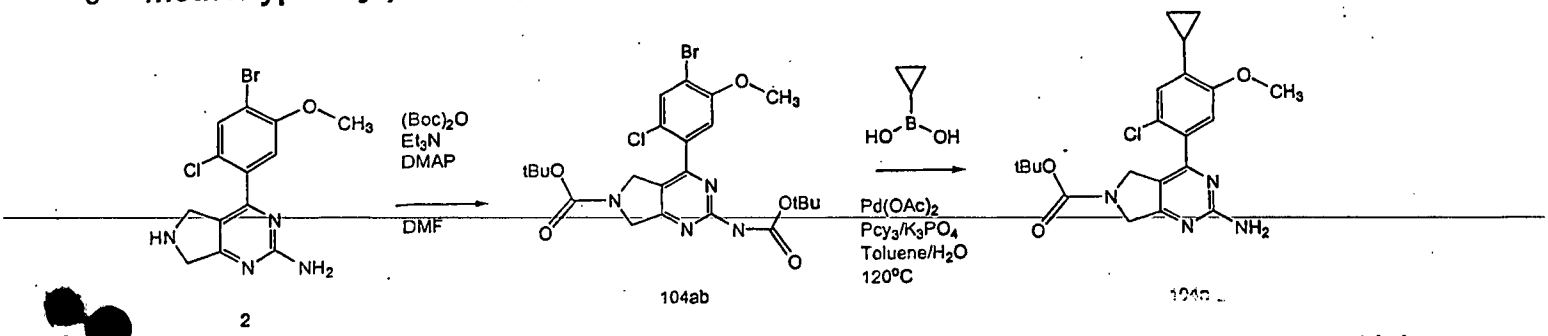



104a 104

To compound **104a** (67 mg, 0.16 mmol) in $CH_2Cl_2$ (4.0 mL) was added 4M HCl in 1,4-dioxane (0.2ml, 0.804mmol). After stirring at ambient temperature for 12 h, the mixture was concentrated and treated with ether and hexane. Removal of the volatile components gave the Boc-deprotected intermediate (65 mg) as a yellow hydrochloride which was carried on directly. LCMS $(M+H)^+$ 317.2, 319.2. Dimethylformamide (2.0 mL) and diisopropylethylamine (0.14, 0.8 mmol) were added followed by isopropyl isocyanate (14.0 mg, 0.16 mmol) to form the urea in a manner similar to Example **15a**. Isolation by preparative HPLC gave compound **104** (13 mg, 0.032mmol) as brown foam in 20% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 0.69 - 0.78 (m, 2 H), 0.90 - 0.98 (m,

2 H), 1.05 (d, J=6.57 Hz, 6 H), 2.04 - 2.18 (m, 1 H),3.77 (t, J=6.95 Hz, 1 H), 3.81 (s, 3 H), 4.25 (s, 2 H), 4.40 (s, 2 H), 6.09 (d, J=7.83 Hz, 1 H), 6.82 (s, 2 H), 6.95 (s, 2 H). LCMS $(M+H)^+$ 402.2, 404.2.

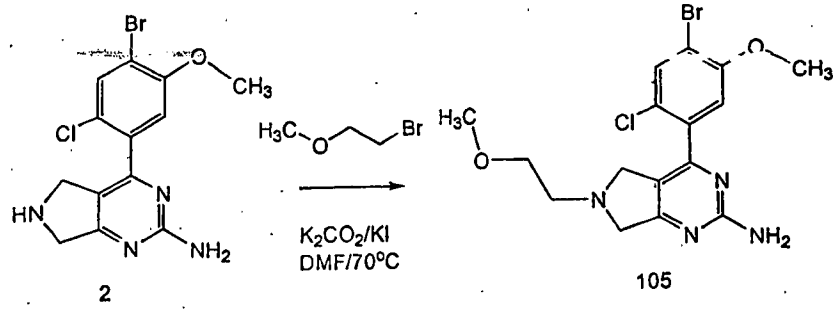
**Preparation of Compound 104a, *tert*-butyl 2-amino-4-(2-chloro-4-cyclopropyl-5-methoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**




2 104ab 104a

To compound **2** (612mg, 1.0mmol) and di-tert-butyldicarbonate (655mg, 3.0mmol.) in DMF (5.0 mL) was added triethylamine (0.84ml, 6.0 mmol) and DMAP (25mg, 0.2 mmol). After stirring 4 h at ambient temperature, the mixture was subjected EtOAc (200ml) extractive work up washing with saturated aqueous $NaHCO_3$ (50ml) and brine (50ml). After drying ($Na_2SO_4$), filtering and concentrating, isolation using silica gel chromatography (0-50% gradient of EtOAc in $CH_2Cl_2$) gave compound **104ab**, *tert*-butyl 4-(4-bromo-2-chloro-5-methoxyphenyl)-2-[(*tert*-butoxycarbonyl) amino]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, (320mg, 0.58mmole) as yellowish foam in 58% yield. 1H NMR (400 MHz, DMF-d7) δ ppm 1.34 - 1.50 (m, 18 H), 3.84 - 3.90 (m, 3 H), 4.30 (d, J=7.33 Hz, 2 H), 4.45 (d, J=6.06 Hz, 2 H), 7.16 (d, J=3.79 Hz, 1 H), 7.88 (d, J=3.54 Hz, 1 H), 7.97 (s, 1 H). LCMS $(M+H)^+$ 556.4, 558.4. Compound **104ab** (167 mg, 0.3 mmol), cyclopropylboronic acid (52mg, 0.6 mmol), $K_3PO_4$ (255mg, 1.20 mmol) and tricyclohexylphosphine (9.0mg, 0.03 mmol) in toluene (4.0 mL) with $H_2O$ (0.1 mL) were purged with $N_2$ for 15 min then $Pd(OAc)_2$ (4.0 mg, 0.02mmol) was added. After heating at 120°C for 6 h, the mixture was filtered through celite washing with EtOAc. The filtrate/washings were subjected to EtOAc (500 ml) extractive work up washing with saturated aqueous $NaHCO_3$ (100ml) and brine (100ml). Following drying ($Na_2SO_4$), filtration and concentration, isolation using silica gel chromatography (0-50% gradient of EtOAc in $CH_2Cl_2$) gave compound **104a** (67mg, 0.324mmole) as a yellowish foam in 54% yield. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.79 - 0.94 (m, 2 H), 0.94 - 1.06 (m, 2 H), 1.43 - 1.54 (m, 9 H), 2.08 - 2.25 (m, 1 H), 3.84 - 3.93 (m, 3 H), 4.48 (d, J=19.70 Hz, 2 H), 4.58 (d, J=23.75 Hz, 2 H), 5.28 (s, 2 H), 6.77 (d, J=10.11 Hz, 1 H), 6.87 (d, J=11.12 Hz, 1 H). LCMS $(M+H)^+$ 417.2, 419.2.

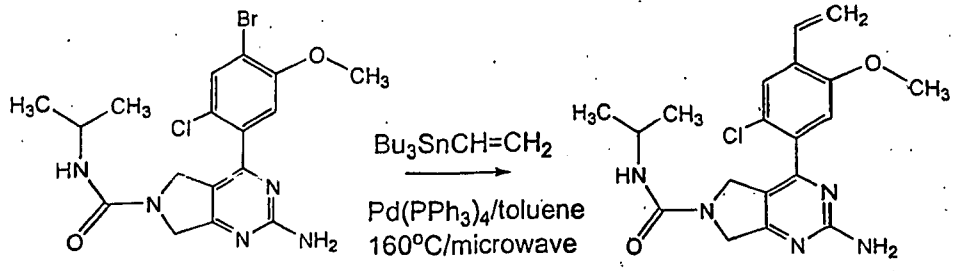
**Example 105: 4-(4-bromo-2-chloro-5-methoxyphenyl)-6-(2-methoxyethyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-2-amine**




2 105

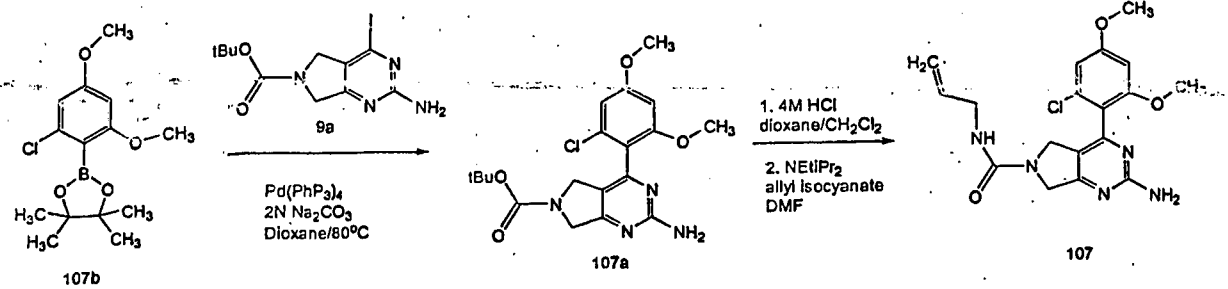
The hydrochloride of compound **2** (70 mg, 0.16 mmol), $K_2CO_3$ (225mg, 1.63 mmol), and 2-bromoethylmethyl ether (113mg, 0.82mmol) in DMF (3mL) were microwaved at 100°C for 2 h. Isolation by preparative HPLC gave compound **105** (13mg, 0.03mmole) as a white solid in 19% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 3.27 - 3.32 (m, 3 H), 3.47 - 3.60 (m, 2 H), 3.66 (br. s., 2 H), 3.84 - 3.93 (m, 3 H), 4.35 - 4.62 (m, 4 H), 7.05 - 7.12 (m, 1 H), 7.14 - 7.25 (m, 2 H), 7.91 (s, 1 H). LCMS $(M+H)^+$ 415.0, 417.0.

**Example 106: 2-amino-4-(2-chloro-4-ethenyl-5-methoxyphenyl)-*N*-(1-methylethyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Compound **55** (66 mg, 0.15 mmol) and ethenyltributylstannane (62mg, 0.2 mmol) in toluene (1mL) and dioxane (1 mL) were purged with $N_2$ and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) was added and the mixture was microwaved at 160°C for 30 min. The mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and subjected to EtOAc (200 ml) extractive work up washing with saturated aqueous $NaHCO_3$ (50ml) and brine (50ml). Following drying ($Na_2SO_4$) and concentration, isolation by preparative HPLC gave compound **106** (11 mg, 0.029 mmole) as a white solid in 19% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 1.02 - 1.10 (m, 6 H), 3.74 - 3.80 (m, 1 H), 3.79 - 3.86 (m, 3 H), 4.28 (s, 2 H), 4.43 (s, 2 H), 5.40 (d, J=12.38 Hz, 1 H), 5.98 (dd, J=17.94, 1.01 Hz, 1 H), 6.09 (d, J=6.82 Hz, 2 H), 6.93 (dd, J=17.68, 11.37 Hz, 1 H), 7.06 (s, 1 H), 7.70 (s, 1 H). LCMS $(M+H)^+$ 386.2, 386.2.

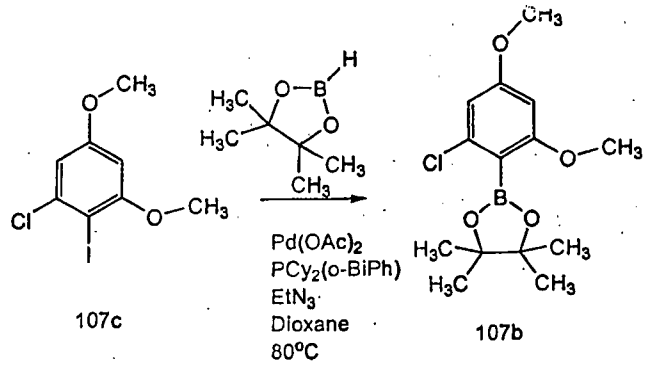
**Example 107: 2-amino-4-(2-chloro-4,6-dimethoxyphenyl)-*N*-prop-2-en-1-yl-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Compound **9a** (199 mg, 0.549 mmol), compound **107b** (164mg, 0.549 mmol), $Pd(PPh_3)_4$ (32 mg, 0.027 mmol) and 2M aqueous $Na_2CO_3$ (0.8 ml, 1.65 mmol) in 1,4-dioxane (4 mL) were reacted in a manner similar to Example **9**. Isolation using silica gel chromatography (gradient of 0-10% MeOH in $CH_2Cl_2$) gave compound **107a**, *tert*-butyl 2-amino-4-(2-chloro-4,6-dimethoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, (204mg, 0.52mmole) as a yellowish solid. LCMS $(M+H)^+$ 407.4, 409.4. To Boc-deprotect, treatment of compound **107a** (204 mg, 0.5 mmol) in $CH_2Cl_2$ (5 mL) with 4M HCl in 1,4-dioxane (1.3mL) in a manner similar to Example **102a** gave the hydrochloride (200 mg) as a yellow grease which was carried on without purification.

LCMS $(M+H)^+$ 307.2, 309.2. A portion of the Boc-deprotected hydrochloride (95mg, 0.25 mmol) in DMF (2.0 mL) was treated with diisopropylethylamine (0.3ml, 1.5 mmol) and allyl isocyanate (21 mg, 0.25 mmol) in a manner similar to Example **15a**. Isolation by preparative HPLC gave compound **107** (15mg, 0.038mmol) as a white solid in 15% yield. 1H NMR (400 MHz, DMSO-d6) δ ppm 3.62 - 3.70 (m, 2 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 4.09 - 4.18 (m, 2 H), 4.43 (s, 2 H), 5.00 (dd, J=10.36, 1.52 Hz, 1 H), 5.10 (dd, J=17.18, 1.52 Hz, 1 H), 5.72 - 5.88 (m, 1 H), 6.57 (t, J=5.56 Hz, 1 H), 6.67 (d, J=2.27 Hz, 1 H), 6.72 - 6.78 (m, 2 H). LCMS $(M+H)^+$ 390.1, 392.

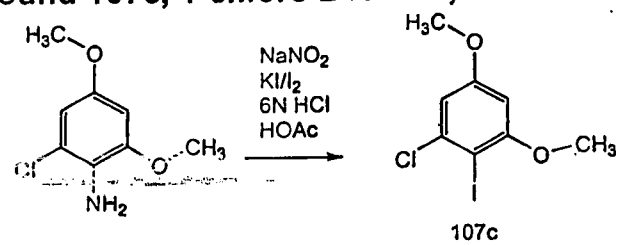
**Preparation of Compound 107b, 2-(2-chloro-4,6-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**




107c 107b

Compound **107c** (1.45g, 4.86mmol), pinacolborane (1.4ml, 9.72 mmol) and $Et_3N$ (2.0ml, 14.6.0mmol), palladium (II) acetate (55mg, 0.243 mmol) and 2-(dicyclohexylphosphino)biphenyl (170mg, 0.7mmol.) in 1,4-dioxane (25 mL). were reacted in a manner similar to Example **18ca**. Isolation using silica gel chromatography (gradient of 0-20% EtOAc in hexane) gave compound **107b** (1.104g, 3.74mmole) as a yellowish solid in 77% yield. NMR data: 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.37 (s, 12 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 6.25 (s, 1 H), 6.44 (s, 1 H).

**Preparation of Compound 107c, 1-chloro-2-iodo-3,5-dimethoxybenzene**

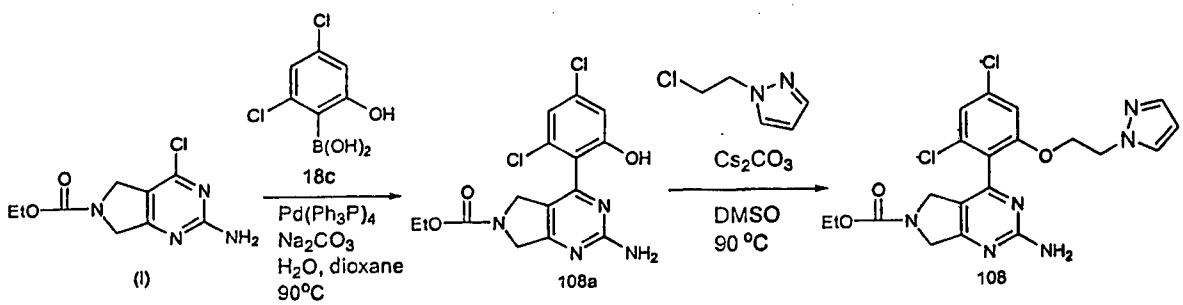



107c

To (2-chloro-4,6-dimethoxyphenyl)amine (1.9 g, 10.0 mmol) in acetic acid (40 mL) was added 6M HCl (10mL). With stirring & cooling in an ice salt bath, sodium nitrite (828 mg, 12.0 mmol) in water (6mL) was added slowly keeping the reaction temperature <5°C. After addition, the mixture was stirred for about 30 min and a solution of potassium iodide (3320 mg, 20.0 mmol) and iodine (761 mg, 3.0 mmol) in water (35 mL)

was added dropwise. The mixture was allowed to warm to ambient temperature over about 90 min and water (120 mL) was added. The mixture was subjected to EtOAc (2x300 mL) extractive work up and the combined extracts were washed with 10% aqueous $Na_2S_2O_3$ solution (2x100ml) and brine (100ml). After drying ($Na_2SO_4$), filtering and concentrating, isolation using silica gel chromatograpy (0-30% gradient of EtOAc in hexane) gave compound **107c** (1.45g, 4.9mmole) as a yellowish solid in 49% yield. 1H NMR (400 MHz, CHLOROFORM-D) d ppm 3.79 (s, 3 H), 3.84 (s, 3 H), 6.30 (d, J=2.53 Hz, 1 H), 6.68 (d, J=2.53 Hz, 1 H).

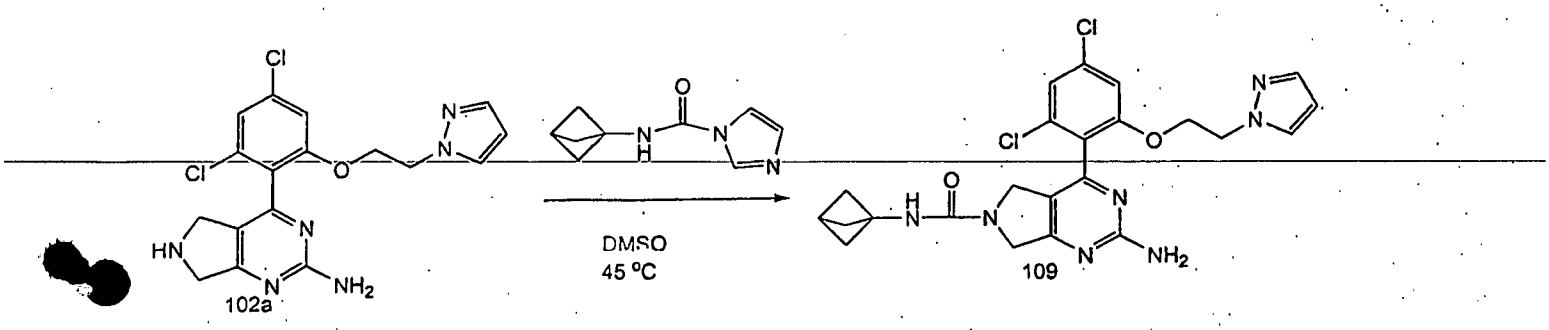
**Example 108: ethyl 2-amino-4-{2,4-dichloro-6-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**




Compound **(i)** (4.04 g, 16.6 mmol), compound **18c** (4.82 g, 23.3 mmol), 2M aqueous sodium carbonate (21 ml, 42 mmol), and tetrakis(triphenylphosphino)palladium (0) (1.82 g, 1.58 mmol) in 1,4 dioxane (200 mL) were reacted in a manner similar to Example **1.** Extractive work up with EtOAc was carried out in a manner similar to Example **18a** first using 0.5N aq NaOH (300 mL) to extract the phenol product into the basic aqueous layer followed by acidification to pH 5 with 1N $KH_2PO_4$ (75 mL) and extraction of phenol product into EtOAc (400 mL). The EtOAc layer was concentrated to give compound **108a,** ethyl 2-amino-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (6.15 g) which was carried on without purification. 1H NMR (400 MHz, DMSO-d6) d ppm 1.07 - 1.34 (m, 3 H) 3.99 - 4.26 (m, 4 H) 4.48 (d, J=11.87 Hz, 2 H) 6.84 (s, 2 H) 7.14 (d, J=1.77 Hz, 1 H) 7.48 - 7.79 (m, 1 H) 10.71 (s, 1 H). LCMS $(M+H)^+$: 369.0 371.0. Compound **108a** (5.11 g, 13.8 mmol), 1-(2-chloro-ethyl)-1H-pyrazole (5.02 g, 38.4 mmol) and cesium carbonate (15.8 g, 48.4 mmol) in DMSO (50.3 mL) were reacted at 90 °C in a manner similar to Example **18.** Following extractive work up from EtOAc (500 mL), washing with water (200 mL), the product was isolated using silica gel chrmoatography (100% EtOAc followed by a gradient of 0-13% MeOH in dichloromethane) to give compound **108** (5.06 g, 13.8 mmol) as a tan powder in 77% yield. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 1.13 - 1.29 (m, 3 H) 3.49 - 3.64 (m, 1 H)

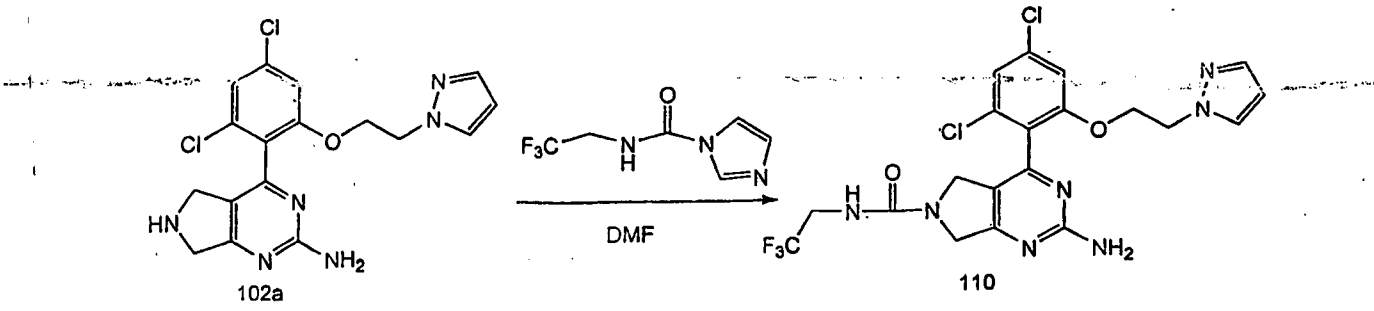
3.91 (d, *J*=13.19 Hz, 1 H) 4.02 - 4.19 (m, 2 H) 4.34 (s, 4 H) 4.40 - 4.48 (m, 2 H) 5.99 - 6.04 (m, 1 H) 6.83 (s, 2 H) 7.23 - 7.28 (m, 2 H) 7.28 - 7.33 (m, 2 H). LCMS $(M+H)^+$: 465.2, 463.2.

**Example 109: 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




Bicyclo[1.1.1]pentan-1-amine-HCl (637 mg, 5.33 mmol) followed by triethylamine (4.00 mL, 28.7 mmol) were added to 1,1-carbonyldiimidazole (870 mg, 5.37 mmol) in DMF (50 mL) at 0 °C. The mixture was stirred at ambient temperature for 1h and crude compound **102a** · HI salt (4.650 g, 5.150 mmol) was added. The mixture heated to 45°C for 0.5h. Following EtOAc extractive work up, washing with water, the crude product was subjected to silica gel chromatography (gradient of 10-15% MeOH in dichloromethane). After isolation, 10% $CH_3CN$ in water was added. Following lyophilization, compound **109** (1.54 g, 3.08 mmol) was obtained as a white powder in 58% yield. $^1H$ NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.95 (s, 6 H) 2.36 (s, 1 H) 3.53 (d, J=13.19 Hz, 1 H) 3.89 (d, J=13.00 Hz, 1 H) 4.33 (s, 6 H) 5.99 - 6.02 (m, 1 H) 6.77 (br. s., 2 H) 6.85 (br. s., 1 H) 7.19 (d, J=2.07 Hz, 1 H) 7.25 (d, J=1.51 Hz, 1 H) 7.30 (d, J=1.70 Hz, 1 H) 7.32 (d, J=1.70 Hz, 1 H). LCMS $(M+H)^+$: 502.2, 500.2.

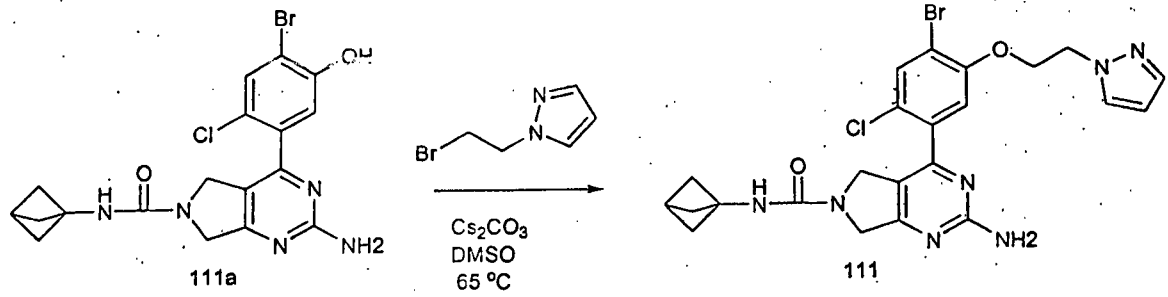
**Example 110: 2-amino-4-{2,4-dichloro-6-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-*N*-(2,2,2-trifluoroethyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




2,2,2-Trifluoroethylamine (19.8 mg, 0.200 mmol), 1,1-carbonyldiimidazole (32.4 mg, 0.200 mmol), compound **102a** ·HCl (89.9 mg, 0.180 mmol) and triethylamine (0.080 mL,

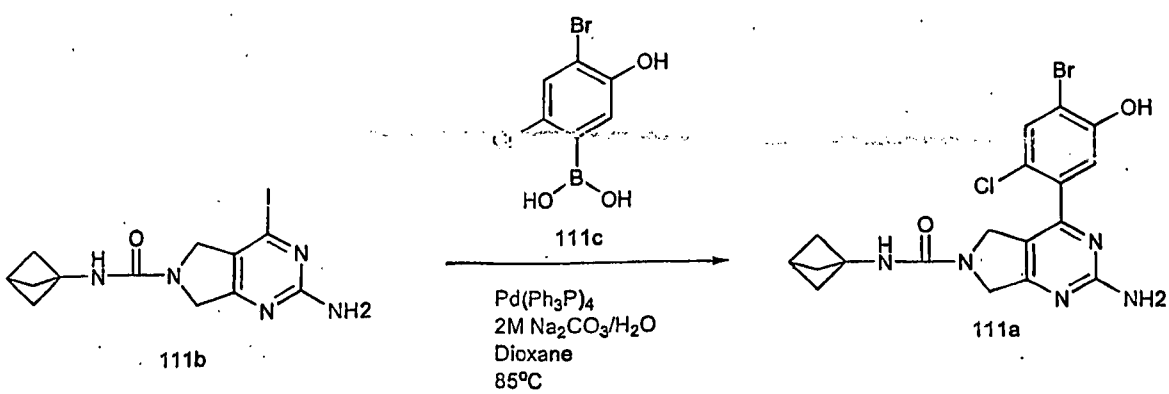
0.57 mmol) in DMF (2 mL) were reacted in a manner similar to Example **18b.** Isolation using preparative HPLC gave compound **110** (37 mg, 0.72 mmol) as a white powder in 40% yield. 1H NMR (400 MHz, DMSO-d6) $\delta$ ppm 3.54 (d, J=12.38 Hz, 1 H) 3.77 - 3.92 (m, 2 H) 3.94 (d, J=12.88 Hz, 1 H) 4.42 - 4.50 (m, 2 H) 5.98 (t, J=2.15 Hz, 1 H) 6.82 (s, 2 H) 7.21 (d, J=2.02 Hz, 1 H) 7.27 (s, 2 H) 7.33 (d, J=1.77 Hz, 1 H). LCMS $(M+H)^+$: 518.0, 516.0.

**Example 111: 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-{4-bromo-2-chloro-5-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**



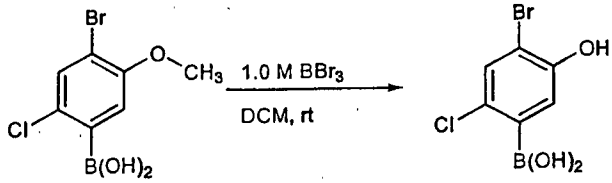

Compound **111a** (44.0 mg, 0.0976 mmol) was alkylated with 1-(2-bromo-ethyl)-1H-pyrazole (32.4 mg, 0.185 mmol) and cesium carbonate (122 mg, 0.374 mmol) in DMSO (1.5 mL) in a manner similar to that described in Example **18.** Isolation using preparative HPLC gave compound **111** (29 mg, 0.053 mmol) as a white powder in 55% yield. 1H NMR (300 MHz, DMSO-d6) d ppm 1.92 (s, 6 H) 2.34 (s, 1 H) 4.21 (s, 2 H) 4.36 - 4.42 (m, 4 H) 4.52 (t, J=4.71 Hz, 2 H) 6.24 (t, J=1.98 Hz, 1 H) 6.88 (s, 2 H) 6.99 (s, 1 H) 7.15 (s, 1 H) 7.44 (d, J=1.70 Hz, 1 H) 7.78 (d, J=2.26 Hz, 1 H) 7.84 (s, 1 H). LCMS $(M+H)^+$: 546.2, 544.2.

**Preparation of Compound 111a, 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-(4-bromo-2-chloro-5-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**



Compound **111b**, 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-iodo-5,7-dihydro-6*H*-pyrrolo[3,4-*d*] pyrimidine-6-carboxamide, was prepared from compound **8b** in a manner similar to Example **18b** except that bicyclo[1.1.1]pentan-1-amine-HCl was subtituted for cyclobutylamine. The coupling of compound **111b** (0.2995 g, 0.8070 mmol) with compound **111c** (0.201 g, 0.800 mmol) was carried out using tetrakis(triphenylphosphino)palladium(0) (0.065 g, 0.070 mmol) and 2M aqueous sodium carbonate (0.80 mL, 1.6 mmol) in 1,4-dioxane (5.0 mL) in a manner similar to that described for Example **1**. Extractive work up involved aqueous base extraction followed by acidification and EtOAc extraction in a manner similar to Example **108a**. Isolation gave compound **111a** (0.316 g) as a tan solid which was carried on without purification. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 1.93 (s, 6 H) 2.34 (s, 1 H) 4.22 (s, 2 H) 4.38 (s, 2 H) 6.87 (br. s., 2 H) 6.91 (s, 1 H) 7.01 (s, 1 H) 7.74 (s, 1 H) 10.83 (br. s., 1 H). LCMS $(M+H)^+$: 452.0, 450.0.

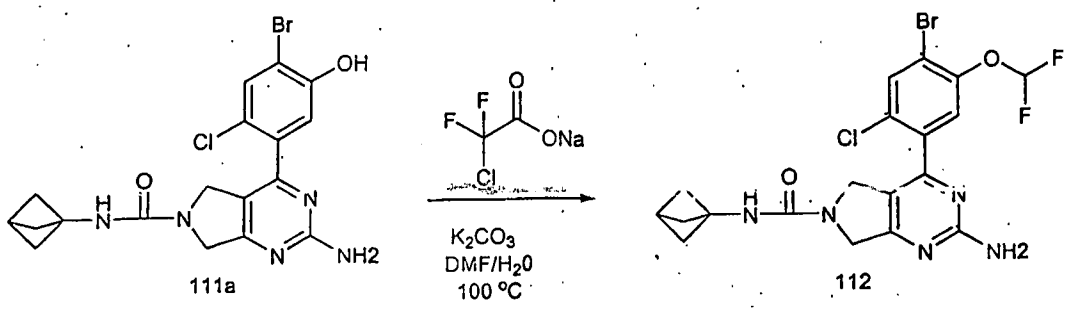
**Preparation of Compound 111c, (4-bromo-2-chloro-5-hydroxyphenyl)boronic acid**




111c

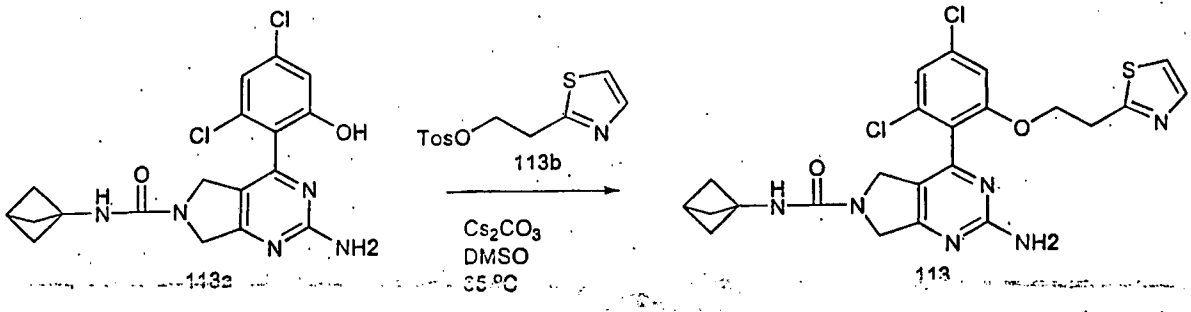
To a suspension of (4-bromo-2-chloro-5-methoxyphenyl)boronic acid (4.96 g, 18.7 mmol) in dichloromethane (125 mL) at 0 °C was added 1 M boron tribromide (52 mL, 52 mmol) in dichloromethane. The reaction mixture was allowed to warm to ambient temperature and stir for 48h. The reaction mixture was then poured over ice, 3N NaOH (52 mL) was added, and the mixture was stirred vigorously for 30 minutes. The layers were separated, and the dichloromethane layer was discarded. The aqueous layer, a slurry, was acidified to pH 5 with concentrated HCl and EtOAc extractive work up gave compound **111c** (4.614 g, 18.36 mmol) as a white powder which was carried on without purification.

**Example 112: 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-[4-bromo-2-chloro-5-(difluoromethoxy) phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**



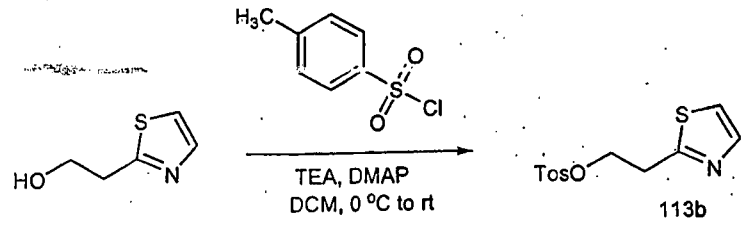

Nitrogen was bubbled through a solution of compound **111a** (53 mg, 0.12 mmol) in DMF (1.0 mL) and $H_2O$ (0.13 mL) for 10 minutes. Potasium carbonate (0.092 g, 0.67 mmol) and sodium chlorodifluoroacetate (0.067 g, 0.44 mmol) were added. The reaction mixture was heated to 100°C for 4h. Isolation using preparative HPLC gave compound **112** (0.019 g, 0.038 mmol) as a white powder in 32% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.93 (s, 6 H) 2.35 (s, 1 H) 4.23 (s, 2 H) 4.39 (s, 2 H) 6.94 (s, 1 H) 6.99 - 7.03 (m, 1 H) 7.36 (t, J=72.90 Hz, 1 H) 7.43 (s, 1 H) 8.10 (s, 1 H). LCMS $(M+H)^+$: 502.2, 500.0.

**Example 113: 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[2-(1,3-thiazol-2-yl) ethoxy]phenyl}-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Compound **113a**, 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-(2,4-dichloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide, was prepared in a similar manner as Example **18a** except that bicyclo[1.1.1]pentan-1-amine-HCl was subtituted for cyclobutylamine. Compound **113a** (65 mg, 0.16 mmol), cesium carbonate (201 mg, 0.617 mmol) and compound **113b** (73 mg, 0.26 mmol) in DMSO (1.5 mL) were heated to 65 °C. After 0.5 h, additional compound **113b** (196 mg ,0.629 mmol) was added in portions over 5 h with continuing heat. Extractive work up from EtOAc, washing with water, followed by isolation using preparative HPLC gave compound **113** (0.0101 g, 0.0195 mmol) as a white solid in 12% yield. 1H NMR (400 MHz, DMSO-d6) $\delta$ ppm 1.95 (s, 6 H) 2.36 (s, 1 H) 3.26 (t, J=5.81 Hz, 2 H) 3.57 (d, J=12.63 Hz, 1 H) 3.90 (d, J=13.14 Hz, 1 H) 4.31 - 4.39 (m, 4 H) 6.75 (s, 2 H) 6.87 (s, 1 H) 7.31 (d, J=1.77 Hz, 1 H) 7.33 (d, J=1.77 Hz, 1 H) 7.35 (d, J=3.28 Hz, 1 H) 7.58 (d, J=3.28 Hz, 1 H). LCMS $(M+H)^+$: 519.2, 517.2.

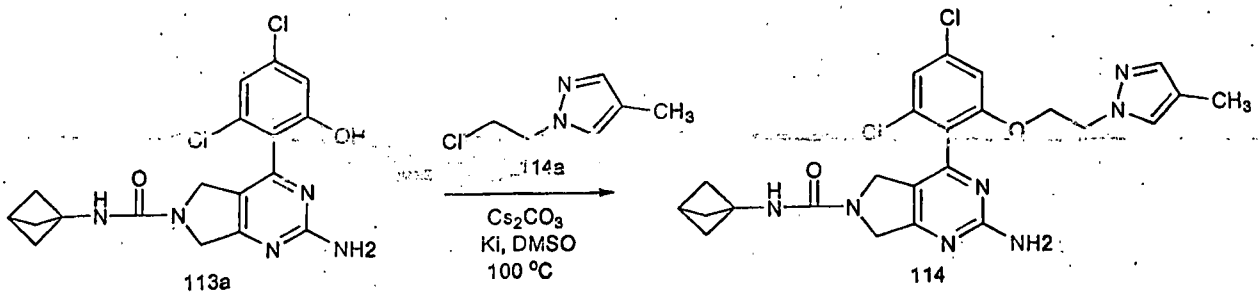
**Preparation of Compound 113b, 2-(1,3-thiazol-2-yl)ethyl 4-methylbenzenesulfonate**




113b

To 2-(1,3-thiazol-2-yl)ethanol (123 mg, 0.952 mmol) (Young et. al. *Eur. J. Med. Chem.*, 28: 201-211; (1993)) and triethylamine (0.15 mL, 1.1 mmol) in dichloromethane (5.0 mL) at 0 °C was added 4-toluensulfonyl chloride (189 mg, 0.991 mmol) and an unmeasured amount of catalytic DMAP. The mixture was stirred overnight and allowed warm to warm to ambient temperature. Extractive work up from dichloromethane (30 mL), washing with saturated aqueous $NH_4Cl$, gave compound **113b** (0.255 g, 0.901mmol) in 95% crude yield. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 2.42 (s, 3 H) 3.34 (t, *J*=6.03 Hz, 2 H) 4.36 (t, *J*=6.03 Hz, 2 H) 7.46 (d, *J*=8.48 Hz, 2 H) 7.60 (d, *J*=3.39 Hz, 1 H) 7.69 (d, *J*=3.39 Hz, 1 H) 7.72 (d, *J*=8.10 Hz, 2 H). LCMS $(M+H)^+$: 284.1.

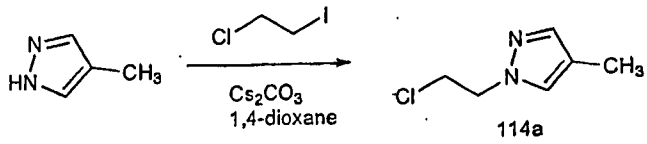
**Example 114: 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[2-(4-methyl-1*H*-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




113a 114

Compound **113a** (59 mg, 0.15 mmol), compound **114a** (49 mg, 0.34 mmol), cesium carbonate (177 mg, 0.543 mmol), and potassium iodide (7 mg) in DMSO (1.5 mL) were heated at 100 °C for 6 h. Isolation by preparative HPLC gave compound **114** (0.0258 g, 0.0501 mmol) as a white solid in 35% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.90 (s, 3 H) 1.94 (s, 6 H) 2.35 (s, 1 H) 3.69 (d, J=13.38 Hz, 1 H) 3.95 (d, J=12.24 Hz, 1 H) 4.20 - 4.39 (m, 6 H) 6.80 (s, 2 H) 6.89 - 6.93 (m, 1 H) 6.97 (s, 1 H) 7.10 (s, 1 H) 7.25 (d, J=1.51 Hz, 1 H) 7.33 (d, J=1.13 Hz, 1 H). LCMS $(M+H)^+$: 516.2, 514.2.

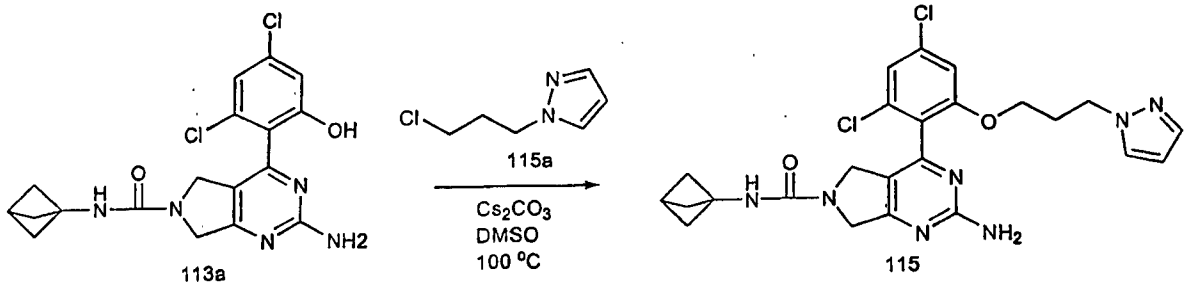
**Preparation of Compound 114a, 1-(2-chloroethyl)-4-methyl-1*H*-pyrazole**




114a

4-Methyl pyrazole (0.177 g, 2.16 mmol), 1-chloro-2-iodoethane (1.20 g, 6.30 mmol) and cesium carbonate (1.10 g, 3.38 mmol) in 1,4-dioxane (5.0 mL) were heated at 95 °C for 24h. After cooling to ambient temperature, dichloromethane (10 mL) was added. Following filtration to remove solids, the filtrate was reduced and subjected to silica gel chromatography (gradient of 0-70% EtOAc in hexane) which gave compound **114a** (0.049 g, 0.34 mmol) as clear oil in 16% yield. 1H NMR (300 MHz, CHLOROFORM-*d*) d ppm 2.12 (s, 3 H) 3.92 (t, *J*=5.84 Hz, 2 H) 4.49 (t, *J*=5.93 Hz, 2 H) 7.33 (s, 1 H) 7.46 (s, 1 H).

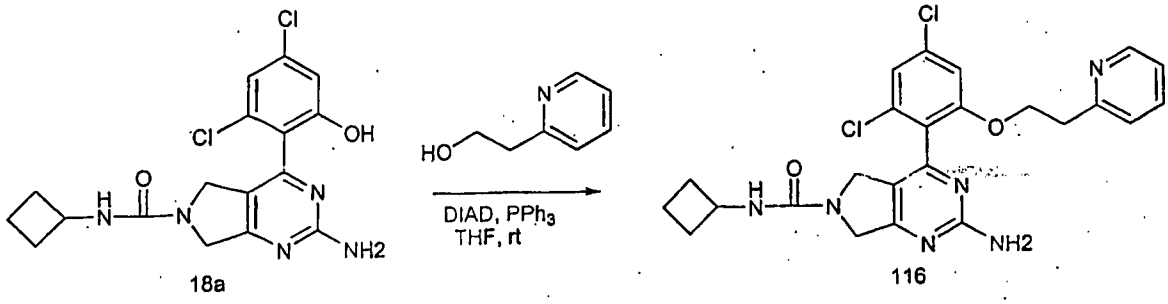
**Example 115: 2-amino-*N*-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[3-(1*H*-pyrazol-1-yl)propoxy]phenyl}-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




113a 115

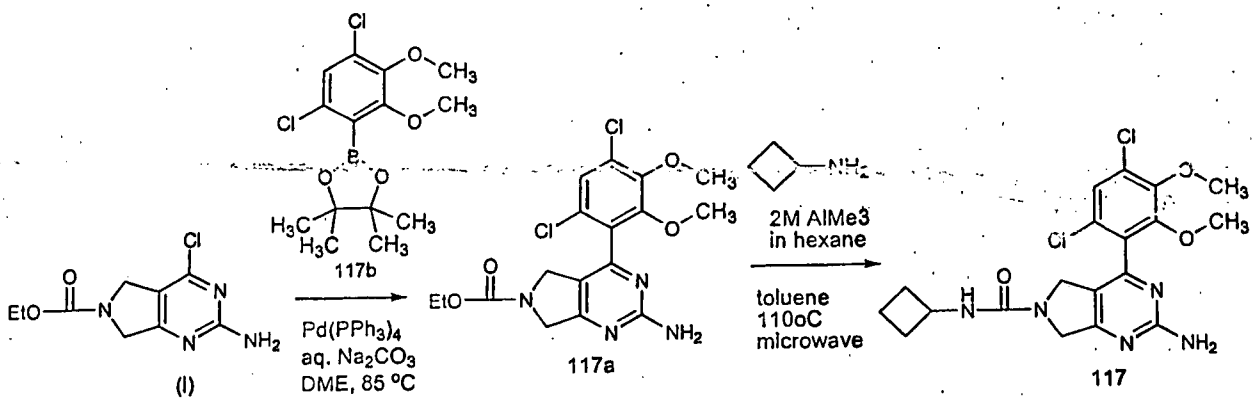
Compound **115a**, 1-(3-chloropropyl)-1*H*-pyrazole, was prepared in a manner similar to compound **114a** except that pyrazole was substituted for 4-methylpyrazole and 1-bromo-3-chloropropane was substituted for 1-chloro-2-iodoethane. 1H NMR (300 MHz, CHLOROFORM-*d*) $\delta$ ppm 2.33 - 2.42 (m, 2 H) 3.47 (t, *J*=6.03 Hz, 2 H) 4.41 (t, *J*=6.40 Hz, 2 H) 6.31 (t, *J*=2.17 Hz, 1 H) 7.49 (d, *J*=2.07 Hz, 1 H) 7.61 (d, *J*=1.51 Hz, 1 H). Compound **113a** (0.0442 g, 0.109 mmol) was then O-alkylated with compound **115a** (0.054 g, 0.37 mmol) and cesium carbonate (0.122g, 0.374 mmol) in DMSO (1.5 mL) at 100°C in a manner similar to Example **18**. Isolation using preparative HPLC gave compound **115** (0.0234, 0.0372 mmol) as a TFA salt in 34% yield. 1H NMR (300 MHz, METHANOL-d4) d ppm 2.03 (s, 6 H) 2.12 - 2.22 (m, J=2.45 Hz, 2 H) 2.37 (s, 1 H) 3.86 - 3.94 (m, 1 H) 3.98 - 4.07 (m, 1 H) 4.12 (t, J=6.59 Hz, 2 H) 4.31 (s, 2 H) 4.57 (s, 2 H) 6.23 - 6.25 (m, 1 H) 7.14 (d, J=1.70 Hz, 1 H) 7.25 (d, J=1.70 Hz, 1 H) 7.45 (d, J=1.51 Hz, 1 H) 7.53 (d, J=2.07 Hz, 1 H). LCMS $(M+H)^+$: 516.2, 514.2.

**Example 116: 2-amino-*N*-cyclobutyl-4-[2,4-dichloro-6-(2-pyridin-2-ylethoxy)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




To compound **18a** (0.032 g, 0.081 mmol), 2-(2-hydroxyethyl)pyridine, and triphenylphosphine (0.053 g, 0.20 mmol) in THF (1.5 mL) was added diisopropyl azodicarboxylate (40 µL, 0.207 mmol). After 3h, DMSO (1.5 mL) was added and the volatile components removed under vacuum. Isolation using preparative HPLC gave compound **116** (0.0208 g, 0.0416 mmol) as a tan powder in 51% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.49 - 1.63 (m, 2 H) 1.88 - 2.00 (m, 2 H) 2.05 - 2.21 (m, 2 H) 2.93 - 3.02 (m, 2 H) 3.38 (d, 1H, overlaps with water peak) 3.86 (d, J=13.00 Hz, 1 H) 4.08 - 4.23 (m, 1 H) 4.28 - 4.45 (m, 4 H) 6.37 (d, J=8.10 Hz, 1 H) 6.77 (s, 2 H) 6.91 (d, J=7.72 Hz, 1 H) 6.99 - 7.06 (m, 1 H) 7.28 - 7.32 (m, 2 H) 7.50 (dt, J=7.58, 1.79 Hz, 1 H) 8.36 (d, J=4.14 Hz, 1 H). LCMS $(M+H)^+$: 501.2, 499.2.

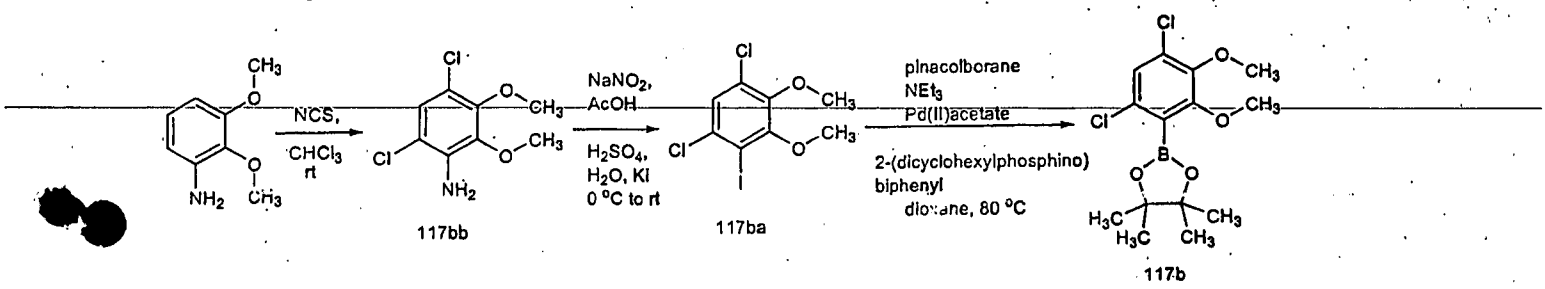
**Example 117: 2-amino-*N*-cyclobutyl-4-(4,6-dichloro-2,3-dimethoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Compound **(i)** (0.263 g, 1.08 mmol), compound **117b** (0.525 g, 1.58 mmol), 2M aqueous sodium carbonate (0.80 mL, 1.6 mmol) and tetrakis(triphenylphosphino)palladium(0) (0.075 g, 0.065 mmol) in DME (10 mL) were reacted in a manner similar to Example **1**. Extractive work up with EtOAc (30 mL), washing with water (30 mL) followed by isolation using silica gel chromatography (gradient of 0-25% MeOH in dichloromethane) gave compound **117a**, ethyl 2-amino-4-(4,6-dichloro-2,3-dimethoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, (0.034 mg, 0.082 mmol) in 8% yield. Compound **117a** (0.034 g, 0.082 mmol), cyclobutylamine (0.040 g, 0.60 mmol) and 2M trimethyl aluminum in hexane (0.25 mL, 0.50 mmol) were reacted in a manner similar to

Example 7. Isolation using preparative HPLC gave compound **117** (0.010 g, 0.023 mmol) in 28% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.49 - 1.61 (m, 2 H) 1.85 - 2.00 (m, 2 H) 2.03 - 2.15 (m, 2 H) 3.69 (s, 3 H) 3.85 (s, 3 H) 4.07 - 4.24 (m, 3 H) 4.43 (s, 2 H) 6.51 (d, J=7.91 Hz, 1 H) 6.89 (br. s., 2 H) 7.60 (s, 1 H). LCMS $(M+H)^+$: 440.2, 438.2.

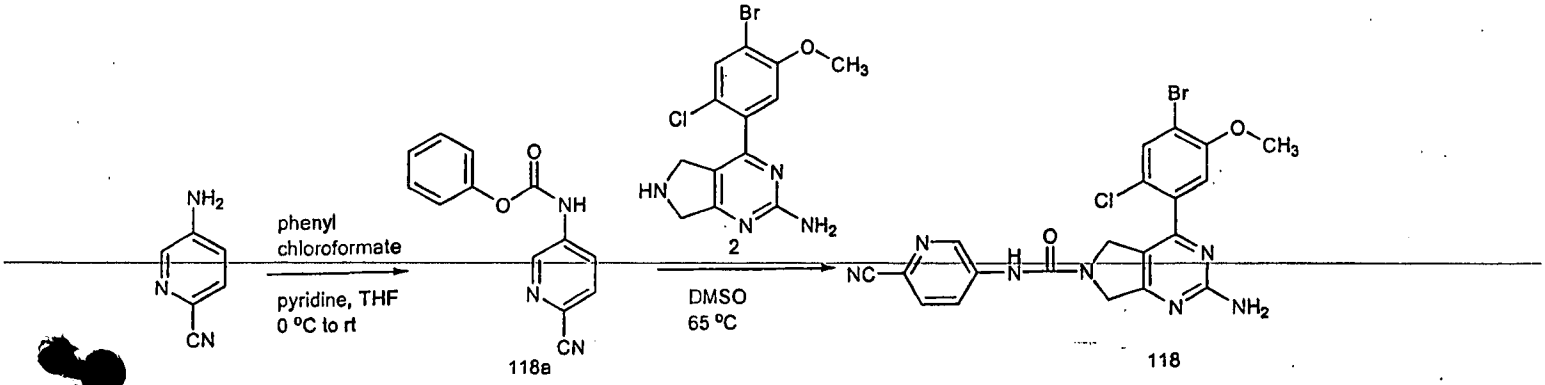
**Preparation of Compound 117b, 2-(4,6-dichloro-2,3-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane**




N-chlorosuccinimide (6.87 g, 50.4 mmol) was added to 2,3-dimethoxyaniline (3.86 g, 25.2 mmol) in chloroform (100 mL) at 0 °C. After allowing to warm to ambient temperature and stir for an additional 4h, isolation by silica gel chromatography (dichloromethane) gave compound **117bb**, 4,6-dichloro-2,3-dimethoxyaniline, (1.97 g, 8.87 mmol) as an orange oil in 35% yield. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 3.74 (s, 3 H) 3.77 (s, 3 H) 5.27 (br. s., 2 H) 7.12 (s, 1 H). With stirring, sodium nitrite (799 mg, 11.6 mmol) in $H_2O$ (4.0 mL) was added dropwise to compound **117bb** (1.97 g, 8.87 mmol) in acetic acid (20.0 mL), $H_2O$ (6.0 mL) and concentrtaed $H_2SO_4$ (6.0 mL) at 0°C. After 3 h at 0 °C, the mixture was poured into a potassium iodide (10.4 g, 62.7 mmol) solution in $H_2O$ (20.0 mL) at 0°C rinsing with additional $H_2O$ (20 mL). The mixture was allowed to slowly warm to ambient temperature and stirred for an additional 16 h. The mixture was then extracted with diethyl ether (100mL) and the $Et_2O$ layer washed with saturated aqueous $Na_2S_2O_3$ (100 mL), 3N NaOH (100 mL) and water (100mL). Isolation using silica gel chromatography (gradient of 0-20% dichloromethane in hexane) gave compound **117ba**, 1,5-dichloro-2-iodo-3,4-dimethoxybenzene, (2.46 g, 7.39 mmol) in 83% yield. 1H-NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 3.81 (s, 3 H) 3.82 (s, 3 H) 7.62 (s, 1 H). Compound **117ba** (2.45 g, 7.36 mmol), pinacolborane (2.1 mL, 14.5 mmol), and triethyl amine (3.00 mL, 21.5 mmol) in 1,4-dioxane (40 mL) were purged with $N_2$ for 15 min and palladium (II) acetate (86 mg, 0.38 mmol) and 2-(dicyclohexylphosphino)biphenyl (263 mg, 0.750 mmol) were added. The mixture was heated to 80 °C for 2.5 h, cooled, and subjected to EtOAc extractive work up, washing with saturated aqueous $NH_4Cl$. Isolation using silica gel chromatography (gradient of 0-

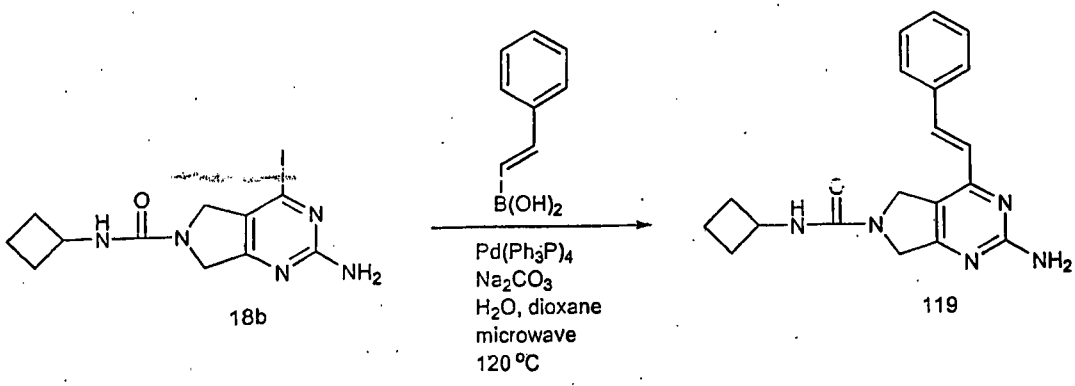
50% dichloromethane in hexane) gave compound **117b** (1.155 g, 3.468 mmol) in 47% yield. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 1.32 (s, 12 H) 3.79 (s, 6 H) 7.36 (s, 1 H).

**Example 118: 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-*N*-(6-cyanopyridin-3-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




Phenylchloroformate (0.70 mL, 5.6 mmol) in THF (10 mL) was added dropwise to 5-amino-2-cyanopyridine (655 mg. 5.50 mmol) and pyridine (0.50 mL, 6.2 mmol) in THF (10.0 mL) at 0 °C. After allowing to warm to ambient temperature and stirring for 1h, the mixture was again cooled to 0°C, and the precipitate removed by filtration. Removal of the volatile components from the filtrate gave compound **118a**, phenyl (6-cyanopyridin-3-yl)carbamate, (0.921, 3.85 mmol) as a pale orange solid in 70% crude yield. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 7.24 - 7.33 (m, 3 H) 7.45 (t, $J$=7.82 Hz, 2 H) 8.01 (d, $J$=8.48 Hz, 1 H) 8.13 (dd, $J$=8.48, 2.55 Hz, 1 H) 8.81 (d, $J$=2.45 Hz, 1 H) 11.01 (s, 1 H). Compound **2** (0.093 g, 0.152 mmol), compound **118a** (0.038 g, 0.160 mmol), and cesium carbonate (0.154 g, 0.473 mmol) in DMSO (1.5 mL) were heated to 65 °C for 20 min. Isolation using preparative HPLC gave compound **118** (0.013 g, 0.026 mmol) as an orange solid in 17% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 3.87 (s, 3 H) 4.52 (br. s., 2 H) 4.64 (br. s., 2 H) 6.97 (br. s., 2 H) 7.19 (s, 1 H) 7.87 - 7.94 (m, 2 H) 8.20 (dd, J=8.57, 2.17 Hz, 1 H) 8.87 (d, J=2.45 Hz, 1 H) 9.04 (br. s., 1 H). LCMS $(M+H)^+$: 502.2, 500.2.

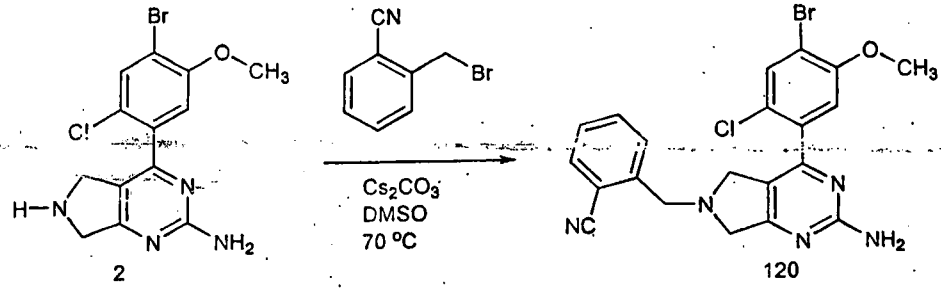
**Example 119: 2-amino-*N*-cyclobutyl-4-[(*E*)-2-phenylvinyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




18b 119

Compound **18b** (0.103 g, 0.287 mmol), trans-2-phenylvinylboronic acid (0.0602 mg, 0.407 mmol) and 2M aqueous sodium carbonate (0.30 mL, 0.60 mmol) in 1,4-dioxane (3.0 mL) were purged with $N_2$. Tetrakis(triphenylphosphino)palladium(0) (0.024 g, 0.021 mmol) was added and the mixture microwaved at 120°C for 1.5 h. After EtOAc (20 mL) extractive work up, washing with water (20 mL), isolation using preparative HPLC gave compound **119** (0.022 g, 0.066 mmol) in 23% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.52 - 1.68 (m, 2 H) 1.92 - 2.07 (m, 2 H) 2.09 - 2.23 (m, 2 H) 4.11 - 4.28 (m, 1 H) 4.37 (s, 2 H) 4.60 (s, 2 H) 6.52 (d, J=7.72 Hz, 1 H) 6.59 (br. s., 2 H) 7.02 (d, J=16.01 Hz, 1 H) 7.34 - 7.48 (m, 3 H) 7.63 - 7.77 (m, 3 H). LCMS $(M+H)^+$: 336.4.

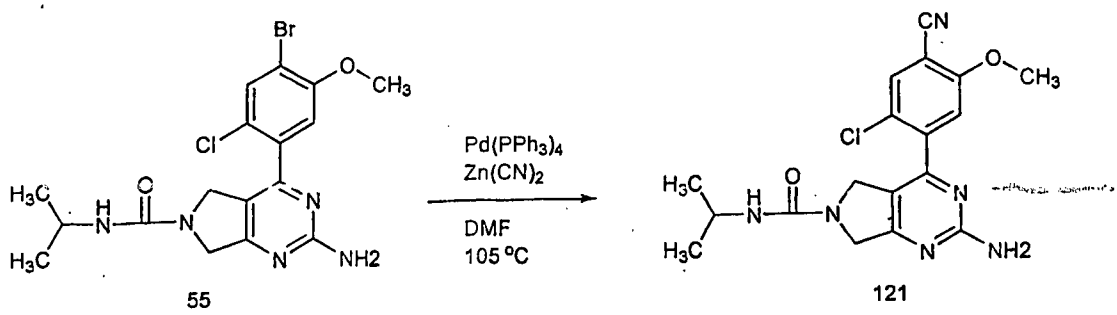
**Example 120: 2-{[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6*H*-pyrrolo [3,4-*d*]pyrimidin-6-yl]methyl}benzonitrile**




2 120

Compound **2** (0.067 g, 0.110 mmol), 2-(bromomethyl)-benzonitrile (0.0215 mg, 0.110 mmol) and cesium carbonate (0.1189 g, 0.365 mmol) in DMSO (1.5 mL) were heated at 70 °C for 10 min. Isolation using preparative HPLC gave compound **120** (0.007 g, 0.01 mmol ) in 10% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 3.67 (s, 2 H) 3.83 (s, 2 H) 3.84 (s, 3 H) 4.03 (s, 2 H) 6.79 (br. s., 2 H) 7.10 (s, 1 H) 7.47 (t, J=7.44 Hz, 1 H) 7.60 - 7.71 (m, 2 H) 7.79 - 7.84 (m, 2 H). LCMS $(M+H)^+$: 472.2, 470.2.

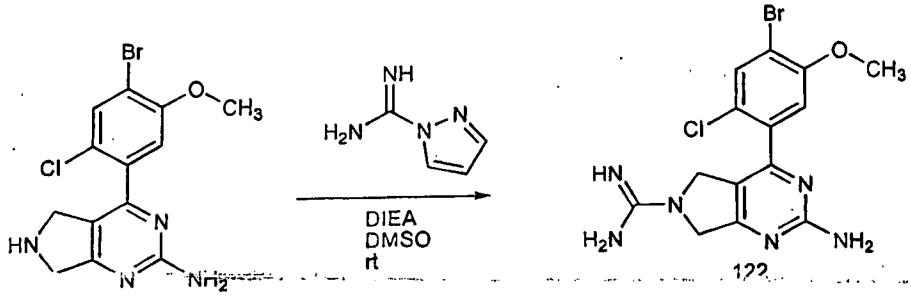
**Example 121: 2-amino-4-(2-chloro-4-cyano-5-methoxyphenyl)-*N*-isopropyl-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




55 121

Compound **55** (0.0247 g, 0.056 mmol) and zinc cyanide (0.0212 g, 0.181 mmol) in DMF (1.5 mL) were purged with $N_2$. Tetrakis(triphenylphosphino)palladium(0) (0.0102 mg, 0.00883 mmol) was added and the mixture was heated at 105 °C for 5h. Ethyl acetate (50 mL) extractive work up, washing with water (50 mL) followed by isolation using preparative HPLC gave compound **121** (0.008 g) as the hydrochloride in 30% yield. 1H NMR (300 MHz, DMSO-d6) d ppm 1.06 (d, J=6.59 Hz, 6 H) 3.71 - 3.85 (m, 1 H) 3.93 (s, 3 H) 4.25 (s, 2 H) 4.43 (s, 2 H) 6.07 (d, J=7.54 Hz, 1 H) 6.95 (br. s., 2 H) 7.34 (s, 1 H) 8.12 (s, 1 H). LCMS $(M+H)^+$: 387.2.

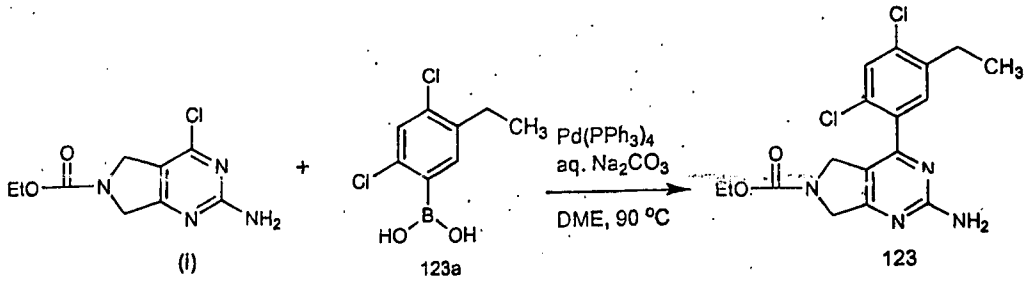
**Example 122: 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboximidamide**




2 122

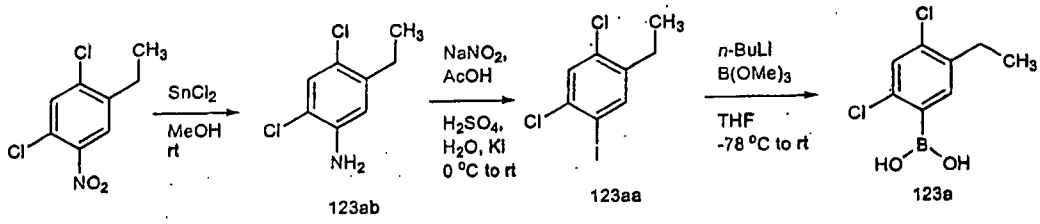
To compound **2** (0.0779 g, 0.105 mmol) in DMSO (1.0 mL) at ambient temperature was added diisopropyl ethylamine (0.10 mL, 0.57 mmol) and (1H)-pyrazole-1-carboxamidine hydrochloride (0.0201 g, 0.137 mmol). After stirring for 16h, isolation using preparative HPLC gave compound **122** (0.016 g, 0.040 mmol) as a white solid in 38% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 3.88 (s, 3 H) 4.45 (s, 2 H) 4.60 (s, 2 H) 7.07 (br. s., 2 H) 7.17 (s, 1 H) 7.31 - 7.47 (br. m, 3 H) 7.90 (s, 1 H). LCMS $(M+H)^+$: 399.0, 397.2.

**Example 123: ethyl 2-amino-4-(2,4-dichloro-5-ethylphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**




Compound **(i)** (0.0953 g, 0.393 mmol), compound **123a** (0.086 mg, 0.39 mmol), 2M aqueous sodium carbonate (0.4 mL, 0.8 mmol), and tetrakis(triphenylphosphino)palladium(0) (0.0227 mg, 0.0196 mmol) in DME (4 mL) were reacted in a manner similar to Example **1**. Isolation using preparative HPLC gave compound **123** (0.047 g, 0.12 mmol) as a white powder in 31% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.13 - 1.24 (m, 6 H) 2.73 (q, J=7.41 Hz, 2 H) 4.01 - 4.14 (m, 2 H) 4.30 - 4.36 (m, 2 H) 4.44 - 4.51 (m, 2 H) 6.94 (br. s., 2 H) 7.42 (s, 1 H) 7.73 (s, 1 H). LCMS $(M+H)^+$: 383.2, 381.2.

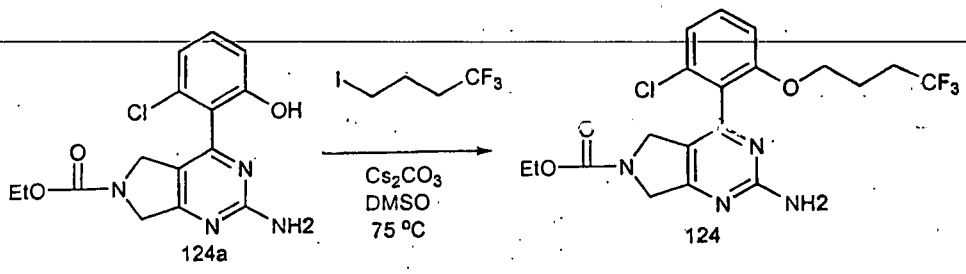
**Preparation of Compound 123a, (2,4-dichloro-5-ethylphenyl)boronic acid**




1,5-Dichloro-2-ethyl-4-nitrobenzene (2.1 g, 9.5 mmol) and $SnCl_2$ (8.1 g, 42.8 mmol) were refluxed in anhydrous methanol until the reduction was complete. Aqueous 10% NaOH and EtOAc were added, and the resulting suspended solids were allowed to settle and most of the EtOAc was decanted. This procedure was repeated several times and the EtOAc batches were combined and filtered through celite, dried ($Na_2SO_4$), filtered, and the volatile components removed. The residue was dissolved in $Et_2O$ and excess 4M HCl in 1,4-dioxane was added. Evaporation of the volatile components gave compound **123ab**, 2,4-dichloro-5-ethylaniline, ( 2.1 g, 9.27 mmol) as a yellow hydrochloride in 97% yield. Compound **123ab** was converted to compound **123aa**, 1,5-dichloro-2-ethyl-4-iodobenzene, (0.577 g, 1.92 mmol) in 36% yield in a manner similar to Example **117ba** except that compound **123ab** was substituted for compound **117bb**. 1H NMR (300 MHz, CHLOROFORM-*d*) $\delta$ ppm 1.22 (t, *J*=7.54 Hz, 3 H) 2.69 (q, *J*=7.54 Hz, 2 H) 7.44 (s, 1 H) 7.70 (s, 1 H). To compound **123aa** (0.576 g, 1.91 mmol) in THF (15.0 mL) at -78 °C was added 2M *n*-BuLi in cyclohexane (1.00 mL, 2.00 mmol) dropwise. After 1h, trimethyl borate (0.30 mL, 2.7 mmol) was added dropwise, and the reaction was allowed to warm

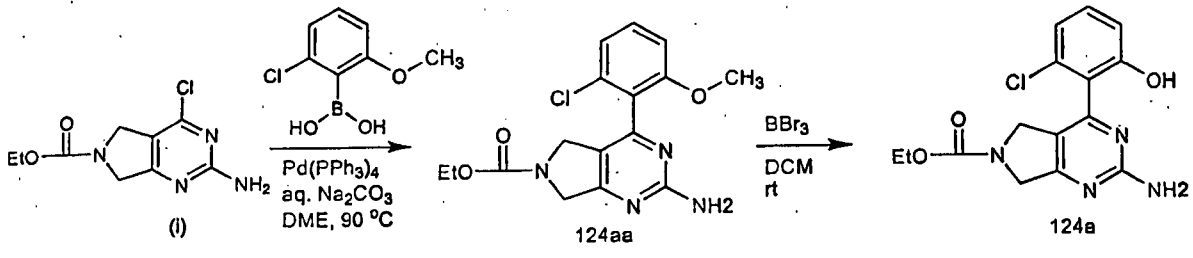
to ambient temperature. Water (50 mL) followed by ether/hexanes (25mL/25 mL) were added, and the layers separated. The organic layer was then extracted with 0.5N NaOH (30 mL), and the aqueous extraction was brought to pH 6 with 1N $KH_2PO_4$ (15 mL) and extracted with EtOAc (50 mL). Removal of the volatile components of the EtOAc layer gave compound **123a** (0.088 g) as white waxy solid which was carried on without purification.

**Example 124: ethyl 2-amino-4-[2-chloro-6-(4,4,4-trifluorobutoxy)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**




Compound **124a** (0.0763 g, 0.228 mmol) was O-alkylated with 1-iodo-4,4,4-trifluorobutane (0.0801 g, 0.337 mmol) and cesium carbonate (0.0992 mg, 0.304 mmol) in DMSO (1.0 mL) in a manner similar to that described for Example **18**. Isolation using preparative HPLC gave compound **124** (0.0353 g, 0.0794 mmol) as a white powder in 35% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.11 - 1.25 (m, 3 H) 1.70 - 1.82 (m, 2 H) 2.03 - 2.23 (m, 2 H) 3.99 - 4.21 (m, 6 H) 4.37 - 4.57 (m, 2 H) 6.83 (br. s., 2 H) 7.11 - 7.20 (m, 2 H) 7.44 (t, J=8.19 Hz, 1 H). LCMS $(M+H)^+$: 445.2.

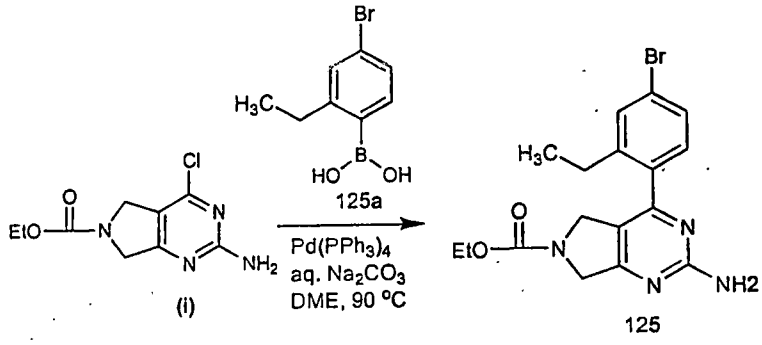
**Preparation of Compound 124a, ethyl 2-amino-4-(2-chloro-6-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**




Compound **(i)** (0.300 g, 1.24 mmol), 2-chloro-6-methoxyphenylboronic acid (0.351 g, 1.88 mmol), 2M aqueous sodium carbonate (1.85 mL, 3.70 mmol) and tetrakis(triphenylphosphino) palladium(0) (0.0789 g, 0.0683 mmol) in DME (10.0 mL) were reacted in a manner similar to that described for Example **1** to give crude compound **124aa**, ethyl 2-amino-4-(2-chloro-6-methoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, (0.481 g) which was carried on without purification. LCMS $(M+H)^+$: 349.2. To compound **124aa** (0.407 g) in dichloromethane

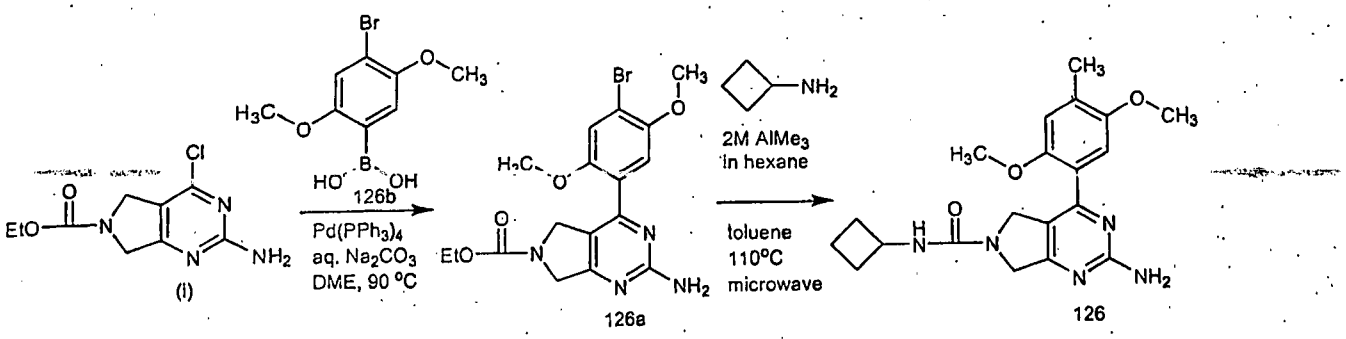
(10.0 mL) at 0°C was added dropwise 1M boron tribromide (0.20 mL, 2.1 mmol) in dichloromethane. The mixture was allowed to warm to ambient temperature and stir for 2 h. Additional boron tribromide (0.20 mL, 2.1 mmol) in dichloromethane was added and the mixture stirred for an additional 4h. The mixture was then poured into cold saturated aqueous $NaHCO_3$ and extracted with dichloromethane/MeOH. Removal of the volatile components gave compound **124a** (0.249 g) as an orange residue which was carried on without purification. LCMS $(M+H)^+$: 335.2.

**Example 125: ethyl 2-amino-4-(4-bromo-2-ethylphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate**



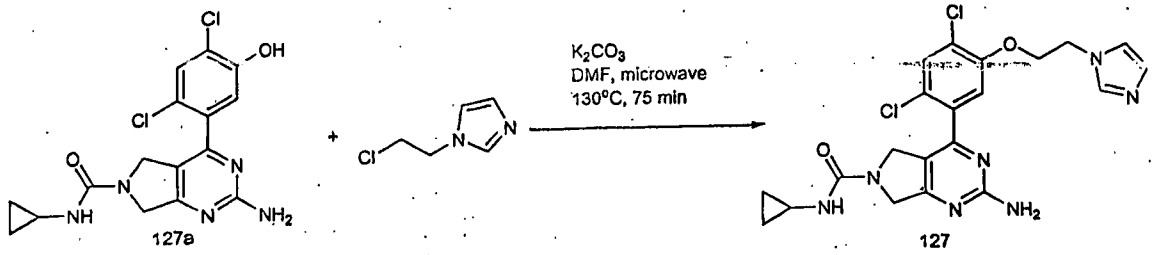

Compound **125a**, 4-bromo-2-ethylphenylboronic acid, was prepared in a similar manner to Example **123a** except that 4-bromo-2-ethyl-1-iodobenzene was substituted for compound **123aa**. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 1.19 (t, $J$=7.35 Hz, 3 H) 3.02 (q, $J$=7.41 Hz, 2 H) 7.33 - 7.41 (m, 2 H) 7.74 (d, $J$=7.91 Hz, 1 H). Compound **(i)** (0.114 g, 0.470 mmol), compound **125a** (0.0852 g, 0.372 mmol), 2M aqueous sodium carbonate (0.50 mL, 1.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.031 g, 0.027 mmol) in DME (3.5 mL) were reacted in a manner similar to that described for Example **1**. Isolation using preparative HPLC gave compound **125** (0.029 g, 0.074 mmol) in 15% yield. 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.02 (t, J=7.54 Hz, 3 H) 1.13 - 1.25 (m, 3 H) 2.55 - 2.63 (m, 2 H) 4.00 - 4.13 (m, 2 H) 4.26 - 4.32 (m, 2 H) 4.44 - 4.50 (m, 2 H) 6.82 (br. s., 2 H) 7.24 (d, J=7.91 Hz, 1 H) 7.48 (dd, J=8.01, 1.60 Hz, 1 H) 7.57 (d, J=1.70 Hz, 1 H). LCMS $(M+H)^+$: 393.2, 391.2.

**Example 126: 2-amino-*N*-cyclobutyl-4-(2,5-dimethoxy-4-methylphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**



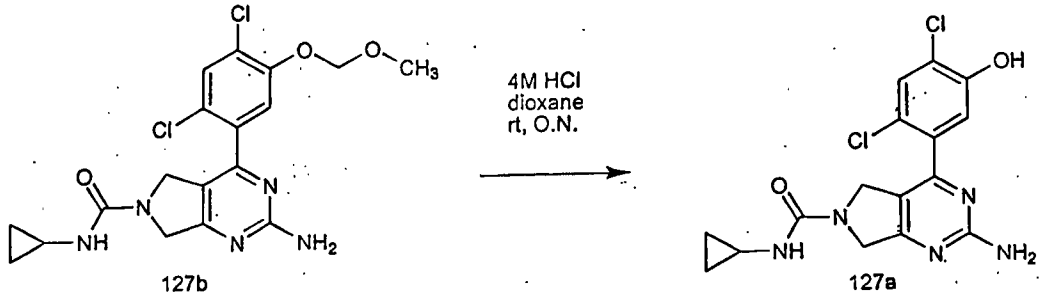

Compound **126b**, 4-dibromo-2,5-dimethoxyphenylboronic acid, was prepared in a similar manner as Example **123a** except that 1,4-dibromo-2,5-dimethoxybenzene was substituted for compound **123aa**. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 3.77 (s, 3 H) 3.78 (s, 3 H) 7.20 (s, 1 H) 7.22 (s, 1 H) 7.83 (s, 2 H). Compound **(i)** (0.114 g, 0.470 mmol), compound **126b** (0.112 g, 0.429 mmol), 2M aqueous sodium carbonate (0.50 mL, 1.0 mmol) and tetrakis(triphenylphosphino)palladium(0) (0.030 g, 0.026 mmol) in DME (3.5 mL) were reacted in a manner similar to Example **1** to give compound **126a**, ethyl 2-amino-4-(4-bromo-2,5-dimethoxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate, (0.065 g, 0.154 mmol) in 36% yield which was carried on without purification. 1H NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm 1.14 - 1.25 (m, 3 H) 3.78 (s, 3 H) 3.80 (s, 3 H) 4.02 - 4.14 (m, 2 H) 4.27 - 4.33 (m, 2 H) 4.42 - 4.48 (m, 2 H) 6.82 (br. s., 2 H) 7.05 (s, 1 H) 7.39 (s, 1 H). LCMS $(M+H)^+$: 425.2, 423.2. Cyclobutylamine (0.10 mL, 1.2 mmol), 2.0 M trimethylaluminum (0.30 mL, 0.6 mmol) in hexane, and compound **126a** (49.2 mg, 0.116 mmol) in toluene (2.0 mL) were microwaved for 1 h in a manner similar to Example 7. Work up, also in a similar manner, and isolation using preparative HPLC gave compound **126** (0.0174 g, 0.0454 mmol) in 30%yield as a TFA salt (conversion of the bromine in compound **126a** to the methyl group of compound **126** was unanticipated). 1H NMR (300 MHz, DMSO-d6) $\delta$ ppm 1.50 - 1.63 (m, 2 H) 1.88 - 2.03 (m, 2 H) 2.06 - 2.17 (m, 2 H) 2.24 (s, 3 H) 3.77 (s, 6 H) 4.10 - 4.20 (m, 1 H) 4.28 (s, 2 H) 4.42 (s, 2 H) 6.53 (d, J=7.72 Hz, 1 H) 6.91 (s, 1 H) 7.04 (s, 1 H). LCMS $(M+H)^+$: 384.4.

**Example 127: 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[2-(1H-imidazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**



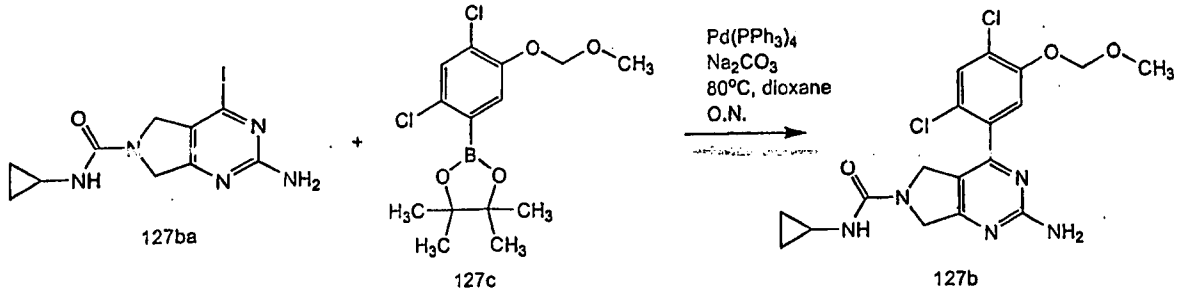

Compound **127a** (70 mg, 0.184 mmol), 1-(2-chloroethyl)-1*H*-imidazole HCl (84 mg, 0.55 mmol), and potassium carbonate (127 mg, 0.92 mmol) in DMF (2 mL) were reacted in a manner similar to Example **100**. Isolation using preparative HPLC gave compound **127** (9.0 mg, 0.02 mmol) as a powder in 11% yield. $^1$H-NMR (DMSO-d6, 300 MHz): $\delta$ 7.71 (s, 1H), 7.63 (s, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 6.85 (m, 3H), 6.43 (s, 1H) 4.37 (s, 4H), 4.31 (m, 2H), 4.18 (s, 2H), 2.69 (bs, 1H), 0.50 (m, 2H), 0.36 (m, 2H).

**Preparation of Compound 127a, 2-amino-*N*-cyclopropyl-4-(2,4-dichloro-5-hydroxyphenyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**




To a suspension of compound **127b** (640 mg, 1.51mol) in MeOH (4 mL) was added 4 M HCl in 1,4-dioxane (4 mL, 16.0 mmol). After stirring overnight, the volatile components were removed and the residue subjected to EtOAc extractive work up, washing with saturated aqueous $NaHCO_3$. Drying ($Na_2SO_4$), filtration, and evaporation of the volatile components gave compound **127a** (426 mg, 1.12 mmol) as a powder in 74% yield which was carried on without purification. 1H NMR (400 MHz, DMSO-d6) d ppm: 10.77 (s, 1 H), 7.62 (s, 1 H), 6.94 (s, 1 H), 6.87 (s, 2 H), 6.47 (d, J=2.78 Hz, 1 H), 4.39 (s, 2 H), 4.23 (s, 2 H), 2.51 - 2.56 (m, 1 H), 0.50 - 0.57 (m, 2 H), 0.36 - 0.43 (m, 2 H). LCMS $(M+H)^+$: 380.2, 382.2

**Preparation of Compound 127b, 2-amino-*N*-cyclopropyl-4-[2,4-dichloro-5-(methoxymethoxy)phenyl]-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**

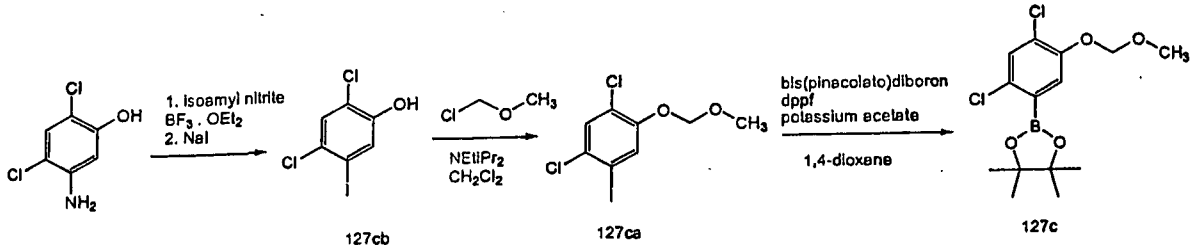



127ba 127c 127b

Compound **127ba**, 2-amino-*N*-cyclopropyl-4-iodo-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide, was prepared from compound **8b** in a manner similar to example **18b** except that cyclopropylamine was substituted for cyclobutylamine.

Compound **127ba** (825 mg, 2.39 mmol), compound **127c** (876 mg, 2.63 mmol), 2M aqueous sodium carbonate (3.6 mL, 7.18 mmol) and tetrakis(triphenylphosphine) palladium(0) (276 mg, 0.239 mmol) in 30 mL 1,4-dioxane were reacted in a manner similar to Example **18a**. After filtering and washing the collected insoluble material with EtOAc, the combined filtrate/washings were concentrated and subjected to EtOAc (100mL) extractive work up, washing with water (200mL), brine (2x100mL), and drying ($Na_2SO_4$). Isolation using silica gel chromatography (gradient 0-5% MeOH in EtOAc) gave compound **127b** (656 mg, 1.55 mmol) as a solid in 65% yield. 1H NMR (400 MHz, DMSO-d6) d ppm: 7.78 (s, 1 H), 7.28 (s, 1 H), 6.90 (s, 2 H), 6.46 (d, J=2.78 Hz, 1 H), 5.32 (s, 2 H), 4.40 (s, 2 H), 4.23 (s, 2 H), 3.41 (s, 3 H), 0.49 - 0.60 (m, 2 H), 0.36 - 0.44 (m, 2 H). LCMS $(M+H)^+$: 424.2, 426.2.

**Preparation of Compound 127c, 2-(2,4-dchlorc-5-methoxymethoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane**

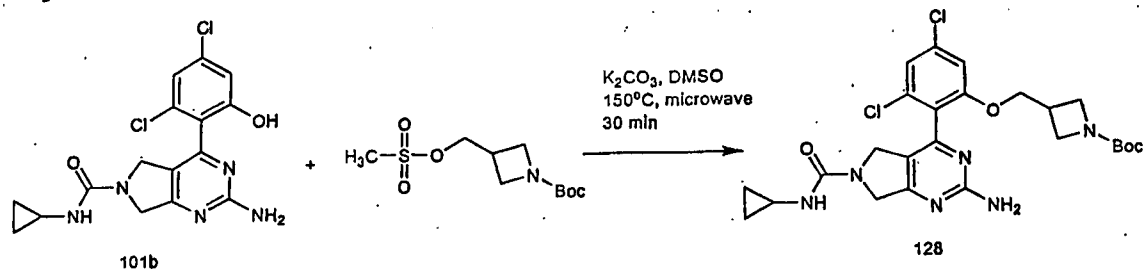



127cb 127ca 127c

$BF_3OEt_2$ (70.6 mL, 560 mmol) was cooled to 0 °C and 5-amino-2,4-dichlorophenol (50.0 g, 280 mmol) in THF (700 mL) was added over 45 min. Then isoamyl nitrite (48.8 mL, 365 mmol) in THF (150 mL) was added over 15 min. After stirring for 30 min at 0 °C a yellow precipitate formed, more $Et_2O$ was added and the yellow solid was collected by filtration, washed with $Et_2O$, and air dried. The collected solid was added in portions to a solution of NaI (54.7 g, 365 mmol) in acetone (1.2 L) and stirred at ambient temperature overnight. The volatile components were reduced, water was added and the mixture was subjected to EtOAc extractive work up, washing with saturated aqueous $NaHSO_3$

and dried ($Na_2SO_4$). Isolation after silica gel chromatography plug ($CH_2Cl_2$) gave a mixture contaminated by the des-iodo impurity. Recrystallization from hexanes (3 crops) gave compound **127cb**, 2,4-dichloro-5-iodophenol, (43.4 g, 150 mmol) as a yellow solid in 54% yield. 1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 3.77 (q, *J*=7.07 Hz, 3 H) 5.27 (s, 2 H) 7.45 (s, 1 H) 7.66 (s, 1 H). Compound **127cb** in $CH_2Cl_2$ (400 mL) was cooled to 0 °C and methoxymethyl chloride (13.7 mL, 180 mmol) followed by diisopropylethyl amine (31.5 mL, 23.3 g, 180 mmol) were added. After warming to ambient temperature overnight, the $CH_2Cl_2$ solution was washed with saturated aqueous $NaHCO_3$ and dried over $Na_2SO_4$. Filtration and evaporation of the volatile components gave compound **127ca**, 1,5-dichloro-2-iodo-4-(methoxymethoxy)benzene, (46.8 g, 141 mmol) as a yellow solid in 94% yield. Compound **127ca** (41.8 g, 125 mmol), bis(pinacolato)diboron (35.1 g, 138 mmol), potassium acetate (24.6 g, 250 mmol), bis(diphenylphosphino)ferrocene-dichloropalladium dichloromethane adduct (6.15 g, 7.5 mmol), and dry 1,4-dioxane (375 mL) were purged with $N_2$ for 1 h and heated to 90 °C. After 5 days, the mixture was cooled to ambient temperature, filtered, and the collected solid washed with $Et_2O$. The combined filtrate/washings were subjected to silica gel chromatography (stepwise gradient of 0 to 17% EtOAc in hexane) and isolation gave compound **127c** (30.2 g, 91 mmol) as a yellow solid in 73% yield (>94% purity by GCMS).

**Example 128: tert-butyl 3-[(2-{2-amino-6-[(cyclopropylamino)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl}-3,5-dichlorophenoxy)methyl]azetidine-1-carboxylate**

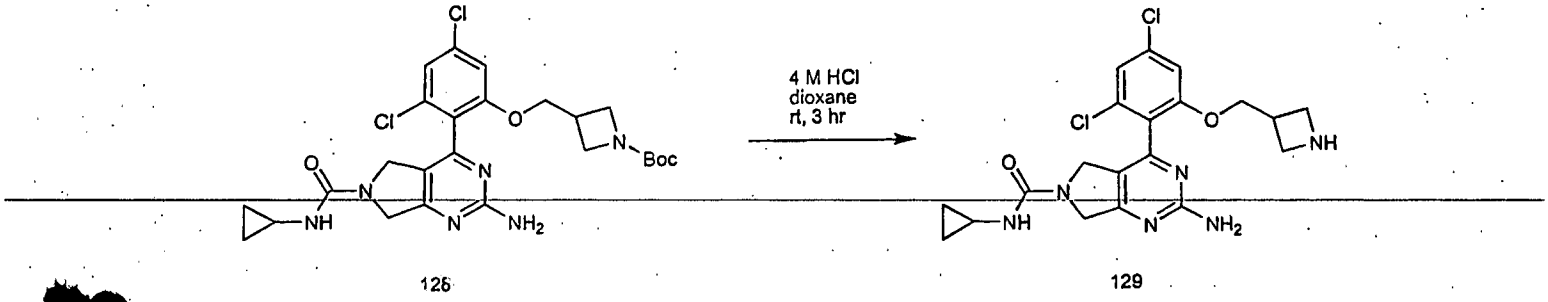



101b 128

Compound **101b** (300 mg, 0.789 mmol), *tert*-butyl 3-{[(methylsulfonyl)oxy]methyl}azetidine-1-carboxylate (419 mg, 1.58 mmol), and potassium carbonate (327 mg, 2.37 mmol) in DMF (10 mL) were microwaved at 150°C for 30 min. Following EtOAc extractive work up, washing with water and brine, and drying ($Na_2SO_4$), isolation using silica gel chromatography (10% MeOH in EtOAc) gave compound **128** (272 mg, 0.495 mmol) in 63% yield. 1H NMR (400 MHz, CHLOROFORM-d) d ppm: 7.15 (d, J=1.77 Hz, 1 H), 6.90 (d, J=1.77 Hz, 1 H), 5.15 (s, 2

H), 4.55 (s, 3 H), 4.35 - 4.42 (m, 1 H), 4.21 - 4.29 (m, 1 H), 4.01 - 4.13 (m, 2 H), 3.86 - 3.96 (m, 2 H), 3.53 - 3.62 (m, 2 H), 2.74 - 2.86 (m, 1 H), 2.64 - 2.74 (m, 1 H), 1.43 (s, 9 H), 0.71 - 0.79 (m, 2 H), 0.48 - 0.56 (m, 2 H). LCMS (M+H)+: 549.2, 550.2.

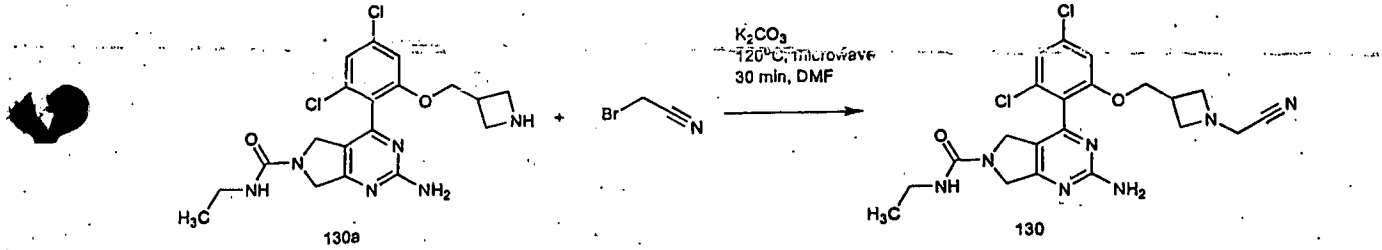
**Example 129: 2-amino-4-[2-(azetidin-3-ylmethoxy)-4,6-dichlorophenyl]-N-cyclopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide**




126 129

To compound **128** (490 mg, 0.892 mmol, 1.0 eq) in 1,4-dioxane (5 mL) was added 4 M HCl in 1,4-dioxane (5 mL). After stirring 3 h, isolation by preparative HPLC gave compound **129** (25 mg, 0.056 mmol) as a solid in 6% yield. 1H NMR (400 MHz, *MeOD*) ppm 8.55 (s, 1 H), 7.15 - 7.35 (m, 2 H), 4.44 - 4.62 (m, 2 H), 4.15 - 4.40 (m, 4 H), 3.85 - 4.03 (m, 2 H), 3.66 - 3.83(m, 2 H), 3.13 - 3.27 (m, 1 H), 2.47 - 2.63 (m, 1 H), 0.58 - 0.75 (m, 2 H), 0.49 (d, *J*=2.02 Hz, 2 H). LCMS (M+H)+: 449.2, 450.2.

**Example 130: 2-amino-4-(2,4-dichloro-6-{[1-(cyanomethyl)azetidin-3-yl]methoxy}phenyl)-*N*-ethyl-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide**



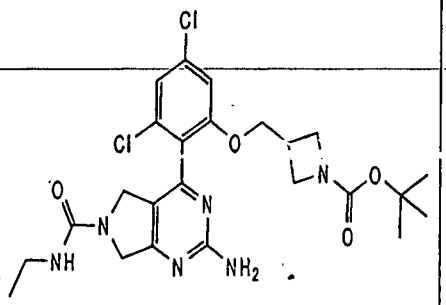
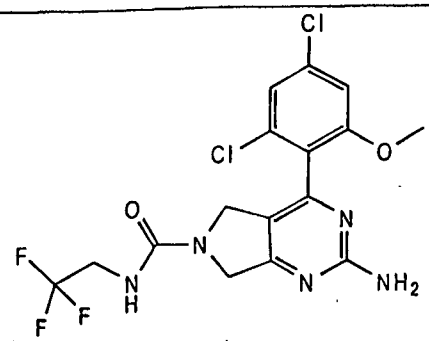
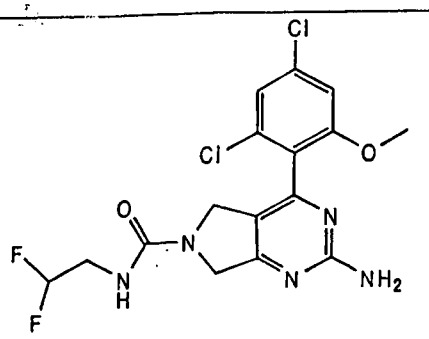

130a 130

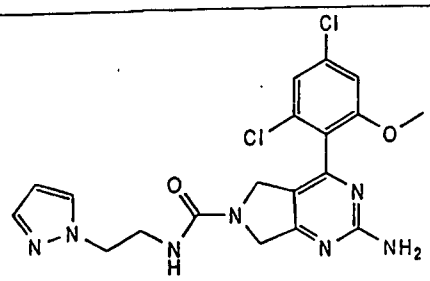
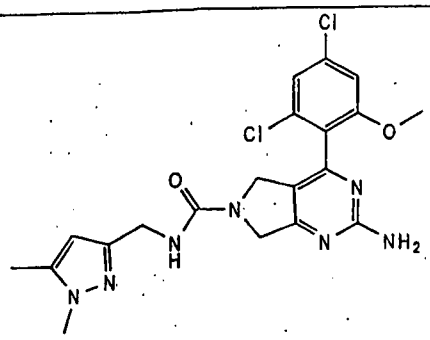
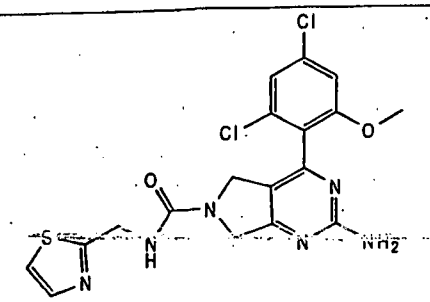
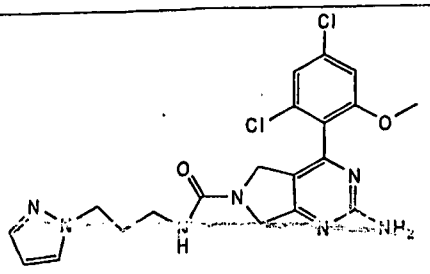
Compound **130a**, 2-amino-4-[2-(azetidin-3-ylmethoxy)-4,6-dichlorophenyl]-*N*-ethyl-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxamide was prepared from compound **131** in a similar manner to Example **129**. A mixture of compound **130a**, (78 mg, 0.180 mmol), bromoacetonitrile (26 mg, 0.216 mmol), and potassium carbonate (124 mg, 0.899 mmol) in DMF (2.5 mL) were microwaved at 120°C for 30 min. Isolation by preparative HPLC gave compound **130** (20.0 mg, 0.042 mmol) as a powder in 23% yield. 1H NMR (400 MHz, DMSO-d6) d ppm: 7.35 (d, J=1.26 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H), 6.81 (br. s., 2 H), 6.34 (t, J=5.31 Hz, 1 H), 4.42 (s, 2 H), 4.04 - 4.20 (m, 4 H),

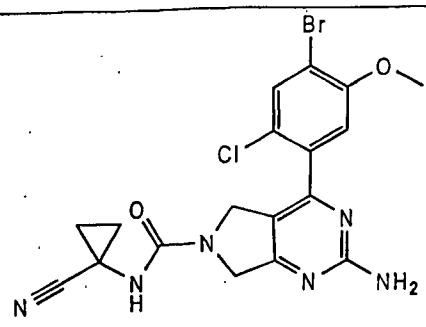
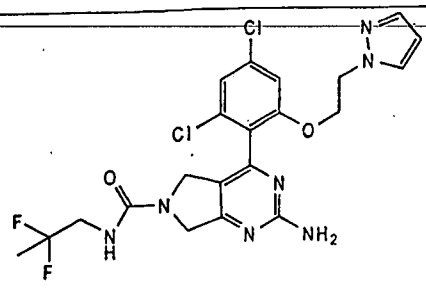
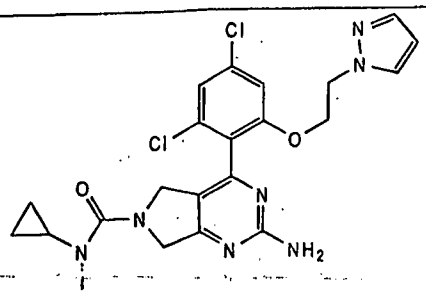
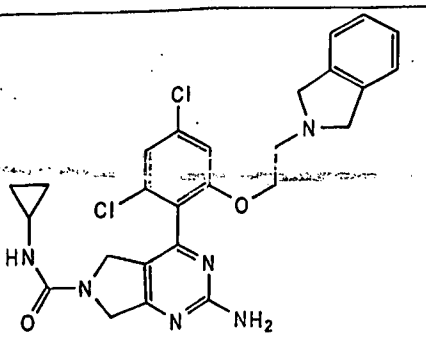
3.43 - 3.48 (m, 2 H), 3.25 - 3.34 (m, 2 H), 3.00 - 3.10 (m, 2 H), 2.87 - 2.99 (m, 2 H), 2.62 - 2.75 (m, 1 H), 1.01 (t, J=7.07 Hz, 3 H). LCMS $(M+H)^+$: 476.0, 478.0.

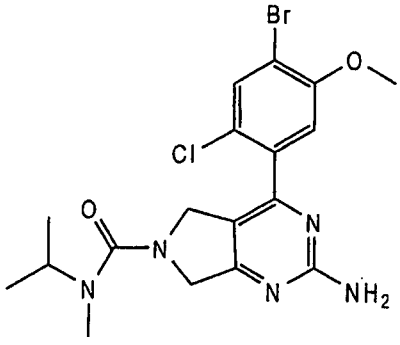
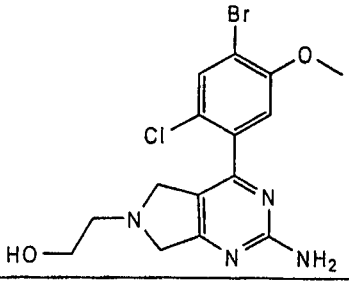
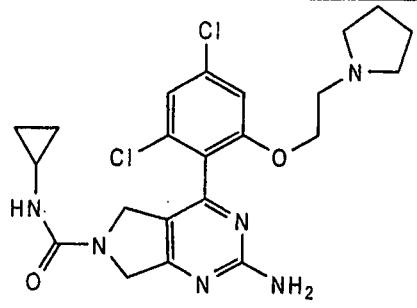
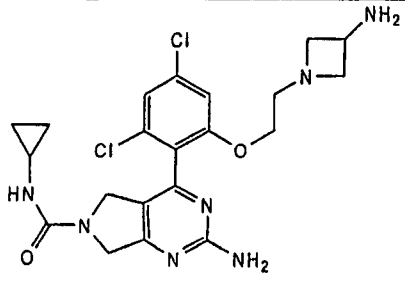
Compouds of Examples 131-2xx were prepared following the methods of Examples 1-18 and 100-130, as shown in the following Table 2.

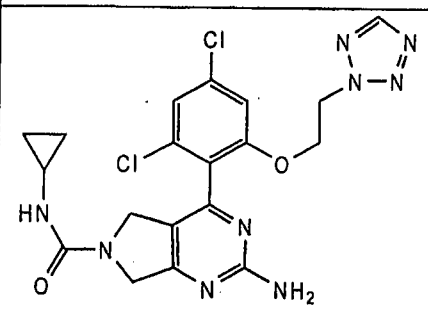
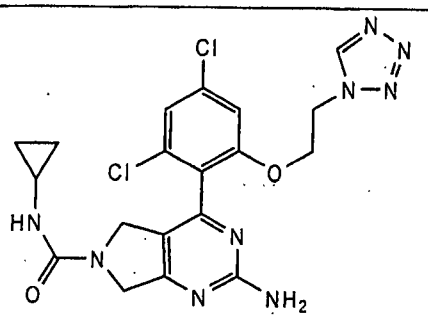
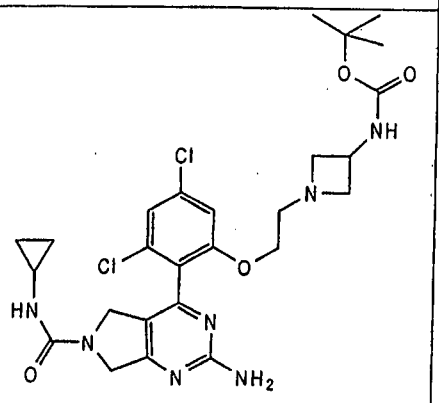
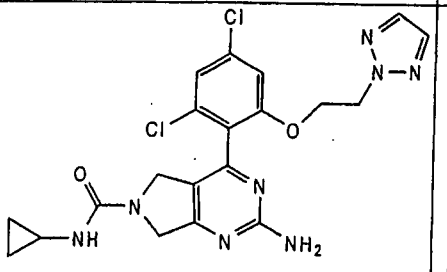
**Table 2**

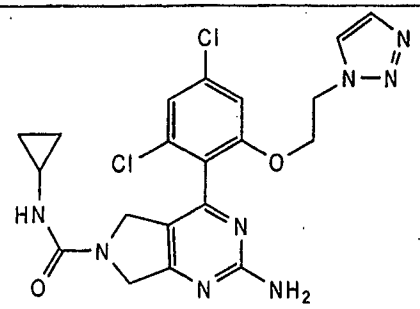
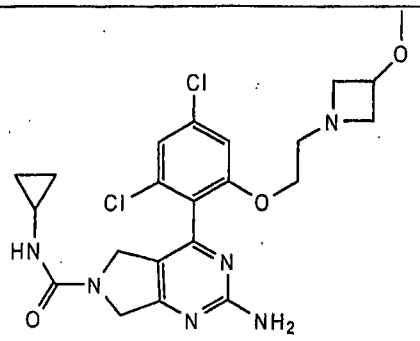
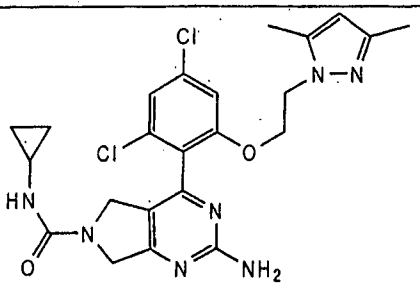
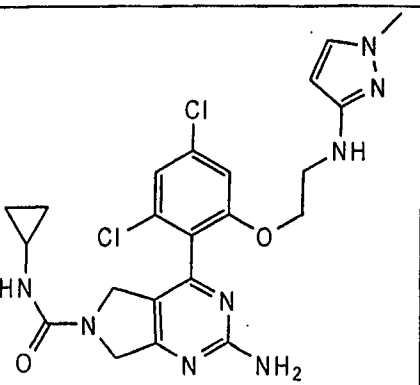
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 131 |  | tert-butyl 3-[(2-{2-amino-6-[(ethylamino)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl}-3,5-dichlorophenoxy)methyl]azetidine-1-carboxylate | Ex. 128 | $^1$H NMR (400 MHz, CHLOROFORM-d) d ppm: 7.15 (d, J=1.77 Hz, 1 H), 6.90 (d, J=1.77 Hz, 1 H), 5.17 (s, 2 H), 4.58 (s, 2 H), 4.37 - 4.45 (m, 1 H), 4.20 - 4.32 (m, 2 H), 4.01 - 4.13 (m, 2 H), 3.87-3.96 (m, 2 H), 3.53 - 3.62 (m, 2 H), 3.27 - 3.38 (m, 2 H), 2.73 - 2.87 (m, 1 H), 1.42 (s, 9 H), 1.17 (t, J=7.20 Hz, 3 H). | 537.1, 539.1 |
| 132 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-(2,2,2-trifluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.78 (s, 3 H), 3.82 (dd, J=9.60, 6.57 Hz, 2 H), 4.16 (s, 2 H), 4.48 (s, 2 H), 6.87 (s, 2 H), 7.07 (br. s., 1 H), 7.28 (d, J=1.52 Hz, 1 H), 7.34 (d, J=1.77 Hz, 1 H) | 436.0, 438.0 |
| 133 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-(2,2-difluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.38 - 3.48 (m, 2 H), 3.72 - 3.82 (m, 3 H), 4.11 - 4.18 (m, 2 H), 4.46 (s, 2 H), 5.74 - 6.15 (m, 1 H), 6.82 (t, J=5.68 Hz, 1 H), 6.86 (s, 2 H), 7.28 (d, J=1.77 Hz, 1 H), 7.34 (d, J=1.77 Hz, 1 H) | 418.0, 420.0 |

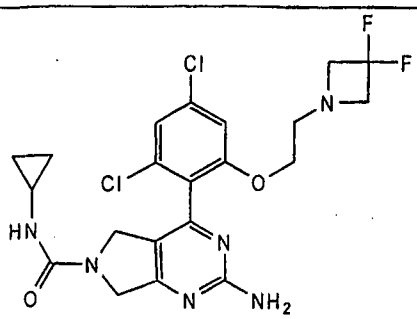
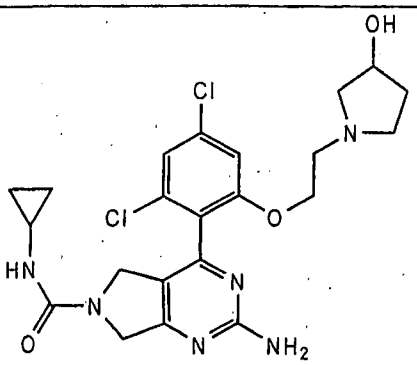
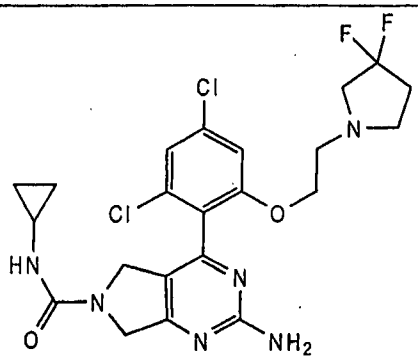
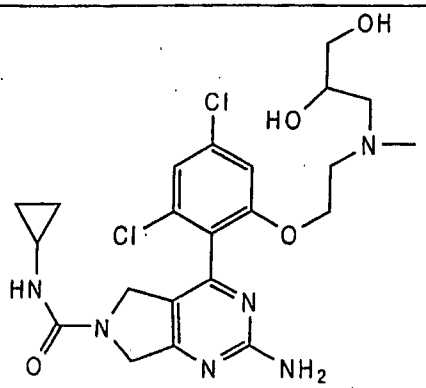
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 134 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-[2-(1H-pyrazol-1-yl)ethyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.35 - 3.40 (m, 2 H), 3.78 (s, 3 H), 4.09 (s, 2 H), 4.15 (t, J=6.57 Hz, 2 H), 4.41 (s, 2 H), 6.20 (t, J=2.02 Hz, 1 H), 6.54 (t, J=5.05 Hz, 1 H), 6.86 (br. s., 2 H), 7.28 (d, J=1.52 Hz, 1 H), 7.34 (d, J=1.77 Hz, 1 H), 7.42 (d, J=1.26 Hz, 1 H), 7.67 (d, J=2.02 Hz, 1 H) | 448.2, 450.2 |
| 135 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-[(1,5-dimethyl-1H-pyrazol-3-yl)methyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.17 (s, 3 H), 3.62 (s, 3 H), 3.77 (s, 3 H), 4.08 (d, J=5.31 Hz, 2 H), 4.12 (s, 2 H), 4.44 (s, 2 H), 5.88 (s, 1 H), 6.73 (t, J=5.68 Hz, 1 H), 6.84 (s, 2 H), 7.28 (d, J=1.52 Hz, 1 H), 7.34 (d, J=1.77 Hz, 1 H) | 462.2, 464.2 |
| 136 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-(1,3-thiazol-2-ylmethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.78 (s, 3 H), 4.18 (s, 2 H), 4.43 - 4.56 (m, 4 H), 6.87 (s, 2 H), 7.28 (s, 1 H), 7.35 (s, 1 H), 7.36 - 7.42 (m, 1 H), 7.55 - 7.60 (m, 1 H), 7.66 - 7.71 (m, 1 H) | 451.0, 453.0 |
| 137 |  | 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-N-[3-(1H-pyrazol-1-yl)propyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.89 (t, J=6.95 Hz, 2 H), 3.02 (q, J=6.40 Hz, 2 H), 3.77 (s, 3 H), 4.06 - 4.15 (m, 4 H), 4.42 (s, 2 H), 6.19 (t, J=2.02 Hz, 1 H), 6.40 (t, J=5.43 Hz, 1 H), 6.84 (s, 2 H), 7.28 (d, J=2.02 Hz, 1 H), 7.34 (d, J=1.77 Hz, 1 H), 7.39 (d, J=1.26 Hz, 1 H), 7.72 (d, J=2.27 Hz, 1 H) | 462.2, 464.2 |

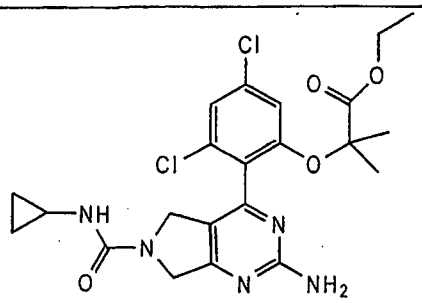
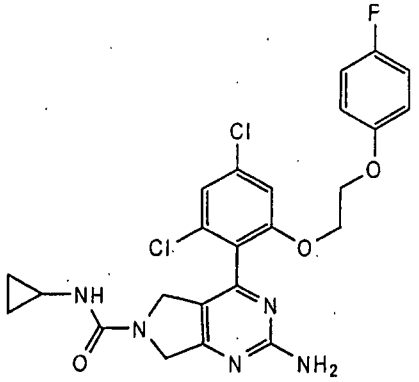
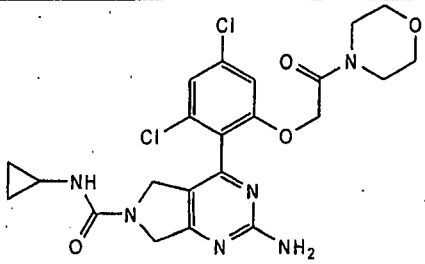
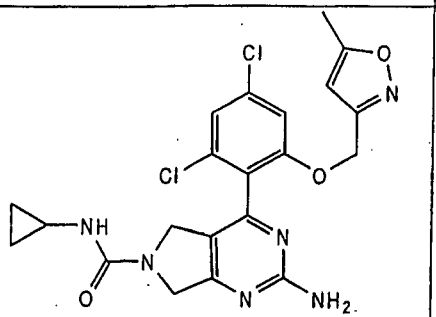
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 138 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(1-cyanocyclopropyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.06 - 1.17 (m, 2 H), 1.35 - 1.47 (m, 2 H), 3.86 (s, 3 H), 4.27 (br. s., 2 H), 4.45 (s, 2 H), 6.93 (s, 2 H), 7.15 (s, 1 H), 7.46 (br. s., 1 H), 7.87 (s, 1 H) | 463.0, 465.0 |
| 139 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(2,2-difluoropropyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.54 - 1.66 (m, 3 H), 3.48 (td, J=13.89, 8.08 Hz, 2 H), 3.58 (d, J=12.88 Hz, 2 H), 3.97 (d, J=12.88 Hz, 1 H), 4.33 (s, 4 H), 4.44 (br. s., 2 H), 6.00 (t, J=2.02 Hz, 1 H), 6.66 (br. s., 1 H), 6.80 (s, 2 H), 7.20 (d, J=2.02 Hz, 1 H), 7.26 (d, J=1.52 Hz, 1 H), 7.29 (d, J=1.52 Hz, 0 H), 7.33 (d, J=1.52 Hz, 1 H) | 512.0, 514.0 |
| 140 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-methyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.50 - 0.63 (m, 2 H), 0.68 (dd, J=6.57, 2.27 Hz, 2 H), 2.63 (ddd, J=6.82, 3.28, 3.03 Hz, 1 H), 2.74 (s, 3 H), 3.82 (d, J=13.39 Hz, 1 H), 4.18 (dd, J=13.39, 1.52 Hz, 1 H), 4.33 (s, 4 H), 4.49 - 4.69 (m, 2 H), 6.06 (t, J=2.02 Hz, 1 H), 6.76 (s, 2 H), 7.19 (d, J=2.02 Hz, 1 H), 7.23 (d, J=1.77 Hz, 1 H), 7.31 (d, J=1.77 Hz, 1 H), 7.33 (d, J=1.52 Hz, 1 H) | 489.0, 491.0 |
| 141 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1,3-dihydro-2H-isoindol-2-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.41 (m, 2 H), 0.45 - 0.57 (m, 2 H), 1.91 (s, 1 H), 2.92 (br. s., 2 H), 3.69 (br. s., 4 H), 4.10 - 4.25 (m, 4 H), 4.26 - 4.36 (m, 1 H), 4.38 - 4.48 (m, 1 H), 6.45 (d, J=2.78 Hz, 1 H), 6.90 (s, 2 H), 7.15 (s, 4 H), 7.31 (d, J=1.77 Hz, 1 H), 7.35 (d, J=1.52 Hz, 1 H) | 525.2, 527.2 |

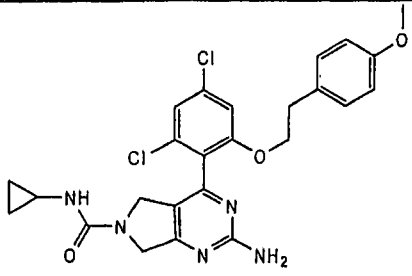
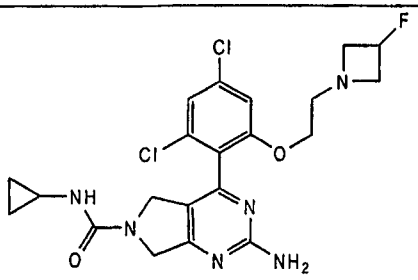
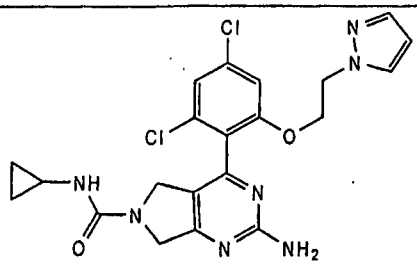
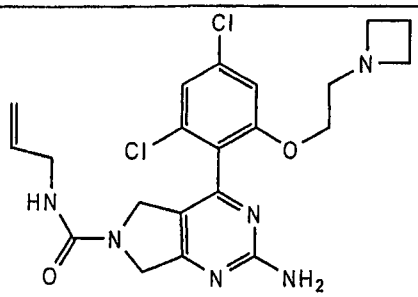
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 142 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-isopropyl-N-methyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.07 (d, J=6.57 Hz, 6 H), 2.64 (s, 3 H), 3.82 - 3.89 (m, 3 H), 3.94 - 4.08 (m, 1 H), 4.40 (s, 2 H), 4.53 (s, 2 H), 6.87 (s, 2 H), 7.16 (s, 1 H), 7.85 (s, 1 H) | 456.0, 458.0 |
| 143 |  | 2-[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]ethanol | Ex. 105 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.44 (d, J=10.36 Hz, 2 H), 3.71 - 3.79 (m, 2 H), 3.85 - 3.91 (m, 3 H), 4.46 (br. s., 2 H), 4.59 (s, 2 H), 5.36 (br. s., 1 H), 7.09 (s, 1 H), 7.17 - 7.24 (m, 2 H), 7.91 (s, 1 H) | 401.0, 403.0 |
| 144 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-6-(2-pyrrolidin-1-ylethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.43 (m, 2 H), 0.46 - 0.58 (m, 2 H), 1.59 (br. s., 4 H), 2.25 - 2.45 (m, 3 H), 2.54 (s, 1 H), 2.62 - 2.84 (m, 2 H), 4.03 - 4.20 (m, 5 H), 4.29 - 4.48 (m, 2 H), 6.54 (s, 1 H), 6.80 (s, 2 H), 7.29 (s, 1 H), 7.34 (d, J=1.52 Hz, 1 H) | 477.2, 479.2 |
| 145 |  | 2-amino-4-{2-[2-(3-aminoazetidin-1-yl)ethoxy]-4,6-dichlorophenyl}-N-cyclopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.46 (m, 2 H), 0.47 - 0.60 (m, 2 H), 1.91 (s, 2 H), 2.59 (dd, J=4.93, 3.16 Hz, 2 H), 2.62 - 2.75 (m, 4 H), 3.98 (t, J=5.05 Hz, 2 H), 4.03 - 4.14 (m, 2 H), 4.14 - 4.25 (m, 2 H), 4.41 (s, 2 H), 6.46 (d, J=2.53 Hz, 1 H), 6.77 (s, 2 H), 7.25 (d, J=1.77 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H) | 478.2, 480.2 |

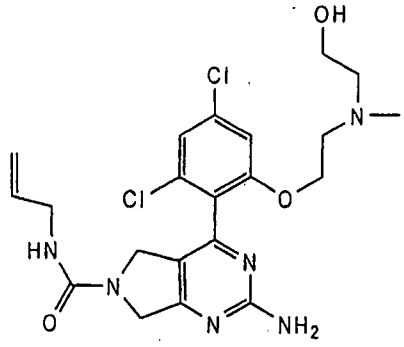
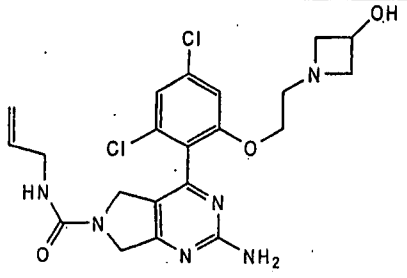
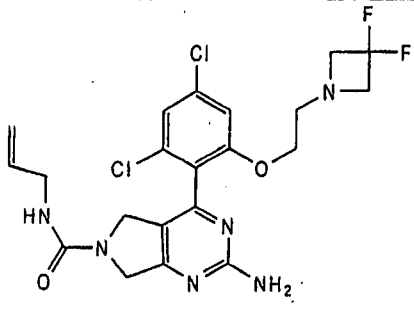
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 146 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(2H-tetrazol-2-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.48 (m, 2 H), 0.47 - 0.59 (m, 2 H), 2.51 - 2.57 (m, 1 H), 3.62 (d, J=13.14 Hz, 1 H), 3.95 (dd, J=13.01, 1.89 Hz, 1 H), 4.28 - 4.45 (m, 3 H), 4.44 - 4.57 (m, 1 H), 4.75 (t, J=5.05 Hz, 2 H), 6.34 (br. s., 1 H), 6.77 (br. s., 2 H), 7.33 (d, J=1.77 Hz, 1 H), 7.36 (d, J=1.77 Hz, 1 H), 8.82 (s, 1 H) | 476.1, 478.1 |
| 147 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-tetrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.36 - 0.48 (m, 2 H), 0.50 - 0.61 (m, 2 H), 2.53 - 2.58 (m, 1 H), 3.36 - 3.42 (m, 1 H), 3.83 (dd, J=13.01, 2.15 Hz, 1 H), 4.25 - 4.47 (m, 2 H), 4.46 - 4.63 (m, 2 H), 4.91 - 5.04 (m, 2 H), 6.34 (br. s., 1 H), 6.72 (s, 2 H), 7.34 (s, 2 H), 8.61 (s, 1 H) | 476.1, 477.1 |
| 148 |  | tert-butyl {1-[2-(2-{2-amino-6-[(cyclopropylamino)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl}-3,5-dichlorophenoxy)ethyl]azetidin-3-yl}carbamate | Ex. 101 | 1H NMR (400 MHz, CHLOROFORM-d) d ppm 1.44 (s, 9 H), 1.66 (br. s., 3 H), 2.70 (br. s., 4 H), 2.75 - 2.89 (m, 2 H), 3.37 - 3.47 (m, 1 H), 3.50 (s, 1 H), 3.86 - 4.03 (m, 2 H), 4.19 (br. s., 1 H), 4.34 (br. s., 2 H), 4.57 (s, 2 H), 4.62 (s, 1 H), 5.08 (br. s., 1 H), 5.30 (br. s., 2 H), 6.85 (d, J=1.52 Hz, 1 H), 7.12 (d, J=1.77 Hz, 1 H) | 578.2, 580.2 |
| 149 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(2H-1,2,3-triazol-2-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.35 - 0.47 (m, 2 H), 0.56 (d, J=7.07 Hz, 2 H), 2.52 - 2.60 (m, 1 H), 3.38 - 3.47 (m, 1 H), 3.84 (d, J=13.14 Hz, 1 H), 4.35 (d, J=4.80 Hz, 2 H), 4.42 - 4.56 (m, 2 H), 4.65 (t, J=4.93 Hz, 2 H), 6.33 (br. s., 1 H), 6.53 (s, 1 H), 6.71 (s, 2 H), 7.26 - 7.37 (m, 1 H), 7.53 (s, 2 H) | 475.1, 477.1 |

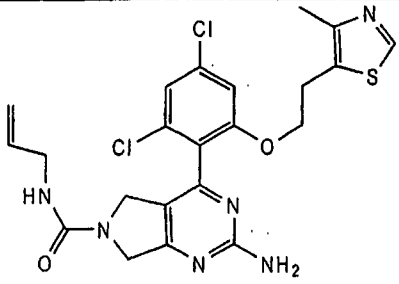
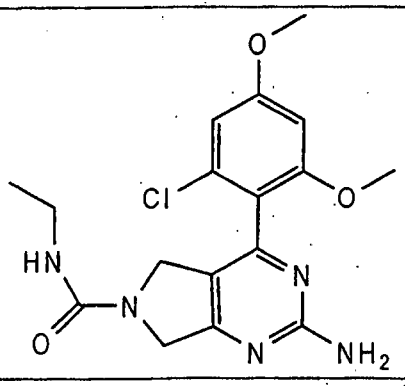
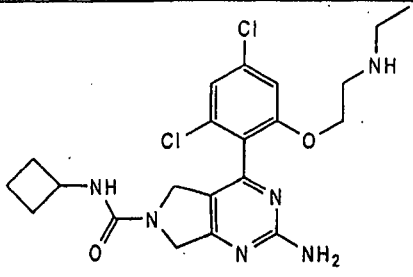
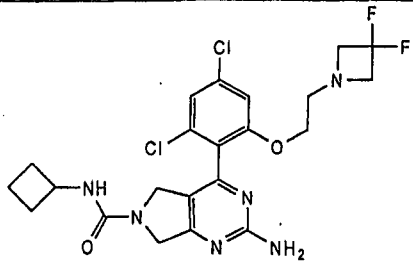
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 150 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-1,2,3-triazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.35 - 0.48 (m, 2 H), 0.49 - 0.60 (m, 2 H), 2.52 - 2.58 (m, 1 H), 3.60 (d, J=13.14 Hz, 1 H), 3.94 (dd, J=12.88, 2.02 Hz, 1 H), 4.30 - 4.51 (m, 4 H), 4.59 - 4.71 (m, 2 H), 6.35 (br. s., 1 H), 6.79 (br. s., 2 H), 7.29 (d, J=1.77 Hz, 1 H), 7.35 (d, J=1.52 Hz, 1 H), 7.48 (s, 1 H), 7.56 (s, 1 H) | 475.1, 477.1 |
| 151 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3-methoxyazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.46 (m, 2 H), 0.49 - 0.59 (m, 2 H), 2.52 - 2.57 (m, 1 H), 2.59 - 2.75 (m, 4 H), 3.07 (s, 3 H), 3.23 - 3.28 (m, 2 H), 3.79 (t, J=5.68 Hz, 1 H), 3.93 - 4.05 (m, 2 H), 4.04 - 4.23 (m, 2 H), 4.29 - 4.48 (m, 2 H), 6.46 (d, J=2.78 Hz, 1 H), 6.82 (s, 2 H), 7.23 (d, J=1.52 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H) | 493.1, 495.1 |
| 152 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3,5-dimethyl-1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.47 (m, 2 H), 0.54 (dd, J=7.07, 2.27 Hz, 2 H), 1.66 (s, 3 H) 2.00 (s, 3 H), 2.54 - 2.58 (m, 1 H), 3.84 (d, J=12.88 Hz, 1 H), 4.00 - 4.17 (m, 2 H), 4.16 - 4.27 (m, 2 H), 4.31 - 4.43 (m, 2 H), 5.49 (s, 1 H), 6.33 (br. s., 1 H), 6.53 (s, 1 H), 6.78 (s, 2 H), 7.25 (d, J=1.77 Hz, 1 H), 7.31 (d, J=1.77 Hz, 1 H) | 502.1, 504.1 |
| 153 |  | 2-amino-N-cyclopropyl-4-(2,4-dichloro-6-{2-[(1-methyl-1H-pyrazol-3-yl)amino]ethoxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.35 - 0.45 (m, 2 H), 0.49 - 0.61 (m, 2 H), 2.53 - 2.58 (m, 1 H), 3.25 (t, J=5.81 Hz, 2 H), 3.60 - 3.67 (m, 3 H), 4.04 - 4.12 (m, 2 H), 4.12 - 4.23 (m, 3 H), 4.40 (s, 2 H), 5.39 (d, J=2.27 Hz, 1 H), 6.41 (br. s., 1 H), 6.62 - 7.04 (m, 2 H), 7.34 (d, J=1.77 Hz, 1 H), 7.38 (d, J=2.02 Hz, 1 H), 7.45 (d, J=1.77 Hz, 1 H) | 503.1, 505.1 |

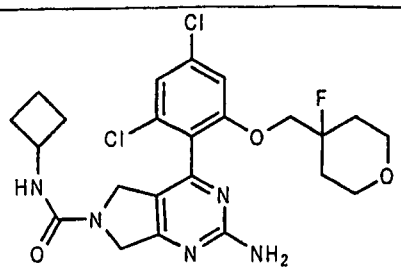
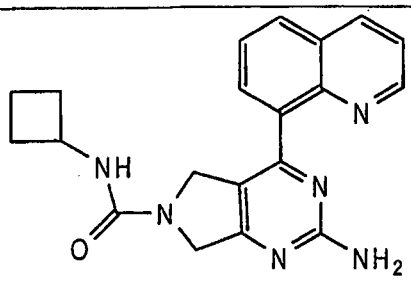
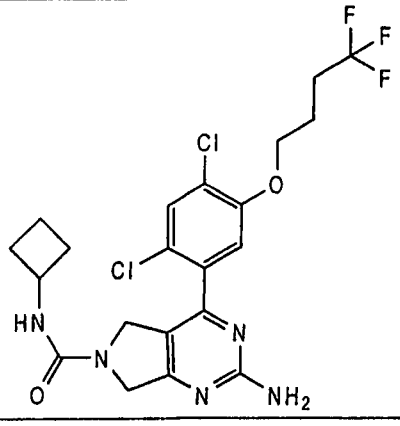
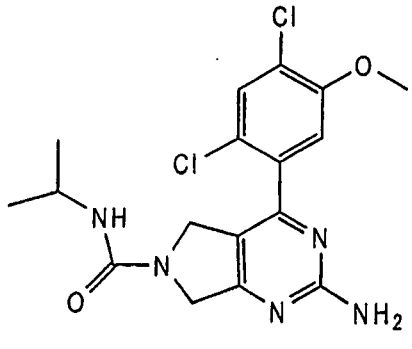
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 154 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3,3-difluoroazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.44 (m, 2 H), 0.47 - 0.59 (m, 2 H), 2.74 (d, J=3.54 Hz, 2 H), 3.22 - 3.35 (m, 4 H), 3.57 (s, 1 H), 3.97 - 4.09 (m, 2 H), 4.08 - 4.17 (m, 2 H), 4.26 - 4.51 (m, 2 H), 6.46 (d, J=2.53 Hz, 1 H), 6.85 (s, 2 H), 7.25 (d, J=1.77 Hz, 1 H), 7.30 - 7.38 (m, 1 H) | 499.1, 500.1 |
| 155 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3-hydroxypyrrolidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.45 (m, 2 H), 0.47 - 0.58 (m, 2 H), 1.34 - 1.49 (m, 2 H), 1.74 - 1.88 (m, 0 H), 2.17 - 2.34 (m, 2 H), 2.34 - 2.45 (m, 1 H), 2.55 - 2.73 (m, 3 H), 3.17 (d, J=4.80 Hz, 2 H), 3.99 - 4.20 (m, 4 H), 4.38 (br. s., 2 H), 4.59 (br. s., 1 H), 6.38 - 6.48 (m, 1 H), 6.78 (s, 2 H), 7.27 (s, 1 H), 7.32 (d, J=1.52 Hz, 1 H) | 493.1, 495.1 |
| 156 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3,3-difluoropyrrolidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.33 - 0.43 (m, 2 H), 0.47 - 0.57 (m, 2 H), 2.09 - 2.32 (m, 2 H), 2.52 - 2.58 (m, 1 H), 3.00 (d, J=3.79 Hz, 3 H), 3.13 - 3.21 (m, 2 H), 4.11 (s, 2 H), 4.16 - 4.26 (m, 2 H), 4.29 - 4.47 (m, 3 H), 6.44 (d, J=2.27 Hz, 1 H), 6.82 (br. s., 2 H), 7.32 (s, 1 H), 7.37 (s, 1 H) | 513.1, 514.1 |
| 157 |  | 2-amino-N-cyclopropyl-4-(2,4-dichloro-6-{2-[(2,3-dihydroxypropyl)(methyl)amino]ethoxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.90 (s, 1 H), 2.06 - 2.12 (m, 3 H), 2.11 - 2.14 (m, 2 H), 2.20 (dd, J=12.88, 7.07 Hz, 2 H), 2.29 - 2.40 (m, 2 H), 2.56 - 2.63 (m, 2 H), 3.17 - 3.27 (m, 2 H), 3.39 - 3.49 (m, 2 H), 4.02 - 4.13 (m, 3 H), 4.13 - 4.30 (m, 2 H), 4.39 (s, 2 H), 6.43 (d, J=2.53 Hz, 1 H), 6.77 (s, 2 H), 7.28 (d, J=1.77 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H) | 512.2, 513.2 |

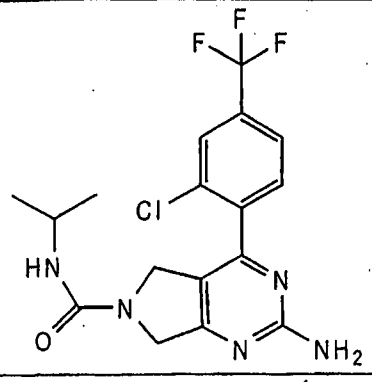
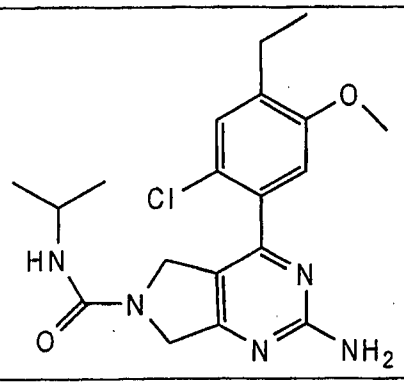
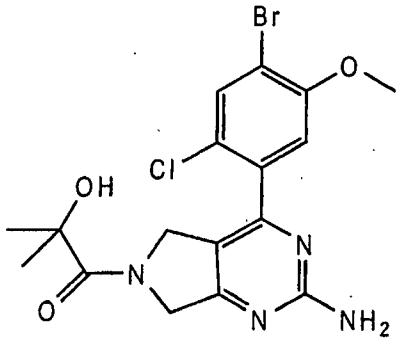
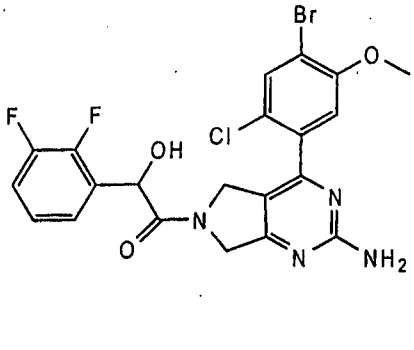
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 158 |  | ethyl 2-(2-{2-amino-6-[(cyclopropylamino)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl}-3,5-dichlorophenoxy)-2-methylpropanoate | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.45 (m, 2 H), 0.48 - 0.58 (m, 2 H), 1.17 (t, J=7.07 Hz, 3 H), 1.24 (s, 1 H), 1.35 (s, 3 H), 1.43 (s, 3 H), 4.10 - 4.23 (m, 4 H), 4.40 (s, 2 H), 6.45 (d, J=2.78 Hz, 1 H), 6.79 - 6.88 (m, 3 H), 7.45 (d, J=2.02 Hz, 1 H) | 494.1, 496.1 |
| 159 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(4-fluorophenoxy)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.43 (m, 2 H), 0.49 - 0.61 (m, 2 H), 1.23 (s, 1 H), 3.96 - 4.28 (m, 5 H), 4.29 - 4.42 (m, 3 H), 6.41 (d, J=2.02 Hz, 1 H), 6.70 - 6.83 (m, 3 H), 6.95 - 7.06 (m, 2 H), 7.31 - 7.41 (m, 2 H), 7.50 - 7.68 (m, 1 H) | 518.1, 520.1 |
| 160 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-6-(2-morpholin-4-yl-2-oxoethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.44 (m, 2 H), 0.47 - 0.59 (m, 2 H), 2.54 (s, 1 H), 3.46 (s, 4 H), 3.47 - 3.60 (m, 4 H), 4.10 (d, J=13.39 Hz, 1 H), 4.19 - 4.32 (m, 1 H), 4.39 (s, 2 H), 4.81 - 4.96 (m, 1 H), 4.96 - 5.09 (m, 1 H), 6.45 (d, J=2.53 Hz, 1 H), 6.79 (br. s., 2 H), 7.18 (d, J=1.26 Hz, 1 H), 7.31 (d, J=1.52 Hz, 1 H) | 507.1, 509.1 |
| 161 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[(5-methylisoxazol-3-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.45 (m, 2 H), 0.48 - 0.59 (m, 2 H), 2.33 - 2.41 (m, 3 H), 2.52 - 2.56 (m, 1 H), 3.96 - 4.16 (m, 2 H), 4.40 (s, 2 H), 5.19 - 5.33 (m, 2 H), 6.04 (s, 1 H), 6.44 (d, J=2.53 Hz, 1 H), 6.84 (s, 2 H), 7.39 (d, J=1.77 Hz, 1 H), 7.42 (d, J=1.77 Hz, 1 H) | 475.1, 477.1 |

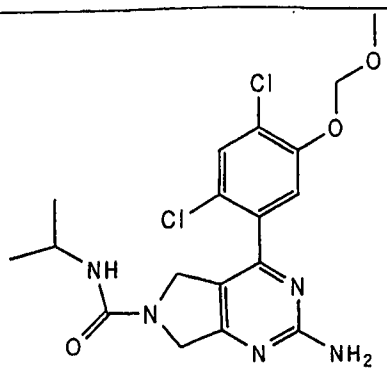
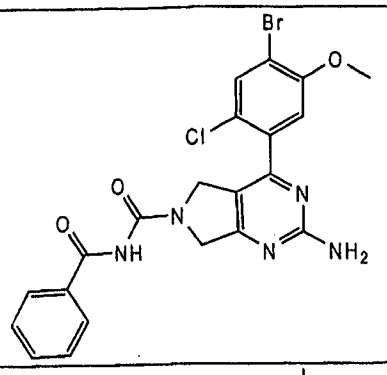
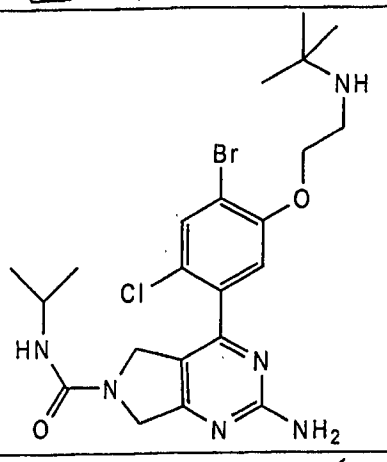
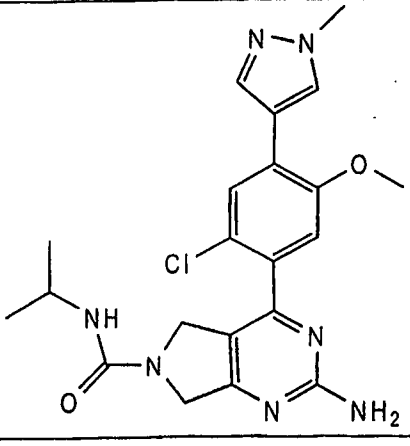
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 162 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(4-methoxyphenyl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.44 (m, 2 H), 0.47 - 0.58 (m, 2 H), 2.65 - 2.84 (m, 2 H), 3.69 (s, 3 H), 3.74 (d, J=13.14 Hz, 1 H), 3.97 (d, J=12.88 Hz, 1 H), 4.06 - 4.23 (m, 3 H), 4.41 (s, 2 H), 6.36 (br. s., 1 H), 6.69 (d, J=8.59 Hz, 2 H), 6.83 (s, 2 H), 6.86 (s, 1 H), 6.88 (s, 1 H), 7.24 (d, J=1.77 Hz, 1 H), 7.29 (d, J=1.77 Hz, 1 H) | 514.1, 515.1 |
| 163 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(3-fluoroazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.44 (m, 2 H), 0.47 - 0.59 (m, 2 H), 2.52 - 2.57 (m, 1 H), 2.66 (br. s., 2 H), 2.90 (d, J=7.83 Hz, 2 H), 4.00 (t, J=4.93 Hz, 2 H), 4.07 - 4.20 (m, 4 H), 4.33 - 4.46 (m, 2 H), 4.84 - 5.11 (m, 1 H), 6.46 (d, J=2.53 Hz, 1 H), 6.81 (s, 2 H), 7.24 (d, J=1.52 Hz, 1 H), 7.29 - 7.36 (m, 1 H) | 481.1, 483.1 |
| 164 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.32 - 0.45 (m, 2 H), 0.50 - 0.59 (m, 2 H), 2.52 - 2.57 (m, 1 H), 3.55 (d, J=12.88 Hz, 1 H), 3.82 - 3.97 (m, 1 H), 4.32 (s, 4 H), 4.35 - 4.42 (m, 2 H), 6.00 (t, J=2.02 Hz, 1 H), 6.33 (br. s., 1 H), 6.78 (s, 2 H), 7.18 (d, J=2.02 Hz, 1 H), 7.25 (d, J=1.77 Hz, 1 H), 7.29 (d, J=1.77 Hz, 1 H), 7.32 (d, J=1.52 Hz, 1 H) | 474.1, 476.1 |
| 165 |  | N-allyl-2-amino-4-[2-(2-azetidin-1-ylethoxy)-4,6-dichlorophenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.85 (t, J=7.07 Hz, 2 H), 2.60 (t, 2 H), 3.01 (br. s., 2 H), 3.67 (t, J=5.31 Hz, 2 H), 3.98 (t, J=4.93 Hz, 2 H), 4.08 - 4.28 (m, 4 H), 4.37 - 4.48 (m, 2 H), 5.00 (dd, J=10.23, 1.64 Hz, 1 H), 5.10 (dd, J=17.18, 1.77 Hz, 1 H), 5.68 - 5.90 (m, 1 H), 6.57 (t, J=5.68 Hz, 1 H), 6.81 (s, 2 H), 7.24 (d, J=1.77 Hz, 1 H), 7.29 - 7.36 (m, 1 H) | 463.2, 464.2 |

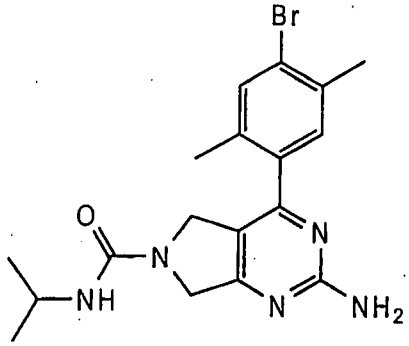
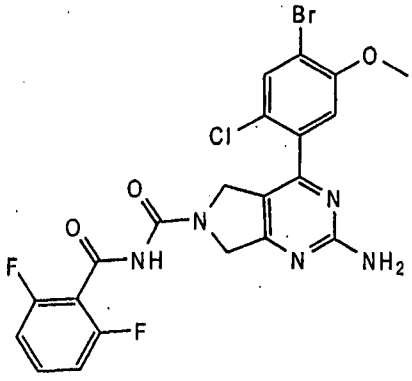
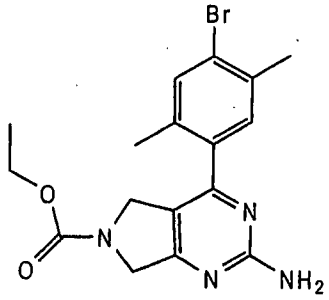
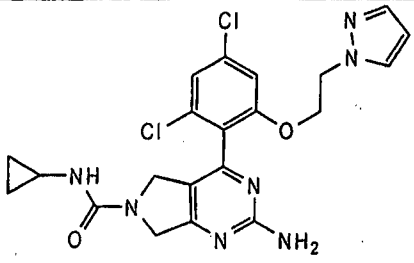
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 166 |  | N-allyl-2-amino-4-(2,4-dichloro-6-{2-[(2-hydroxyethyl)(methyl)amino]ethoxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.08 (s, 3 H), 2.33 (t, J=6.19 Hz, 2 H), 2.56 - 2.63 (m, 2 H), 3.67 (t, J=5.31 Hz, 3 H), 3.97 - 4.17 (m, 4 H), 4.25 (d, J=13.14 Hz, 2 H), 4.43 (br. s., 2 H), 5.00 (dd, J=10.23, 1.64 Hz, 1 H), 5.10 (dd, J=17.31, 1.64 Hz, 1 H), 5.73 - 5.88 (m, 1 H), 6.55 (t, J=5.56 Hz, 1 H), 6.79 (s, 2 H), 7.29 (d, J=1.77 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H) | 481.2, 483.2 |
| 167 |  | N-allyl-2-amino-4-{2,4-dichloro-6-[2-(3-hydroxyazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.56 (d, J=6.57 Hz, 2 H), 3.63 - 3.72 (m, 2 H), 3.93 - 4.04 (m, 4 H), 4.06 - 4.18 (m, 2 H), 4.18 - 4.29 (m, 2 H), 4.39 - 4.49 (m, 2 H), 5.01 (dd, J=10.23, 1.64 Hz, 1 H), 5.06 - 5.16 (m, 1 H), 5.20 (br. s., 1 H), 5.73 - 5.89 (m, 1 H), 6.51 - 6.61 (m, 2 H), 6.81 (s, 2 H), 7.25 (d, J=1.77 Hz, 1 H), 7.31 - 7.36 (m, 1 H) | 479.2, 481.2 |
| 168 |  | N-allyl-2-amino-4-{2,4-dichloro-6-[2-(3,3-difluoroazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 101 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.73 (d, J=4.04 Hz, 2 H), 3.20 - 3.29 (m, 2 H), 3.66 (t, J=5.31 Hz, 2 H), 3.99 - 4.09 (m, 2 H), 4.15 (s, 2 H), 4.29 - 4.51 (m, 4 H), 4.99 (dd, J=10.23, 1.64 Hz, 1 H), 5.09 (dd, J=17.43, 1.77 Hz, 1 H), 5.73 - 5.85 (m, 1 H), 6.56 (t, J=5.56 Hz, 1 H), 6.85 (s, 2 H), 7.24 (d, J=1.77 Hz, 1 H), 7.33 (d, J=1.77 Hz, 1 H) | 499.0, 501.0 |

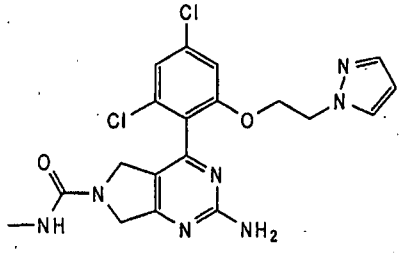
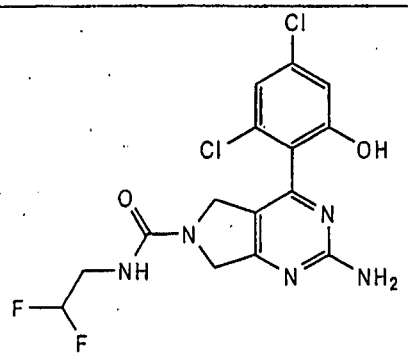
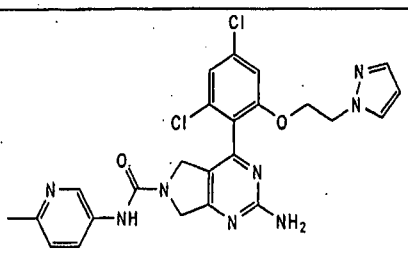
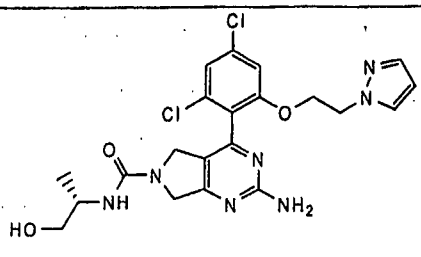
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 169 |  | N-allyl-2-amino-4-{2,4-dichloro-6-[2-(4-methyl-1,3-thiazol-5-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.02 (s, 3 H), 2.99 - 3.12 (m, 2 H), 3.55 - 3.65 (m, 1 H), 3.68 (t, J=5.18 Hz, 2 H), 3.87 - 4.00 (m, 1 H), 4.01 - 4.12 (m, 1 H), 4.23 - 4.34 (m, 1 H), 4.33 - 4.54 (m, 2 H), 5.02 (dd, J=10.36, 1.52 Hz, 1 H), 5.13 (dd, J=17.18, 1.52 Hz, 1 H), 5.74 - 5.93 (m, 1 H), 6.46 (br. s., 1 H), 6.80 (s, 2 H), 7.26 (d, J=1.52 Hz, 1 H), 7.32 (d, J=1.77 Hz, 1 H), 8.56 (s, 1 H) | 505.0, 507.0 |
| 170 |  | 2-amino-4-(2-chloro-4,6-dimethoxyphenyl)-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 107 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.01 (t, J=7.20 Hz, 3 H), 2.97 - 3.12 (m, 2 H), 3.73 (s, 3 H), 3.80 - 3.87 (m, 3 H), 4.05 - 4.17 (m, 2 H), 4.37 - 4.53 (m, 2 H), 6.35 (t, J=5.43 Hz, 1 H), 6.68 (d, J=2.27 Hz, 1 H), 6.75 (d, J=2.27 Hz, 2 H), 7.21 (s, 1 H) | 378.1, 380.1 |
| 171 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[2-(ethylamino)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.87 (t, J=7.07 Hz, 3 H), 1.44 - 1.61 (m, 2 H), 1.83 - 1.96 (m, 4 H), 2.02 - 2.14 (m, 2 H), 2.38 - 2.45 (m, 2 H), 2.73 (t, J=4.93 Hz, 2 H), 4.01 - 4.19 (m, 4 H), 4.40 (br. s., 2 H), 6.51 (d, J=7.83 Hz, 1 H), 6.82 (s, 2 H), 7.31 (s, 1 H), 7.34 (s, 1 H) | 465.1, 467.1 |
| 172 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[2-(3,3-difluoroazetidin-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.54 (dd, J=9.85, 7.33 Hz, 2 H), 1.85 - 1.97 (m, 2 H), 2.08 (dd, J=6.82, 3.54 Hz, 2 H), 2.74 (br. s., 2 H), 3.36 - 3.47 (m, 2 H), 3.98 - 4.08 (m, 2 H), 4.09 - 4.17 (m, 3 H), 4.26 - 4.48 (m, 2 H), 6.47 - 6.57 (m, 2 H), 6.85 (s, 2 H), 7.25 (d, J=1.77 Hz, 1 H), 7.34 (d, J=1.52 Hz, 1 H) | 513.1, 515.1 |

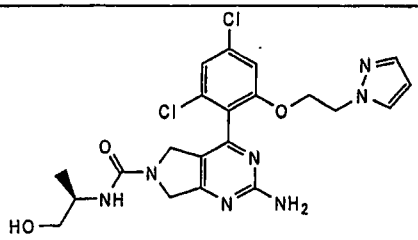
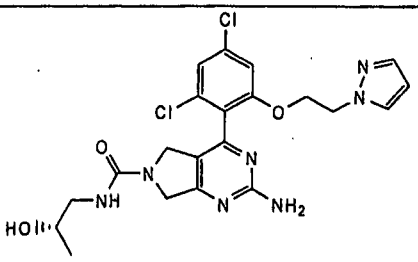
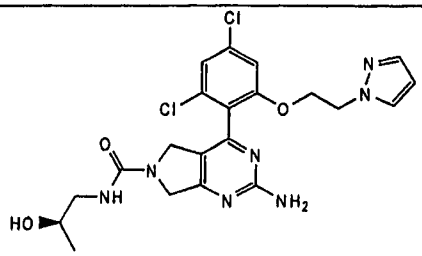
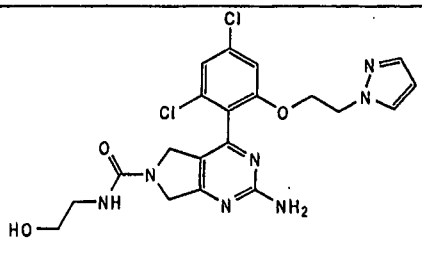
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 173 |  | -amino-N-cyclobutyl-4-{2,4-dichloro-6-[(4-fluorotetrahydro-2H-pyran-4-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.46 - 1.60 (m, 4 H), 1.91 (br. s., 2 H), 2.09 (dd, J=6.82, 3.28 Hz, 2 H), 3.28 - 3.40 (m, 4 H), 3.42 - 3.52 (m, 2 H), 3.56 - 3.68 (m, 2 H), 4.09 - 4.16 (m, 3 H), 4.36 - 4.44 (m, 2 H), 6.52 - 6.59 (m, 2 H), 6.82 (s, 1 H), 7.37 (dd, J=8.08, 1.77 Hz, 2 H) | |
| 174 |  | 2-amino-N-cyclobutyl-4-quinolin-8-yl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18a | 1H NMR (400 MHz, DMSO-d6) d ppm 1.44 - 1.62 (m, 2 H), 1.81 - 1.94 (m, 2 H), 1.99 - 2.18 (m, 2 H), 3.95 - 4.19 (m, 3 H), 4.42 (d, J=18.44 Hz, 2 H), 6.42 (d, J=7.83 Hz, 1 H), 6.75 (s, 2 H), 7.59 - 7.66 (m, 1 H), 7.69 - 7.77 (m, 1 H), 7.78 - 7.84 (m, 1 H), 8.08 - 8.17 (m, 1 H), 8.43 - 8.55 (m, 1 H), 8.93 (dd, J=4.17, 1.64 Hz, 1 H) | 361.4 |
| 175 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-5-(4,4,4-trifluorobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.45 - 1.65 (m, 2 H) 1.86 - 2.01 (m, 4 H) 2.03 - 2.15 (m, 2 H) 2.37 - 2.46 (m, 2 H) 4.06 - 4.21 (m, 3 H) 4.26 (s, 2 H) 4.41 (s, 2 H) 6.53 (d, J=8.08 Hz, 1 H) 6.89 (s, 2 H) 7.23 (s, 1 H) 7.77 (s, 1 H) | 504.2, 506.2 |
| 177 |  | 2-amino-4-(2,4-dichloro-5-methoxyphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.05 (d, J=6.57 Hz, 6 H) 3.77 (d, J=7.07 Hz, 1 H) 3.87 (s, 3 H) 4.25 (s, 2 H) 4.41 (s, 2 H) 6.07 (d, J=7.58 Hz, 1 H) 6.89 (s, 2 H) 7.20 (s, 1 H) 7.74 (s, 1 H) | 396.0, 397.0 |

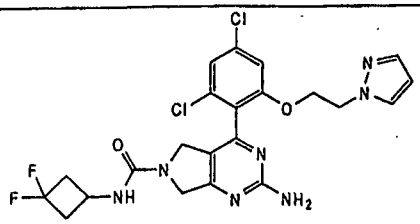
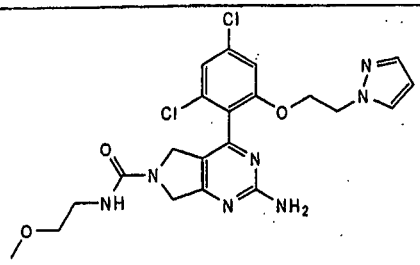
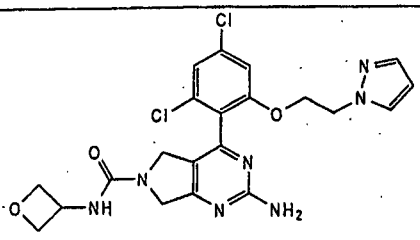
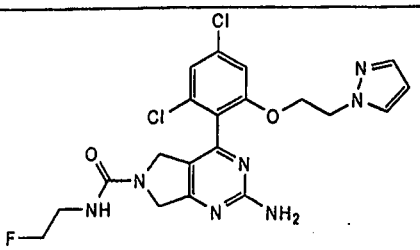
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 178 |  | 2-amino-4-[2-chloro-4-(trifluoromethyl)phenyl]-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18a | 1H NMR (400 MHz, DMSO-d6) d ppm 1.05 (d, J=6.32 Hz, 6 H) 3.77 (d, J=6.82 Hz, 1 H) 4.25 (s, 2 H) 4.43 (s, 2 H) 6.08 (d, J=7.83 Hz, 1 H) 6.93 (s, 2 H) 7.70 (d, J=7.83 Hz, 1 H) 7.86 (d, J=7.83 Hz, 1 H) 8.06 (s, 1 H) | 400.1, 402.1 |
| 179 |  | 2-amino-4-(2-chloro-4-ethyl-5-methoxyphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 104 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.00 - 1.11 (m, 6 H) 1.10 - 1.21 (m, 3 H) 2.54 - 2.67 (m, 2 H) 3.76 - 3.83 (m, 3 H) 4.27 (s, 2 H) 4.37 - 4.44 (m, 2 H) 6.10 (d, J=7.83 Hz, 1 H) 6.82 (s, 2 H) 6.96 (s, 1 H) 7.27 - 7.35 (m, 1 H) | 390.4, 392.4 |
| 180 |  | 1-[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]-2-methyl-1-oxopropan-2-ol | Ex. 6 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.31 (d, J=13.89 Hz, 6 H) 3.85 (s, 3 H) 4.44 (d, J=61.39 Hz, 2 H) 4.91 (d, J=48.25 Hz, 2 H) 5.35 (d, J=25.52 Hz, 1 H) 6.92 (s, 2 H) 7.16 (d, J=14.65 Hz, 1 H) 7.87 (d, J=5.05 Hz, 1 H) | |
| 181 |  | 2-[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]-1-(2,3-difluorophenyl)-2-oxoethanol | Ex. 6 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.82 - 3.89 (m, 3 H), 4.40 (d, J=6.06 Hz, 2 H), 4.49 - 4.58 (m, 2 H), 4.76 - 5.02 (m, 1 H), 5.60 (d, J=24.25 Hz, 1 H), 6.86 - 7.05 (m, 2 H), 7.11 - 7.21 (m, 1 H), 7.22 - 7.31 (m, 2 H), 7.33 - 7.44 (m, 1 H), 7.86 (d, J=1.01 Hz, 1 H) | |

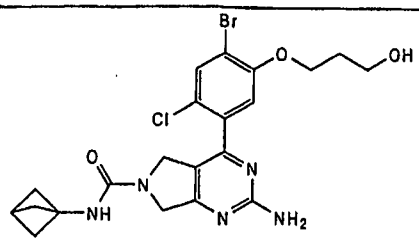
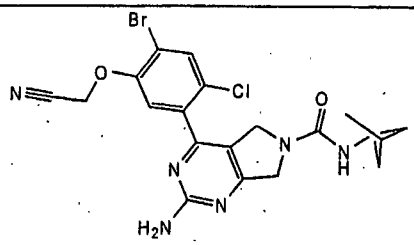
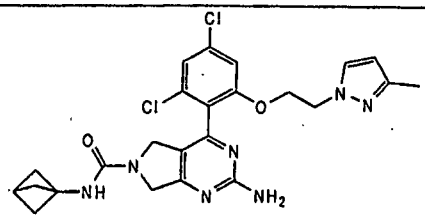
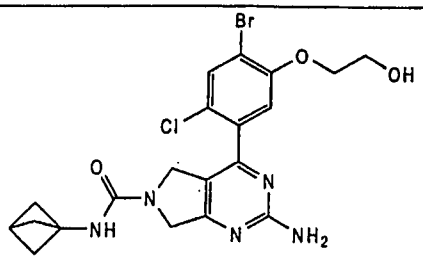
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 182 |  | 2-amino-4-[2,4-dichloro-5-(methoxymethoxy)phenyl]-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.06 (d, J=6.57 Hz, 6 H), 3.39 - 3.45 (m, 3 H), 3.78 (dd, J=14.15, 6.57 Hz, 1 H), 4.25 (s, 2 H), 4.42 (s, 2 H), 5.33 (s, 2 H), 6.08 (d, J=7.58 Hz, 1 H), 6.92 (s, 2 H), 7.29 (s, 1 H), 7.80 (s, 1 H) | 427.2, 429.2 |
| 183 |  | 2-amino-N-benzoyl-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15a | 1H NMR (400 MHz, DMSO-d6) d ppm 3.85 (d, J=10.61 Hz, 3 H), 4.45 (s, 2 H), 4.60 (s, 2 H), 4.75 (s, 1 H), 6.97 (s, 2 H), 7.16 (s, 1 H), 7.44 - 7.57 (m, 2 H), 7.61 (s, 1 H), 7.78 - 7.85 (m, 1 H), 7.85 - 7.93 (m, 2 H) | 505.2, 506.2 |
| 184 |  | 2-amino-4-{4-bromo-5-[2-(tert-butylamino)ethoxy]-2-chlorophenyl}-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.05 (t, J=3.16 Hz, 15 H), 1.90 (s, 1 H), 2.87 (t, J=5.43 Hz, 2 H), 3.78 (dd, J=14.02, 6.69 Hz, 1 H), 4.09 (t, J=5.68 Hz, 2 H), 4.25 (s, 2 H), 4.41 (s, 2 H), 6.07 (d, J=7.58 Hz, 1 H), 6.88 (s, 2 H), 7.19 (s, 1 H), 7.86 (s, 1 H) | 527.1, 528.1 |
| 185 |  | 2-amino-4-[2-chloro-5-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl]-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 104 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.05 (t, J=5.81 Hz, 6 H), 3.78 (s, 1 H), 3.86 - 3.92 (m, 6 H), 4.30 (s, 2 H), 4.43 (s, 2 H), 6.05 - 6.16 (m, 1 H), 6.85 (s, 2 H), 7.08 (s, 1 H), 7.80 (s, 1 H), 8.03 (s, 1 H), 8.25 (s, 1 H) | 442.2, 444.2 |

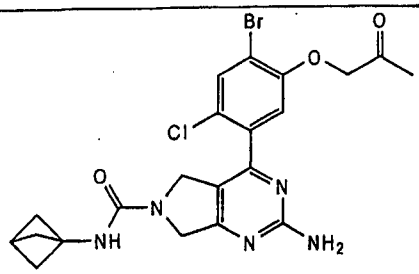
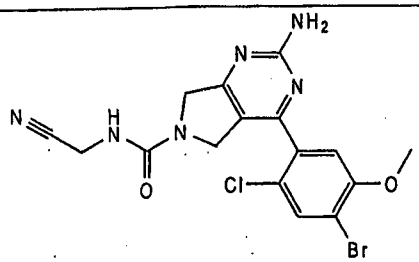
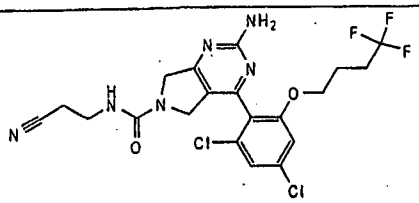
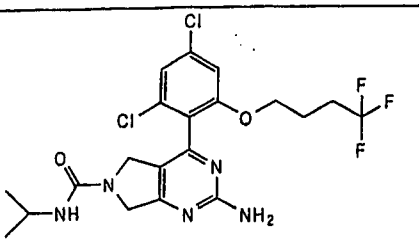
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 186 |  | 2-amino-4-(4-bromo-2,5-dimethylphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15a | 1H NMR (400 MHz, DMSO-d6) d ppm 1.05 (d, J=6.57 Hz, 6 H), 2.17 (s, 3 H), 2.33 (s, 3 H), 3.72 - 3.84 (m, 1 H), 4.24 (s, 2 H), 4.41 (s, 2 H), 6.06 (d, J=7.33 Hz, 1 H), 7.28 (s, 1 H), 7.56 (s, 1 H) | 405.1, 406.1 |
| 187 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2,6-difluorobenzoyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15a | 1H NMR (400 MHz, DMSO-d6) d ppm 3.86 (d, J=10.86 Hz, 3 H), 4.34 (s, 1 H), 4.48 (s, 1 H), 4.59 (s, 1 H), 4.74 (s, 1 H), 6.97 (s, 2 H), 7.03 - 7.11 (m, 1 H), 7.11 - 7.23 (m, 2 H), 7.46 - 7.59 (m, 1 H), 7.58 - 7.68 (m, 1 H), 7.86 (d, J=13.64 Hz, 1 H) | 540.2, 542.2 |
| 188 |  | ethyl 2-amino-4-(4-bromo-2,5-dimethylphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 1 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.09 - 1.30 (m, 3 H), 2.18 (d, J=7.83 Hz, 3 H), 2.33 (s, 3 H), 4.08 (dd, J=14.02, 6.95 Hz, 2 H), 4.32 (d, J=5.05 Hz, 2 H), 4.46 (d, J=10.36 Hz, 2 H), 6.81 (s, 2 H), 7.29 (d, J=5.05 Hz, 1 H),7.55 (s, 1 H) | 391.1, 392.1 |
| 189 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 100 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.33 - 0.44 (m, 2 H), 0.49 - 0.58 (m, 2 H), 2.51 - 2.56 (m, 1 H), 3.55 (d, J=12.88 Hz, 1 H), 3.82 - 3.94 (m, 1 H), 4.29 - 4.35 (m, 4 H), 4.36 - 4.42 (m, 2 H), 6.00 (t, J=2.02 Hz, 1 H), 6.32 (br. s., 1 H), 6.77 (br. s., 2 H), 7.18 (d, J=2.27 Hz, 1 H), 7.24 (d, J=1.77 Hz, 1 H), 7.29 (d, J=1.52 Hz, 1 H), 7.31 (d, J=1.52 Hz, 1 H) | 474.2, 476.2 |

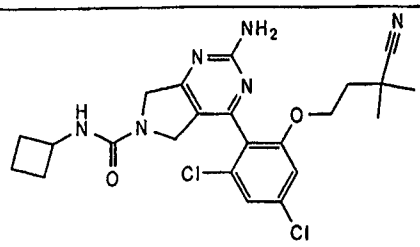
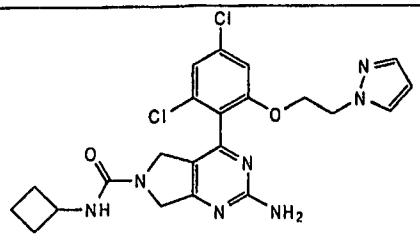
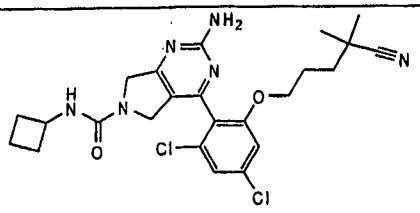
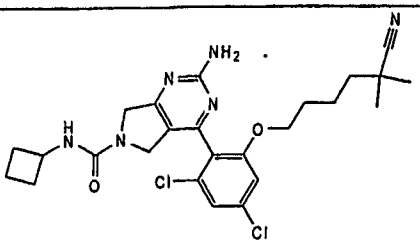
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 190 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-methyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 106 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.59 (d, J=4.29 Hz, 3 H) 3.60 (d, J=12.63 Hz, 1 H) 3.92 (dd, 1 H) 4.29 - 4.36 (m, 4 H) 4.36 - 4.46 (m, 2 H) 6.00 (t, J=2.02 Hz, 1 H) 6.18 (d, J=4.29 Hz, 1 H) 6.78 (s, 2 H) 7.19 (d, J=2.02 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.29 (d, J=1.52 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 450.2, 448.2 |
| 191 |  | 2-amino-4-(2,4-dichloro-6-hydroxyphenyl)-N-(2,2-difluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.35 - 3.49 (m, 2 H) 4.19 (s, 2 H) 4.45 (s, 2 H) 5.96 (tt, 1 H) 6.76 - 6.89 (m, 3 H) 6.96 (d, J=1.77 Hz, 1 H) 7.15 (d, J=2.02 Hz, 1 H) 10.66 (s, 1 H) | 406.0, 404.2 |
| 192 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(6-methylpyridin-3-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 109 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.42 (s, 3 H) 3.69 (d, J=12.63 Hz, 1 H) 4.13 (d, J=12.63 Hz, 1 H) 4.31 - 4.40 (m, 4 H) 4.49 - 4.63 (m, 2 H) 6.01 (t, J=1.89 Hz, 1 H) 6.84 (s, 2 H) 7.22 - 7.27 (m, 3 H) 7.29 (d, J=1.52 Hz, 1 H) 7.34 (d, J=1.77 Hz, 1 H) 7.91 (dd, J=8.46, 2.40 Hz, 1 H) 8.43 (s, 1 H) 8.61 (s, 1 H) | 527.2, 525.2 |
| 193 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-[(1S)-2-hydroxy-1-methylethyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | | 494.2, 492.2 |

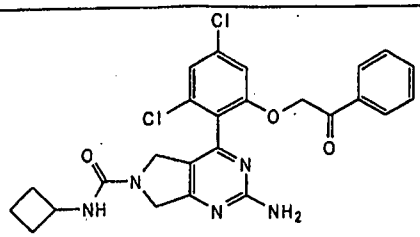
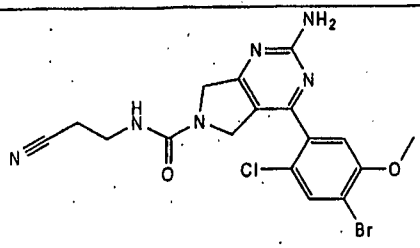
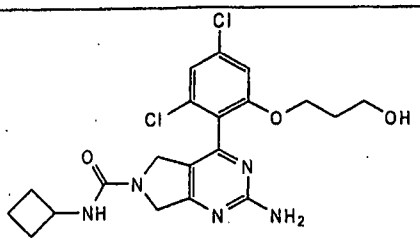
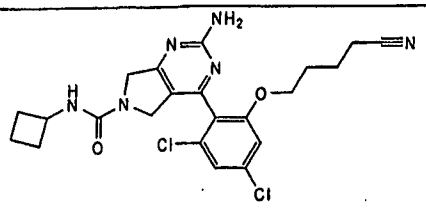
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 194 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-[(1R)-2-hydroxy-1-methylethyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | | 494.2, 492.2 |
| 195 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-[(2S)-2-hydroxypropyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.01 (dd, J=6.19, 1.39 Hz, 3 H) 2.96 - 3.03 (m, J=5.56, 5.56 Hz, 2 H) 3.58 - 3.70 (m, 2 H) 3.95 (d, J=12.63 Hz, 1 H) 4.30 - 4.37 (m, 4 H) 4.39 - 4.47 (m, 2 H) 6.01 (q, J=1.94 Hz, 1 H) 6.21 - 6.30 (m, 1 H) 6.78 (s, 2 H) 7.19 (d, J=2.27 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.30 - 7.32 (m, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 494.2, 492.2 |
| 196 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-[(2R)-2-hydroxypropyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.01 (dd, J=6.32, 1.26 Hz, 3 H) 2.95 - 3.02 (m, J=5.56, 5.56 Hz, 2 H) 3.58 - 3.70 (m, 2 H) 3.95 (d, J=12.63 Hz, 1 H) 4.30 - 4.38 (m, 4 H) 4.39 - 4.47 (m, 2 H) 6.01 (q, J=1.85 Hz, 1 H) 6.22 - 6.30 (m, 1 H) 6.78 (s, 2 H) 7.19 (d, J=2.27 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.29 - 7.31 (m, 1 H) 7.32 (d, J=1.52 Hz, 1 H) | 494.2, 492.2 |
| 197 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(2-hydroxyethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.06 - 3.15 (m, 2 H) 3.37 - 3.43 (m, 2 H) 3.59 (d, J=13.00 Hz, 1 H) 3.93 (d, J=12.62 Hz, 1 H) 4.33 (s, 4 H) 4.38 - 4.48 (m, 2 H) 6.01 (t, J=1.98 Hz, 1 H) 6.22 - 6.28 (m, 1 H) 6.79 (s, 2 H) 7.19 (d, J=2.26 Hz, 1 H) 7.25 (d, J=1.70 Hz, 1 H) 7.30 - 7.33 (m, 1.70 Hz, 2 H) | 480.2, 478.2 |

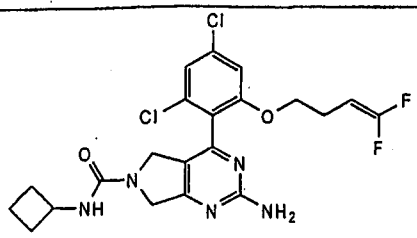
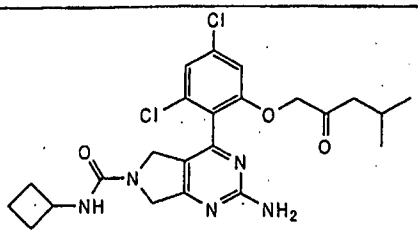
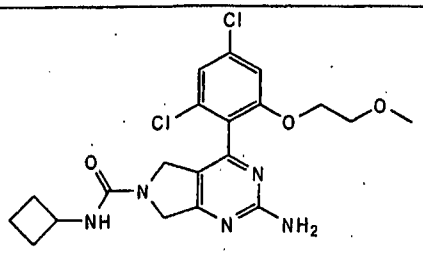
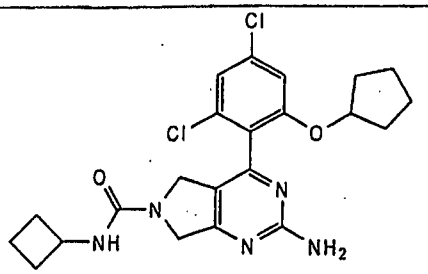
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 198 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(3,3-difluorocyclobutyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.57 - 2.70 (m, 2 H) 2.77 - 2.90 (m, 2 H) 3.60 (d, J=12.88 Hz, 1 H) 3.95 (d, J=12.88 Hz, 1 H) 3.99 - 4.08 (m, 1 H) 4.31 - 4.37 (m, 4 H) 4.39 - 4.47 (m, 2 H) 6.00 (t, J=2.02 Hz, 1 H) 6.60 (d, J=6.32 Hz, 1 H) 6.77 (s, 2 H) 7.20 (d, J=2.02 Hz, 1 H) 7.26 (d, J=1.52 Hz, 1 H) 7.29 (d, J=1.52 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 526.0, 524.0 |
| 199 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(2-methoxyethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.16 - 3.22 (m, 2 H) 3.24 (s, 3 H) 3.31 - 3.37 (m, 2 H) 3.57 (d, J=12.88 Hz, 1 H) 3.92 (d, J=13.14 Hz, 1 H) 4.30 - 4.36 (m, 4 H) 4.37 - 4.45 (m, 2 H) 6.00 (t, J=1.89 Hz, 1 H) 6.28 - 6.35 (m, 1 H) 6.79 (s, 2 H) 7.19 (d, J=1.77 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.30 (d, J=1.26 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 494.2, 492.2 |
| 200 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-oxetan-3-yl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.60 (d, J=13.00 Hz, 1 H) 3.97 (d, J=12.81 Hz, 1 H) 4.33 (s, 4 H) 4.38 - 4.52 (m, 4 H) 4.61 - 4.81 (m, 3 H) 5.97 - 6.02 (m, 1 H) 6.80 (s, 2 H) 6.89 (d, J=5.65 Hz, 1 H) 7.20 (d, J=1.88 Hz, 1 H) 7.25 - 7.30 (m, 2 H) 7.33 (d, J=1.51 Hz, 1 H) | 492.2, 490.2 |
| 201 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(2-fluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.26 - 3.41 (m, 2 H) 3.57 (d, J=13.00 Hz, 1 H) 3.93 (d, J=12.81 Hz, 1 H) 4.30 - 4.54 (m, 8 H) 6.00 (t, J=1.88 Hz, 1 H) 6.50 (s, 1 H) 6.79 (s, 2 H) 7.20 (d, J=2.07 Hz, 1 H) 7.25 (d, J=1.70 Hz, 1 H) 7.30 (d, J=1.51 Hz, 1 H) 7.32 (d, J=1.51 Hz, 1 H) | 482.2, 480.2 |

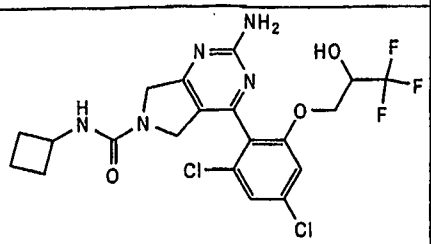
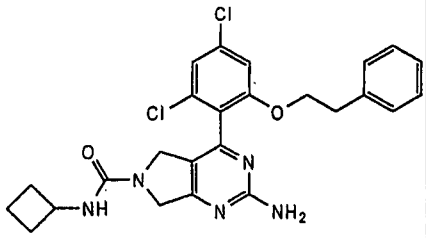
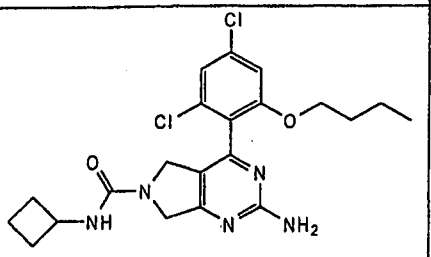
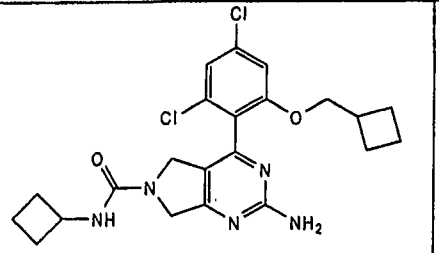
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 202 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-[4-bromo-2-chloro-5-(3-hydroxypropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.82 - 1.90 (m, 2 H) 1.93 (s, 6 H) 2.34 (s, 1 H) 3.57 (t, J=6.22 Hz, 2 H) 4.12 (t, J=6.12 Hz, 2 H) 4.23 (s, 2 H) 4.39 (s, 2 H) 6.90 (s, 2 H) 7.01 (s, 1 H) 7.15 (s, 1 H) 7.85 (s, 1 H) | 510.2, 508.2 |
| 203 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-[4-bromo-2-chloro-5-(cyanomethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.93 (s, 6 H) 2.34 (s, 1 H) 4.23 (s, 2 H) 4.40 (s, 2 H) 5.31 (s, 2 H) 6.93 (s, 2 H) 6.98 (s, 1 H) 7.36 (s, 1 H) 7.98 (s, 1 H) | 491.2, 489.2 |
| 204 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[2-(3-methyl-1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, METHANOL-d4) d ppm 2.05 (s, 6 H) 2.19 (s, 3 H) 2.38 (s, 1 H) 3.65 (d, J=12.81 Hz, 1 H) 4.06 (d, J=12.81 Hz, 1 H) 4.32 (s, 4 H) 4.53 (s, 2 H) 5.89 (d, J=2.07 Hz, 1 H) 7.08 (d, J=2.26 Hz, 1 H) 7.18 (d, J=1.70 Hz, 1 H) 7.24 (d, J=1.70 Hz, 1 H) | 516.2, 514.2 |
| 205 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-[4-bromo-2-chloro-5-(2-hydroxyethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.93 (s, 6 H) 2.34 (s, 1 H) 3.72 (t, J=4.71 Hz, 2 H) 4.09 (t, J=4.80 Hz, 2 H) 4.23 (s, 2 H) 4.39 (s, 2 H) 6.89 (s, 2 H) 7.01 (s, 1 H) 7.18 (s, 1 H) 7.85 (s, 1 H) | 496.2, 494.2 |

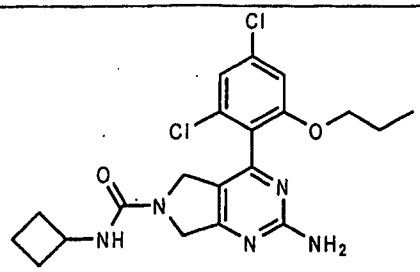
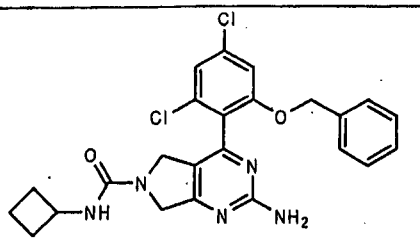
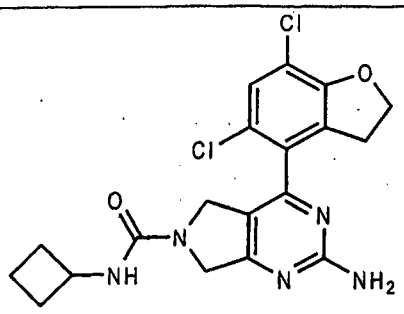
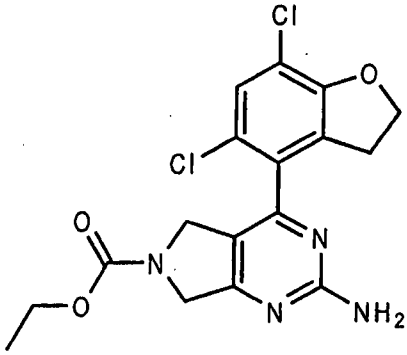
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 206 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-[4-bromo-2-chloro-5-(2-oxopropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.93 (s, 6 H) 2.14 (s, 3 H) 2.34 (s, 1 H) 4.18 (s, 2 H) 4.38 (s, 2 H) 4.99 (s, 2 H) 6.88 (s, 2 H) 7.00 (s, 1 H) 7.07 (s, 1 H) 7.87 (s, 1 H) | 508.2, 506.2 |
| 207 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(cyanomethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 2<br>Ex. 109 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.87 (s, 3 H) 4.06 (d, J=5.09 Hz, 2 H) 4.31 (s, 2 H) 4.47 (s, 2 H) 6.93 (s, 2 H) 7.17 (s, 1 H) 7.18 (t, J=5.36 Hz, 1 H) 7.87 (s, 1 H) | 439.0, 437.0 |
| 208 |  | 2-amino-N-(2-cyanoethyl)-4-[2,4-dichloro-6-(4,4,4-trifluorobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.70 - 1.82 (m, 2 H) 2.02 - 2.20 (m, 2 H) 2.62 (t, J=6.31 Hz, 2 H) 3.25 (q, J=6.09 Hz, 2 H) 4.04 - 4.20 (m, 4 H) 4.35 - 4.50 (m, 2 H) 6.81 (t, J=5.46 Hz, 1 H) 6.85 (s, 2 H) 7.31 (d, J=1.51 Hz, 1 H) 7.36 (d, J=1.32 Hz, 1 H) | 505.2, 503.2 |
| 209 |  | 2-amino-4-[2,4-dichloro-6-(4,4,4-trifluorobutoxy)phenyl]-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 8a,<br>Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.05 (d, J=5.27 Hz, 6 H) 1.69 - 1.83 (m, 2 H) 2.01 - 2.20 (m, 2 H) 3.70 - 3.85 (m, 1 H) 4.04 - 4.18 (m, J=7.54 Hz, 4 H) 4.37 - 4.44 (m, 2 H) 6.04 (d, J=7.72 Hz, 1 H) 6.81 (br. s., 2 H) 7.31 (d, J=1.32 Hz, 1 H) 7.36 (d, J=1.51 Hz, 1 H) | 494.2, 492.2 |

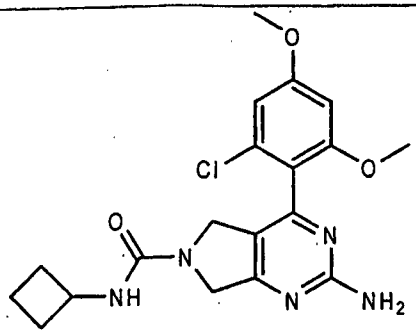
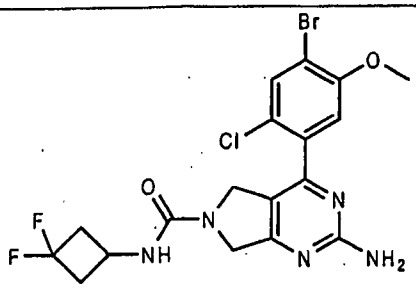
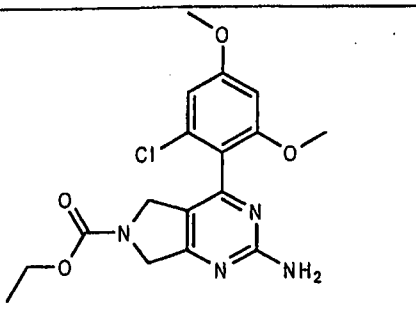
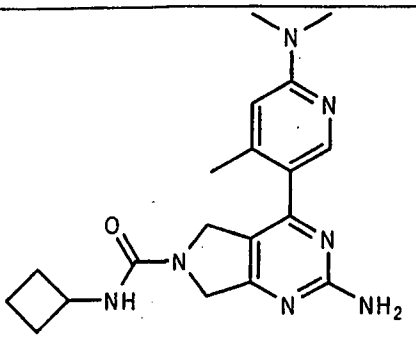
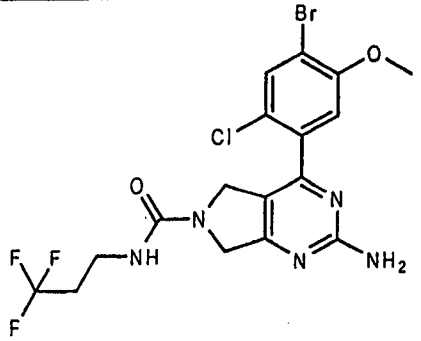
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 210 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(3-cyano-3-methylbutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.19 (d, J=3.01 Hz, 6 H) 1.46 - 1.60 (m, 2 H) 1.81 - 1.99 (m, 4 H) 2.02 - 2.15 (m, 2 H) 4.07 - 4.23 (m, 5 H) 4.30 - 4.45 (m, 2 H) 6.51 (d, J=7.72 Hz, 1 H) 6.80 (s, 2 H) 7.36 - 7.39 (m, J=3.20 Hz, 2 H) | 491.2, 489.2 |
| 211 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.62 (m, 2 H) 1.85 - 2.01 (m, 2 H) 2.04 - 2.18 (m, 2 H) 3.57 (d, J=13.00 Hz, 1 H) 3.93 (d, J=12.24 Hz, 1 H) 4.08 - 4.20 (m, 1 H) 4.29 - 4.46 (m, 6 H) 5.98 - 6.00 (m, 1 H) 6.40 (d, J=7.72 Hz, 1 H) 6.79 (s, 2 H) 7.19 (d, J=2.26 Hz, 1 H) 7.26 (d, J=1.32 Hz, 1 H) 7.28 (d, J=1.51 Hz, 1 H) 7.33 (d, J=1.32 Hz, 1 H) | 490.2, 488.2 |
| 212 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[(4-cyano-4-methylpentyl)oxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.17 (s, 6 H) 1.32 - 1.42 (m, 2 H) 1.48 - 1.72 (m, 4 H) 1.83 - 1.99 (m, 2 H) 2.02 - 2.15 (m, 2 H) 4.02 - 4.20 (m, 5 H) 4.33 - 4.47 (m, 2 H) 6.52 (d, J=7.72 Hz, 1 H) 6.83 (s, 2 H) 7.29 (d, J=1.32 Hz, 1 H) 7.34 (d, J=1.70 Hz, 1 H) | 505.2, 503.2 |
| 213 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[(5-cyano-5-methylhexyl)oxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.18 (d, J=2.07 Hz, 6 H) 1.25 - 1.64 (m, 8 H) 1.83 - 1.99 (m, 2 H) 2.02 - 2.15 (m, 2 H) 4.00 - 4.18 (m, 5 H) 4.40 (s, 2 H) 6.50 (d, J=7.72 Hz, 1 H) 6.81 (s, 2 H) 7.29 (d, J=1.51 Hz, 1 H) 7.33 (d, J=1.70 Hz, 1 H) | 519.2, 517.2 |

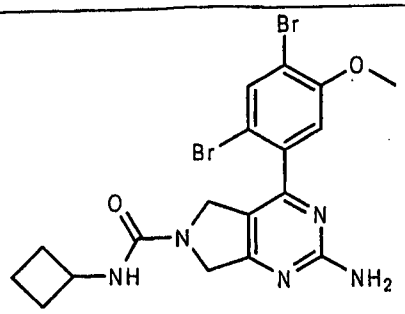
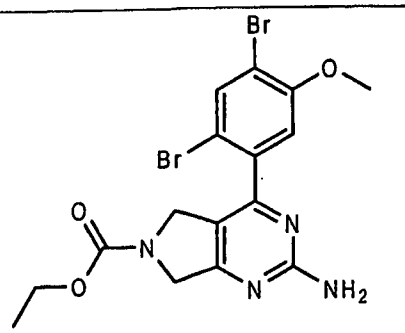
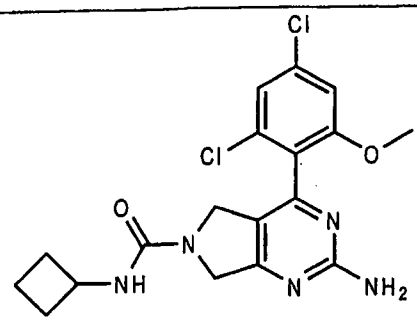
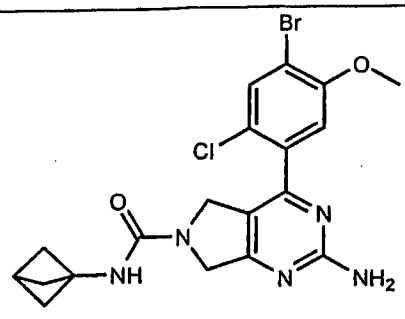
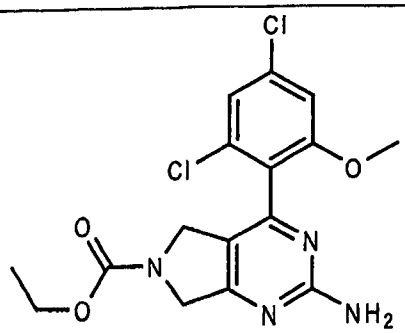
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 214 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(2-oxo-2-phenylethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.47 - 1.61 (m, 2 H) 1.87 - 1.99 (m, 2 H) 2.05 - 2.14 (m, 2 H) 4.07 - 4.21 (m, 2 H) 4.29 (d, J=13.14 Hz, 1 H) 4.41 (s, 2 H) 5.66 (d, J=17.94 Hz, 1 H) 5.79 (d, J=17.68 Hz, 1 H) 6.54 (d, J=7.83 Hz, 1 H) 6.83 (s, 2 H) 7.29 (d, J=1.77 Hz, 1 H) 7.34 (d, J=1.77 Hz, 1 H) 7.54 (t, J=7.71 Hz, 2 H) 7.67 (t, J=7.45 Hz, 1 H) 7.93 (d, J=7.33 Hz, 2 H) | 514.2, 512.2 |
| 215 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-cyanoethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 2, Ex. 109 | 1H NMR (300 MHz, DMSO-d6) d ppm 2.63 (t, J=6.40 Hz, 2 H) 3.21 - 3.30 (m, 2 H) 3.86 (s, 3 H) 4.28 (s, 2 H) 4.44 (s, 2 H) 6.83 (t, J=4.52 Hz, 1 H) 6.93 (s, 2 H) 7.18 (s, 1 H) 7.87 (s, 1 H) | 453.0, 451.0 |
| 216 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(3-hydroxypropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.47 - 1.60 (m, 2 H) 1.62 - 1.73 (m, 2 H) 1.84 - 1.99 (m, 2 H) 2.02 - 2.15 (m, 2 H) 3.31 (t, J=5.56 Hz, 2 H) 4.04 - 4.18 (m, 5 H) 4.41 (s, 2 H) 6.51 (d, J=7.54 Hz, 1 H) 6.82 (s, 2 H) 7.28 (s, 1 H) 7.32 (s, 1 H) | 454.2, 452.2 |
| 217 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(4-cyanobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.43 - 1.72 (m, 6 H) 1.84 - 2.00 (m, 2 H) 2.03 - 2.17 (m, 2 H) 2.40 (t, J=7.06 Hz, 2 H) 4.02 - 4.21 (m, 5 H) 4.41 (s, 2 H) 6.50 (d, J=7.91 Hz, 1 H) 6.81 (s, 2 H) 7.29 (d, J=1.70 Hz, 1 H) 7.34 (d, J=1.51 Hz, 1 H) | 477.2, 475.2 |

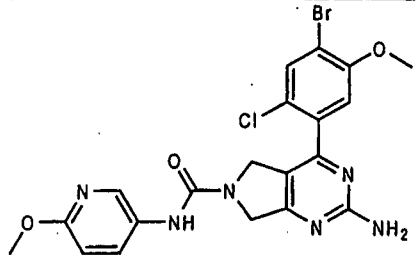
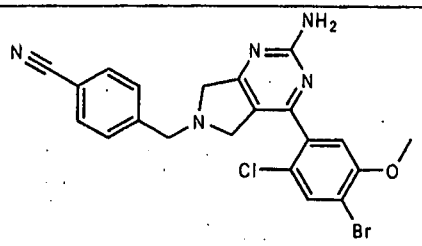
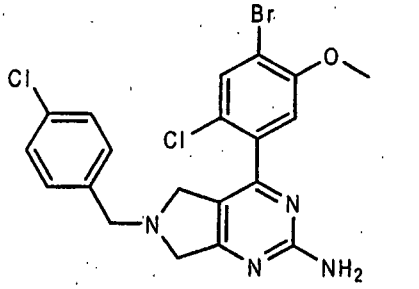
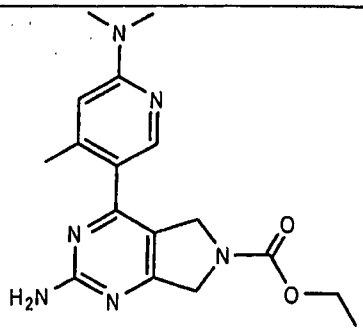
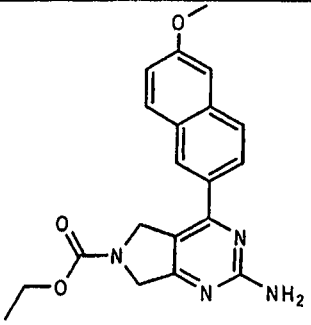
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 218 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[(4,4-difluorobut-3-en-1-yl)oxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.46 - 1.61 (m, 2 H) 1.82 - 1.99 (m, 2 H) 2.02 - 2.14 (m, 2 H) 2.15 - 2.28 (m, 2 H) 3.94 - 4.46 (m, 8 H) 6.48 (d, J=8.48 Hz, 1 H) 6.79 (s, 2 H) 7.28 (d, J=1.32 Hz, 1 H) 7.34 (d, 1 H) | 486.2, 484.2 |
| 219 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[(4-methyl-2-oxopentyl)oxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 0.80 (dd, J=6.59, 2.45 Hz, 6 H) 1.48 - 1.60 (m, 2 H) 1.86 - 2.15 (m, 5 H) 2.24 (dd, J=6.78, 2.07 Hz, 2 H) 4.06 - 4.29 (m, 3 H) 4.41 (s, 2 H) 4.81 (d, J=17.52 Hz, 1 H) 4.93 (d, J=17.33 Hz, 1 H) 6.52 (d, J=7.72 Hz, 1 H) 6.83 (s, 2 H) 7.13 (d, J=1.32 Hz, 1 H) 7.35 (d, J=1.70 Hz, 1 H) | 494.0, 492.0 |
| 220 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(2-methoxyethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.60 (m, 2 H) 1.83 - 1.99 (m, 2 H) 2.02 - 2.14 (m, 2 H) 3.12 (s, 3 H) 3.45 - 3.52 (m, 2 H) 4.06 - 4.22 (m, 5 H) 4.40 (br. s., 2 H) 6.49 (d, J=8.10 Hz, 1 H) 6.81 (br. s., 2 H) 7.31 (d, J=1.51 Hz, 1 H) 7.34 (d, J=1.70 Hz, 1 H) | 454.0, 452.0 |
| 221 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(cyclopentyloxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.39 - 1.98 (m, 12 H) 2.02 - 2.15 (m, 2 H) 4.03 - 4.18 (m, 3 H) 4.40 (s, 2 H) 4.89 - 4.97 (m, 1 H) 6.52 (d, J=7.91 Hz, 1 H) 6.80 (s, 2 H) 7.26 (d, J=1.70 Hz, 1 H) 7.30 (d, J=1.70 Hz, 1 H) | 464.0, 462.0 |

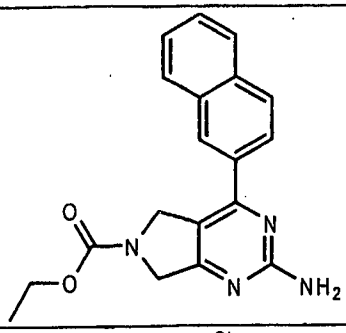
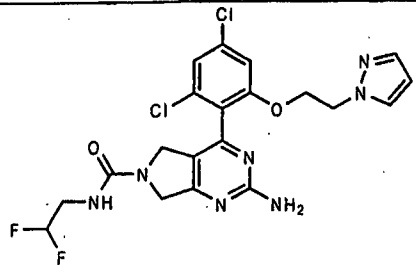
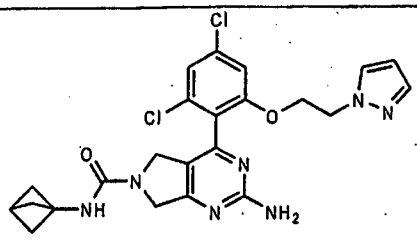
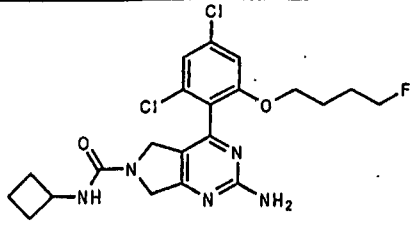
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 222 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(3,3,3-trifluoro-2-hydroxypropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.59 (m, 2 H) 1.84 - 1.99 (m, 2 H) 2.03 - 2.14 (m, 2 H) 4.04 - 4.25 (m, 6 H) 4.39 (s, 2 H) 6.48 (d, J=7.35 Hz, 1 H) 6.63 (br. s., 1 H) 6.78 (s, 2 H) 7.38 (s, 1 H) 7.41 (s, 1 H) | 508.0, 506.0 |
| 223 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(2-phenylethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.62 (m, 2 H) 1.84 - 2.01 (m, 2 H) 2.04 - 2.19 (m, 2 H) 2.70 - 2.92 (m, 2 H) 3.60 (d, J=12.62 Hz, 1 H) 3.94 (d, J=13.19 Hz, 1 H) 4.07 - 4.46 (m, 5 H) 6.39 (d, J=7.72 Hz, 1 H) 6.83 (br. s., 2 H) 6.98 (d, J=6.41 Hz, 2 H) 7.04 - 7.19 (m, 3 H) 7.26 (s, 1 H) 7.30 (s, 1 H) | 500.0, 498.0 |
| 224 |  | 2-amino-4-(2-butoxy-4,6-dichlorophenyl)-N-cyclobutyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.78 (t, J=7.45 Hz, 3 H) 1.14 - 1.25 (m, 2 H) 1.46 - 1.58 (m, 4 H) 1.86 - 1.97 (m, 2 H) 2.04 - 2.13 (m, 2 H) 3.98 - 4.05 (m, 2 H) 4.08 - 4.16 (m, 3 H) 4.40 (s, 2 H) 6.52 (d, J=7.83 Hz, 1 H) 6.82 (s, 2 H) 7.28 (d, J=1.77 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 452.0, 450.0 |
| 225 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(cyclobutylmethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.45 - 2.00 (m, 11 H) 2.02 - 2.16 (m, 2 H) 3.98 (d, J=5.84 Hz, 2 H) 4.08 - 4.20 (m, 3 H) 4.36 - 4.48 (m, 2 H) 6.51 (d, J=7.91 Hz, 1 H) 6.81 (s, 2 H) 7.28 (s, 1 H) 7.33 (s, 1 H) | 464.2, 462.2 |

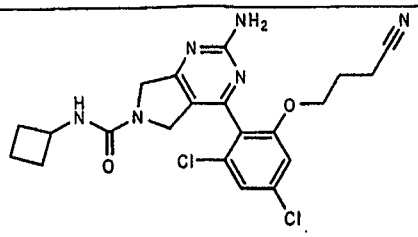
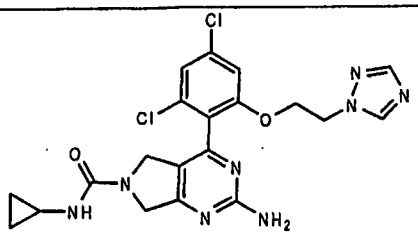
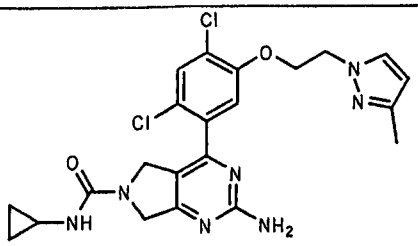
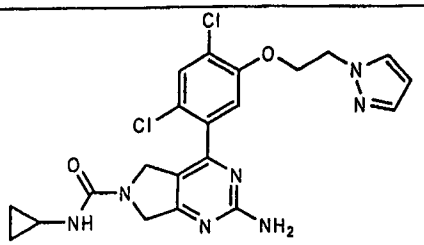
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 226 |  | 2-amino-N-cyclobutyl-4-(2,4-dichloro-6-propoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 0.76 (t, J=7.35 Hz, 3 H) 1.47 - 1.62 (m, 4 H) 1.83 - 2.01 (m, 2 H) 2.02 - 2.15 (m, 2 H) 3.93 - 4.05 (m, 2 H) 4.07 - 4.17 (m, 3 H) 4.40 (s, 2 H) 6.51 (d, J=8.29 Hz, 1 H) 6.82 (br. s., 2 H) 7.27 (d, J=1.32 Hz, 1 H) 7.32 (d, J=1.32 Hz, 1 H) | 438.2, 436.2 |
| 227 |  | 2-amino-4-[2-(benzyloxy)-4,6-dichlorophenyl]-N-cyclobutyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.60 (m, 2 H) 1.84 - 2.01 (m, 2 H) 2.03 - 2.15 (m, 2 H) 4.07 - 4.20 (m, 3 H) 4.40 (s, 2 H) 5.20 (s, 2 H) 6.51 (d, J=7.91 Hz, 1 H) 6.85 (br. s., 2 H) 7.19 - 7.25 (m, 2 H) 7.26 - 7.34 (m, 3 H) 7.36 (s, 2 H) | 486.2, 484.2 |
| 228 |  | 2-amino-N-cyclobutyl-4-(5,7-dichloro-2,3-dihydro-1-benzofuran-4-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 7 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.47 - 1.61 (m, 2 H) 1.87 - 1.99 (m, 2 H) 2.05 - 2.13 (m, 2 H) 2.99 - 3.21 (m, 2 H) 4.07 - 4.21 (m, 2 H) 4.27 (d, J=13.14 Hz, 1 H) 4.36 - 4.48 (m, 2 H) 4.61 - 4.74 (m, 2 H) 6.54 (d, J=7.83 Hz, 1 H) 6.90 (br. s., 2 H) 7.53 (s, 1 H) | 422.2, 420.2 |
| 229 |  | ethyl 2-amino-4-(5,7-dichloro-2,3-dihydro-1-benzofuran-4-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 1 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.13 - 1.27 (m, 3 H) 2.95 - 3.26 (m, 2 H) 3.98 - 4.16 (m, 2 H) 4.22 - 4.39 (m, 2 H) 4.41 - 4.58 (m, 2 H) 4.61 - 4.76 (m, 2 H) 6.94 (br. s., 2 H) 7.51 (s, 1 H) | 397.2, 395.2 |

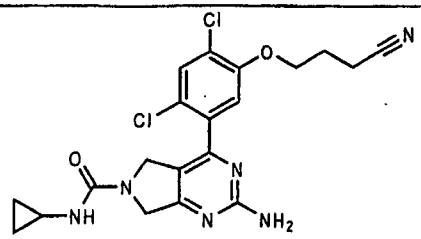
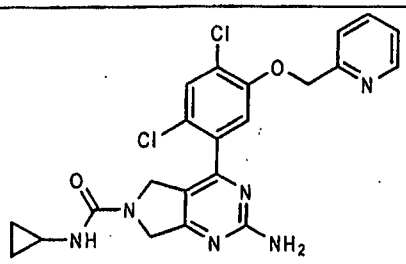
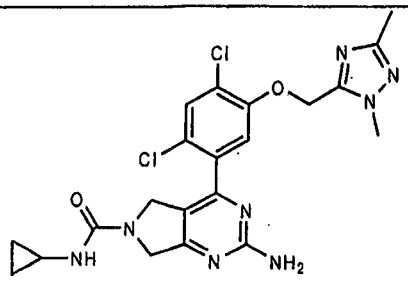
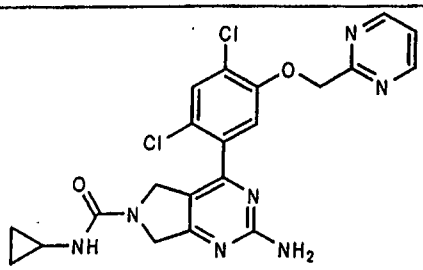
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 230 |  | 2-amino-4-(2-chloro-4,6-dimethoxyphenyl)-N-cyclobutyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 117 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.60 (m, 2 H) 1.84 - 2.00 (m, 2 H) 2.03 - 2.15 (m, 2 H) 3.72 (s, 3 H) 3.83 (s, 3 H) 4.04 - 4.19 (m, 3 H) 4.40 (s, 2 H) 6.51 (d, J=7.91 Hz, 1 H) 6.67 (d, J=2.07 Hz, 1 H) 6.71 - 6.77 (m, 3 H) | 406.0, 404.0 |
| 231 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(3,3-difluorocyclobutyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 2, Ex. 109 | 1H NMR (300 MHz, DMSO-d6) d ppm 2.53 - 2.89 (m, 4 H) 3.87 (s, 3 H) 3.95 - 4.08 (m, 1 H) 4.28 (s, 2 H) 4.44 (s, 2 H) 6.75 (d, J=6.78 Hz, 1 H) 6.91 (br. s., 2 H) 7.17 (s, 1 H) 7.87 (s, 1 H) | 489.8, 487.8 |
| 232 |  | ethyl 2-amino-4-(2-chloro-4,6-dimethoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 117a | 1H NMR (300 MHz, DMSO-d6) d ppm 1.13 - 1.24 (m, 3 H) 3.72 (s, 3 H) 3.83 (s, 3 H) 4.00 - 4.19 (m, 4 H) 4.47 (d, J=8.48 Hz, 2 H) 6.66 (d, J=2.26 Hz, 1 H) 6.74 (d, J=2.07 Hz, 1 H) 6.79 (br. s., 2 H) | 379.2 |
| 233 |  | 2-amino-N-cyclobutyl-4-[6-(dimethylamino)-4-methylpyridin-3-yl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 117 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.63 (m, 2 H) 1.87 - 2.02 (m, 2 H) 2.04 - 2.17 (m, 2 H) 2.28 (s, 3 H) 3.06 (s, 6 H) 4.06 - 4.22 (m, 1 H) 4.34 - 4.48 (m, 4 H) 6.52 - 6.69 (m, 4 H) 8.05 (s, 1 H) | 343.4 |
| 234 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(3,3,3-trifluoropropyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 2, Ex. 109 | 1H NMR (300 MHz, DMSO-d6) d ppm 2.32 - 2.47 (m, 2 H) 3.22 - 3.30 (m, 2 H) 3.86 (s, 3 H) 4.27 (s, 2 H) 4.42 (s, 2 H) 6.63 (t, J=5.27 Hz, 1 H) 6.90 (br. s., 2 H) 7.17 (s, 1 H) 7.86 (s, 1 H) | 496.0, 493.9 |

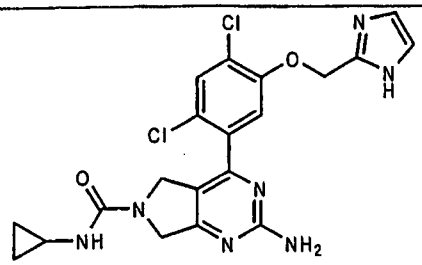
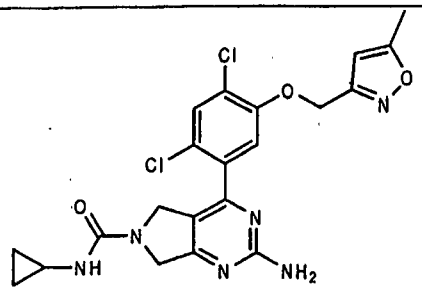
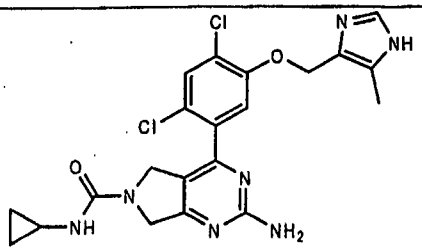
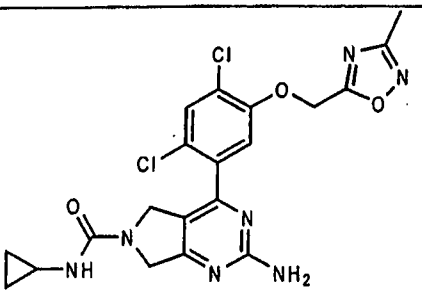
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 235 |  | 2-amino-N-cyclobutyl-4-(2,4-dibromo-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 117 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.47 - 1.63 (m, 2 H) 1.84 - 2.01 (m, 2 H) 2.02 - 2.16 (m, 2 H) 3.85 (s, 3 H) 4.05 - 4.20 (m, 1 H) 4.24 (s, 2 H) 4.41 (s, 2 H) 6.52 (d, J=7.91 Hz, 1 H) 6.88 (br. s., 2 H) 7.15 (s, 1 H) 7.96 (s, 1 H) | 498.2 |
| 236 |  | ethyl 2-amino-4-(2,4-dibromo-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 117a | 1H NMR (300 MHz, DMSO-d6) d ppm 1.13 - 1.27 (m, 3 H) 3.85 (s, 3 H) 4.02 - 4.16 (m, 2 H) 4.29 - 4.35 (m, 2 H) 4.45 - 4.52 (m, 2 H) 6.94 (br. s., 2 H) 7.12 (s, 1 H) 7.96 (s, 1 H) | 473.2 |
| 237 |  | 2-amino-N-cyclobutyl-4-(2,4-dichloro-6-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 117 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.48 - 1.61 (m, 2 H) 1.85 - 2.00 (m, 2 H) 2.03 - 2.15 (m, 2 H) 3.77 (s, 3 H) 4.04 - 4.19 (m, 3 H) 4.41 (s, 2 H) 6.50 (d, J=7.91 Hz, 1 H) 6.82 (br. s., 2 H) 7.28 (d, J=1.70 Hz, 1 H) 7.34 (d, J=1.70 Hz, 1 H) | 408.2 |
| 238 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 2, Ex. 109 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.93 (s, 6 H) 2.34 (s, 1 H) 3.86 (s, 3 H) 4.23 (s, 2 H) 4.39 (s, 2 H) 6.87 (br. s., 2 H) 6.99 (s, 1 H) 7.15 (s, 1 H) 7.85 (s, 1 H) | 466.0, 464.0 |
| 239 |  | ethyl 2-amino-4-(2,4-dichloro-6-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 117a | 1H NMR (300 MHz, DMSO-d6) d ppm 1.13 - 1.24 (m, 3 H) 3.77 (s, 3 H) 4.00 - 4.12 (m, 2 H) 4.14 (s, 1 H) 4.17 (s, 1 H) 4.47 (s, 1 H) 4.49 (s, 1 H) 6.87 (br. s., 2 H) 7.25 (d, J=1.51 Hz, 1 H) 7.32 (d, J=1.51 Hz, 1 H) | 385.2, 383.2 |

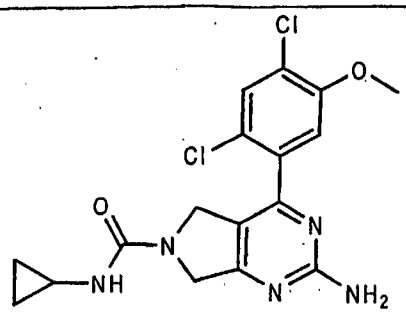
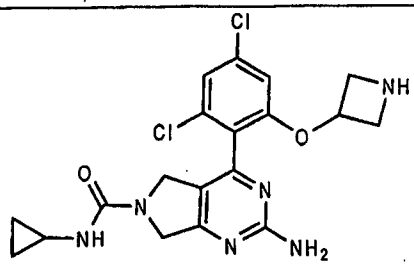
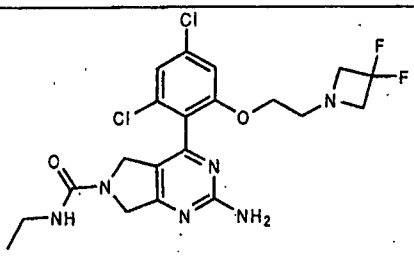
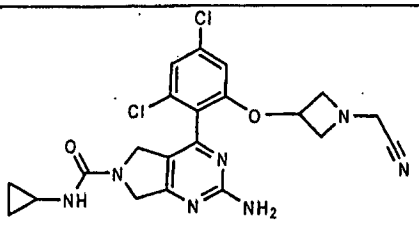
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 240 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(6-methoxypyridin-3-yl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 118 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.79 (s, 3 H) 3.87 (s, 3 H) 4.46 (s, 2 H) 4.58 (s, 2 H) 6.73 (d, J=8.85 Hz, 1 H) 6.94 (s, 2 H) 7.19 (s, 1 H) 7.79 (dd, J=8.95, 2.54 Hz, 1 H) 7.88 (s, 1 H) 8.21 (d, J=2.64 Hz, 1 H) 8.37 (s, 1 H) | 507.2, 505.2 |
| 241 |  | 4-{[2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl]methyl}benzonitrile | Ex. 120 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.63 (s, 2 H) 3.78 (s, 2 H) 3.84 (s, 3 H) 3.94 (s, 2 H) 6.76 (br. s., 2 H) 7.09 (s, 1 H) 7.54 (d, J=8.10 Hz, 2 H) 7.76 - 7.83 (m, 3 H) | 472.2, 470.2 |
| 242 |  | 4-(4-bromo-2-chloro-5-methoxyphenyl)-6-(4-chlorobenzyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Ex. 120 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.59 (s, 2 H) 3.75 (s, 2 H) 3.82 - 3.86 (m, 5 H) 6.77 (br. s., 2 H) 7.09 (s, 1 H) 7.35 - 7.39 (m, 4 H) 7.79 (s, 1 H) | 481.0, 479.0 |
| 243 |  | ethyl 2-amino-4-[6-(dimethylamino)-4-methylpyridin-3-yl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 117a | 1H NMR (300 MHz, DMSO-d6) d ppm 1.15 - 1.26 (m, 3 H) 2.28 (s, 3 H) 3.06 (s, 6 H) 4.02 - 4.15 (m, 2 H) 4.40 - 4.50 (m, 4 H) 6.56 (s, 1 H) 6.67 (s, 2 H) 8.06 (d, J=3.58 Hz, 1 H) | 343.4 |
| 244 |  | ethyl 2-amino-4-(6-methoxy-2-naphthyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 1 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.24 (t, J=7.06 Hz, 3 H) 3.91 (s, 3 H) 4.14 (q, J=6.78 Hz, 2 H) 4.44 - 4.51 (m, 2 H) 4.86 (s, 2 H) 7.24 (dd, J=8.95, 2.35 Hz, 1 H) 7.40 (d, J=1.88 Hz, 1 H) 7.93 - 8.04 (m, 3 H) 8.32 (d, J=3.20 Hz, 1 H) | 365.4 |

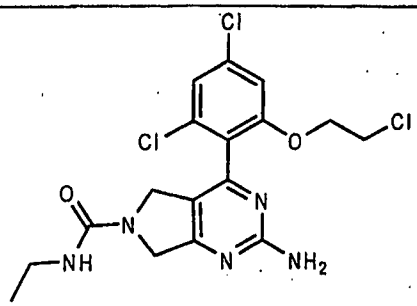
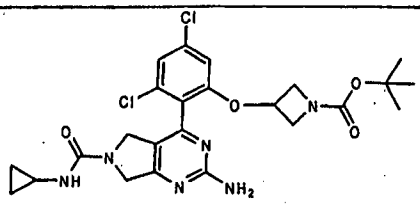
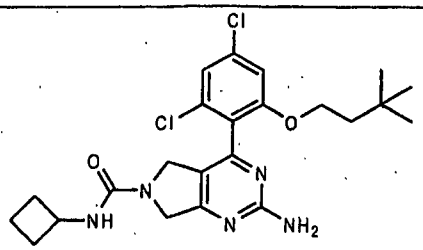
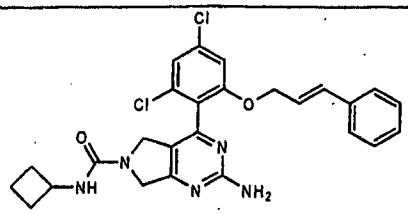
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 245 |  | ethyl 2-amino-4-(2-naphthyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 1 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.20 - 1.28 (m, 3 H) 4.14 (q, J=7.16 Hz, 2 H) 4.45 - 4.51 (m, 2 H) 4.87 (s, 2 H) 6.86 (br. s., 2 H) 7.57 - 7.67 (m, 2 H) 7.95 - 8.14 (m, 4 H) 8.38 (d, J=3.58 Hz, 1 H) | 335.2 |
| 246 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(2,2-difluoroethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (300 MHz, DMSO-d6) d ppm 3.33 - 3.51 (m, 2 H) 3.56 (d, J=12.81 Hz, 1 H) 3.94 (d, J=12.62 Hz, 1 H) 4.29 - 4.38 (m, 4 H) 4.40 - 4.50 (m, 2 H) 5.77 - 6.20 (m, 2 H) 6.70 (br. s., 1 H) 6.80 (br. s., 2 H) 7.20 (d, J=2.07 Hz, 1 H) 7.26 (d, J=1.51 Hz, 1 H) 7.30 (d, J=1.51 Hz, 1 H) 7.32 (d, J=1.70 Hz, 1 H) | 500.2, 498.2 |
| 247 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 110 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.95 (s, 6 H) 2.36 (s, 1 H) 3.53 (d, J=13.19 Hz, 1 H) 3.89 (d, J=13.00 Hz, 1 H) 4.33 (s, 6 H) 5.99 - 6.02 (m, 1 H) 6.77 (br. s., 2 H) 6.85 (br. s., 1 H) 7.19 (d, J=2.07 Hz, 1 H) 7.25 (d, J=1.51 Hz, 1 H) 7.30 (d, J=1.70 Hz, 1 H) 7.32 (d, J=1.70 Hz, 1 H) | 502.2, 500.2 |
| 248 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(4-fluorobutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.61 (d, J=5.27 Hz, 6 H) 1.84 - 1.98 (m, 2 H) 2.03 - 2.15 (m, 2 H) 4.03 - 4.28 (m, 6 H) 4.37 - 4.43 (m, 3 H) 6.51 (d, J=7.91 Hz, 1 H) 6.82 (br. s., 2 H) 7.29 (d, J=1.32 Hz, 1 H) 7.34 (d, J=1.13 Hz, 1 H) | 470.2, 468.2 |

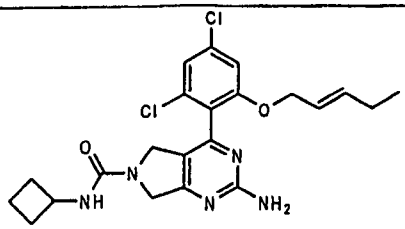
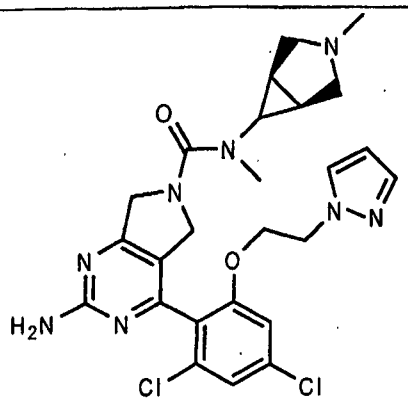
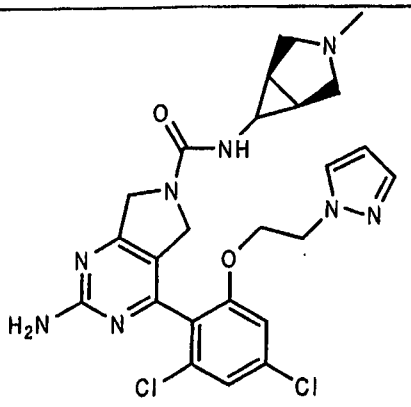
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 249 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(3-cyanopropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.47 - 1.59 (m, 2 H) 1.82 - 1.98 (m, 4 H) 2.04 - 2.13 (m, 2 H) 2.38 (t, J=7.20 Hz, 2 H) 4.06 - 4.18 (m, 5 H) 4.40 (br. s., 2 H) 6.50 (d, J=7.83 Hz, 1 H) 6.82 (br. s., 2 H) 7.33 (d, J=1.77 Hz, 1 H) 7.37 (d, J=1.77 Hz, 1 H) | 463.2, 461.2 |
| 250 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-1,2,4-triazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.96 (s, 1 H), 7.73 (s, 1 H), 7.33 (d, J=1.77 Hz, 1 H), 7.29 (d, J=1.77 Hz, 1 H), 6.75 (s, 2 H), 6.35 (br. s., 1 H), 4.37 - 4.51 (m, 4 H), 4.25 - 4.36 (m, 2 H), 3.87 (dd, J=13.01, 2.15 Hz, 1 H), 3.44 - 3.52 (m, 1 H), 2.52 - 2.57 (m, 1 H), 0.50 - 0.58 (m, 2 H), 0.42 (d, J=3.28 Hz, 2 H). | 475.0, 477.0 |
| 251 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[2-(3-methyl-1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 7.46 (s, 2H), 6.72 (s, 1H), 5.97 (s, 1H), 5.19 (s, 2H), 4.52 (s, 2H), 4.51 (s, 1H), 4.46 (t, 2H, J = 5 Hz), 4.38 (s, 2H), 4.31 (t, 2H, J = 5 Hz), 2.67 (bs, 1H), 2.20 (s, 3H), 0.70 (q, 2H, J = 5 Hz), 0.51 (m, 2H). | 488.0, 490.0 |
| 252 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 7.60 (s, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 6.72 (s, 1H), 6.24 (s, 1H), 5.18 (s, 2H), 4.54 (m, 5H), 4.38 (s, 2H), 4.32 (t, 2H, J = 5 Hz), 2.66 (bs, 1H), 0.73 (q, 2H, J = 6 Hz), 0.51 (m, 2H). | 474.0, 476.0 |

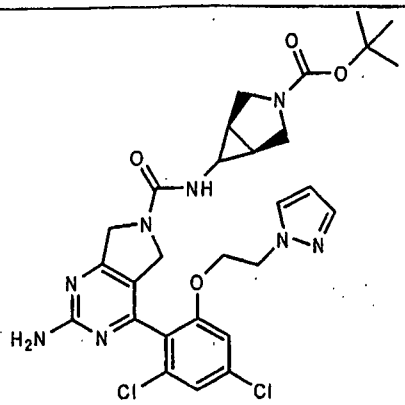
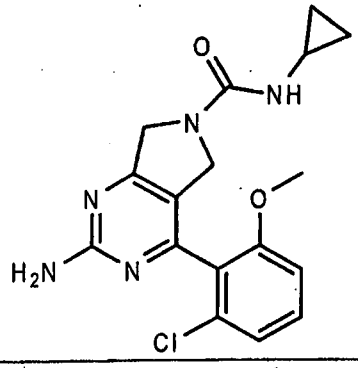
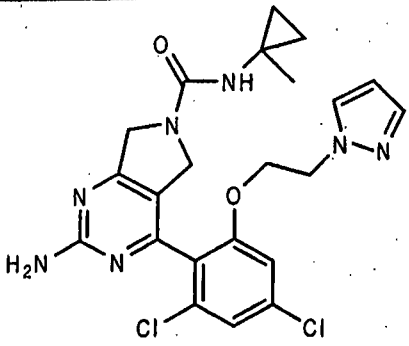
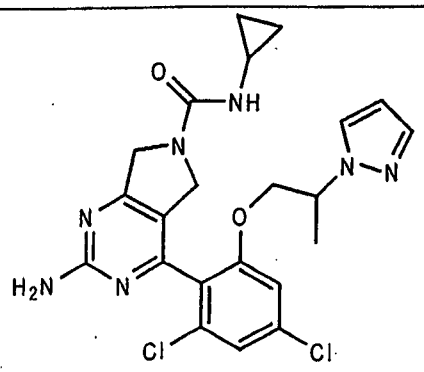
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 253 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-5-(3-cyanopropoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 7.48 (s, 1H), 6.87 (s, 1H), 5.18 (s, 2H), 4.56 (s, 3H), 4.48 (s, 2H), 4.12 (t, 2H, J = 6 Hz), 2.68 (bs, 2H), 2.65 (t, 2H, J = 6 Hz), 2.19 (q, 2H, J = 6 Hz), 0.72 (m, 2H), 0.50 (m, 2H). | 446.0, 448.0 |
| 254 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-5-(pyridin-2-ylmethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 8.55 (d, 1H, J = 6 Hz), 7.72 (t, 1H, J = 6 Hz), 7.60 (d, 1H, J = 6 Hz), 7.51 (s, 1H), 7.25 (m, 1H), 6.95 (s, 1H), 5.24 (s, 2H), 5.14 (s, 2H), 4.55 (s, 2H), 4.49 (s, 1H), 4.32 (s, 2H), 2.68 (bs, 1H), 0.73 (q, 2H, J = 6 Hz), 0.50 (m, 2H). | 471.0, 473.0 |
| 255 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[(1,3-dimethyl-1H-1,2,4-triazol-5-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex 127 | 1H-NMR (CDCl3, 300 MHz): d 7.49 (s, 1H), 7.16 (s, 1H), 5.23 (s, 2H), 5.20 (s, 2H), 4.57 (s, 1H), 4.56 (s, 2H), 4.38 (s, 2H), 3.93 (s, 3H), 2.69 (bs, 1H), 2.33 (s, 3H), 0.74 (q, 2H, J = 6 Hz), 0.51 (m, 2H). | 489.0, 491.0 |
| 256 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-5-(pyrimidin-2-ylmethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 8.79 (d, 2H, J = 6 Hz), 7.51 (s, 1H), 7.27 (t, 1H), 6.97 (s, 1H, J = 6 Hz), 5.37 (s, 2H), 5.17 (s, 2H), 4.52 (s, 2H), 5.41 (s, 1H)., 4.32 (s, 2H), 2.68 (bs, 1H), 0.73 (m, 2H), 0.50 (s, 2H). | 473.0, 475.0 |

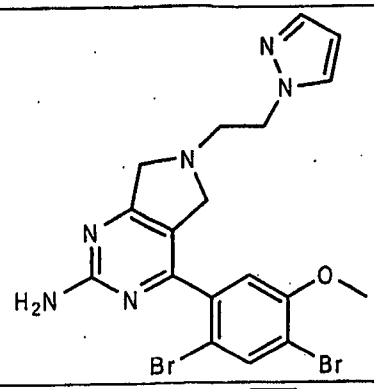
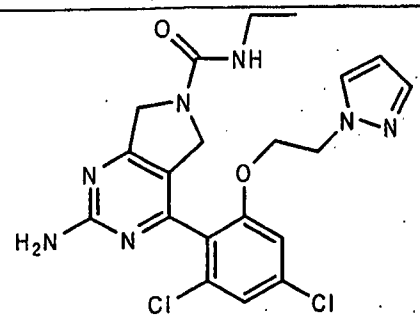
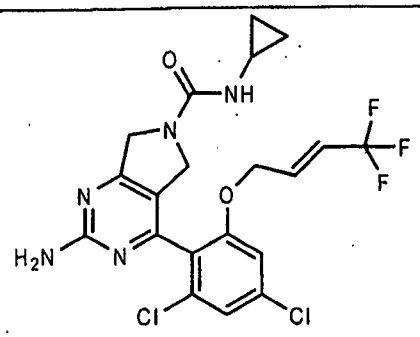
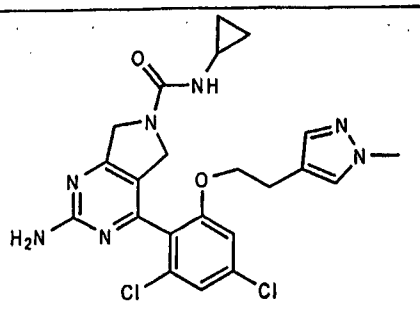
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 257 |  | 2-amino-N-cyclopropyl-4-[2,4-dichloro-5-(1H-imidazol-2-ylmethoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (DMSO-d6, 300 MHz): d 7.59 (s, 1H), 7.46 (s, 1H), 6.85 (bs, 2H), 6.77 (s, 1H), 6.44 (s, 1H), 4.50 (d, 1H, J = 3 Hz), 4.39 (m, 4H), 4.14 (s, 1H), 2.06 (2H), 0.50 (m, 2H), 0.39 (m, 2H). | 460.0, 462.0 |
| 258 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[(5-methylisoxazol-3-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 7.50 (s, 1H), 7.01 (s, 1H), 6.16 (s, 1H), 5.21 (s, 2H), 5.16 (s, 2H), 4.66 (s, 1H), 4.59 (s, 2H), 4.42 (s, 2H), 2.70 (bs, 1H), 2.44 (s, 3H), 0.76 (m, 2H), 0.54 (m, 2H). | 477.0, 479.0 |
| 259 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[(5-methyl-1H-imidazol-4-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (DMSO-d6, 300 MHz): d 7.42 (s, 1H), 7.36 (s, 1H), 6.77 (s, 1H), 6.42 (s, 1H), 4.68 (s, 2H), 4.30 (d, 2H, J = 3 Hz), 4.21 (s, 2H), 2.10 (bs, 2H) 2.06 (s, 3H) 0.51 (m, 2H), 0.39 (m, 2H). | 476.0, 478.0 |
| 260 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-5-[(3-methyl-1,2,4-oxadiazol-5-yl)methoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H-NMR (CDCl3, 300 MHz): d 7.56 (s, 1H), 7.01 (s, 1H), 5.34 (s, 2H), 5.16 (s, 1H), 4.59 (s, 2H), 4.42 (s, 2H), 2.65 (bs, 1H), 2.44 (s, 3H), 0.74 (m, 2H), 0.52 (m, 2H). | 475.0, 477.0 |

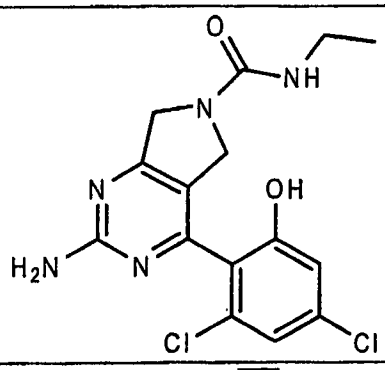
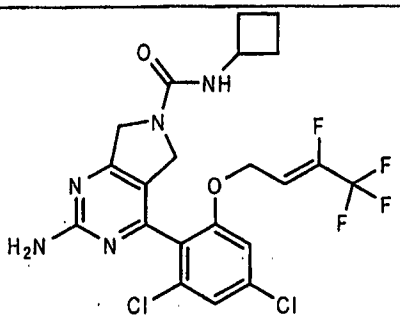
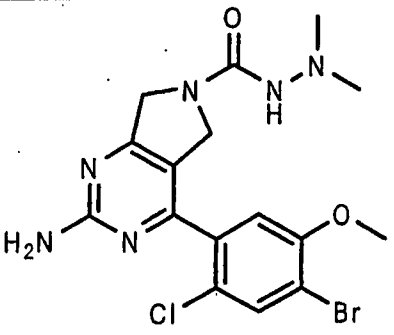
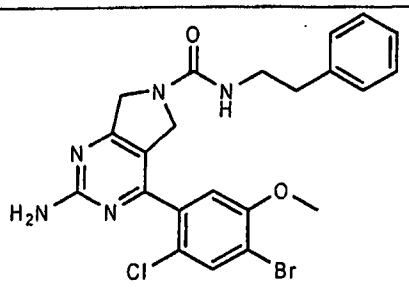
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 261 |  | 2-amino-N-cyclopropyl-4-(2,4-dichloro-5-methoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 14 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.74 (s, 1 H), 7.20 (s, 1 H), 6.89 (s, 2 H), 6.47 (d, J=2.78 Hz, 1 H), 4.41 (s, 2 H), 4.24 (s, 2 H), 3.87 (s, 3 H), 2.52 - 2.55 (m, 1 H), 0.50 - 0.57 (m, 2 H), 0.35 - 0.42 (m, 2 H). | 394.1, 396.1 |
| 262 |  | 2-amino-4-[2-(azetidin-3-yloxy)-4,6-dichlorophenyl]-N-cyclopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 129 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.39 (d, J=1.77 Hz, 1 H), 7.01 (d, J=1.77 Hz, 1 H), 6.84 (s, 2 H), 6.45 (d, J=2.53 Hz, 1 H), 5.02 - 5.13 (m, 1 H), 4.42 (s, 2 H), 4.05 - 4.19 (m, 2 H), 3.89 - 4.04 (m, 2 H), 3.45 - 3.55 (m, 2 H), 3.17 - 3.45 (m, 2 H), 0.47 - 0.58 (m, 2 H), 0.33 - 0.44 (m, 2 H). | 435.2, 437.2 |
| 263 |  | 2-amino-4-{2,4-dichloro-6-[2-(3,3-difluoroazetidin-1-yl)ethoxy]phenyl}-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 15 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.34 (d, J=1.77 Hz, 1 H), 7.25 (d, J=1.77 Hz, 1 H), 6.85 (s, 2 H), 6.35 (t, J=5.31 Hz, 1 H), 4.30 - 4.47 (m, 2 H), 4.13 (s, 2 H), 4.00 - 4.08 (m, 2 H), 3.36 - 3.42 (m, 2 H), 3.21 - 3.29 (m, 2 H), 3.01 - 3.10 (m, 2 H), 2.70 - 2.77 (m, 2 H), 1.01 (t, J=7.20 Hz, 3 H). | 487.0, 489.0 |
| 264 |  | 2-amino-N-cyclopropyl-4-(2,4-dichloro-6-{[1-(cyanomethyl)azetidin-3-yl]oxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 130 | 1H NMR (400 MHz, CHLOROFORM-d) d ppm: 7.16 (d, J=1.77 Hz, 1 H), 6.59 (d, J=1.77 Hz, 1 H), 5.24 (s, 2 H), 4.75 - 4.84 (m, 1 H), 4.53 - 4.66 (m, 3 H), 4.33 - 4.43 (m, 2 H), 3.76 - 3.90 (m, 2 H), 3.51 (s, 2 H), 3.27 - 3.38 (m, 2 H), 2.64 - 2.75 (m, 1 H), 0.67 - 0.80 (m, 2 H), 0.46 - 0.56 (m, 2 H). | 474.0, 476.0 |

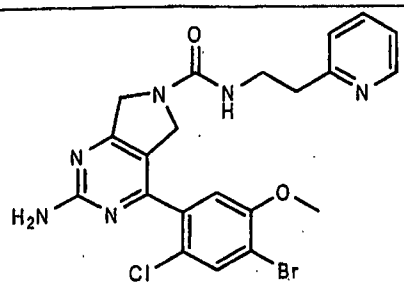
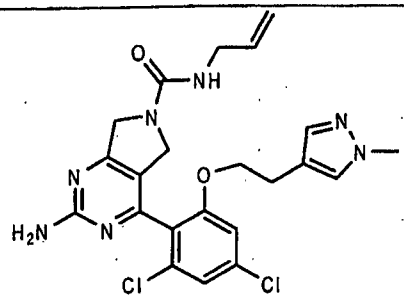
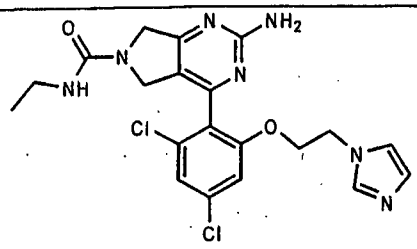
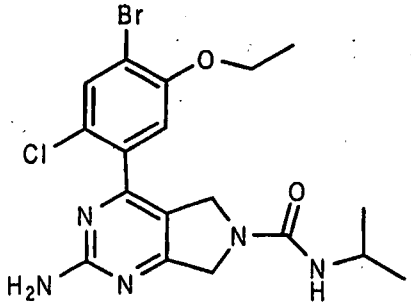
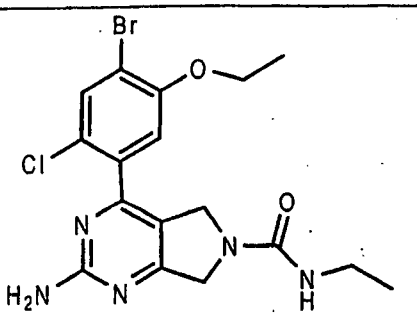
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 265 |  | 2-amino-4-[2,4-dichloro-6-(2-chloroethoxy)phenyl]-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 14 | 1H NMR (400 MHz, CHLOROFORM-d) d ppm: 7.17 (d, J=1.77 Hz, 1 H), 6.89 (d, J=1.77 Hz, 1 H), 5.18 (s, 2 H), 4.61 (s, 2 H), 4.31 - 4.43 (m, 2 H), 4.16 - 4.26 (m, 3 H), 3.62 - 3.69 (m, 2 H), 3.27 - 3.37 (m, 2 H), 1.17 (t, J=7.20 Hz, 3 H). | 430.0, 432.0 |
| 266 |  | tert-butyl 3-(2-{2-amino-6-[(cyclopropylamino)carbonyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-yl}-3,5-dichlorophenoxy)azetidine-1-carboxylate | Ex. 128 | 1H NMR (400 MHz, CHLOROFORM-d) d ppm: 7.15 (d, J=1.26 Hz, 1 H), 6.52 (s, 1 H), 5.24 - 5.38 (m, 2 H), 4.78 - 4.90 (m, 1 H), 4.65 (br. s., 1 H), 4.56 (br. s., 2 H), 4.32 - 4.43 (m, 1 H), 4.19 - 4.32 (m, 3 H), 3.76 - 3.93 (m, 2 H), 2.60 - 2.75 (m, 1 H), 1.42 (s, 9 H), 0.74 (t, J=5.94 Hz, 2 H), 0.46 - 0.59 (m, 2 H). | 534.1, 536.1 |
| 267 |  | 2-amino-N-cyclobutyl-4-[2,4-dichloro-6-(3,3-dimethylbutoxy)phenyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.32 (s, 2 H), 6.80 (br. s., 2 H), 6.52 (d, J=7.83 Hz, 1 H), 4.39 (d, J=4.04 Hz, 2 H), 4.09 - 4.17 (m, 3 H), 4.00 - 4.08 (m, 2 H), 2.03 - 2.15 (m, 2 H), 1.84 - 1.99 (m, 2 H), 1.49 - 1.62 (m, 2 H), 1.45 (t, J=6.69 Hz, 2 H), 0.80 (s, 9 H). | 478.0, 480.0 |
| 268 |  | 2-amino-N-cyclobutyl-4-(2,4-dichloro-6-{[(2E)-3-phenylprop-2-en-1-yl]oxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.22 - 7.42 (m, 7 H), 6.87 (s, 2 H), 6.46 - 6.57 (m, 2 H), 6.28 - 6.40 (m, 1 H), 4.81 (d, J=4.80 Hz, 2 H), 4.42 (s, 2 H), 4.17 (s, 2 H), 4.06 - 4.15 (m, 1 H), 2.02 - 2.14 (m, 2 H), 1.82 - 1.98 (m, 2 H), 1.46 - 1.60 (m, 2 H). | 510.0, 512.0 |

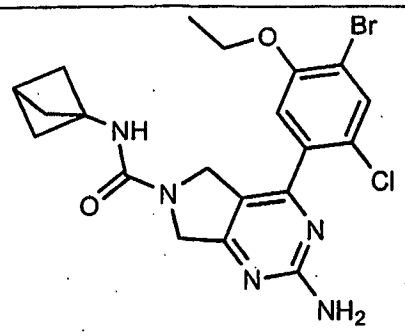
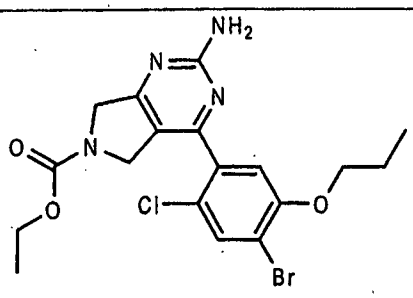
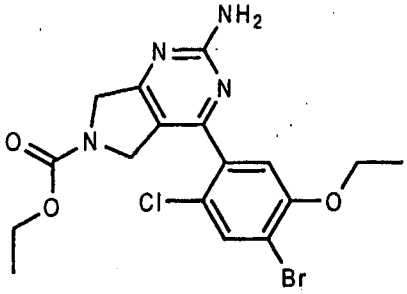
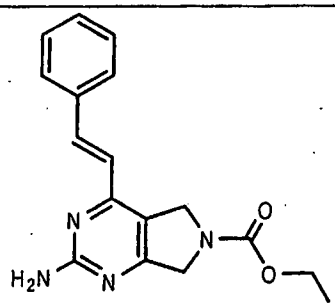
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 269 |  | 2-amino-N-cyclobutyl-4-{2,4-dichloro-6-[(2E)-pent-2-en-1-yloxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 127 | 1H NMR (400 MHz, DMSO-d6) d ppm: 7.33 (d, J=1.77 Hz, 1 H), 7.28 (d, J=1.52 Hz, 1 H), 6.83 (br. s., 2 H), 6.48 - 6.55 (m, 1 H), 5.64 - 5.76 (m, 1 H), 5.42 - 5.53 (m, 1 H), 4.57 (d, J=5.56 Hz, 2 H), 4.40 (s, 2 H), 4.07 - 4.17 (m, 3 H), 2.04 - 2.13 (m, 2 H), 1.85 - 2.02 (m, 4 H), 1.46 - 1.59 (m, 2 H), 0.88 (t, J=7.45 Hz, 3 H). | 462.0, 464.0 |
| 270 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-methyl-N-[(1R,5S)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.66 (s, 1 H) 1.85 (s, 1 H) 2.19 (s, 3 H) 2.26 - 2.35 (m, 2 H) 2.85 - 2.91 (m, 1 H) 2.97 - 3.12 (m, 2 H) 3.56 - 3.65 (m, 2 H) 4.04 - 4.11 (m, 2 H) 4.28 - 4.42 (m, 4 H) 5.86 - 5.91 (m, 1 H) 7.17 (d, J=2.02 Hz, 1 H) 7.19 (d, J=1.52 Hz, 1 H) 7.29 (s, 1 H) 7.35 (s, 1 H) | 543.2, 544.2 |
| 271 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-[(1R,5S)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.81 - 1.97 (m, 2 H) 2.54 (s, 3 H) 2.60 - 2.72 (m, J=1.52 Hz, 2 H) 3.03 (s, 2 H) 3.11 - 3.20 (m, 1 H) 3.60 - 3.70 (m, J=19.45 Hz, 1 H) 3.85 (d, J=12.63 Hz, 2 H) 4.29 - 4.33 (m, 4 H) 4.37 (d, J=7.58 Hz, 2 H) 5.94 - 6.02 (m, 1 H) 7.17 (d, J=1.77 Hz, 1 H) 7.23 (d, J=1.52 Hz, 1 H) 7.29 (d, J=1.52 Hz, 1 H) 7.30 (d, J=1.52 Hz, 1 H) | 464.0, 466.0 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 272 |  | tert-butyl (1R,5S)-6-{[(2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidin-6-yl)carbonyl]amino}-3-azabicyclo[3.1.0]hexane-3-carboxylate | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.20 - 1.26 (m, 2 H) 1.54 - 1.67 (m, J=23.49 Hz, 2 H) 2.13 - 2.23 (m, J=2.02 Hz, 1 H) 2.82 - 2.94 (m, 2 H) 3.30 - 3.36 (m, 1 H) 3.45 (dd, J=10.74, 4.17 Hz, 2 H) 3.52 - 3.59 (m, 1 H) 3.84 - 3.96 (m, 1 H) 4.32 (s, 2 H) 4.38 (d, J=6.82 Hz, 1 H) 6.00 (t, J=1.89 Hz, 1 H) 6.42 (s, 1 H) 6.79 (s, 1 H) 7.22 (dd, J=26.78, 1.77 Hz, 1 H) 7.31 (dd, J=8.34, 1.52 Hz, 1 H) | 615.2, 617.2 |
| 273 |  | 2-amino-4-(2-chloro-6-methoxyphenyl)-N-cyclopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.33 - 0.43 (m, 2 H) 0.47 - 0.60 (m, 2 H) 2.49 - 2.58 (m, 1 H) 3.73 (s, 3 H) 4.08 (s, 2 H) 4.40 (s, 2 H) 6.46 (d, J=2.78 Hz, 1 H) 6.78 (s, 2 H) 7.14 (dd, J=8.08, 5.56 Hz, 2 H) 7.44 (t, J=8.21 Hz, 1 H) | 360.2, 362.2 |
| 274 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-(1-methylcyclopropyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.44 - 0.48 (m, 2 H) 0.55 - 0.68 (m, 2 H) 1.29 (s, 3 H) 3.50 (d, J=13.39 Hz, 1 H) 3.86 (dd, J=13.01, 1.89 Hz, 1 H) 4.26 - 4.34 (m, 4 H) 4.34 - 4.44 (m, 2 H) 5.99 (t, J=2.02 Hz, 1 H) 6.46 - 6.55 (m, 1 H) 6.77 (s, 2 H) 7.18 (d, J=2.02 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.28 (d, J=1.26 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 488.2, 490.2 |
| 275 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)propoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.35 - 0.45 (m, 2 H) 0.49 - 0.64 (m, 2 H) 1.34 (d, J=2.02 Hz, 3 H) 2.52 - 2.58 (m, 1 H) 3.35 - 3.40 (m, 1 H) 3.75 - 3.88 (m, 1 H) 4.14 - 4.44 (m, 4 H) 4.51 - 4.65 (m, 1 H) 6.01 (t, J=2.02 Hz, 1 H) 6.27 - 6.44 (m, 1 H) 6.74 - 6.79 (m, 2 H) 7.21 - 7.27 (m, 2 H) 7.29 - 7.36 (m, 2 H) | 488.1, 490.1 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 276 |  | 4-(2,4-dibromo-5-methoxyphenyl)-6-[2-(1H-pyrazol-1-yl)ethyl]-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-amine | Ex. 105 | 1H NMR (400 MHz, DMSO-d6) d ppm 3.80 - 3.91 (m, J=3.79 Hz, 3 H) 4.25 (s, 1 H) 4.27 - 4.41 (m, 6 H) 4.45 (s, 1 H) 6.24 (d, J=2.02 Hz, 1 H) 6.94 (s, 2 H) 7.13 (d, J=2.78 Hz, 1 H) 7.45 (s, 1 H) 7.79 (d, J=1.77 Hz, 1 H) 7.86 (d, J=8.84 Hz, 1 H) | 494.0, 496.1 |
| 277 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.02 (t, J=7.20 Hz, 3 H) 2.98 - 3.14 (m, 2 H) 3.59 (d, J=12.88 Hz, 1 H) 3.87 - 3.97 (m, 1 H) 4.33 (s, 4 H) 4.36 - 4.47 (m, 2 H) 6.00 (t, J=2.02 Hz, 1 H) 6.23 (t, J=4.80 Hz, 1 H) 6.78 (s, 2 H) 7.19 (d, J=1.77 Hz, 1 H) 7.25 (d, J=1.77 Hz, 1 H) 7.29 (d, J=1.26 Hz, 1 H) 7.32 (d, J=1.77 Hz, 1 H) | 462.1, 464.1 |
| 278 |  | 2-amino-N-cyclopropyl-4-(2,4-dichloro-6-{[(2E)-4,4,4-trifluorobut-2-en-1-yl]oxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.33 - 0.43 (m, 2 H) 0.47 - 0.59 (m, 2 H) 4.02 - 4.18 (m, 2 H) 4.39 (d, J=7.33 Hz, 2 H) 4.74 - 4.91 (m, 2 H) 5.61 - 5.74 (m, 1 H) 6.43 (d, J=2.53 Hz, 1 H) 6.57 - 6.67 (m, 1 H) 7.32 (d, J=1.77 Hz, 1 H) 7.40 (d, J=1.77 Hz, 1 H) | 488.0, 490.1 |
| 279 |  | 2-amino-N-cyclopropyl-4-{2,4-dichloro-6-[2-(1-methyl-1H-pyrazol-4-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 0.34 - 0.44 (m, 2 H) 0.53 (dd, J=6.82, 2.27 Hz, 2 H) 2.53 - 2.56 (m, 1 H) 2.61 - 2.70 (m, 2 H) 3.70 (s, 3 H) 3.85 (d, J=13.14 Hz, 1 H) 3.96 - 4.05 (m, 1 H) 4.06 - 4.16 (m, 2 H) 4.35 - 4.50 (m, 2 H) 6.41 (d, J=2.02 Hz, 1 H) 6.85 (s, 2 H) 7.00 (s, 1 H) 7.17 (s, 1 H) 7.27 (d, J=1.77 Hz, 1 H) 7.31 (d, J=1.77 Hz, 1 H) | 488.1, 490.1 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 280 |  | 2-amino-4-(2,4-dichloro-6-hydroxyphenyl)-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.00 (t, J=7.20 Hz, 3 H) 2.97 - 3.13 (m, 2 H) 4.14 (s, 2 H) 4.38 - 4.48 (m, 2 H) 6.35 (t, J=5.43 Hz, 1 H) 6.76 - 6.83 (m, 2 H) 6.95 (d, J=1.77 Hz, 1 H) 7.14 (d, J=1.77 Hz, 1 H) 10.68 (s, 1 H) | 368.1, 370.0 |
| 281 |  | 2-amino-N-cyclobutyl-4-(2,4-dichloro-6-{[(2Z)-3,4,4,4-tetrafluorobut-2-en-1-yl]oxy}phenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.46 - 1.65 (m, 2 H) 1.85 - 2.00 (m, 2 H) 2.02 - 2.14 (m, 2 H) 4.01 - 4.24 (m, 3 H) 4.35 - 4.44 (m, 2 H) 5.63 - 5.84 (m, 1 H) 6.49 (d, J=7.83 Hz, 1 H) 6.86 (d, J=2.53 Hz, 2 H) 7.42 - 7.49 (m, 1 H) 7.53 - 7.69 (m, 1 H) | 520.0, 522.0 |
| 282 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N',N'-dimethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carbohydrazide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.46 - 2.57 (m, 6 H) 3.86 (s, 3 H) 4.20 - 4.34 (m, 2 H) 4.37 - 4.57 (m, 1 H) 6.91 (s, 2 H) 7.16 (s, 1 H) 7.56 (s, 1 H) 7.87 (s, 1 H) | 441.9, 442.9 |
| 283 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-phenylethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.65 - 2.82 (m, 2 H) 3.16 - 3.30 (m, 2 H) 3.87 (s, 3 H) 4.27 (s, 2 H) 4.43 (s, 2 H) 6.53 (t, J=5.43 Hz, 1 H) 6.92 (s, 2 H) 7.10 - 7.22 (m, 4 H) 7.24 - 7.37 (m, 2 H) 7.88 (s, 2 H) | 502.9, 503.9 |

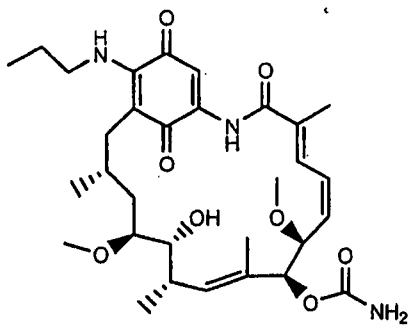
| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 284 |  | 2-amino-4-(4-bromo-2-chloro-5-methoxyphenyl)-N-(2-pyridin-2-ylethyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 102 | 1H NMR (400 MHz, DMSO-d6) d ppm 2.81 - 2.93 (m, 2 H) 3.35 - 3.45 (m, 2 H) 4.19 - 4.29 (m, 2 H) 4.36 - 4.50 (m, 2 H) 6.54 (t, J=5.68 Hz, 1 H) 6.91 (s, 2 H) 7.12 - 7.27 (m, 3 H) 7.61 - 7.74 (m, 1 H) 7.87 (s, 1 H) 8.47 (d, J=1.01 Hz, 1 H) | 503.8, 504.9 |
| 285 |  | N-allyl-2-amino-4-{2,4-dichloro-6-[2-(1-methyl-1H-pyrazol-4-yl)ethoxy]phenyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 18 | 1H NMR (400 MHz, MeOD) d ppm 2.77 (t, J=5.43 Hz, 2 H) 3.77 (s, 3 H) 3.79 (d, J=5.31 Hz, 2 H) 3.96 - 4.12 (m, 2 H) 4.14 - 4.25 (m, 2 H) 4.49 - 4.69 (m, 2 H) 5.06 (dd, J=10.11, 1.26 Hz, 1 H) 5.16 (dd, J=17.18, 1.52 Hz, 1 H) 5.81 - 5.96 (m, 1 H) 7.04 (s, 1 H) 7.12 - 7.17 (m, 2 H) 7.19 (d, J=1.77 Hz, 1 H) | 488.1, 489.1 |
| 286 |  | 2-amino-4-{2,4-dichloro-6-[2-(1H-imidazol-1-yl)ethoxy]phenyl}-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.04 (t, J = 7.1 Hz, 3H), 3.04-3.13 (m, 2H), 3.75 (d, J=13.2 Hz, 1H), 4.01 (d, J =13.2 Hz, 1H), 4.19-4.56 (m, 6H), 6.27 (br s, 1H), 6.71 (s, 1H), 6.75-6.86 (m, 3H), 7.28 (s, 2H), 7.37 (s, 1H). | 462.2, 464.2 |
| 287 |  | 2-amino-4-(4-bromo-2-chloro-5-ethoxyphenyl)-N-isopropyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (400 MHz, DMSO-d6) d ppm 1.06 (d, J = 6.5 Hz, 6H), 1.35 (t, J = 6.9 Hz, 3H), 3.75 (m, 1H), 4.09-4.17 (m, 2H), 4.25 (s, 2H), 4.42 (s, 2H), 6.07 (d, J = 8.6 Hz, 1H), 6.88 (s, 2H), 7.15 (s, 1H), 7.86 (s, 1H). | 454.2, 456.2 |
| 288 |  | 2-amino-4-(4-bromo-2-chloro-5-ethoxyphenyl)-N-ethyl-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 0.98-1.07 (m, 3H), 1.30-1.41 (m, 3H), 3.01-3.14 (m, 2H), 4.08-4.20 (m, 2H), 4.26 (s, 2H), 4.43 (s, 2H), 6.39 (br s, 1H), 6.92 (br s, 2H), 7.17 (s, 1H), 7.87 (s, 1H) | 440.2, 442.2 |

| Ex. No. | Structure | Name | Synthetic Method | $^1$H NMR | MS |
|---|---|---|---|---|---|
| 289 |  | 2-amino-N-bicyclo[1.1.1]pent-1-yl-4-(4-bromo-2-chloro-5-ethoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxamide | Ex. 111 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.36 (t, J = 7.2 Hz, 3H), 1.95 (s, 6H), 2.36 (s, 1H), 4.10-4.18 (m, 2H, partially obscured), 4.25 (s, 2H), 4.40 (s, 2H), 6.90 (br s, 2H), 7.02 9br s, 1H), 7.16 (s, 1H), 7.87 (s, 1H) | 478.2, 480.2 |
| 290 |  | ethyl 2-amino-4-(4-bromo-2-chloro-5-propoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 108 | 1H NMR (300 MHz, DMSO-d6) d ppm 0.96-1.04 (m, 3H), 1.14-1.29 (m, 3H), 1.69-1.82 (m, 2H), 3.98-4.16 (m, 4H), 4.32-4.39 (m, 2H), 4.46-4.56 (m, 2H), 6.97 (br s, 2H), 7.15 (s, 1H), 7.86 (s, 1H) | 455.0, 457.0 |
| 291 |  | ethyl 2-amino-4-(4-bromo-2-chloro-5-ethoxyphenyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 108 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.13-1.26 (m, 3H), 1.31-1.40 (m, 3H), 4.04-4.17 9m, 4H), 4.31-4.38 (m, 2H), 4.47-4.54 (m, 2H), 6.96 (br s, 2H), 7.15 | 441.0, 443.0 |
| 292 |  | ethyl 2-amino-4-[(E)-2-phenylvinyl]-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate | Ex. 1 | 1H NMR (300 MHz, DMSO-d6) d ppm 1.22-1.30 (m, 3H), 4.09-4.16 (m, 2H), 4.42 (d, J = 7.6 Hz, 2H), 4.67 (d, J = 7.5 Hz), 6.62 (s, 2H), 7.11 (dd, J = 6.9, 15.8 Hz, 1H), 7.36-7.48 (m, 3H), 7.71-7.79 (m, 3H). | 311.4 |

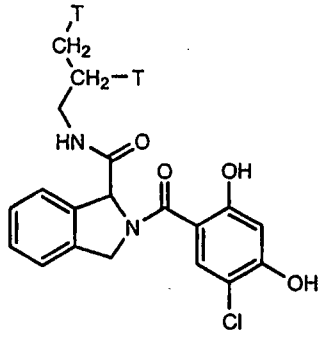
**HSP-90 Biochemical Assay**

Compounds of the present invention were evaluated for potency against HSP-90 using a SPA (scintillation proximity assay) competition binding assay. Briefly, either full length or N-terminal HSP-90 that contains a 6-His tag on its C-terminus binds to copper on Yttrium-silicate scintillant beads via the His-tag. Tritiated propyl-Geldanamycin (pGA), whose structure is shown below, is an analog of a natural inhibitor of HSP-90 called Geldanamycin. Tritiated pGA, which contains a tritiated propyl-amine group

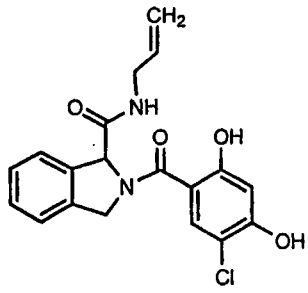
added at the #17 position, binds HSP-90 and brings the isotope into proximity with the beads. 17-n-propylamino-Geldanamycin can be prepared as described in U.S. Patent No. 4,261,989, which is incorporated herein by reference. A second tritiated compound that can also be used in this assay is shown below and is designated as Compound A.



pGA



Compound A



parent compound of compound A

The "T" in the structure of Compound A above indicates the position of the labeled tritiated hydrogen atoms. This compound has a $K_d$ of 40 nM and can be prepared as follows. Compound A can be prepare from the parent compound of Compound A, (*N*-allyl-2-(5-chloro-2,4-dihydroxybenzoyl)isoindoline-1-carboxamide) as described in the following. Allylamine (2.5 mL, 5 mmol, 2M in THF) was added to a solution of Boc(R,S)-1,3-dihydro-2H-isoindole carboxylic acid (263 mg, 1 mmole), diisopropylethyl amine (0.9 mL, 5 mmol), and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium phosphorus pentafloride (HATU) (420 mg, 1.1 mmol) in 5 mL of DMF under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 12 hours. Saturated $NaHCO_3$ (30 mL) was added to the reaction mixture to quench the reaction. EtOAc (2x50 mL) was then added to extract the aqueous solution. Dry EtOAc layer over $Na_2SO_4$. The $Na_2SO_4$ was filtered off and the filtrate was evaporated to give a brown oil residue. The residue was purified by silica gel chromatography (gradient elution 40→ 50% EtOAc in hexanes) to give the desired intermediate product (321 mg, qunatitative yield) *tert*-butyl 1-[(allylamino)carbonyl]-1,3-dihydro-2*H*-isoindole-2-carboxylate.

Hydrogen chloride (3 mL, 12 mmol; 4 M in dioxane) was added to a solution of *tert*-butyl 1-[(allylamino)carbonyl]-1,3-dihydro-2*H*-isoindole-2-carboxylate (1 mmol) in DCM (5 mL) at room temperature. The reaction was heated and stirred at room temperature for 12 hours. The reaction mixture was evaporated to give an oil residue. The residue (*N*-allylisoindoline-1-carboxamide) was used for the next step reaction without further purification.

*N*-allylisoindoline-1-carboxamide (1 mmol) was then added to a solution of 5-chloro-2,4-bis(methoxymethoxy)benzoic acid (which can be prepared as shown in WO

2006/117669) (340 mg, 1.2 mmol), 4-methylmorpholine (2.2 mL, 20 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (460 mg, 2.4 mmol), and 1-hydroxy benzotriazole (330 mg, 2.4 mmol) in 12 mL of DMF under a nitrogen atmosphere. The reaction was allowed to stir at room temperature for 12 hours. $H_2O$ (50 mL) was added to the reaction mixture to quench the reaction. EtOAc (2 x 100 mL) was then added to extract the aqueous solution. Dry EtOAc layer over $Na_2SO_4$. The $Na_2SO_4$ was filtered off and the filtrate was evaporated to give a brown oil residue. The residue was purified by silica gel chromatography (gradient elution 50→ 60% EtOAc in hexanes) to give the desired intermediate product (423 mg, 91.8% yield) *N*-allyl-2-[5-chloro-2,4-bis(methoxymethoxy)benzoyl]isoindoline-1-carboxamide.

Hydrogen chloride (4 mL, 16 mmol; 4 M in dioxane) was added to a solution of *N*-allyl-2-[5-chloro-2,4-bis(methoxymethoxy)benzoyl]isoindoline-1-carboxamide (392 mg, 0.85 mmol) in DCM (5 mL). The reaction was stirred at room temperature for 12 hours. The reaction mixture was neutralized with saturated $NaHCO_3$ (aq) and then extracted with EtOAc (2 x 50 mL). The combined organic layers were dried, filtered, and evaporated to give the desired final product as the parent compound (*N*-allyl-2-(5-chloro-2,4-dihydroxybenzoyl)isoindoline-1-carboxamide) as a white solid (221 mg, 69.7% yield). $^1$H NMR (400 MHz, DMSO-D6) $\delta$ ppm 3.57 (d, *J*=79.33 Hz, 2 H) 4.65 - 4.93 (m, 1 H) 4.97 - 5.19 (m, 1 H) 5.42 - 5.70 (m, 1 H) 5.68 - 5.95 (m, 1 H) 6.40 - 6.71 (m, 1 H) 6.92 (s, 1 H) 7.15 - 7.67 (m, 4 H) 8.28 (s, 1 H) 10.06 (s, 1 H) 10.40 (s, 1 H). Anal. Calcd for $C_{19}H_{17}ClN_2O_4$: C, 61.21; H, 4.60; N, 7.51. Found: C, 61.02; H, 4.63; N, 7.36.

Once the parent compound was made, Compound A was prepared using standard hydrogenation methods using tritium gas.

The beta signal emitted from the isotope excites the scintillant, which creates a measurable signal. As competitive compounds are added to the assay mixture, they compete with bound tritiated pGA or Compound A at the ATP-binding site on the N-terminal of HSP-90. When a compound displaces the labeled pGA or Compond A, the signal is reduced (the beta-particles are no longer in proximity with the bead). This reduction in signal is used to quantify the extent to which the inhibitor/compound is competitive with pGA or Compound A.

The SPA assay for $^3$H-pGA (designated G1) and Compound A (designated G2) binding to HSP-90 was performed in 96-well flat bottom white plates (Corning #3604). For G1, typical reaction solutions contained 30 nM HSP-90 and 200 nM $^3$H-pGA in

binding buffer (100 mM Hepes, pH 7.5 and 150 mM KCl). For G2, typical reaction solutions contained 5 nM HSP-90 and 50 nM of Compound A. For G1, the $^3$H-pGA was first diluted to 33% label with unlabeled pGA that was synthesized and purified to give a final concentration of 200 nM. For G2, labeled Compound A was diluted with unlabeled Compound A to provide a ratio of labeled:unlabeled of 1:2 for a final concentration of 50 nM. Inhibitors were added to the HSP-90/$^3$H-pGA (or HSP-90/Compound A) solutions at eleven different concentrations for $K_i$ determinations. The range of inhibitor concentrations were 100 $\mu$M, or an appropriate range, for solid samples and 10 $\mu$M for targeted library compounds and 4 mM liquid stocks. To determine percent inhibition, the compound was tested at 1 and 10 $\mu$M. The final DMSO in the samples was 4%. Copper-Ysi beads (Amersham, #RPNQ0096) that have been diluted in binding buffer were added to each well to give a final concentration of 100 $\mu$g/well. The plates were sealed, covered with a foil-covered lid and shaken for 30 minutes at room temperature. The beads were allowed to settle for 30 minutes after which the plates were counted using a Packard TopCount NXT instrument. This procedure has also been adapted for medium throughput using a Beckman Biomek FX. Samples were run in duplicate and on two separate days to assure an accurate value of $K_i$.

For $K_i$ determinations, the corrected cpm's (actual cpm's minus background) were plotted vs. inhibitor concentration using GraphPad Prism software. The data were fit to a generic $IC_{50}$ equation, $Y = YI / (1 + [X]/IC_{50})$, where YI = Y-intercept and [X] is the competing ligand/inhibitor. The $IC_{50}$ was then used to calculate the Ki by using the Cheng-Prusoff equation:

$$Ki\{cl\} = \frac{IC_{50}\{cl\}}{1 + ([hl]/Kd\{hl\})}$$

Where cl = cold ligand concentration (varies), [hl] = concentration of hot ligand (200 nM or 50 nM) and Kd{hl} = 240 nM (for $^3$H-pGA) or 40 nM (for Compound A). Error was calculated as follows: $IC_{50}$ error / $IC_{50}$ value = fractional error and fractional error * $K_i$ value = $K_i$ error.

In the cases in which inhibitor binds to HSP-90 so tightly that the population of free inhibitor molecules is significantly depleted by formation of the enzyme-inhibitor complex, the above equation is no longer valid. This is normally true when the observed $IC_{50}$ is about the same as the HSP-90 concentration. For a tight binding inhibitor, the following equation can be applied:

$$\frac{EL}{EL_o} = \frac{-(K_I^{app} + I_o - E_o) + \sqrt{(K_I^{app} + I_o - E_o)^2 + 4 \times E_o \times K_I^{app}}}{2 \times E_o}$$

Where $K_I^{app} = K_I \times (1 + \frac{L_o}{K_L})$

EL and $EL_o$ are the radioligand-HSP-90 complexes in the presence and absence of inhibitor, respectively. $EL/EL_o$ represents the fractional signal in the presence of inhibitor. Io, $E_o$, and $L_o$ are the inhibitor, HSP-90, and radioligand concentrations, respectively. $K_I$ is the inhibition constant for the ligand, while $K_L$ is the binding affinity constant between the enzyme (HSP-90) and the ligand.

The Ki assay data of the compound of Examples 1-292 are listed in the following Table 3.

**Table 3**

| Example No. | (G1):Ki ($\mu$M) | (G2):Ki ($\mu$M) |
|---|---|---|
| 1 | 0.54 | 0.112 |
| 2 | 2.77 | |
| 3 | 0.052 | |
| 4 | 1.7 | 0.475 |
| 5 | 0.244 | |
| 6 | 4.6 | |
| 7 | 0.952 | 0.12 |
| 8 | 0.369 | |
| 9 | 4 | |
| 10 | | 19.2 |
| 11 | | 2.4 |
| 12 | | 16 |
| 13 | 0.388 | |
| 14 | 1.74 | |
| 15 | 0.57 | |
| 17 | | 17.5 |
| 18 | 0.008 | |
| 20 | | 27 |
| 22 | | 21.5 |
| 23 | | 0% inhibition at 10$\mu$M |
| 24 | | 38 |
| 25 | | 0% inhibition at 10$\mu$M |
| 26 | 44 | |
| 27 | | 0% inhibition at 10$\mu$M |
| 29 | | 0.304 |

| | | |
|---|---|---|
| 30 | | 0.56 |
| 31 | | 0.36 |
| 32 | 1.9 | 0.499 |
| 33 | 1.3 | 0.268 |
| 34 | 2.6 | 0.74 |
| 35 | 1.5 | 0.437 |
| 36 | 7.3 | 2.86 |
| 37 | 4 | 1.54 |
| 38 | 2.5 | 0.822 |
| 39 | 1.66 | 0.300 |
| 40 | 4 | 0.831 |
| 41 | 2.5 | 0.56 |
| 42 | 0.56 | 0.082 |
| 43 | 0.47 | 0.105 |
| 44 | 0.72 | 0.17 |
| 45 | 0.78 | 0.167 |
| 46 | | 0% inhibition at 10$\mu$M |
| 47 | | 32 |
| 48 | | 20 |
| 49 | | 3.4 |
| 50 | | 11.4 |
| 51 | 2.71 | |
| 52 | 0.626 | |
| 53 | 0.289 | |
| 54 | 0.4 | |
| 55 | 0.143 | |
| 56 | 0.104 | |
| 57 | 0.304 | |
| 58 | 0.648 | |
| 59 | 9.78 | |
| 60 | 0.343 | |
| 61 | 0.154 | |
| 62 | 0.058 | |
| 63 | 3.32 | |
| 64 | 0.134 | |
| 65 | 0.409 | |
| 66 | 0.3 | |
| 67 | 0.169 | |
| 68 | 0.249 | |
| 69 | 0.089 | |
| 70 | 0.209 | |
| 71 | 0.209 | |
| 72 | 0.535 | |
| 73 | 0.314 | |
| 74 | 0.631 | |
| 75 | 1.59 | |

| | | |
|---|---|---|
| 76 | 0.431 | |
| 77 | 0.155 | |
| 78 | 0.157 | |
| 79 | 0.111 | |
| 80 | 0.081 | |
| 81 | 36 | |
| 82 | 2.4 | |
| 83 | 2.95 | |
| 84 | 4.34 | |
| 85 | 24 | |
| 86 | 1.65 | |
| 87 | 1.95 | |
| 88 | 3.78 | |
| 89 | 2.38 | |
| 90 | | 1.93 |
| 91 | | 0.745 |
| 92 | | 0.619 |
| 93 | | 0.349 |
| 94 | 0.82 | 0.216 |
| 95 | 12 | 3.71 |
| 96 | 1.66 | 0.3 |
| 97 | | 1.5 |
| 98 | 1.5 | 0.245 |
| 100 | | 0.014 |
| 101 | | 0.115 |
| 101a | | 0.149 |
| 102 | | 0.00918 |
| 102b | | 12 |
| 103 | | 0.0265 |
| 104 | | 0.765 |
| 105 | | 1.22 |
| 106 | | 0.319 |
| 107 | | 0.99 |
| 108 | | 0.0202 |
| 108a | | 1.9 |
| 109 | | 0.00825 |
| 110 | | 0.0101 |
| 111 | | 0.064 |
| 112 | | 0.17 |
| 113 | | 0.0245 |
| 114 | | 0.0165 |
| 115 | | 0.0665 |
| 116 | | 0.0274 |
| 117 | | 0.547 |
| 118 | | 0.19 |
| 119 | | 8.77 |
| 120 | | 0.324 |

| | | |
|---|---|---|
| 121 | | 0.354 |
| 122 | | 1.05 |
| 123 | | 36 |
| 124 | | 0.844 |
| 125 | | 9.38 |
| 126 | | 2.35 |
| 127 | | 0.0688 |
| 127a | | 0.0628 |
| 127b | | 0.0839 |
| 128 | | 0.648 |
| 129 | | 0.449 |
| 130 | | 0.154 |
| 131 | | 0.775 |
| 132 | | 0.268 |
| 133 | | 0.273 |
| 134 | | 1.63 |
| 135 | | 1.14 |
| 136 | | 0.267 |
| 137 | | 0.332 |
| 138 | | 0.132 |
| 139 | | 0.0128 |
| 140 | | 0.132 |
| 141 | | 0.154 |
| 142 | | 0.303 |
| 143 | | 1.3 |
| 144 | | 0.473 |
| 145 | | 0.434 |
| 146 | | 0.00792 |
| 147 | | 0.0517 |
| 148 | | 2.26 |
| 149 | | 0.329 |
| 150 | | 0.0528 |
| 151 | | 0.463 |
| 152 | | 0.332 |
| 153 | | 0.811 |
| 154 | | 0.029 |
| 155 | | 0.546 |
| 156 | | 0.0267 |
| 157 | | 1.2 |
| 158 | | 4.72 |
| 159 | | 0.062 |
| 160 | | 0.685 |
| 161 | | 0.592 |
| 162 | | 0.03 |
| 163 | | 0.104 |
| 164 | | 0.00838 |
| 165 | | 0.392 |

| | | |
|---|---|---|
| 166 | | 2.99 |
| 167 | | 2.81 |
| 168 | | 0.067 |
| 169 | | 0.14 |
| 170 | | 1.3 |
| 171 | | 0.247 |
| 172 | | 0.0162 |
| 173 | | 1.02 |
| 174 | | 17.1 |
| 175 | | 0.378 |
| 176 | | 0.319 |
| 177 | | 0.235 |
| 178 | | 2.14 |
| 179 | | 1.15 |
| 180 | | 2.28 |
| 181 | | 0.735 |
| 182 | | 0.24 |
| 183 | | 0.504 |
| 184 | | 0.658 |
| 185 | | 2.88 |
| 186 | | 0.802 |
| 187 | | 0.577 |
| 188 | | 1.77 |
| 189 | | 0.0116 |
| 190 | | 0.0201 |
| 191 | | 0.396 |
| 192 | | 0.014 |
| 193 | | 0.0296 |
| 194 | | 0.0466 |
| 195 | | 0.0467 |
| 196 | | 0.0355 |
| 197 | | 0.0139 |
| 198 | | 0.0091 |
| 199 | | 0.0427 |
| 200 | | 0.0144 |
| 201 | | 0.0117 |
| 202 | | 0.0631 |
| 203 | | 0.02 |
| 204 | | 0.00862 |
| 205 | | 0.0487 |
| 206 | | 0.0353 |
| 207 | | 0.07 |
| 208 | | 0.0379 |
| 209 | | 0.0214 |
| 210 | | 0.306 |
| 211 | | 0.00665 |
| 212 | | 0.224 |

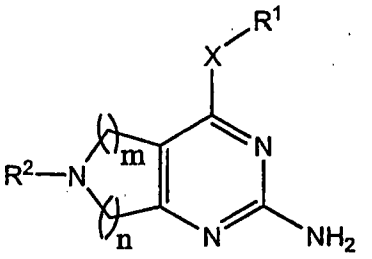
| | | |
|---|---|---|
| 213 | | 0.03 |
| 214 | | 0.255 |
| 215 | | 1.05 |
| 216 | | 0.185 |
| 217 | | 0.0135 |
| 218 | | 0.00593 |
| 219 | | 0.0676 |
| 220 | | 0.121 |
| 221 | | 0.243 |
| 222 | | 0.0568 |
| 223 | | 0.0073 |
| 224 | | 0.0549 |
| 225 | | 0.0794 |
| 226 | | 0.105 |
| 227 | | 0.48 |
| 228 | | 0.179 |
| 229 | | 1.25 |
| 230 | | 0.225 |
| 231 | | 0.069 |
| 232 | | 3.18 |
| 233 | | 2.26 |
| 234 | | 0.184 |
| 235 | | 0.0318 |
| 236 | | 0.21 |
| 237 | | 0.205 |
| 238 | | 0.0455 |
| 239 | | 0.699 |
| 240 | | 0.13 |
| 241 | | 0.472 |
| 242 | | 1.08 |
| 243 | | 3.82 |
| 244 | | 39 |
| 245 | | 14.9 |
| 246 | | 0.00853 |
| 247 | | 0.00661 |
| 248 | | 0.016 |
| 249 | | 0.039 |
| 250 | | 0.0092 |
| 251 | | 0.144 |
| 252 | | 0.104 |
| 253 | | 0.0255 |
| 254 | | 0.145 |
| 255 | | 0.275 |
| 256 | | 0.164 |
| 257 | | 6.29 |
| 258 | | 0.114 |
| 259 | | 5.85 |

| | | |
|---|---|---|
| 260 | | 0.213 |
| 261 | | 0.0831 |
| 262 | | 0.267 |
| 263 | | 0.0355 |
| 264 | | 0.195 |
| 265 | | 0.098 |
| 266 | | 0.504 |
| 267 | | 0.0642 |
| 268 | | 0.46 |
| 269 | | 0.0911 |
| 270 | | 0.00352 |
| 271 | | 0.0148 |
| 272 | | 0.0649 |
| 273 | | 1.32 |
| 274 | | 0.0149 |
| 275 | | 0.0141 |
| 276 | | 0.775 |
| 277 | | 0.0125 |
| 278 | | 0.0352 |
| 279 | | 0.0108 |
| 280 | | 0.565 |
| 281 | | 0.098 |
| 282 | | 0.22 |
| 283 | | 0.53 |
| 284 | | 0.635 |
| 285 | | 0.023 |
| 286 | | 0.00693 |
| 287 | | 0.155 |
| 288 | | 0.0814 |
| 289 | | 0.0557 |
| 290 | | 0.807 |
| 291 | | 0.224 |
| 292 | | 2.51 |

## Claims

We claim:

1. A compound of formula (I)



(I)

wherein:

m is 1 or 2, n is 1 or 2, when m is 2, n is 1;

X is a bond or a diradical selected from the group consisting of -O-, -S-, -($C_1$-$C_3$ alkylene)-, -O-($C_1$-$C_3$ alkylene)-, -NH-($C_1$-$C_3$ alkylene)-, –S-($C_1$-$C_3$ alkylene)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, –NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- and -$S(O)_2$-NH-, wherein each end of the diradical may be connected to $R^1$ or to the aminopyrimidine ring of formula I;

where permissible, each nitrogen or carbon atom of X is optionally further substituted by one group selected from -($C_1$-$C_3$ alkylene)$_t$-CN, -($C_1$-$C_3$ alkylene)$_t$-F, -($C_1$-$C_3$ alkylene)$_t$-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_3$ alkylene)$_t$-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_3$ alkylene)$_t$-OH, -($C_1$-$C_3$ alkylene)$_t$-$NH_2$, -($C_1$-$C_3$ alkylene)$_t$-NH($C_1$-$C_3$ alkyl) and -($C_1$-$C_3$ alkylene)$_t$-N($C_1$-$C_3$ alkyl)($C_1$-$C_3$ alkyl), and t is 0 or 1;

$R^1$ is selected from the group consisting of $C_6$-$C_{12}$ aryl, 5 to 12 member heteroaryl, $C_3$-$C_{12}$ cycloalkyl, 3-12 member heterocyclyl and $C_5$-$C_{12}$ unsaturated nonaromatic carbocyclyl, and each $R^1$ is optionally further substituted with 1-5 R, provided that when $R^1$ is phenyl, then $R^1$ is further substituted with at least two R and at least one of the R is not a halogen;

R is selected from the group consisting of $R^x$, -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_7$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(7-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(7-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -

$(C_1\text{-}C_6$ alkylene$)_p$-O-$(C_2\text{-}C_6$ alkynylene$)_p$-$(C_3\text{-}C_{10}$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_p$-O-$(C_2\text{-}C_6$ alkynylene$)_p$-(5-10 member heteroaryl) and -$(C_1\text{-}C_6$ alkylene$)_p$-O-$(C_2\text{-}C_6$ alkynylene$)_p$-(3-10 member heterocyclyl);

$R^2$ is selected from the group consisting of -$(C_1\text{-}C_6$ alkylene$)_p$-C(O)-$R^b$, -$(C_1\text{-}C_6$ alkylene$)_p$-C(O)-O-$R^a$, -$(C_1\text{-}C_6$ alkylene$)_p$-C(O)-N$(R^a)_2$, -$(C_1\text{-}C_6$ alkylene$)_p$-S(O)-$R^a$, -$(C_1\text{-}C_6$ alkylene$)_p$-S(O)$_2$-$R^a$, -$(C_1\text{-}C_6$ alkylene$)_p$-S(O)$_2$-N$(R^a)_2$, -$(C_1\text{-}C_6$ alkylene$)_p$-S(O)$_2$-O-$R^a$, and $R^3$, wherein $R^3$ is selected from –$(C_1\text{-}C_6$ alkylene)-$(C_1\text{-}C_3$ perfluoroalkyl), $C_2\text{-}C_8$ alkenyl, $C_2\text{-}C_8$ alkynyl, -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_3\text{-}C_{12}$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_p$-(3-12 member heterocyclyl), -$(C_1\text{-}C_6$ alkylene$)_p$-(5-12 member heteroaryl) and -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_5\text{-}C_{12}$ unsaturated nonaromatic carbocyclyl);

each $R^a$ is independently selected from the group consisting of H, $C_1\text{-}C_8$ alkyl, $C_2\text{-}C_8$ alkenyl, $C_2\text{-}C_8$ alkynyl, $C_1\text{-}C_8$ perfluoroalkyl, -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_6\text{-}C_{12}$ aryl), -$(C_1\text{-}C_6$ alkylene$)_p$-(5 to 12 member heteroaryl), -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_3\text{-}C_{12}$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_p$-(3-12 member heterocyclyl), -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_5\text{-}C_{12}$ unsaturated nonaromatic carbocyclyl);

two $R^a$ attached to the same nitrogen atom, together with the nitrogen atom, may optionally form a 3-12 member heterocyclyl or a 5-12 member heteroaryl; the said 3-12 member heterocyclyl and the said 5-12 member heteroaryl is optionally further substituted by 1-5 $R^x$;

$R^b$ is selected from the group consisting of –N$R^a$N$(R^a)_2$, -N$R^a$O$R^a$, $C_2\text{-}C_8$ alkenyl, $C_2\text{-}C_8$ alkynyl, $C_1\text{-}C_8$ perfluoroalkyl, -$(C_3\text{-}C_6$ alkylene)-$(C_1\text{-}C_3$ perfluoroalkyl), -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_6\text{-}C_{12}$ aryl), -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_3\text{-}C_{12}$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_p$-(3-12 member heterocyclyl), -$(C_1\text{-}C_6$ alkylene$)_p$-(5-12 member heteroaryl), -$(C_1\text{-}C_6$ alkylene$)_p$-$(C_5\text{-}C_{12}$ unsaturated nonaromatic carbocyclyl);

p is 0 or 1;

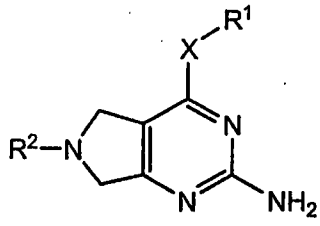
each R, $R^a$, $R^b$ and $R^3$ is optionally further substituted with 1-5 $R^x$;

each $R^x$ is independently selected from the group consisting of –oxo-, -$(C_1\text{-}C_4$ alkylene)-, halogen, -CN, -OH, $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ perfluoroalkyl, -$(C_1\text{-}C_6$ alkylene)-halogen, -$(C_1\text{-}C_6$ alkylene)-OH, -$(C_1\text{-}C_6$ alkylene)-CN, -$(C_1\text{-}C_6$ alkylene$)_q$-$(C_3\text{-}C_6$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-(3-6 member heterocyclyl), -$(C_1\text{-}C_6$ alkylene$)_q$-(5-6 member heteroaryl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-$(C_1\text{-}C_6$ alkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-$(C_3\text{-}C_6$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-$(C_1\text{-}C_6$ alkylene)-$(C_3\text{-}C_6$ cycloalkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-O-$(C_1\text{-}C_6$ alkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-NH-$(C_1\text{-}C_6$ alkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-C(O)-N$(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), -$(C_1\text{-}C_6$ alkylene$)_q$-O-$(C_1\text{-}C_6$

alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-halogen, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-($C_1$-$C_3$ perfluoroalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(3-6 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)$_q$-(5-6 member heteroaryl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-O-($C_1$-$C_6$ alkylene)-N($C_1$-$C_6$ alkyl)$_2$, -($C_1$-$C_6$ alkylene)$_q$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-NH-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-N($C_1$-$C_6$ alkyl)($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$- NHC(O)-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-NH-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-$NH_2$, -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH($C_1$-$C_3$ alkyl), -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-NH-($C_1$-$C_3$ alkylene)$_q$-($C_3$-$C_6$ cycloalkyl) and -($C_1$-$C_6$ alkylene)$_q$-$SO_2$-N($C_1$-$C_3$ alkyl)$_2$; each q is independently 0 or 1; where permissible, each carbon atom of $R^x$ is optionally further substituted by 1-3 fluorine;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein m is 1 and n is 1, and the compound is of formula II,



II

or a pharmaceutically acceptable salt thereof.

3. The compound of any of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein X is a bond or –O-, $R^1$ is $C_6$-$C_{12}$ aryl, 5 to 12 member heteroaryl, or 3-12 member heterocyclyl, and $R^1$ is further substituted with 2-5 R.

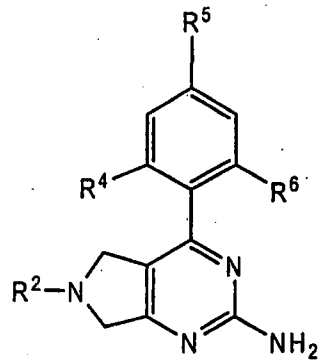
4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein X is a bond and $R^1$ is a $C_6$-$C_{12}$ aryl further substituted with 2-5 R.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein $R^1$ is phenyl further substituted with 2-5 R and at least one of the R is not a halogen.

6. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R is selected from the group consisting of F, Cl, Br, -OH, -CN, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$

alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); wherein each R is optionally further substituted by 1-5 $R^x$.

7. The compound of claim 2, of formula V,



V

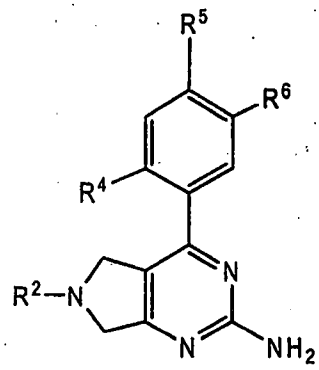
wherein

$R^4$ and $R^5$ are independently F, Cl, Br, -OH, -CN, unsubstituted $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, unsubstituted -($C_1$-$C_6$ alkylene)-OH or unsubstituted -O-($C_1$-$C_6$ alkyl);

$R^6$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); and $R^6$ is optionally further substituted with 1-5 $R^x$;

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 2, of formula VI



VI

wherein

$R^4$ and $R^5$ are independently F, Cl, Br, -OH, -CN, unsubstituted $C_1$-$C_3$ alkyl, $C_1$-$C_3$ perfluoroalkyl, unsubstituted -($C_1$-$C_6$ alkylene)-OH or unsubstituted -O-($C_1$-$C_6$ alkyl);

$R^6$ is selected from the group consisting of -($C_1$-$C_6$ alkylene)-OH, -O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)-O-($C_1$-$C_6$ alkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_1$-$C_6$ alkylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(5-10 member heteroaryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkenylene)$_p$-(3-10 member heterocyclyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_6$-$C_{10}$ aryl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-($C_3$-$C_{10}$ cycloalkyl), -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(5-10 member heteroaryl) and -($C_1$-$C_6$ alkylene)$_p$-O-($C_2$-$C_6$ alkynylene)$_p$-(3-10 member heterocyclyl); and $R^6$ is optionally further substituted with 1-5 $R^x$;

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 7 or claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is –O-($C_1$-$C_6$ alkylene)-(5-10 member heteroaryl), and $R^6$ is optionally further substituted with 1-5 $R^x$.

10. The compound of claim 7 or claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is –O-($C_1$-$C_6$ alkylene)-(5 member heteroaryl), and $R^6$ is optionally further substituted with 1-5 $R^x$.

11. The compound of claim 7 or claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is –O-($C_1$-$C_6$ alkylene)-(3-10 member heterocyclyl), and $R^6$ is optionally further substituted with 1-5 $R^x$.

12. The compound of claim 7 or claim 8, or a pharmaceutically acceptable salt thereof, wherein $R^6$ is –O-($C_1$-$C_6$ alkyl) or –O-($C_2$-$C_6$ alkenyl), and $R^6$ is optionally further substutituted with 1-5 $R^x$.

13. The compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is –C(O)-N($R^a$)$_2$.

14. The compound of any of claim 1-12, or a pharmaceutically acceptable salt thereof, wherein $R^2$ is –C(O)-O$R^a$.

15. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutuically acceptable salt thereof, and a pharmaceutical acceptable carrier.

16. The use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cancer.

17. A method of modulating the activity of HSP-90, comprising contacting a cell with a compound of claim 1, or a pharmaceutically acceptable salt thereof.

# COMPUESTOS DE 2-AMINO PIRIMIDINA

Esta solicitud reivindica el beneficio de la Solicitud de Patente Provisional de Estados Unidos Nº 60/888.433 presentada el 6 de febrero de 2007 y 61/020.661 presentada el 11 de enero de 2008, cuya descripción se incorpora por este documento como referencia en su totalidad.

Campo de la Invención

La presente invención se refiere a compuestos y sales farmacéuticamente aceptables y solvatos de los mismos, su síntesis y su uso como moduladores o inhibidores de HSP-90. Los compuestos de la presente invención son útiles para modular (por ejemplo, inhibir) la actividad de HSP-90 y para tratar enfermedades o afecciones mediadas por HSP-90, tales como por ejemplo, patologías asociadas con crecimiento celular anormal tales como cáncer.

Antecedentes

Las chaperonas moleculares juegan papeles importantes en la función celular asegurando el plegamiento apropiado de proteínas tras la síntesis así como su replegamiento en condiciones de estrés desnaturalizante. Regulando el equilibrio entre síntesis y degradación de proteínas, las chaperonas moleculares son una parte significativa de la respuesta celular al estrés. Además, regulando el plegamiento apropiado de diversas proteínas celulares, las chaperonas juegan un papel importante en la regulación de funciones celulares, tales como proliferación celular y apoptosis. (Véase, por ejemplo, Jolly, y col., J. *Natl. Cancer Inst.* 92: 1564-1572 (2000)). Las proteínas de choque térmico (HSP) son una clase de chaperonas que se acumulan en la célula en respuesta a diversos estreses del entorno, tales como choque

térmico, estrés oxidativo o la presencia de alcoholes o metales pesados. Además de su papel en la protección de la célula de tales estreses del entorno, las HSP también pueden jugar un papel significativo como chaperonas para una diversidad de proteínas celulares en condiciones sin estrés. Los miembros de la familia HSP se clasifican de acuerdo con su peso molecular (por ejemplo, HSP-27, HSP-70 y HSP-90). La evidencia de expresión diferencial de HSP en diversos estados de progresión tumoral sugiere que las HSP juegan un papel en el cáncer. (Véase, por ejemplo, Martin, y col. *Cancer Res.* 60: 2232-2238 (2000)).

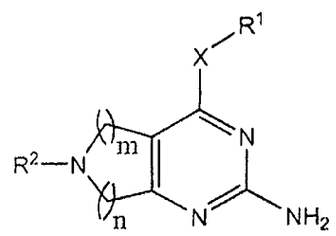
HSP-90 es un homodímero con actividad y funciones de ATPasa en una serie de interacciones complejas con una diversidad de proteínas de sustrato (Young, y col., *J. Cell Biol.* 154: 267-273 (2001)). Sin embargo, HSP-90 es única con respecto a otras chaperonas, ya que la mayoría de sus proteínas de sustrato conocidas son proteínas de transducción de señal. Por tanto, HSP-90 juega un papel imprescindible en la regulación de redes de transducción de señal celulares (Véase, por ejemplo, Xu, y col., *Proc. Natl. Acad. Sci.* 90: 7074-7078 (1993)). En particular, las proteínas de sustrato de HSP-90 incluyen muchas proteínas mutadas o sobre expresadas implicadas en el cáncer, tales como p53, Bcr-AB1 quinasa, Raf-1 quinasa, Akt quinasa, Npm-Alk quinasa, quinasa transmembrana $p185^{ErbB2}$, Cdk4, Cdk6, Wee1 (una quinasa dependiente de ciclo celular), HER2/Neu (ErbB2) y factor 1$\alpha$ inducible por hipoxia (HIF-1$\alpha$). Por tanto, la inhibición de HSP-90 da como resultado la degradación selectiva de estas proteínas de señalización importantes implicadas en apoptosis, proliferación celular y regulación del ciclo celular (Holstein, y col. *Cancer Res.* 61: 4003-4009 (2001)). En consecuencia, HSP-90

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es una diana terapéutica atractiva debido a los papeles importantes que juegan estas proteínas de señalización en patologías que implican crecimiento celular anormal, tales como cáncer. Por tanto, es deseable descubrir y desarrollar inhibidores nuevos de actividad de HSP-90 que puedan proporcionar un beneficio terapéutico a pacientes que sufren de patologías relacionadas con crecimiento celular anormal tales como cáncer.

Sumario

En una realización, la presente invención proporciona un compuesto de fórmula (I)



(I)

en la que:

m es 1 ó 2, n es 1 ó 2, cuando m es 2, n es 1;

X es un enlace o un dirradical seleccionado del grupo constituido por -O- , -S-, -(alquileno $C_1$-$C_3$)-, -O-(alquileno $C_1$-$C_3$)-, -NH-(alquileno $C_1$-$C_3$)-, -S-(alquileno $C_1$-$C_3$)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, -NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- y -$S(O)_2$-NH-, donde cada extremo del dirradical puede estar conectado a $R^1$ o al anillo de aminopirimidina de fórmula I;

cuando se permita, cada átomo de nitrógeno o carbono de X está opcionalmente sustituido adicionalmente con un grupo seleccionado de -(alquileno $C_1$-$C_3$)$_t$CN, -(alquileno $C_1$-$C_3$)$_t$F, -(alquileno $C_1$-$C_3$)$_t$(perfluoroalquilo

$C_1$-$C_3$), -(alquileno $C_1$-$C_3$)$_t$O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_3$)$_r$ OH, -(alquileno $C_1$-$C_3$)$_t$$NH_2$, -(alquileno $C_1$-$C_3$)$_t$NH(alquilo $C_1$-$C_3$) y -(alquileno $C_1$-$C_3$)$_t$N(alquil $C_1$-$C_3$)(alquilo $C_1$-$C_3$) y t es 0 ó 1;

$R^1$ se selecciona del grupo constituido por arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros, cicloalquilo $C_3$-$C_{12}$, heterociclilo de 3-12 miembros y carbociclilo $C_5$-$C_{12}$ insaturado no aromático, y cada $R^1$ está sustituido opcionalmente además con 1-5 R, con la condición de que cuando $R^1$ es fenilo, entonces $R^1$ esté sustituido adicionalmente con al menos dos R y al menos uno de los R no es un halógeno;

R se selecciona del grupo constituido por $R^x$, -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_7$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 7-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 7-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), (alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)-(cicloalquilo ($C_3$-$C_{10}$), -(alquileno ($C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros);

$R^2$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)$_p$-C(O)-$R^b$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-O-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-S(O)-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$$R^a$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-N($R^a$)$_2$, -

(alquileno $C_1$-$C_6$)$_p$-$S(O)_2$-$OR^a$ y $R^3$, donde $R^3$ se selecciona de -(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), $C_2$-$C_B$ alquenilo, alquinilo $C_2$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros) y -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

cada $R^a$ se selecciona independientemente del grupo constituido por H, alquilo $C_1$-$C_8$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5 a 12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

dos $R^a$ unidos al mismo átomo de nitrógeno, junto con el átomo de nitrógeno, pueden formar opcionalmente un heterociclilo de 3-12 miembros o un heteroarilo de 5-12 miembros; donde dicho heterociclilo de 3-12 miembros y dicho heteroarilo de 5-12 miembros están opcionalmente sustituidos adicionalmente con 1-5 $R^x$;

$R^b$ se selecciona del grupo constituido por-$NR^aN(R^a)_2$, -$NR^aOR^a$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_3$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)p-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

p es 0 ó 1;

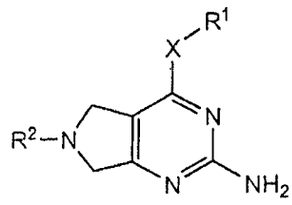
cada R, $R^a$, $R^b$ y $R^3$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$;

cada $R^x$ se selecciona independientemente del grupo constituido por -oxo-, -(alquileno $C_1$-$C_4$)-, halógeno, -CN, -OH, alquilo $C_1$-$C_6$, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, perfluoroalquilo $C_1$-$C_6$, -(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)-OH, -(alquileno $C_1$-$C_6$)-CN, -(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), (alquileno $C_1$-$C_6$)$_q$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-N(alquilo $C_1$-$C_6$)$_2$, -(alquileno $C_1$-$C_6$)$_q$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$- NHC(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH(alquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$) y -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-N(alquilo $C_1$-$C_3$)$_2$; cada q es independientemente 0 ó 1; cuando se permita, cada átomo de carbono de $R^x$

está opcionalmente sustituido adicionalmente con 1-3 flúor;

o una sal farmacéuticamente aceptable del mismo.

En un aspecto preferido de esta realización, y en combinación con cualquier otro aspecto no incoherente, m es 1, n es 1, y el compuesto es de fórmula II,



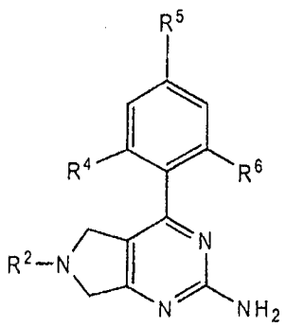
II

En otro aspecto preferido de esta realización, y junto con cualquier otro aspecto no incoherente, X es un enlace o -O-, $R^1$ es arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros o heterociclilo de 3-12 miembros, y $R^1$ está sustituido adicionalmente con 2-5 R. Más preferiblemente, X es un enlace y $R^1$ es un arilo $C_5$-$C_{12}$ sustituido adicionalmente con 2-5 R. Aún más preferiblemente, $R^1$ es fenilo sustituido adicionalmente con 2-5 R y al menos uno de los R no es un halógeno.

En otro aspecto preferido de esta realización, y en combinación con cualquier otro aspecto no incoherente, R se selecciona del grupo constituido por F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-

(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); donde cada R está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En otro aspecto preferido de esta realización, y en combinación con cualquier otro aspecto no incoherente, m es 1, n es 1 y el compuesto es de fórmula V,



V

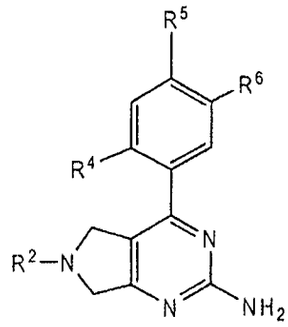
en la que

$R^4$ y $R^5$ son independientemente F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$ sin sustituir, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH sin sustituir o -O-(alquilo $C_1$-$C_6$) sin sustituir;

$R^6$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-

10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_5$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En otro aspecto preferido de esta realización, y en combinación con cualquier otro aspecto no incoherente, m es 1, n es 1 y el compuesto es de fórmula VI,



VI

en la que

$R^4$ y $R^5$ son independientemente F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$ sin sustituir, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH sin sustituir o -O-(alquilo $C_1$-$C_6$) sin sustituir;

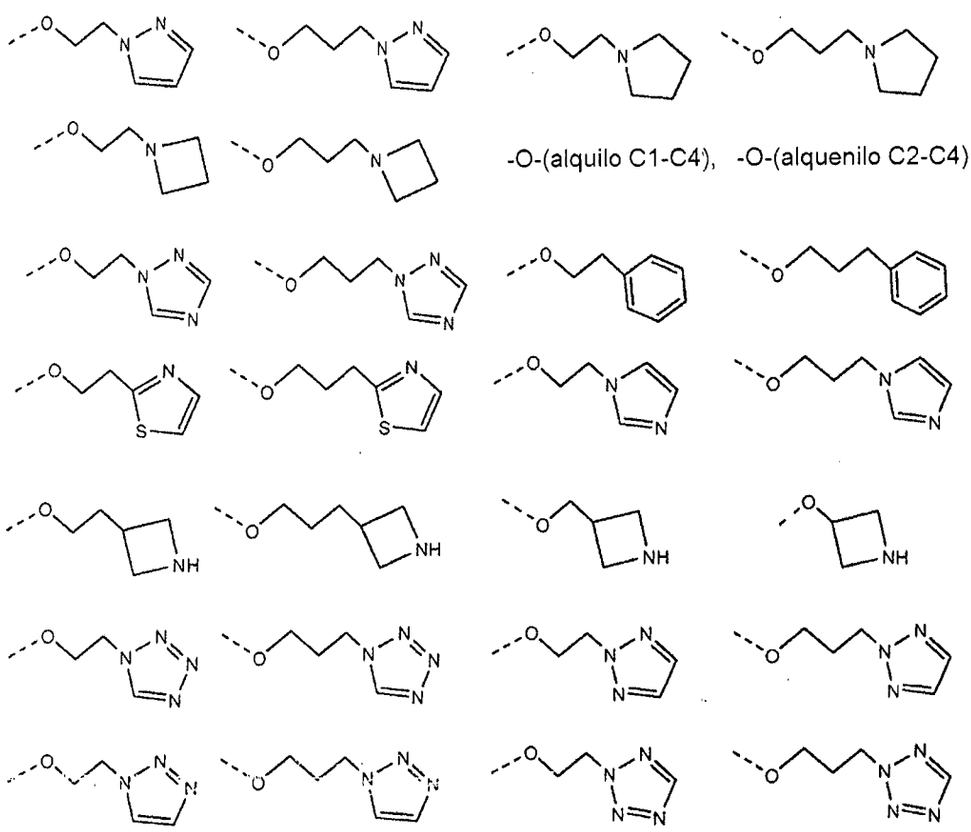
$R^6$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-

(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En la fórmula V y en la fórmula VI, preferiblemente, $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heteroarilo de 5-10 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$; más preferiblemente, $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heteroarilo de 5 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$; además, preferiblemente, $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heterociclilo de 3-10 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$; además, preferiblemente, $R^6$ es -O-(alquileno $C_1$-$C_6$)-fenilo, y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$; además, preferiblemente, $R^6$ es -O-(alquilo $C_1$-$C_6$) o -O-(alquenilo $C_2$-$C_6$), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$. El sustituyente preferido de $R^6$ es F, Cl, alquilo $C_1$-$C_3$, -O-(alquilo $C_1$-$C_3$), -OH, -CN y -(alquileno $C_1$-$C_3$)-CN. Más preferiblemente, $R^6$ incluye el siguiente grupo, donde cada grupo está sin sustituir o sustituido con 1-5 $R^x$; preferiblemente, el siguiente grupo está sin

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sustituir o sustituido con 1-5 grupos de F, Cl, alquilo $C_1$-$C_3$, -O-(alquilo $C_1$-$C_3$), -OH, -CN o -(alquileno $C_1$-$C_3$)-CN:

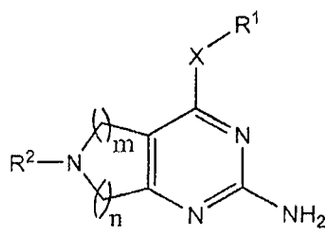



En otro aspecto preferido de esta realización, y junto con cualquier otro aspecto no incoherente, particularmente junto con el aspecto en el que el compuesto es de fórmula V, además particularmente junto con el aspecto en el que el compuesto es de fórmula VI, $R^2$ es -C(O)-N($R^a$)$_2$. Preferiblemente, un primer $R^a$ es H o alquilo $C_1$-$C_3$ sin sustituir; y un segundo $R^a$ se selecciona de alquilo $C_1$-$C_6$, ciclopropilo, ciclobutilo, biciclo[1.1.1]pent-1-ilo, (1S,5R)-3-aza-biciclo[3.1.0]hex-6-ilo, heteroarilo de 5-6 miembros, heterociclilo de 3-7 miembros y alquenilo $C_2$-$C_6$, y el segundo $R^a$ está opcionalmente sustituido adicionalmente con 1-5 grupos seleccionados de F, Cl, alquilo $C_1$-$C_3$, -O-(alquilo $C_1$-$C_3$), -OH, -CN y -(alquileno $C_1$-$C_3$)-CN. Más preferiblemente, el

primer $R^a$ es H.

En otro aspecto preferido de esta realización, y junto con cualquier otro aspecto no incoherente, particularmente junto con el aspecto en el que el compuesto es de fórmula V, además particularmente junto con el aspecto en el que el compuesto es de fórmula VI, $R^2$ es -C(O)-$OR^a$. Preferiblemente, $R^a$ se selecciona de alquilo $C_1$-$C_6$, ciclopropilo, ciclobutilo, biciclo[1.1.1]pent-1-ilo, heteroarilo de 5-6 miembros, heterociclilo de 3-7 miembros y alquenilo $C_2$-$C_6$, y $R^a$ está opcionalmente sustituido adicionalmente con 1-5 grupos seleccionados de F, Cl, alquilo $C_1$-$C_3$, -O-(alquilo $C_1$-$C_3$), -OH, -CN y -(alquileno $C_1$-$C_3$)-CN.

En otra realización, la presente invención proporciona un compuesto de fórmula (I)



(I)

en la que:

m es 1 ó 2, n es 1 ó 2, cuando m es 2, n es 1;

X es un enlace o un dirradical seleccionado del grupo constituido por -O-, -S-, -(alquileno $C_1$-$C_3$)-, -O-(alquileno $C_1$-$C_3$)-, -NH-(alquileno $C_1$-$C_3$)-, -S-(alquileno $C_1$-$C_3$)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, -NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- y -$S(O)_2$-NH-, donde cada extremo del dirradical puede estar conectado a $R^1$ o al anillo de aminopirimidina de fórmula I;

cuando se permita, cada átomo de nitrógeno o carbono de X está opcionalmente sustituido adicionalmente con un grupo seleccionado de -

(alquileno $C_1$-$C_3$)$_t$-CN, -(alquileno $C_1$-$C_3$)$_t$-F, -(alquileno $C_1$-$C_3$)$_t$-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_3$)$_t$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_3$)$_t$-OH, -(alquileno $C_1$-$C_3$)$_t$-$NH_2$, -(alquileno $C_1$-$C_3$)$_t$-NH(alquilo $C_1$-$C_3$) y -(alquileno $C_1$-$C_3$)$_t$-N(alquil $C_1$-$C_3$)(alquilo $C_1$-$C_3$), y t es 0 ó 1;

$R^1$ se selecciona del grupo constituido por arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros, cicloalquilo $C_3$-$C_{12}$, heterociclilo de 3-12 miembros y carbociclilo $C_5$-$C_{12}$ insaturado no aromático, y cada $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$, con la condición de que cuando $R^1$ es fenilo, $R^1$ esté sustituido adicionalmente con al menos dos $R^x$ y uno de los $R^x$ no sea un halógeno;

los sustituyentes preferidos de $R^1$ se seleccionan de F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -O-(alquileno $C_1$-$C_6$)-halógeno, -O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -O-(alquileno $C_1$-$C_6$)-N(alquil $C_1$-$C_6$)$_2$, -O-(alquileno $C_1$-$C_6$)-$NH_2$ y -O-(alquileno $C_1$-$C_6$)-NH(alquilo $C_1$-$C_6$);

$R^2$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)$_p$-C(O)-$R^b$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-O-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-S(O)-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-$S(O)_2$-$R^a$, -(alquileno ($C_1$-$C_6$)$_p$-$S(O)_2$-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-$S(O)_2$-O-$R^1$ y $R^3$, donde $R^3$ se selecciona de -(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), alquinilo $C_2$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros) y -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

cada $R^a$ se selecciona independientemente del grupo constituido por H, alquilo $C_1$-$C_8$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -

(alquileno $C_1$-$C_6)_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6)_p$-(heteroarilo de 5 a 12 miembros), -(alquileno $C_1$-$C_6)_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6)_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6)_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

dos $R^a$ unidos al mismo átomo de nitrógeno, junto con el átomo de nitrógeno, pueden formar opcionalmente un heterociclilo de 3-12 miembros o un heteroarilo de 5-12 miembros; donde dicho heterociclilo de 3-12 miembros y dicho heteroarilo de 5-12 miembros están opcionalmente sustituidos adicionalmente con 1-5 $R^x$;

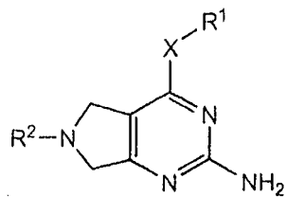
$R^b$ se selecciona del grupo constituido por alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_3$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_5)_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6)_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6)_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6)_p$-(heteroarilo de 5-12 miembros), -(alquileno $C_1$-$C_6)_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

p es 0 ó 1; cada $R^a$, $R^b$ y $R^3$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$;

cada $R^x$ se selecciona independientemente del grupo constituido por -oxo-, -(alquileno $C_1$-$C_4$)-, halógeno, -CN, -OH, alquilo $C_1$-$C_6$, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, perfluoroalquilo $C_1$-$C_6$, -(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)-OH, -(alquileno $C_1$-$C_6$)-CN, -(alquileno $C_1$-$C_6)_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6)_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6)_q$-(heteroarilo de 5-6 miembros), (alquileno $C_1$-$C_6)_q$-C(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6)_q$-C(O)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6)_q$-C(O)-(alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6)_q$-C(O)-O-(alquilo $C_1$-$C_6$), -

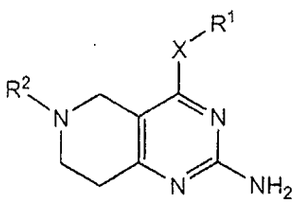
(alquileno $C_1$-$C_6$)$_q$-C(O)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_8$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-N(alquilo $C_1$-$C_6$)$_2$, -(alquileno $C_1$-$C_6$)$_q$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-NH-(alquilo $C_1$-$C_6$)-, (alquileno $C_1$-$C_6$)$_q$-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$- NHC(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-SO2-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-SO2-NH(alquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH-(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$) y -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-N(alquilo $C_1$-$C_3$)$_2$; cada q es independientemente 0 ó 1; cuando se permita, cada átomo de carbono de R* está opcionalmente sustituido adicionalmente con 1-3 flúor; o una sal farmacéuticamente aceptable del mismo.

En el primer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 1 y n es 1, y el compuesto es de fórmula II,



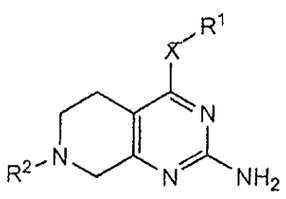
II

En el segundo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 1 y n es 2, y el compuesto es de fórmula III,



III

En el tercer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 2 y n es 1, y el compuesto es de fórmula IV,



IV

En el cuarto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es un enlace y $R^1$ es un arilo $C_6$-$C_{12}$ opcionalmente sustituido con 1-5 $R^x$. Preferiblemente, $R^1$ es fenilo sustituido con 2-5 $R^x$ y al menos uno de los $R^x$ no es un halógeno. Más preferiblemente, $R^1$ es fenilo sustituido con 2-3 grupos seleccionados de F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$,

perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -O-(alquileno $C_1$-$C_6$)-halógeno, -O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -O-(alquileno $C_1$-$C_6$)-N(alquilo $C_1$-$C_6$)$_2$, -O-(alquileno $C_1$-$C_6$)-$NH_2$ y -O-(alquileno $C_1$-$C_6$)-NH(alquilo $C_1$-$C_6$), con la condición de que al menos uno de dichos 2-3 grupos no sea un halógeno.

En el quinto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es un enlace, $R^1$ es heteroarilo de 5-12 miembros y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el sexto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es un enlace, $R^1$ es heterociclilo de 3-12 miembros, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el séptimo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es un enlace, $R^1$ es cicloalquilo $C_3$-$C_{12}$ y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el octavo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -O- o -O-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es arilo $C_6$-$C_{12}$ y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el noveno aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -O- o -O-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heteroarilo de 5-12 miembros, y $R^1$ está opcionalmente sustituido

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adicionalmente con 1-5 $R^x$.

En el décimo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -O- o -O-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heterociclilo de 3-12 miembros, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimoprimer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -O- o -O-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es cicloalquilo $C_3$-$C_{12}$, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimosegundo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -NH-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es arilo $C_6$-$C_{12}$, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimotercer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -NH-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heteroarilo de 5-12 miembros, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimocuarto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -NH-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heterociclilo de 3-12 miembros, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimoquinto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -NH-(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es cicloalquilo $C_3$-$C_{12}$, y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimosexto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, donde X es -(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es arilo $C_6$-$C_{12}$ y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el decimonoveno aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heteroarilo de 5-12 miembros y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el vigésimo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente en combinación con el aspecto particular uno, dos o tres, X es -(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es heterociclilo de 3-12 miembros y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el vigesimoprimer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, especialmente junto con el aspecto particular uno, dos o tres, X es -(alquileno $C_1$-$C_3$)- sin sustituir, $R^1$ es cicloalquilo $C_3$-$C_{12}$ y $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

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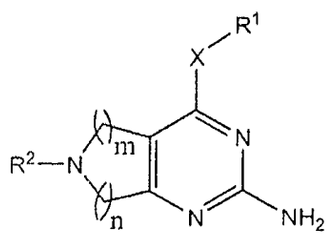
En el vigesimosegundo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, incluyendo cualquiera de los aspectos particulares uno a veintiuno, $R^2$ es -C(O)-$OR^a$ o -(alquileno $C_1$-$C_6$)-C(O)-O-$R^a$.

En el vigesimotercer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, incluyendo cualquiera de los aspectos particulares uno a veintiuno, $R^2$ es -C(O)-$N(R^a)_2$ o -(alquileno $C_1$-$C_6$)-(C(O)-$N(R^a)_2$.

En el vigesimocuarto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, incluyendo cualquiera de los aspectos particulares uno a veintiuno, $R^2$ se selecciona de -$S(O)_2$-$R^a$, -$S(O)_2$-$N(R^a)_2$, -$S(O)_2$-O-$R^a$, -(alquileno $C_1$-$C_6$)-$S(O)_2$-$R^a$, -(alquileno $C_1$-$C_6$)-$S(O)_2$-O-$R^a$ y -(alquileno $C_1$-$C_6$)-$S(O)_2$-$N(R)_2$.

En el vigesimoquinto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, incluyendo cualquiera de los aspectos particulares uno a veintiuno, $R^2$ es -C(O)-$R^b$ o -(alquileno $C_1$-$C_6$)-C(O))-$R^b$.

En otra realización, la presente invención proporciona un compuesto de fórmula I,




I

en la que:

m es 1 ó 2, n es 1 ó 2 , cuando m es 2, n es 1;

X es un enlace o un dirradical seleccionado del grupo constituido por -O- y -O-(alquileno $C_1$-$C_3$)- sin sustituir, donde cada extremo del dirradical puede estar conectado a $R^1$ o al anillo de aminopirimidina de fórmula I;

$R^1$ es fenilo, heteroarilo de 5-12 miembros o heterociclilo de 3-12 miembros;

cuando $R^1$ es fenilo, $R^1$ está sustituido adicionalmente con 2-5 grupos seleccionados de F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -O-(alquileno $C_1$-$C_6$)-halógeno, -O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -O-(alquileno $C_1$-$C_6$)-N(alquil $C_1$-$C_6$)$_2$, -O-(alquileno $C_1$-$C_6$)-$NH_2$ y -O-(alquileno $C_1$-$C_6$)-NH(alquilo $C_1$-$C_6$); y al menos uno de los sustituyentes de $R^1$ no es un halógeno;

cuando $R^1$ es heteroarilo de 5-12 miembros o heterociclilo de 3-12 miembros, $R^1$ está opcionalmente sustituido adicionalmente con 1-5 grupos seleccionados de F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -O-(alquileno $C_1$-$C_6$)-halógeno, -O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -O-(alquileno $C_1$-$C_6$)-N(alquil $C_1$-$C_6$)$_2$, -O-(alquileno $C_1$-$C_6$)-$NH_2$ y -O-(alquileno $C_1$-$C_6$)-NH(alquilo $C_1$-$C_6$);

$R^2$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)$_p$-C(O)-O-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-$R^b$ y -(alquileno $C_1$-$C_6$)$_p$-$SO_2$-$R^a$;

$R^a$ se selecciona del grupo constituido por H, alquilo $C_1$-$C_8$, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5 a 12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros) y -

(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

dos $R^a$ unidos al mismo átomo de nitrógeno, junto con el átomo de nitrógeno, pueden formar opcionalmente un heterociclilo de 3-12 miembros o un heteroarilo de 5-12 miembros; donde dicho heterociclilo de 3-12 miembros y dicho heteroarilo de 5-12 miembros están opcionalmente sustituidos adicionalmente con 1-5 grupos seleccionados de alquilo $C_1$-$C_3$, -CN, -F, -Cl, -Br, -O-(alquilo $C_1$-$C_3$) y perfluoroalquilo $C_1$-$C_3$;

$R^b$ se selecciona del grupo constituido por alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_3$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros), -(alquileno $C_1$-$C_5$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

cada $R^a$ y $R^b$ está independientemente opcional y adicionalmente sustituido con 1-5 grupos seleccionados de alquilo $C_1$-$C_3$, -CN, -F, -Cl, -Br, -O-(alquilo $C_1$-$C_3$), perfluoroalquilo $C_1$-$C_3$, -$NH_2$, -NH-(alquilo $C_1$-$C_3$), -N(alquilo $C_1$-$C_3$)$_2$ y OH;

p es 0 ó 1; o una sal farmacéuticamente aceptable del mismo.

En el primer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 1 y n es 1.

En el segundo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 1 y n es 2.

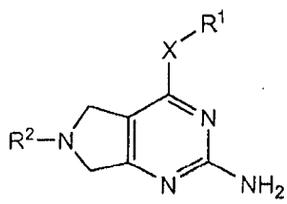
En el tercer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, m es 2 y n es 1.

En el cuarto aspecto particular de esta realización, y junto con cualquier

otro aspecto particular no incoherente, X es un enlace.

En el quinto aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, X es dirradical de -O o -O-(alquileno $C_1$-$C_3$)- sin sustituir.

En otra realización, la presente invención proporciona un compuesto de fórmula



II

en la que:

X es un enlace o un dirradical seleccionado del grupo constituido por -O-, -NH-, -S-, -(alquileno $C_1$-$C_3$)-, -O-(alquileno $C_1$-$C_3$)-, -NH-(alquileno $C_1$-$C_3$)-, -S-(alquileno $C_1$-$C_3$)-, -C(O)-, -C(O)-O, -C(O)-NH-, -OC(O)-NH-, -NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- y -$S(O)_2$-NH-, donde cada extremo del dirradical puede estar conectado a $R^1$ o al anillo de aminopirimidina de fórmula II;

cuando se permita, cada átomo de nitrógeno o carbono de X está opcionalmente sustituido adicionalmente con un grupo seleccionado de -(alquileno $C_1$-$C_3$)$_t$-CN, -(alquileno $C_1$-$C_3$)$_t$-F, -(alquileno $C_1$-$C_3$)$_t$-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_3$)$_t$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_3$)$_t$-OH, -(alquileno $C_1$-$C_3$)$_t$-$NH_2$, -(alquileno $C_1$-$C_3$)$_t$-NH(alquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_3$)$_t$-N(alquil $C_1$-$C_3$)(alquilo $C_1$-$C_3$), y t es 0 ó 1;

$R^1$ se selecciona del grupo constituido por arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros, cicloalquilo $C_3$-$C_{12}$, heterociclilo de 3-12 miembros y carbociclilo

$C_5$-$C_{12}$ insaturado no aromático, y cada $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$;

$R^2$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)$_p$-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-O-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-S(O)-$R^1$-(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$$R^a$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-N($R^a$)$_2$ y -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-O-$R^a$;

cada $R^a$ se selecciona independientemente del grupo constituido por H, alquilo $C_1$-$C_8$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5 a 12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros) y -(alquileno $C_1$-$C_6$)$_p$-(carbocicilo $C_5$-$C_{12}$ insaturado no aromático), $R^a$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$;

dos $R^a$ unidos al mismo átomo de nitrógeno, junto con el átomo de nitrógeno, pueden formar opcionalmente un heterociclilo de 3-12 miembros o un heteroarilo de 5-12 miembros; donde dicho heterociclilo de 3-12 miembros y dicho heteroarilo de 5-12 miembros están opcionalmente sustituidos adicionalmente con 1-5 $R^x$;

cada p es independientemente 0 ó 1;

cada $R^x$ se selecciona independientemente del grupo constituido por -oxo-, -(alquileno $C_1$-$C_4$)-, halógeno, -CN, -OH, alquilo $C_1$-$C_6$, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, perfluoroalquilo $C_1$-$C_6$, -(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)-OH, -(alquileno $C_1$-$C_6$)-CN, -(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquilo $C_1$-$C_6$), -

(alquileno $C_1$-$C_6$)$_q$-C(O)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-{heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-N(alquilo $C_1$-$C_6$)$_2$, -(alquileno $C_1$-$C_6$)$_q$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$- NHC(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH(alquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$) y -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-N(alquilo $C_1$-$C_3$)$_2$; q es independientemente 0 ó 1; cuando se permita, cada átomo de carbono de R* está opcionalmente sustituido adicionalmente con 1-3 flúor;

o una sal farmacéuticamente aceptable del mismo.

En el primer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, X es un enlace o un dirradical seleccionado del grupo constituido por -O- y -O-(alquileno $C_1$-$C_3$)- sin sustituir; $R^x$ se selecciona del grupo constituido por F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$,

perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -O-(alquileno $C_1$-$C_6$)-halógeno, -O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -O-(alquileno $C_1$-$C_6$)-N(alquil $C_1$-$C_6$)$_2$, -O-(alquileno $C_1$-$C_6$)-$NH_2$ y -O-(alquileno $C_1$-$C_6$)-NH(alquilo $C_1$-$C_6$. Preferiblemente, X es un enlace, $R^1$ se selecciona del grupo constituido por fenilo, heteroarilo de 5-12 miembros y heterociclilo de 3-12 miembros, $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$. Más preferiblemente, $R^1$ es fenilo opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el segundo aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, X es un dirradical -O-(alquileno $C_1$-$C_3$)-, $R^1$ es fenilo o heteroarilo de 5-12 miembros, $R^1$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En el tercer aspecto particular de esta realización, y junto con cualquier otro aspecto particular no incoherente, X es un dirradical -O-, $R^1$ es fenilo opcionalmente sustituido adicionalmente con 1-5 $R^x$.

En otra realización, la presente invención proporciona una composición farmacéutica que comprende un compuesto de fórmula I, II, III, IV, V o VI, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

En otra realización, la presente invención proporciona un uso de un compuesto de fórmula I, II, III, IV, V o VI, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para el tratamiento del cáncer.

En otra realización, la presente invención proporciona un procedimiento para modular la actividad de HSP-90, que comprende poner en contacto una

célula con un compuesto de fórmula I, II, III, IV, V o VI o una sal farmacéuticamente aceptable del mismo.

Esta invención también se refiere a un procedimiento para el tratamiento de crecimiento celular anormal en un mamífero, incluyendo un ser humano, que comprende administrar a dicho mamífero una cantidad de un compuesto de la Fórmula I, como se ha definido anteriormente o una sal farmacéuticamente aceptable o solvato del mismo, que sea eficaz para tratar el crecimiento celular anormal.

En una realización de este procedimiento, el crecimiento celular anormal es cáncer, incluyendo pero sin limitación, mesotelioma, hepatobiliar (conducto hepático y biliar), un tumor primario o secundario del SNC, un tumor cerebral primario o secundario, cáncer de pulmón (NSCLC y SCLC), cáncer de huesos, cáncer pancreático, cáncer de piel, cáncer de la cabeza o cuello, melanoma cutáneo o intraocular, cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal, cáncer de estómago, gastrointestinal (gástrico, colorrectal y duodenal), cáncer mamario, cáncer uterino, carcinoma de las trompas de Falopio, carcinoma del endometrio, carcinoma del cérvix, carcinoma de la vagina, carcinoma de la vulva, enfermedad de Hodgkin, cáncer del esófago, cáncer del intestino delgado, cáncer del sistema endocrino, cáncer de la glándula tiroides, cáncer de la glándula paratiroides, cáncer de la glándula adrenal, sarcoma de tejido blando, cáncer de la uretra, cáncer del pene, cáncer de próstata, cáncer testicular, leucemia crónica o aguda, leucemia mieloide crónica, linfomas linfocíticos, cáncer de la vejiga, cáncer del riñón o uréter, carcinoma de células renales, carcinoma de la pelvis renal, neoplasias del sistema nervioso central (SNC), linfoma del SNC primario, linfoma no Hodgkin,

tumores del eje espinal, glioma de tronco cerebral, adenoma de pituitaria, cáncer adrenocortical, cáncer de vesícula biliar, mieloma múltiple, colangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma o una combinación de uno o más de los cánceres anteriores.

En otra realización de dicho procedimiento, dicho crecimiento celular anormal es una enfermedad proliferativa benigna, que incluye, pero sin limitación, psoriasis, hipertrofia prostática benigna o reestenosis.

En una realización preferida de la presente invención el cáncer se selecciona entre cáncer de pulmón (NSCLC y SCLC), cáncer de la cabeza o cuello, cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal, cáncer de estómago, cáncer mamario, cáncer del riñón o uréter, carcinoma de células renales, carcinoma de la pelvis renal, neoplasias del sistema nervioso central (SNC), linfoma de SNC primario, linfoma no Hodgkin, tumores del eje espinal o una combinación de uno o más de los cánceres anteriores.

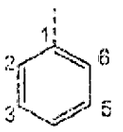
En otra realización preferida de la presente invención el cáncer se selecciona entre cáncer de pulmón (NSCLC y SCLC), cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal o una combinación de uno o más de los cánceres anteriores.

En una realización más preferida de la presente invención el cáncer se selecciona entre cáncer de pulmón (NSCLC y SCLC), cáncer ovárico, cáncer de colon, cáncer rectal o una combinación de uno o más de los cánceres anteriores.

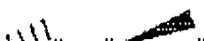
En otra realización de dicho procedimiento, dicho crecimiento celular anormal es una enfermedad proliferativa benigna, que incluye, pero sin limitación, psoriasis, hipertrofia prostática benigna o reestenosis.

Esta invención también se refiere a una composición farmacéutica para el tratamiento de crecimiento celular anormal en un mamífero, incluyendo un ser humano, que comprende una cantidad de un compuesto de la Fórmula I, como se ha definido anteriormente, o una sal farmacéuticamente aceptable o solvato del mismo, que es eficaz para tratar crecimiento celular anormal y un vehículo farmacéuticamente aceptable. En una realización de dicha composición, dicho crecimiento celular anormal es cáncer, incluyendo, pero sin limitación, mesotelioma, hepatobiliar (conducto hepático y biliar), un tumor primario o secundario del SNC, un tumor primario o secundario del cerebro, cáncer de pulmón (NSCLC y SCLC), cáncer de huesos, cáncer pancreático, cáncer de piel, cáncer de la cabeza o cuello, melanoma cutáneo o intraocular, cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal, cáncer de estómago, gastrointestinal (gástrico, colorectal y duodenal), cáncer mamario, cáncer uterino, carcinoma de las trompas de Falopio, carcinoma del endometrio, carcinoma del cérvix, carcinoma de la vagina, carcinoma de la vulva, enfermedad de Hodgkin, cáncer del esófago, cáncer del intestino delgado, cáncer del sistema endocrino, cáncer de la glándula tiroides, cáncer de la glándula paratiroides, cáncer de la glándula adrenal, sarcoma de tejido blando, cáncer de la uretra, cáncer del pene, cáncer de próstata, cáncer testicular, leucemia crónica o aguda, leucemia mieloide crónica, linfomas linfocíticos, cáncer de la vejiga, cáncer del riñón o uréter, carcinoma de células renales, carcinoma de la pelvis renal, neoplasias del sistema nervioso central (SNC), linfoma del SNC primario, linfoma no Hodgkin, tumores del eje espinal, glioma de tronco cerebral, adenoma de la pituitaria, cáncer adrenocortical, cáncer de vesícula biliar, mieloma múltiple, colangiocarcinoma, fibrosarcoma,

neuroblastoma, retinoblastoma o una combinación de uno o más de los cánceres anteriores. En otra realización de dicha composición farmacéutica, dicho crecimiento celular anormal es una enfermedad proliferativa benigna, que incluye, pero sin limitación, psoriasis, hipertrofia prostática benigna o reestenosis.

Como se usa en este documento, el símbolo [------] cuando se incorpora en la estructura química de un sustituyente significa que el átomo al que [------] está unido es el punto de unión de ese sustituyente a alguna posición de otra molécula. Por ejemplo, X en la molécula hipotética $CH_3CH$-X puede definirse como que X es 

. En cuyo caso, la situación de [------] unido a la posición numerada de forma arbitraria C-1, significa que C-1 del anillo fenilo está unida al carbono del metileno.

Los símbolos "" y "  ", cuando se usan juntos en una sola molécula sin indicación adicional de lo contrario, por ejemplo, nombre químico o descripción adjunta, simplemente indican la estereoquímica relativa de *trans* o *cis* cuando sea aplicable. El símbolo "" y el símbolo "", usados conjuntamente o por separado, en combinación con una indicación de que representan la estereoquímica absoluta, por ejemplo, una indicación de "*S*" o "*R*" en la estructura química correspondiente o el nombre químico adjunto, indican la estereoquímica absoluta del centro quiral correspondiente.

"Alifático" se refiere a hidrocarburos $C_1$-$C_{12}$ de cadena lineal, ramificados o cíclicos que están completamente saturados o que contienen una o más

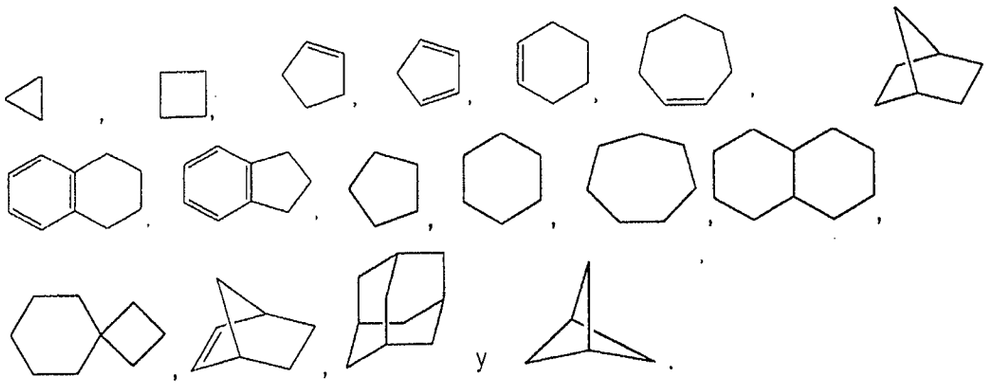
unidades de instauración pero que no son aromáticos. Los ejemplos de grupos alifáticos incluyen grupos alquilo, alquenilo y alquinilo lineales, ramificados o cíclicos e híbridos de los mismos tales como (cicloalquil)alquilo, (cicloalquenil)alquilo, etc. Un grupo alifático puede estar opcionalmente sustituido con 1-6 sustituyentes. Los sustituyentes adecuados en un grupo alifático incluyen: heterociclil arilo $C_6$-$C_{10}$ de 3-12 miembros, heteroarilo de 5-12 miembros, halógeno, -$NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, -$CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, $SO_2R$, -$SONR_2$, -$SO_2NR_2$, donde R es H, alquilo $C_1$-$C_{10}$, heterociclilo de 3-10 miembros, arilo $C_6$-$C_{10}$ o heteroarilo de 5-12 miembros.

"Alquilo $C_1$-$C_{12}$" se refiere a un radical hidrocarburo de cadena lineal o ramificada, saturado, que tiene de 1 a 12 átomos de carbono. Un grupo alquilo $C_1$-$C_{12}$ puede estar opcionalmente sustituido con al menos un sustituyente. Los sustituyentes adecuados en un grupo alquilo $C_1$-$C_{12}$ incluyen, pero sin limitación, heterociclilo de 3-12 miembros, arilo $C_6$-$C_{10}$, heteroarilo de 5-12 miembros, halógeno -$NO_2$, -$NR_2$, -CN, -COR, -COOR, -$CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, -$SO_2R$, -$SONR_2$, -$SO_2NR_2$, donde cada R es independientemente –H, alquilo $C_1$-$C_{10}$, heterociclilo de 3-12 miembros, arilo $C_6$-$C_{10}$ o heteroarilo de 5-12 miembros. Los ejemplos de grupos alquilo $C_1$-$C_{12}$ incluyen, pero sin limitación, metilo, etilo, propilo, isopropilo, butilo, sec-butilo, iso-butilo, *terc*-butilo, pentilo, neo-pentilo, sec-pentilo, hexilo, heptilo, octilo y similares, incluyendo las formas sustituidas de los mismos. Además, el término "alquilo" se refiere a un radical hidrocarburo de cadena lineal o ramificada saturado, de 1 a 20 átomos de carbono, o de 1 a 12 átomos de carbonos, o de 1 a 8 átomos de carbono, o de 1 a 6 átomos de carbono, o de 1 a 4 átomos de carbono. "Alquilo inferior" se refiere específicamente a un grupo alquilo que

tiene de 1 a 4 átomos de carbono. El alquilo puede estar sustituido o sin sustituir. Los sustituyentes adecuados en un grupo alquilo son los mismos que los descritos para un grupo alquilo $C_1$-$C_{12}$.

"Cicloalquilo" se refiere a un radical hidrocarburo saturado cíclico, que tiene de 3 a 20 átomos de carbono. Un grupo cicloalquilo puede ser monocíclico y, cuando se permita puede ser bicíclico o policíclico. Un grupo cicloalquilo puede estar opcionalmente sustituido con al menos un sustituyente. Los sustituyentes adecuados en un grupo cicloalquilo son los mismos que se han descrito para un grupo alquilo. Los ejemplo de grupos cicloalquilo incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, norbornilo, adamantilo, y similares, incluyendo las formas sustituidas de los mismos.

"Carbociclilo no aromático" se refiere a un grupo de anillo monocíclico de 3 a 12 miembros, todos carbono, un grupo de sistemas de anillos bicíclicos o multicíclicos, con todos los miembros carbono, donde uno o más de los anillos pueden contener uno o más dobles enlaces o un anillo aromático como parte del sistema de anillos bicíclicos o multicíclicos, pero el anillo monocíclico, y el sistema de anillos bicíclicos o multicíclicos no tiene un sistema de electrones pi completamente conjugados. Son ejemplos, sin limitación, de carbociclilo no aromático ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexadienilo, adamantilo, cicloheptilo, cicloheptatrienilo y similares. Un carbociclilo no aromático puede estar sustituido o sin sustituir. Los grupos sustituyentes típicos son los mismos que los del grupo alquilo, como se ha definido en este documento. Los ejemplos ilustrativos de carbociclilo no aromático se obtienen a partir de, pero sin limitación, lo siguiente:



"Carbociclilo no aromático insaturado" o "carbociclilo insaturado no aromático" se refieren un carbociclilo no aromático, como se ha definido en este documento, que contiene al menos un doble enlace carbono-carbono o un triple enlace carbono-carbono, o un anillo aromático como parte del sistema de anillos bicíclicos o multicíclicos.

"Alquenilo $C_2$-$C_{12}$" se refiere a un radical hidrocarburo insaturado, de cadena lineal o ramificada, que tiene de 2 a 12 átomos de carbono. Un grupo alquenilo $C_2$-$C_{12}$ puede tener uno o más puntos de instauración (es decir, uno o más dobles enlaces carbono-carbono). En el caso en el que el alquenilo $C_2$-$C_{12}$ tiene más de un doble enlace carbono-carbono, los dobles enlaces carbono-carbono pueden estar conjugados o no conjugados. Un grupo alquenilo $C_2$-$C_{12}$ puede estar opcionalmente sustituido con al menos un sustituyente. Los sustituyentes adecuados en un grupo alquenilo $C_2$-$C_{12}$ son los mismos que los que se han descrito para un grupo alquilo $C_1$-$C_{12}$. Los ejemplos de alquenilo $C_2$-$C_{12}$ incluyen, pero sin limitación, etenilo, 1-propenilo, 2-propenilo, 1-butenilo, 2-butenilo, iso-butenilo, y similares, incluyendo las formas sustituidas de los mismos. Además, el término "alquenilo" se refiere a un radical hidrocarburo insaturado, de cadena lineal o ramificada, que tiene de 2 a 20 átomos de carbono o de 2 a 12 átomos de carbono, o de 2 a 8 átomos de carbono, o de 2

a 6 átomos de carbono, o de 2 a 4 átomos de carbono. Un grupo alquenilo puede tener uno o más puntos de instauración (es decir, uno o más dobles enlaces carbono-carbono). En el caso en el que un grupo alquenilo tiene más de un doble enlace carbono-carbono, los dobles enlaces carbono-carbono pueden estar conjugados o no conjugados. Un grupo alquenilo puede estar sustituido o no sustituido. Los sustituyentes adecuados en un grupo alquenilo son los mismos que los que se han descrito para un grupo alquilo $C_1$-$C_{12}$.

"Alcoxi" o "alcoxilo" se refiere a $-OR^c$ donde $R^c$ es alquilo $C_1$-$C_{12}$, alquenilo $C_2$-$C_{12}$, alquinilo $C_2$-$C_{12}$, cicloalquilo $C_3$-$C_{12}$ o (alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_{12}$). Un "alcoxi $C_1$-$C_{12}$" o "alcoxilo $C_1$-$C_{12}$" se refiere a un grupo alcoxi, como se ha definido en este documento, en el que $R^c$ tiene de 1 a 12 átomos de carbono en total.

"Alcoxialquilo" se refiere a un alquilo, como se ha definido en este documento, que está sustituido con al menos un grupo alcoxi como se ha definido en este documento. Un "alquilalcoxi $C_2$-$C_6$" se refiere a un alquilalcoxi en el que el número total de carbonos del alquilo y sus sustituyentes alcoxi es de 2 a 6.

"Alquilamino" se refiere a $-NR^pR^q$ donde cada $R^p$ y $R^q$ es independientemente H, alquilo $C_1$-$C_{12}$, alquenilo $C_2$-$C_{12}$, alquinilo $C_2$-$C_{12}$, cicloalquilo $C_3$-$C_{12}$ o (alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_{12}$) con la condición de que $R^p$ y $R^q$ no sean los dos H. Un "monoalquilamino" se refiere a un grupo alquilamino, como se ha definido en este documento, en el que uno de $R^p$ y $R^q$ es H. Un "dialquilamino" se refiere a un grupo alquilamino, como se ha definido en este documento, en el que ninguno de $R^p$ y $R^q$ es H. Un "alquilamino $C_1$-$C_{12}$" se refiere a un grupo alquilamino que contiene de 1 a 10 átomos de carbono.

"Alquinilo $C_2$-$C_{12}$" se refiere a un radical hidrocarburo de cadena lineal o ramificada que tiene de 2-12 átomos de carbono y al menos un triple enlace carbono-carbono. En el caso en el que el alquinilo $C_2$-$C_{12}$ tiene más de un doble enlace carbono-carbono, los dobles enlaces carbono-carbono pueden estar conjugados o no conjugados. Un grupo alquinilo $C_2$-$C_{12}$ puede estar opcionalmente sustituido con al menos un sustituyente. Los sustituyentes adecuados en un grupo alquinilo $C_2$-$C_{12}$ son los mismos que los que se han descrito para un grupo alquilo $C_1$-$C_{12}$. Los ejemplos de alquinilo $C_2$-$C_{12}$ incluyen, pero sin limitación, etinilo, 1-propinilo, 2-propinilo, 1-butinilo, 2-butinilo, y similares, incluyendo las formas sustituidas de los mismos. Además, el término "alquinilo" se refiere a un radical hidrocarburo de cadena lineal o ramificada de 2 a 20 átomos de carbono, o de 2 a 12 átomos de carbono, o de 2 a 8 átomos de carbono, o de 2 a 6 átomos de carbono, o de 2 a 4 átomos de carbono, y que tiene al menos un triple enlace carbono-carbono. El alquinilo puede estar sustituido o sin sustituir. Los sustituyentes adecuados en un grupo alquinilo son los mismos que los que se han descrito para un grupo alquilo $C_1$-$C_{12}$.

"Amino" se refiere a $-NH_2$.

"Arilo $C_6$-$C_{10}$" se refiere a un anillo monocíclico o a un anillo policíclico con todos los miembros carbono de 6 a 10 átomos de carbono que tiene un sistema de electrones pi completamente conjugados. Un grupo arilo $C_6$-$C_{10}$ puede estar opcionalmente sustituido con al menos un sustituyente. Los sustituyentes adecuados en un grupo arilo $C_6$-$C_{10}$ son los mismos que los que se han descrito para un grupo alquilo $C_1$-$C_{12}$. Los ejemplos de arilo $C_6$-$C_{10}$ incluyen, pero sin limitación, fenilo y naftilo. Además, el término "arilo" se refiere a un anillo monocíclico o anillo policíclico con todos los miembros carbono, de 6

a 20 átomos de carbono, que tiene un sistema de electrones pi completamente conjugados. El grupo arilo puede estar sustituido o sin sustituir. Los ejemplos de arilo incluyen, pero sin limitación, antracenilo, fenantrenilo y perilenilo.

"Aralquilo" se refiere a alquilo, como se ha definido en este documento, que está sustituido con un grupo arilo $C_{6-10}$ como se ha definido anteriormente; por ejemplo $-CH_2$fenilo, $-(CH_2)_2$fenilo, $-(CH_3)_2$fenilo, $CH_3CH(CH_3)CH_2$fenilo y similares y derivados de los mismos. Un aralquilo $C_1$-$C_6$ se refiere a un alquilo $C_1$-$C_6$ que está sustituido con un grupo arilo $C_1$-$C_6$.

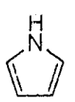
Un grupo "heteroaralquilo" se refiere a alquilo, como se ha definido en este documento, que está sustituido con un grupo heteroarilo de 5 a 12 miembros; por ejemplo, $-CH_2$piridinilo, $-(CH_2)_2$pirimidinilo, $-(CH_3)_2$imidazolilo y similares, y derivados de los mismos. Un heteroaralquilo $C_1$-$C_6$ se refiere a un alquilo $C_1$-$C_6$ que está sustituido con un grupo heteroarilo de 5-12 miembros.

"Heteroarilo" se refiere a un grupo monocíclico o de anillos condensados de 5 a 12 átomos de anillo que contiene uno, dos, tres o cuatro heteroátomos de anillo seleccionados de N, O y S, siendo los átomos restantes del anillo C, y, además, que tiene un sistema de electrones pi completamente conjugados. Son ejemplos, sin limitación, de grupos heteroarilo sin sustituir pirrol, furano, tiofeno, imidazol, oxazol, tiazol, pirazol, piridina, pirimidina, quinolina, isoquinolina, purina, tetrazol, triazina y carbazol. El grupo heteroarilo puede estar sustituido o sin sustituir. Los sustituyentes típicos incluyen alifático $C_1$-$C_{12}$, heterociclilo de 3-10 miembros, arilo de 6-10 miembros, halógeno, $-NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, $-CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, $SO_2R$, $-SONR_2$, $-SO_2NR_2$ donde R es un alifático $C_1$-$C_{10}$, heterociclilo de 3-10 miembros, arilo $C_6$-$C_{10}$ o heteroarilo de 5-10 miembros.

225

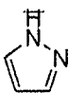
Un "heteroarilo farmacéuticamente aceptable" es uno que es suficientemente estable para unirse a un compuesto de la invención, formularse en una composición farmacéutica y posteriormente administrarse a un paciente que lo necesita.

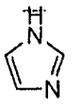
Los ejemplos de grupos heteroarilo monocíclicos típicos incluyen, pero sin limitación:


pirrol (pirrolilo)


furano (furanilo)


tiofeno (tiofenilo)


pirazol (pirazolilo)

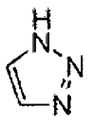

imidazol (imidazolilo)

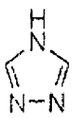

isoxazol (isoxazolilo)


oxazol (oxazolilo)


isotiazol (isotiazolilo)


tiazol (tiazolilo)


1,2,3-triazol (1,2,3,-triazolilo)


1,3,4-triazol (1,3,4-triazolilo)


1-oxa-2,3-diazol (1-oxa-2,3-diazolilo)


1-oxa-2,4-diazol (1-oxa-2,4-diazolilo)

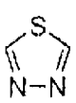

1-oxa-2,5-diazol (1-oxa-2,5-diazolilo)

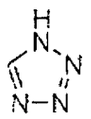

1-oxa-3,4-diazol (1-oxa-3,4-diazolilo)

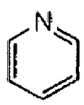

1-tia-2,3-diazol (1-tia-2,3-diazolilo)

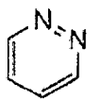

1-tia-2,4-diazol (1-tia-2,4-diazolilo)

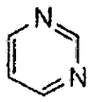

1-tia-2,5-diazol (1-tia-2,5-diazolilo)

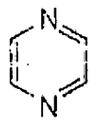

1,-tia-3,4-diazol (1,-tia-3,4-diazolilo)


tetrazol (tetrazolilo)


piridina (piridinilo)

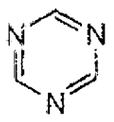

piridazina (piridazinilo)


pirimidina (pirimidinilo)



pirazina

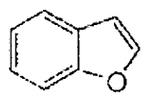
(pirazinilo)



1,3,5-triazina

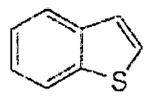
triazinilo

Los ejemplos de grupos heteroarilo bicíclicos incluyen, pero sin limitación



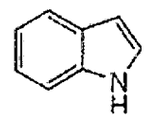
benzofurano

(benzofuranilo)



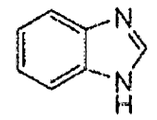
benzotiofeno

(benzotiofenilo)



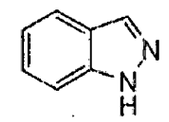
indol

(indolilo)



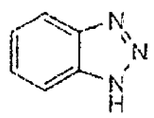
bencimidazol

(bencimidazolilo)



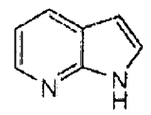
indazol

(indazolilo)



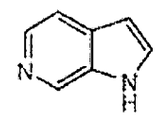
benzotriazol

(benzotriazolilo)



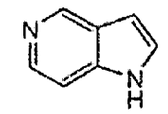
pirrol[2,3-b]piridina

(pirrol[2,3-b]piridinilo)



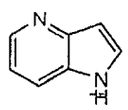
pirrol[2,3-c]piridina

(pirrol[2,3-c]piridinilo)



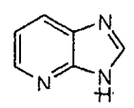
pirrol[3,2-c]piridina

(pirrol[3,2-c]piridinilo)



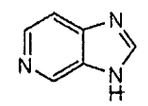
pirrol[3,2-b]piridina

(pirrol[3,2-b]piridinilo)



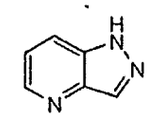
imidazol[4,5-b]piridina

(imidazol[4,5-b]piridinilo)



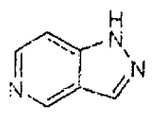
imidazol[4,5-c]piridina

(imidazol[4,5-c]piridinilo)



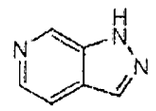
pirazol[4,3-d]piridina

(pirazol[4,3-d]piridinilo)



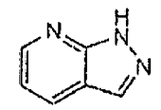
pirazol[4,3-c]piridina

(pirazol[4,3-c]piridinilo)



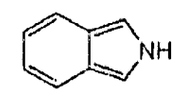
pirazol[3,4-c]piridina

(pirazol[3,4-c]piridinilo)



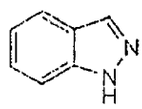
pirazol[3,4-b]piridina

(pirazol[3,4-b]piridinilo)

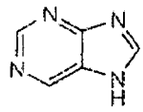


isoindol

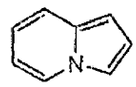
(isoindolilo)



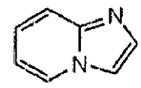
indazol (indazolilo)



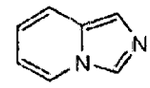
purina (purinilo)



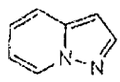
indolizina (indolinililo)



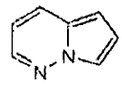
imidazol[1,2-q]piridina (imidazol[1,2-q]piridinilo)



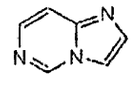
imidazol[1,5-a]piridina (imidazol[1,5-a]piridinilo)



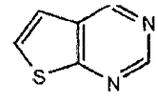
pirazol[1,5-a]piridina (pirazol[1,5-a]piridinilo)



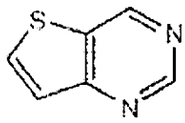
pirrol[1,2,b]piridazina (pirrol[1,2,b]piridazinilo)



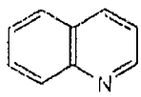
imidazol[1,2-c]pirimidina (imidazol[1,2-c]pirimidinilo)



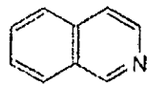
tienopirimidina (tienopirimidinilo)



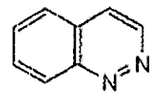
tienopirimidina (tienopirimidinilo)



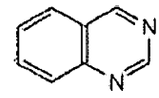
quinolina (quinolinilo)



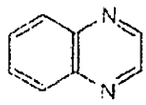
isoquinolina (isoquinolinilo)



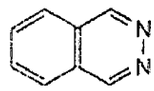
cinolina (cinolinilo)



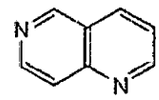
quinazolina (azaquinazolina)



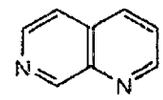
quinoxalina (quinoxalinilo)



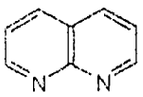
ftalazina (ftalazinilo)



1,6-naftiridina (1,6-naftiridinilo)

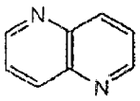


1,7-naftiridina (1,7-naftiridinilo)



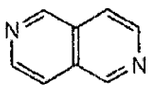
1,8-naftiridina

(1,8-naftiridinilo)



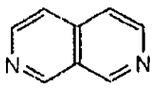
1,5-naftiridina

(1,5-naftiridinilo)



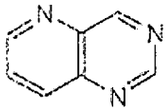
2,6-naftiridina

(2,6-naftiridinilo)



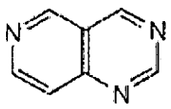
2,7-naftiridina

(2,7-naftiridinilo)



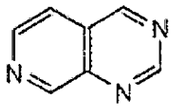
piridо[3,2d]pirimidina

(piridо[3,2d]pirimidinilo)



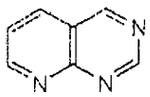
piridо[4,3-d]pirimidina

(piridо[4,3-d]pirimidinilo)



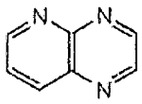
piridо[3,4-d]pirimidina

(piridо[3,4-d]pirimidinilo)



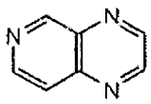
piridо[2,3-d]pirimidina

(piridо[2,3-d]pirimidinilo)



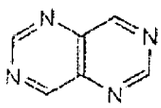
piridо[2,3-b]pirazina

(piridо[2,3-b]pirazinilo)



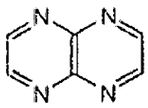
piridо[3,4-b]pirazina

(piridо[3,4-b]pirazinilo)



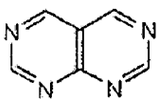
pirimido[5,4-d]pirimidina

(pirimido[5,4-d]pirimidinilo)



pirazino[2,3-b]pirazina

(pirazino[2,3-b]pirazinilo)



pirimido[4,5-d]pirimidina

(pirimido[4,5-d]pirimidinilo)

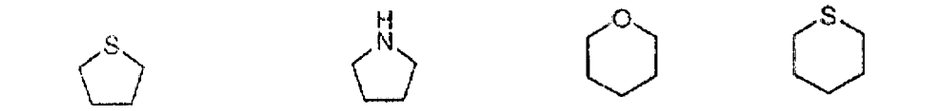
"Heteroalicíclico" o "heterociclilo" se refiere a un grupo monocíclico o policíclico que tiene de 3 a 12 átomos de anillo, donde de 1 a 4 átomos del anillo son heteroátomos seleccionados de N, O y S. "Heteroalicíclico" o "heterociclilo" también puede tener uno o más dobles enlaces. Sin embargo, "heteroalicíclico" o "heterociclilo" no tiene un sistema de electrones pi completamente conjugados. "Heteroalicíclico" o "heterociclilo" puede estar sustituido o sin sustituir. Los sustituyentes típicos incluyen, pero sin limitación, alifático $C_1$-$C_{12}$, arilo de 6-10 miembros, arilo de 6-10 miembros, halógeno, -

$NO_2$, $NH_2$, $NR_2$, -CN, -COR, -COOR, $-CONR_2$, -OH, -OR, -OCOR, -SR, -SOR, $-SO_2R$, donde R es un alquilo $C_1$-$C_{10}$, heterociclilo de 3-10 miembros, arilo $C_6$-$C_{10}$ o heteroarilo de 5-10 miembros.

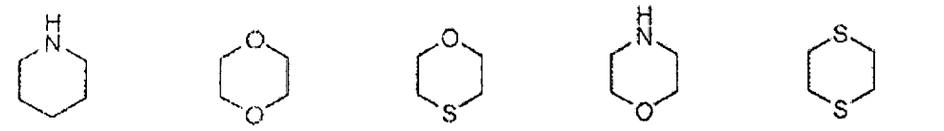
Los ejemplos de grupos heterociclilo saturados incluyen, pero sin limitación:



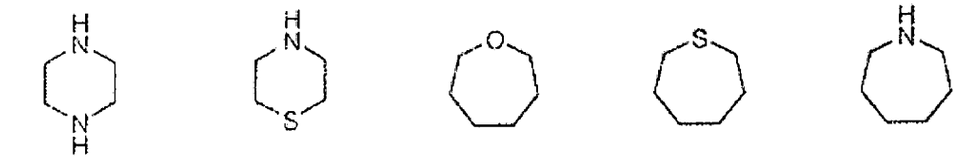
oxirano (oxiranilo) | tiarano (tiaranilo) | aziridina (aziridinilo) | oxetano | tiatano (oxetanilo) | azetidina (tiatanilo) | tetrahidrofurano (azetidinilo) (tetrahidrofuranilo)



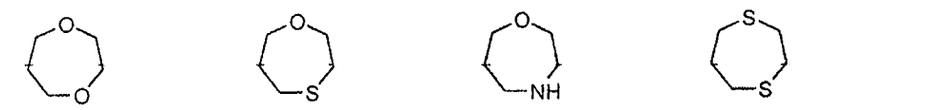
tetrahidrotiofeno (tetrahidrotiofenilo) | pirrolidona (pirrolidinilo) | tetrahidropirano (tetrahidropiranilo) | tetrahidrotiopirano (tetrahidrotiopiranilo)



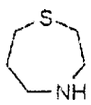
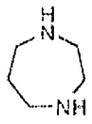
piperidina (piperidinilo) | 1,4-dioxano (1,4-dioxanilo) | 1,4-oxatiano (1,4-oxatianilo) | morfolina (morfolinilo) | 1,4-ditiano (1,4-ditianilo)



piperazina (piperazinilo) | 1,4-azatiano (1,4-azatianilo) | oxepano (oxepanilo) | tiepano (tiepanilo) | azepano (azepanilo)



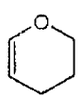
1,4-dioxepano (1,4-dioxepanilo) | 1,4-oxatiepano (1,4-oxatiepanilo) | 1,4-oxaazepano (1,4-oxaazepanilo) | 1,4-ditiepano (1,4-ditiepanilo)

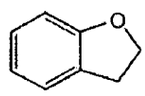





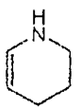
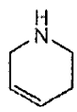
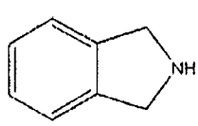
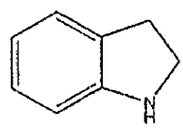
1,4-tioazepano (1,4-tioazepanilo) | 1,4-diazepano (1,4-diazepanilo) | tropano (tropanilo) | (1*S*,5*R*)-3-aza-biciclo[3.1.0]hexano (1*S*,5*R*)-3-aza-biciclo[3.1.0]hexanilo)

Ejemplos de grupos heterociclilo parcialmente insaturados incluyen, pero sin limitación:



3,4-dihidro-2H-pirano (3,4-dihidro-2H-piranilo) | 5,6-dihidro-2H-pirano (5,6-dihidro-2H-piranilo) | 2H-pirano (2H-piranilo) | 2,3-dihidrobenzofurano (2,3-dihidrobenzofuranilo)

1,2,3,4-tetrahidropiridina (1,2,3,4-tetrahidropiridinilo) | 1,2,5,6-tetrahidropiridina (1,2,5,6-tetrahidropiridinilo) | isoindolina (isoindolinilo) | indolina (indolinilo)

Un "dirradical" se refiere a un grupo que tiene dos valencias abiertas y está conectado adicionalmente a otros dos grupos, o forma un doble enlace con el mismo átomo de un grupo, o forma dos enlaces sencillos con el mismo átomo de un grupo. Son ejemplos de dirradicales, pero sin limitación, $-CH_2-$, -O-, $-O-CH_2-$, -(alquileno $C_1$-$C_3$)-NH- y $-CH_2-CH_2-$. Cuando se hace referencia a un dirradical como, por ejemplo, $-O-CH_2-$ o -(alquileno $C_1$-$C_3$)-NH-, se entiende que

cada extremo del dirradical puede conectarse igualmente a otro resto. Por ejemplo, si K se define como A-L-B, y L es un dirradical seleccionado de -O-$CH_2$-, y -(alquileno $C_1$-$C_3$)-, se entiende que K se selecciona por lo tanto de A-O-$CH_2$-B, A-$CH_2$-O-B, y A-(alquileno $C_1$-$C_3$)-B. En este documento A y B se consideran restos orgánicos diferentes.

Cuando se añade "eno" después del "il" al final de cualquiera de los términos definidos previamente para formar un nuevo término, el nuevo término se refiere a un dirradical formado retirando un átomo de hidrógeno del término original del que procede el nuevo término. Por ejemplo, un alquileno se refiere a un grupo dirradical formado retirando un átomo de hidrógeno de un grupo alquilo y un "metileno" se refiere a un radical divalente –$CH_2$- obtenido retirando un átomo de hidrógeno de metilo. Ejemplos adicionales de dichos dirradicales incluyen, pero sin limitación: alquenileno, alquinileno, cicloalquileno, fenileno, heterociclileno, heteroarileno y (carbociclileno insaturado no aromático), que se obtienen a partir de alquenilo, alquinilo, cicloalquilo, fenilo, heterociclilo, heteroarilo y (carbociclilo insaturado no aromático), respectivamente. Por ejemplo, "ciclopropileno" se refiere tanto a  , como a  . Por ejemplo, "alquileno $C_1$-$C_2$" se refiere a todos los siguientes: -$CH_2$-, -$CH(CH_3)$- y –$CH_2$-$CH_2$-.

"oxo" u "-oxo-" se refiere a una sustitución con un doble enlace de oxígeno "=O".

"Hidroxi" o "hidroxilo" se refieren a –OH.

"Perfluoroalquilo" se refiere a un grupo alquilo en el que todos los átomos de hidrógeno se han reemplazado por átomos de flúor.

"Opcional" u "opcionalmente" significa que el siguiente evento o circunstancia descrita puede producirse pero no necesariamente se produce, y que la descripción incluye casos en los que el evento o circunstancia se produce y casos en los que no. Por ejemplo, "grupo heterociclilo opcionalmente sustituido con un grupo alquilo" significa que el alquilo puede estar presente pero no necesariamente lo está, y la descripción incluye situaciones en las que el grupo heterociclilo está sustituido con un grupo alquilo y situaciones en las que el grupo heterociclilo no está sustituido con el grupo alquilo.

Cuando un grupo está "opcionalmente sustituido" u "opcionalmente sustituido adicionalmente" con algunos sustituyentes, indica un átomo de carbono o nitrógeno de este grupo en el que uno o más átomos de hidrógeno están unidos al átomo de carbono o nitrógeno, estando dicho átomo de carbono o nitrógeno opcionalmente sustituido con algunos sustituyentes distintos. Por ejemplo, "R es H, alquilo $C_1$-$C_3$ o fenilo, y R está opcionalmente sustituido adicionalmente con 1-3 grupos seleccionados de –F, oxo y perfluoroalquilo $C_1$-$C_3$" significa que R es 1) H (cuando R es H, R no puede estar sustituido adicionalmente); 2) alquilo $C_1$-$C_3$ opcionalmente sustituido adicionalmente con 1-3 grupos seleccionados de –F, oxo y perfluoroalquilo $C_1$-$C_3$, y 3) fenilo opcionalmente sustituido adicionalmente con 1-3 grupos seleccionados de –F y perfluoroalquilo $C_1$-$C_3$. La sustitución opcional de oxo no se aplica cuando R es fenilo ya que ningún átomo individual del grupo fenilo posee dos átomos de hidrógeno para ser sustituidos con oxo, es decir un enlace =O. Cuando un grupo está sustituido adicionalmente con un "-(alquileno $C_1$-$C_4$)-", significa que el "-(alquileno $C_1$-$C_4$)-", junto con átomo de nitrógeno o el átomo de carbono del grupo al que el "alquileno $C_1$-$C_4$" está unido, forma un

carbo o hetero espiro ciclo.

Una "composición farmacéutica" se refiere a una mezcla de uno o más de los compuestos descritos en este documento, o sales fisiológica/farmacéuticamente aceptables, solvatos, hidratos o profármacos de los mismos, con otros componentes químicos tales como vehículos y excipientes fisiclógica/farmacéuticamente aceptables. El propósito de una composición farmacéutica es facilitar la administración de un compuesto a un organismo.

Como se usa en este documento, un "vehículo fisiológica/farmacéuticamente aceptable" se refiere a un vehículo o diluyente que no provoca irritación significativa a un organismo y que no anula la actividad biológica ni las propiedades del compuesto administrado.

Un "excipiente farmacéuticamente aceptable" se refiere a una sustancia inerte añadida a una composición farmacéutica para facilitar adicionalmente la administración de un compuesto. Los ejemplos, sin limitación, de excipientes incluyen carbonato cálcico, fosfato cálcilo, diversos azúcares y tipos de almidón, derivados de celulosa, gelatina, aceites vegetales y polietilenglicoles.

Como se usa en este documento, la expresión "sal farmacéuticamente aceptable" se refiere a las sales que mantienen la eficacia biológica y las propiedades del compuesto de partida. Dichas sales incluyen:

(1) sales de adición de ácidos, que pueden obtenerse por reacción de la base libre del compuesto de partida con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido fosfórico, ácido sulfúrico y ácido perclórico y similares, o con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido (D) o (L)-málico, ácido maleico, ácido metanosulfónico,

ácido etanosulfónico, ácido *p*-toluenosulfónico, ácido salicílico, ácido tartárico, ácido cítrico, ácido succínico o ácido malónico y similares; o

(2) sales formadas cuando un protón ácido presente en el compuesto de partida se reemplaza por un ión metálico, por ejemplo, un ión de metal alcalino, un ión de metal alcalinotérreo, o un ión de aluminio; o se coordina con una base orgánica tal como etanolamina, dietanolamina, trietanolamina, trometamina, N-metilglucamina y similares.

"PK" se refiere a receptor proteína tirosina quinasa (RTK), tirosina quinasa no receptora o "celular" (CTK) y serina-treonina quinasa (STK).

"Modulación" o "modular" se refieren a la alteración de la actividad catalítica de RTK, CTK y STK. En particular, modular se refiere a la activación de la actividad catalítica de RTK, CTK y STK, preferiblemente la activación o inhibición de la actividad catalítica de RTK, CTK y STK, dependiendo de la concentración del compuesto o sal a la cual se expone el RTK, CTK o STK o, más preferiblemente, la inhibición de la actividad catalítica de RTL, CTK y STK.

"Actividad catalítica" se refiere a la velocidad de fosforilación de tirosina bajo la influencia, directa o indirecta, de RTK y/o CTK o la fosforilación de serina y treonina bajo la influencia, directa o indirecta, de STK.

"Poner en contacto" se refiere a juntar un compuesto de los presentes contenidos y una PK diana de una manera tal que el compuesto pueda influir en la actividad catalítica de la PK, directamente, es decir, interaccionando con la misma quinasa o indirectamente, es decir, interaccionando con otra molécula de la cual depende la actividad catalítica de la quinasa. Tal "contacto" se puede conseguir "*in vitro*", es decir, en un tubo de ensayo, una placa de petri o similar. En un tubo de ensayo, poner en contacto puede implicar sólo un compuesto y

una PK de interés o puede implicar células enteras. Las células también se pueden mantener o cultivar en placas de cultivo celular y contactarse con un compuesto en ese entorno. En este contexto, la capacidad de un compuesto particular de influir en un trastorno relacionado con PK, es decir, la $CI_{50}$ del compuesto, se puede determinar antes de intentar el uso de compuestos *in vivo* con organismos vivos más complejos. Para células fuera del organismo existen múltiples procedimientos, y son conocidos por los especialistas en la técnica, para poner las PK en contacto con los compuestos que incluyen, pero sin limitación, microinyección celular directa y numerosas técnicas de transportador transmembrana.

"*In vitro*" se refiere a procedimientos realizados en un entorno artificial tal como, por ejemplo, sin limitación, en un tubo de ensayo o medio de cultivo.

"*In vivo*" se refiere a procedimientos realizados dentro de un organismo vivo tal como, sin limitación, un ratón, rata o conejo.

"Trastorno relacionado con PK", "trastorno dirigido por PK" y "actividad de PK anormal" se refieren a una afección caracterizada por actividad catalítica inapropiada de PK, es decir, actividad disminuida o, más comúnmente, exceso de actividad, donde la PK particular puede ser una RTK, una CTK o una STK. La actividad catalítica inapropiada puede surgir como el resultado de: (1) expresión de PK en células que normalmente no expresan PK, (2) expresión de PK aumentada que conduce a proliferación, diferenciación y/o crecimiento celular indeseado o (3) expresión de PK disminuida que conduce a reducciones indeseadas en la proliferación, diferenciación y/o crecimiento celular. El exceso de actividad de una PK se refiere a amplificación del gen que codifica una PK particular o producción de un nivel de actividad de PK que se puede relacionar

con un trastorno de proliferación, diferenciación y/o crecimiento celular (es decir, a medida que el nivel de PK aumenta, la gravedad de uno o más de los síntomas del trastorno celular aumenta). Actividad disminuida es, por supuesto, lo contrario, donde la gravedad de uno o más síntomas de un trastorno celular aumenta a medida que la actividad de PK disminuye.

"Trata", "tratar" y "tratamiento" se refieren un procedimiento para aliviar o anular un trastorno celular mediado por PK y/o sus síntomas consiguientes. Con respecto particularmente al cáncer, estos términos simplemente se refieren a que la esperanza de vida de un individuo afectado con un cáncer aumentará o que uno o más de los síntomas de la enfermedad se reducirán.

"Organismo" se refiere a cualquier entidad viviente constituida al menos por una célula. Un organismo vivo puede ser tan simple como, por ejemplo, una célula eucariota única o tan complejo como un mamífero, incluyendo un ser humano.

"Cantidad terapéuticamente eficaz" se refiere a la cantidad del compuesto que se está administrando que aliviará hasta cierto punto uno o más de los síntomas del trastorno que se está tratando. Con referencia al tratamiento de cáncer, una cantidad terapéuticamente eficaz se refiere a la cantidad que tiene al menos uno de los siguientes efectos:

(1) reducir el tamaño del tumor;

(2) inhibir (es decir, retrasar hasta cierto punto, preferiblemente detener) la metástasis del tumor;

(3) inhibir hasta cierto punto (es decir, retrasar hasta cierto punto, preferiblemente detener) el crecimiento tumoral y

(4) aliviar hasta cierto punto (o, preferiblemente, eliminar) uno o más

síntomas asociados con el cáncer.

"Supervisar" se refiere a observar o detectar el efecto de poner en contacto un compuesto con una célula que expresa una PK particular. El efecto observado o detectado puede ser un cambio en el fenotipo celular, en la actividad catalítica de una PK o un cambio en la interacción de una PK con un compañero de unión natural. Las técnicas para observar o detectar tales efectos se conocen en el campo. El efecto se selecciona entre un cambio o una ausencia de cambio en un fenotipo celular, un cambio o ausencia de cambio en la actividad catalítica de dicha proteína quinasa o un cambio o ausencia de cambio en la interacción de dicha proteína quinasa con un compañero de unión natural en un aspecto final de esta invención.

"Fenotipo celular" se refiere al aspecto exterior de una célula o tejido o la función biológica de la célula o tejido. Los ejemplos, sin limitación de un fenotipo celular son tamaño celular, crecimiento celular, proliferación celular, diferenciación celular, supervivencia celular, apoptosis y captación y uso de nutrientes. Tales características fenotípicas se pueden medir mediante técnicas conocidas en el campo.

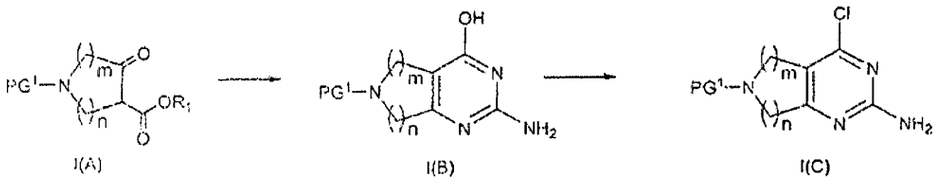
"Compañero de unión natural" se refiere a un polipéptido que se une a una PK particular en una célula. Los compañeros de unión naturales pueden jugar un papel en la propagación de una señal en un procedimiento de transducción de señal mediado por PK. Un cambio en la interacción del compañero de unión natural con la PK se puede manifestar como una concentración aumentada o disminuida del complejo PK/compañero de unión natural y, como resultado, en un cambio observable en la capacidad de la PK de mediar la transducción de señal.

El término "estereoisómero" se refiere a compuestos que tienen constitución química idéntica, pero difieren con respecto al orden de sus átomos o grupos en el espacio. En particular, el término "enantiómeros" se refiere a dos estereoisómeros de un compuesto que son imágenes especulares que no se pueden sobreponer el uno del otro. Las expresiones "racémico" o "mezcla racémica", como se usan en este documento, se refieren a una mezcla 1:1 de enantiómeros de un compuesto particular. Por otra parte, el término "diastereómeros", se refiere a la relación entre un par de estereoisómeros que comprenden dos o más centros asimétricos y no son imágenes especulares el uno del otro.

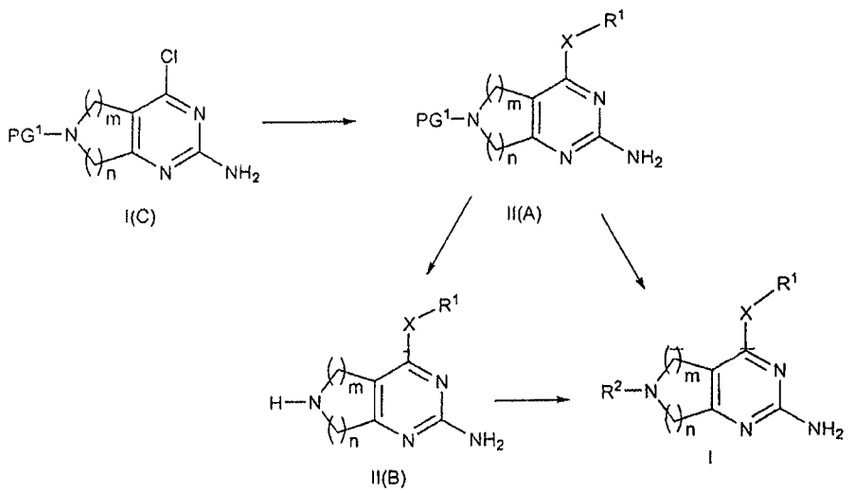
Descripción Detallada

Los compuestos de la presente invención, es decir, los compuestos de fórmula I, así como los compuestos de fórmula II, III y IV, pueden prepararse siguiendo los Esquemas de reacción 1, 2, y 3.

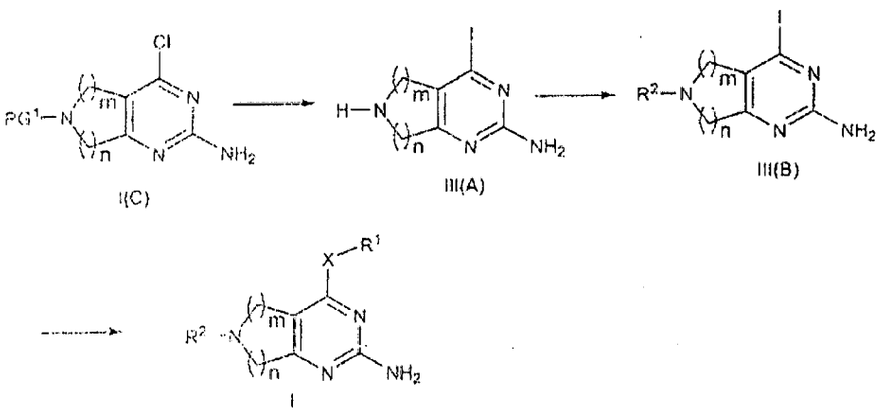
**Esquema 1**




**Esquema 2**


Cl
PG1
N
m
n
N
NH2
I(C)
R1
X
II(A)
H
II(B)
R2
I

**Esquema 3**




El Esquema 1 ilustra la síntesis del intermedio **I(C)** usado para preparar compuestos de fórmula **I.** El beta ceto éster **I(A)** puede prepararse basándose en procedimientos conocidos (véase, por ejemplo, Viscontini y Buhler *Helvetica Chimica Acta,* 50(5): 1289-93; (1967), Rosowsky et. al. *J. Heterocyclic Chem.,* 26: 509-16 (1989)). $PG^1$, el grupo protector de nitrógeno, puede seleccionarse de manera que sea compatible con la química posterior. Los grupos protectores y consideraciones generales para su uso se describen en T. Greene y P. Wuts "Protective Groups in Organic Synthesis", 3ª Edición 1999, John Wiley & Sons y se conocen bien por los especialistas en la técnica. El compuesto **I(A)** se condensa con guanidina dando el compuesto **I(B)**. Esto puede realizarse típicamente calentando el compuesto **I(A)** con guanidina o un equivalente de guanidina en un disolvente prótico. Una condición de reacción típica sería calentar a reflujo el compuesto **I(A)** con carbonato de guanidina en *terc*-butanol como disolvente. La conversión del grupo hidroxilo del compuesto **I(B)** en cloro da **I(C).** Esto puede realizarse típicamente calentando el compuesto **I(B)** con $POCl_3$ en un disolvente aprótico. Una condición de reacción típica sería calentamiento a reflujo el compuesto **I(B)** junto con un exceso de $POCl_3$ en acetonitrilo en forma pura o en acetonitrilo seco como disolvente.

El Esquema 2 ilustra la ruta a través de la cual pueden prepararse compuestos de fórmula **I** a partir del intermedio **I(C)**. En el Esquema 2, el grupo saliente cloro del compuesto **I(C)** se reemplaza por un grupo $R^1$-X- dando el compuesto **II(A)**. Esta reacción puede realizarse típicamente por desplazamiento del grupo saliente cloro usando una diversidad de nucleófilos tales como carbono, oxígeno, nitrógeno, azufre u otros nucleófilos. Una reacción de desplazamiento nucleófilo típica para la transformación del compuesto **I(C)** en el compuesto **II(A)** sería tratar el compuesto **I(C)** con un nucleófilo en presencia de una base tal como carbonato de cesio usando DMF o DMSO como disolvente para dar el compuesto **II(A)**. Como alternativa, el desplazamiento del grupo saliente cloro del compuesto **I(C)** mediante $R^1$-X- para dar el compuesto **II(A)** también puede realizarse usando una metodología de acoplamiento cruzado usando condiciones de Suzuki, Stille, Negishi o similares. Una reacción de acoplamiento cruzado típica para la transformación del compuesto **I(C)** en el compuesto **II(A)** sería tratar el compuesto **I(C)** con un ácido o éster borónico en presencia de una base tal como carbonato sódico y catalizador de Pd(0) en una mezcla de disolventes tales como agua y 1,4-dixoano para dar el compuesto **II(A)**. Después se retira el grupo protector de nitrógeno, $PG^1$, del compuesto **II(A)** dando el compuesto **II(B)**. Esto puede realizarse típicamente, cuando $PG^1$ forma un grupo protector de carbamato de etilo, calentando a reflujo el compuesto **II(A)** con yoduro de trimetilsililo en un disolvente tal como $CH_3CN$. Como alternativa, también puede usarse HBr en ácido acético o KOH en isopropanol. Una condición típica para la transformación del compuesto **II(A)** en el compuesto **II(B)** sería tratar el compuesto **II(A)** con TMSI (5 equivalentes) en $CH_3CN$ a la temperatura de

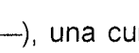
reflujo para dar el compuesto **II(B).** El resto dihidropirrolo amino del compuesto **II(B)** actúa después como un nucleófilo en reacciones con un resto $R^2$ electrófilo dando el compuesto **I.** Esta reacción nucleófila puede ser alquilación, acilación, sulfonilación y otras reacciones aplicables a alquilaminas secundarias. Una reacción de alquilación del compuesto **II(B)** puede realizarse haciendo reaccionar el compuesto **II(B)** con un resto de alquilación $R^2$. Una condición de reacción de alquilación típica es hacer reaccionar el compuesto **II(B)** con un resto de bromuro de alquilo $R^2$ en presencia de TEA a temperatura ambiente para dar el compuesto **I** en forma de un N-alquilo. Una reacción de acilación del compuesto **II(B)** puede realizarse haciendo reaccionar el compuesto **II(B)** con un resto de acilación $R^2$. Una condición de reacción de acilación típica es hacer reaccionar el compuesto **II(B)** con un resto de éster activado $R^2$ o un haluro de acilo $R^2$ en presencia de TEA para dar el compuesto **I** en forma de una amida. Otra condición de reacción de acilación típica es hacer reaccionar el compuesto **II(B)** con un resto de isocianato o equivalente de isocianato $R^2$ en presencia de TEA para dar el compuesto **I** en forma de una urea. Una reacción de sulfonilación del compuesto **II(B)** puede realizarse haciendo reaccionar el compuesto **II(B)** con un resto de sulfonilación $R^2$. Una reacción de sulfonilación típica es hacer reaccionar el compuesto **II(B)** con un resto de cloruro de sulfonilo $R^2$ en presencia de TEA para dar el compuesto **I** en forma de una sulfonamida.

Otro procedimiento para la preparación del compuesto **I** en forma de una urea toma el compuesto **II(A)**, en el que $PG^1$ forma un grupo protector de carbamato de etilo, y convierte directamente el compuesto **II(A)** en el compuesto **I.** Esta reacción puede realizarse típicamente usando una amina

nucleófila en presencia de trimetilaluminio en un disolvente tal como tolueno. Una condición típica es tratar una amina nucleófila en tolueno a 0°C con una solución de trimetilaluminio en hexanos. Después de calentar a temperatura ambiente, se añade el compuesto **II(A)** y la mezcla se calienta con radiación de microondas para preparar el compuesto **I.**

El Esquema 3 ilustra otra ruta a través de la cual pueden prepararse compuestos de fórmula **I** a partir del intermedio **I(C).** En el Esquema 3, cuando $PG^1$ forma un grupo protector de carbamato de etilo, el grupo protector $PG^1$ del compuesto **I(C)** se retira con la conversión simultánea de cloro en yodo en una sola etapa. Esto puede realizarse típicamente calentando el compuesto **I(C)** con TMSI en un disolvente aprótico. Una condición de reacción típica es calentar a reflujo el compuesto **I(C)** en $CH_3CN$ con cinco equivalentes de TMSI. Después de la activación con metanol, se obtiene el compuesto **III(A)** en forma de una sal HI. El resto de dihidropirrolo amino del compuesto **III(A)** actúa después como un nucleófilo en reacciones con un resto electrófilo $R^2$ dando el compuesto **III(B).** Esta reacción nucleófila puede ser alquilación, acilación, sulfonilación y otras reacciones aplicables a alquilaminas secundarias. Puede realizarse una reacción de alquilación del compuesto **III(A)** haciendo reaccionar el compuesto **III(A)** con un resto de alquilación $R^2$. Una condición de reacción de alquilación típica es hacer reaccionar el compuesto **III(A)** con un resto de bromuro de alquilo $R^2$ en presencia de TEA a temperatura ambiente para dar el compuesto **III(B)** en forma de un N-alquilo. Puede realizarse una reacción de acilación del compuesto **III(A)** haciendo reaccionar el compuesto **III(A)** con un resto de acilación $R^2$. Una condición de reacción de acilación típica es hacer reaccionar el compuesto **III(A)** con un resto de éster activado $R^2$ o haluro de

acilo $R^2$ en presencia de TEA para dar el compuesto **III(B)** en forma de una amida. Otra condición de reacción de acilación típica es hacer reaccionar el compuesto **III(A)** con un resto isocianato o equivalente de isocianato $R^2$ en presencia de TEA para dar el compuesto **III(B)** en forma de una urea. Puede realizarse una reacción de sulfonilación del compuesto **III(A)** haciendo reaccionar el compuesto **III(A)** con un resto de sulfonilación $R^2$. Una condición de reacción de sulfonilación típica es hacer reaccionar **III(A)** con un resto de cloruro de sulfonilo $R^2$ en presencia de TEA a 0ºC para dar el compuesto **III(B)** en forma de una sulfonamida. El grupo yodo del compuesto **III(B)** se desplaza después por $R^1$-X- usando la metodología de acoplamiento cruzado dando el compuesto **I**. Esta reacción puede realizarse típicamente usando condiciones de Suzuki, Stille, Negishi o similares. Una reacción de acoplamiento cruzado típica para la transformación del compuesto **III(B)** en el compuesto **I** sería tratar el compuesto **III(B)** con un ácido o éster borónico en presencia de una base tal como carbonato sódico y catalizador de Pd(0) en una mezcla de disolventes tales como agua y 1,4-dixoano para dar el compuesto **I**.

Los compuestos de la presente invención pueden tener átomos de carbono asimétricos. Los enlaces carbono-carbono de los compuestos de la presente invención pueden representarse en este documento usando una línea continua (—), una cuña continua (  ) o una cuña discontinua (). El uso de una línea continua para representar enlaces con átomos de carbono asimétricos pretende indicar que se incluyen todos los estereoisómeros posibles (por ejemplo, enantiómeros específicos, mezclas racémicas, etc.) en ese átomo de carbono. El uso de una cuña continua o discontinua para representar enlaces con átomos de carbono asimétricos pretende indicar que

sólo se incluye el estereoisómero mostrado. Es posible que los compuestos de la invención puedan contener más de un átomo de carbono asimétrico. En estos compuestos, el uso de una línea sólida para representar enlaces con átomos de carbono asimétricos pretende indicar que se incluyen todos los estereoisómeros posibles. Por ejemplo, a menos que se indique lo contrario, se entiende que los compuestos de la presente invención pueden existir en forma de enantiómeros y diastereómeros o en forma de racematos y mezclas de los mismos. El uso de una línea continua para representar enlaces con uno o más átomos de carbono asimétricos en un compuesto de la invención y el uso de una cuña continua o discontinua para representar enlaces con otros átomos de carbono asimétricos en el mismo compuesto pretende indicar que está presente una mezcla de diastereómeros.

Las técnicas convencionales para la preparación/aislamiento de enantiómeros individuales incluyen síntesis quiral a partir de un precursor ópticamente puro adecuado o resolución del racemato usando, por ejemplo, cromatografía líquida de alta presión (HPLC) quiral. Como alternativa, el racemato (o un precursor racémico) puede hacerse reaccionar con un compuesto ópticamente activo adecuado, por ejemplo, un alcohol o, en caso de que el compuesto contenga un resto ácido o básico, un ácido o base tal como ácido tartárico o 1-feniletilamina. La mezcla diastereomérica resultante puede separarse por cromatografía y/o cristalización fraccionada y uno o los dos diastereoisómeros pueden convertirse en el o los enantiómeros puros correspondientes por medios bien conocidos por un especialista en la técnica. Los compuestos quirales de la invención (y precursores quirales de los mismos) pueden obtenerse en forma enantioméricamente enriquecida usando

cromatografía, típicamente HPLC, sobre una resina asimétrica con una fase móvil que consta de un hidrocarburo, típicamente heptano o hexano, que contiene del 0 al 50% de isopropanol, típicamente del 2 al 20% y del 0 al 5% de una alquilamina, típicamente el 0,1% de dietilamina. La concentración del eluato produce la mezcla enriquecida. Los conglomerados estereoisoméricos pueden separarse por técnicas convencionales conocidas por los especialistas en la técnica. Véase, por ejemplo, "Stereochemistry of Organic Compounds" por E. L. Eliel (Wiley, Nueva York, 1994), cuya descripción se incorpora en este documento como referencia en su totalidad.

Cuando un compuesto de la invención contiene un grupo alquenilo o alquenileno, son posibles isómeros geométricos *cis/trans* (o Z/E). Los isómeros cis/trans pueden separarse por técnicas convencionales bien conocidas por los especialistas en la técnica, por ejemplo, cromatografía y cristalización fraccionada. Cuando los isómeros estructurales son interconvertibles a través de una barrera de baja energía, puede producirse isomería tautomérica ("tautomería"). Ésta puede tomar la forma de tautomería de protones en compuestos de la presente invención que contienen, por ejemplo, un grupo imino, ceto u oxima, o la denominada tautomería de valencia en compuestos que contienen un resto aromático. Se deduce que un compuesto individual puede mostrar más de un tipo de isomería. Dentro del alcance de la invención se incluyen todos los estereoisómeros, isómeros geométricos y formas tautoméricas de los compuestos de la invención, incluyendo compuestos que muestran más de un tipo de isomería, y mezclas de uno o más de los mismos.

Las sales de la presente invención pueden prepararse de acuerdo con procedimientos conocidos por los especialistas en la técnica. Los ejemplos de

sales incluyen, pero sin limitación, sales acetato, acrilato, bencenosulfonato, benzoato (tales como clorobenzoato, metilbenzoato, dinitrobenzoato, hidroxibenzoato y metoxibenzoato), bicarbonato, bisulfato, bisulfito, bitartrato, borato, bromuro, butino-1,4-dioato, edetato cálcico, camsilato, carbonato, cloruro, caproato, caprilato, clavulanato, citrato, decanoato, diclorhidrato, dihidrogenofosfato, edetato, edisilato, estolato, esilato, etilsuccinato, formiato, fumarato, gluceptato, gluconato, glutamato, glicolato, glicolilarsanilato, heptanoato, hexino-1,6-dioato, hexilresorcinato, hidrabamina, bromhidrato, clorhidrato, γ-hidroxibutirato, yoduro, isobutirato, isotionato, lactato, lactobionato, laurato, malato, maleato, malonato, mandelato, mesilato, metafosfato, metano-sulfonato, metilsulfato, monohidrogenfosfato, mucato, napsilato, naftaleno-1-sulfonato, naftaleno-2-sulfonato, nitrato, oleato, oxalato, pamoato (embonato), palmitato, pantotenato, fenilacetatos, fenilbutirato, fenilpropionato, ftalato, fosfato/difosfato, poligalacturonato, propanosulfonato, propionato, propiolato, pirofosfato, pirosulfato, salicilato, estearato, subacetato, suberato, succinato, sulfato, sulfonato, sulfito, tanato, tartrato, teoclato, tosilato, yoduro de trietilo y valerato.

Los compuestos de la presente invención que son de carácter básico pueden formar una gran diversidad de sales con diversos ácidos inorgánicos y orgánicos. Aunque dichas sales deben ser farmacéuticamente aceptables para la administración a animales, a menudo es deseable en la práctica aislar inicialmente el compuesto de la presente invención a partir de la mezcla de reacción en forma de una sal farmacéuticamente inaceptable y después simplemente convertir ésta última de nuevo en el compuesto de base libre por tratamiento con un reactivo alcalino y posteriormente convertir esta última base

libre en una sal de adición de ácidos farmacéuticamente aceptable. Las sales de adición de ácidos de los compuestos básicos de esta invención pueden prepararse por tratamiento del compuesto básico con una cantidad sustancialmente equivalente del ácido mineral u orgánico seleccionado en un medio disolvente acuoso o en un disolvente orgánico adecuado, tal como metanol o etanol. Después de la evaporación del disolvente, se obtiene la sal sólida deseada. La sal de ácidos deseada también puede precipitarse en una solución de la base libre en un disolvente orgánico mediante la adición de un ácido mineral u orgánico apropiado a la solución.

Los compuestos de la presente invención que son de carácter ácido pueden formar sales básicas con diversos catiónicos farmacológicamente aceptables. Los ejemplos de dichas sales incluyen las sales de metales alcalinos o de metales alcalinotérreos y, particularmente, las sales de sodio y potasio. Todas estas sales se preparan por técnicas convencionales. Las bases químicas que se usan como reactivos para preparar las sales de bases farmacéuticamente aceptables de esta invención son las que forman sales de bases no tóxicas con los compuestos ácidos de la presente invención. Dichas sales de bases no tóxicas incluyen las obtenidas a partir de cationes farmacológicamente aceptables tales como sodio, potasio, calcio y magnesio, etc. Estas sales pueden prepararse por cualquier procedimiento adecuado, por ejemplo, el tratamiento del ácido libre con una base orgánica o inorgánica, tal como una amina (primaria, secundaria o terciaria), un hidróxido de metal alcalino o un hidróxido de metal alcalinotérreo o similares. Los ejemplos ilustrativos de sales adecuadas incluyen sales orgánicas obtenidas a partir de aminoácidos, tales como glicina y arginina, amoniaco, aminas primarias,

secundarias y terciarias y aminas cíclicas, tales como piperidina, morfolina y piperazina, y sales inorgánicas obtenidas a partir de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, cinc, aluminio y litio. Estas sales también pueden prepararse por tratamiento de los compuestos ácidos correspondientes con una solución acuosa que contiene los cationes farmacológicamente aceptables deseados, y después evaporando la solución resultante a sequedad, preferiblemente a presión reducida. Como alternativa, también pueden prepararse mezclando soluciones alcanólicas inferiores de los compuestos ácidos y el alcóxido de metal alcalino deseado, y después evaporando la solución resultante a sequedad de la misma manera que antes. En cualquier caso, preferiblemente se emplean cantidades estequiométricas de reactivos con el fin de asegurar que la reacción se completa y que se obtienen rendimientos máximos del producto final deseado.

Si el compuesto de la invención es una base, la sal farmacéuticamente aceptable deseada puede prepararse por cualquier procedimiento adecuado disponible en la técnica, por ejemplo, tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, o con un ácido orgánico, tal como ácido acético, ácido maleico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, un ácido piranosidílico, tal como ácido glucurónico o ácido galacturónico, un alfa-hidroxiácido, tal como ácido cítrico o ácido tartárico, un aminoácido, tal como ácido aspártico o ácido glutámico, un ácido aromático, tal como ácido benzoico o ácido cinámico, un ácido sulfónico, tal como ácido p-toluenosulfónico o ácido etanosulfónico o similares.

En el caso de compuestos que son sólidos, entienden los especialistas en la técnica que los compuestos y sales de la invención pueden existir en diferentes formas cristalinas o polimórficas, o en una forma amorfa, incluyéndose todas esas dentro del alcance de la presente invención.

La invención también incluye compuestos de la invención marcados con isótopos, en los que uno o más átomos se reemplazan por un átomo que tiene el mismo número atómico, pero una masa atómica o un número másico diferente de la masa atómica o número másico que se encuentra normalmente de forma natural. Los ejemplos isótopos adecuados para la inclusión en los compuestos de la invención incluyen isótopos de hidrógeno tales como $^{2}H$ y $^{3}H$, de carbono tales como $^{11}C$, $^{13}C$ y $^{14}C$, de cloro tales como $^{36}Cl$, de flúor tales como $^{18}F$, de yodo tales como $^{123}I$ y $^{125}I$, de nitrógeno tales como $^{13}N$ y $^{15}N$, de oxígeno tales como $^{15}O$, $^{17}O$ y $^{18}O$, de fósforo tales como $^{32}P$, y de azufre tales como $^{35}S$. Algunos compuestos de la invención marcados con isótopos, por ejemplo, los que incorporan un isótopo radiactivo, son útiles en estudios de distribución de fármacos y/o sustratos en tejidos. Los isótopos radiactivos tritio, $^{3}H$ y carbono-14, $^{14}C$, son particularmente útiles para este propósito gracias a su facilidad de incorporación y a los rápidos medios de detección. La sustitución con isótopos más pesados tales como deuterio, $^{2}H$, puede producir ciertas ventajas terapéuticas debidas a una mayor estabilidad metabólica, por ejemplo, una mayor semivida *in vivo* o la necesidad de dosificaciones reducidas, y por lo tanto puede preferirse en algunas circunstancias. La sustitución con isótopos emisores de positrones, tales como $^{11}C$, $^{18}F$, $^{15}O$ y $^{13}N$, puede ser útil en estudios Topografía de Emisión de Positrones (PET) para examinar la ocupación del receptor por el sustrato. Los compuestos de la

invención marcados con isótopos pueden prepararse generalmente por técnicas convencionales conocidas por los especialistas en la técnica o por procedimientos análogos a los descritos en este documento, usando un reactivo marcado con isótopos apropiado en lugar del reactivo no marcado empleado de otra forma.

Los compuestos de la invención pueden existir tanto en formas no solvatadas como solvatadas. El término "solvato" se usa en este documento para describir un complejo molecular que comprende un compuesto de la invención y una cantidad de una o más moléculas de disolventes farmacéuticamente aceptables. El término "hidrato" se emplea cuando dicho disolvente es agua. Los ejemplos de formas de solvato incluyen, pero sin limitación, compuestos de la invención junto con agua, isopropopanol, etanol, metanol, dimetilsulfóxido (DMSO), acetato de etilo, ácido acético, etanolamina o mezclas de los mismos. Se contempla específicamente que, en la presente invención, una molécula de disolvente puede asociarse con una molécula de los compuestos de la presente invención, tal como un hidrato.

Además se contempla específicamente que, en la presente invención, más de una molécula de disolvente puede asociarse con una molécula de los compuestos de la presente invención, tal como un dihidrato. Además se contempla específicamente que, en la presente invención, menos de una molécula de disolvente puede asociarse con una molécula de los compuestos de la presente invención, tal como un hemihidrato. Además, los solvatos de la presente invención se contemplan como solvatos de compuestos de la presente invención que mantienen la eficacia biológica de la forma no hidrato de los compuestos.

Los profármacos de los compuestos descritos en este documento también están dentro del alcance de la invención. Por lo tanto, algunos derivados de los compuestos de la presente invención, que pueden tener poca o ninguna actividad farmacológica por sí mismos, cuando se administran en o sobre el cuerpo pueden convertirse en compuestos de la presente invención que tienen la actividad deseada, por ejemplo, por escisión hidrolítica. Dichos derivados se denominan "profármacos". Puede encontrarse información adicional sobre el uso de profármacos en Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi y W. Stella) y Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association). Por ejemplo, los profármacos de acuerdo con la invención pueden producirse reemplazando funcionalidades apropiadas presentes en los compuestos de la presente invención por ciertos restos conocidos por los especialistas en la técnica como "pro-restos" que se describen, por ejemplo, en Design Prodrugs por H. Bundgaard (Elsevier, 1985).

Algunos ejemplos de profármacos de acuerdo con la invención incluyen:

(i) cuando los compuestos de la presente invención contienen una funcionalidad ácido carboxílico (-COOH), un compuesto profármaco en el que el hidrógeno de la funcionalidad ácido carboxílico del compuesto se reemplaza por alquilo($C_1$-$C_8$) para formar el éster correspondiente;

(ii) cuando los compuestos de la presente invención contienen una funcionalidad alcohol (-OH), un compuesto profármaco en el que el hidrógeno de la funcionalidad alcohol del compuesto se reemplaza por alcanoiloximetilo ($C_1$-$C_6$) para formar el éter correspondiente; y

(iii) cuando los compuestos de la presente invención contienen una

funcionalidad amino primaria o secundaria (-$NH_2$ o –NHR donde R ≠ H), un compuesto profármaco en el que el, como puede ser el caso, uno o los dos hidrógenos de la funcionalidad amino del compuesto **I** se reemplazan por alcanoílo ($C_1$-$C_{10}$) para formar la amida correspondiente.

En las referencias mencionadas anteriormente pueden encontrarse ejemplos adicionales de grupos de reemplazo de acuerdo con los ejemplos anteriores y ejemplos de otros tipo de profármacos. Además, algunos compuestos de la presente invención pueden actuar por sí mismos como profármacos de otros compuestos de la presente invención.

También se incluyen dentro del alcance de la invención metabolitos de compuestos de la presente invención, es decir, compuestos formados *in vivo* después de la administración del fármaco. Algunos ejemplos de metabolitos de acuerdo con la invención incluyen:

(i) cuando los compuestos de la presente invención contienen un grupo metilo, un derivado de hidroximetilo del mismo (por ejemplo, -$CH_3$ -> -$CH_2OH$);

(ii) cuando los compuestos de la presente invención contienen un grupo alcoxi, un derivado de hidroxi del mismo (por ejemplo, -OR -> -OH);

(iii) cuando los compuestos de la presente invención contienen un grupo amino terciario, un derivado de amino secundario del mismo (por ejemplo, -$NR^1R^2$ -> -$NHR^1$ o -$NHR^2$);

(iv) cuando los compuestos de la presente invención contienen un grupo amino secundario, un derivado primario del mismo (por ejemplo, -$NHR^1$ -> -$NH_2$);

(v) cuando los compuestos de la presente invención contienen un resto fenilo, un derivado de fenol del mismo (por ejemplo, -Ph -> -PhOH); y

(vi) cuando los compuestos de la presente invención contienen un grupo amida, un derivado de ácido carboxílico del mismo (por ejemplo, $-CONH_2$ -> COOH).

Los compuestos de la invención deseados para uso farmacéutico pueden administrarse como productos cristalinos o amorfos, o mezclas de los mismos. Pueden obtenerse, por ejemplo, en forma de bloques sólidos, polvos o películas por procedimientos tales como precipitación, cristalización, liofilización, secado por pulverización o secado por evaporación. Para este propósito pueden usarse secado por microondas o radiofrecuencia.

Los compuestos pueden administrarse solos o en combinación con uno o más compuestos distintos de la invención, o en combinación con uno o más fármacos distintos (o cualquier combinación de los mismos). En general, se administrarán como una formulación junto con uno o más excipientes farmacéuticamente aceptables. El término "excipiente" se usa en este documento para describir cualquier ingrediente distinto del compuesto o compuestos de la invención. La elección del excipiente dependerá en gran medida de factores tales como la vía de administración particular, el efecto del excipiente sobre la solubilidad y la estabilidad, y la naturaleza de la forma farmacéutica.

Las composiciones farmacéuticas adecuadas para la liberación de compuestos de la invención y procedimientos para su preparación serán evidentes para los especialistas en la técnica. Dichas composiciones y procedimientos para su preparación pueden encontrarse, por ejemplo, en "Remington's Pharmaceutical Sciences", 19ª Edición (Mack Publishing

Company, 1995), cuya descripción se incorpora en este documento como referencia en su totalidad.

Administración Oral

Los compuestos de la invención se pueden administrar por vía oral. La administración oral puede incluir la deglución, de forma que el compuesto entre en el tracto gastrointestinal, o se puede emplear la administración bucal o sublingual mediante la cual el compuesto entra al torrente sanguíneo directamente desde la boca.

Las formulaciones adecuadas para administración oral incluyen formulaciones sólidas tales como comprimidos, cápsulas que contienen partículas, líquidos o polvos, grageas (que incluyen las llenas de líquido), caramelos masticables, multi y nanopartículas, geles, solución sólida, liposomas, películas (que incluyen mucoadhesivas), óvulos, pulverizaciones y formulaciones líquidas.

Las formulaciones líquidas incluyen suspensiones, soluciones, jarabes y elíxires. Tales formulaciones se pueden usar como cargas en cápsulas suaves o duras y típicamente incluyen un vehículo, por ejemplo, agua, etanol, polietilén glicol, propilen glicol, metilcelulosa o un aceite adecuado y uno o más agentes emulsificantes y/o agentes de suspensión. Las formulaciones líquidas también se pueden preparar mediante la reconstitución de un sólido, por ejemplo, a partir de una bolsita.

Los compuestos de la invención también se pueden usar en formas farmacéuticas de disolución rápida y de disgregación rápida tales como las que se describen en Expert Opinion in Therapeutic Patents, 11 (6), 981-986 por Liang y Chen (2001), cuya descripción se incorpora en este documento como

referencia en su totalidad.

Para formas farmacéuticas de comprimidos, dependiendo de la dosis, el fármaco puede formar del 1% en peso al 80% en peso de la forma farmacéutica y más típicamente del 5% en peso al 60% de la forma farmacéutica. Además del fármaco, los comprimidos generalmente contienen un disgregante. Los ejemplos de disgregantes incluyen almidón glicolato de sodio, carboximetilcelulosa de sodio, carboximetilcelulosa de calcio, croscarmelosa sódica, crospovidona, polivinilpirrolidona, metilcelulosa, celulosa microcristalina, hidroxipropil celulosa sustituida con alquilo inferior, almidón, almidón pregelatinizado y alginato de sodio. En general, el disgregante comprenderá del 1% en peso al 25% en peso, preferiblemente del 5% en peso al 20% en peso de la forma farmacéutica.

Generalmente se usan aglutinantes para impartir cualidades cohesivas a una formulación de comprimido. Los aglutinantes adecuados incluyen celulosa microcristalina, gelatina, azúcares, polietilén glicol, gomas naturales y sintéticas, polivinilpirrolidona, almidón pregelatinizado, hidroxipropil celulosa e hidroxipropil metilcelulosa. Los comprimidos también pueden contener diluyentes, tales como lactosa (monohidrato, monohidrato secado por pulverización, anhidra y similares), manitol, xilitol, dextrosa, sucrosa, sorbitol, celulosa microcristalina, almidón y fosfato de calcio dibásico dihidrato.

Los comprimidos también pueden incluir opcionalmente agentes tensioactivos, tales como lauril sulfato de sodio y polisorbato 80 y emolientes tales como dióxido de silicio y talco. Cuando están presentes, los agentes tensioactivos están típicamente en cantidades del 0,2% en peso al 5% en peso del comprimido y los emolientes típicamente del 0,2% en peso al 1% en peso del

comprimido.

Los comprimidos generalmente también contienen lubricantes tales como estearato de magnesio, estearato de calcio, estearato de zinc, estearil fumarato de sodio y mezclas de estearato de magnesio con lauril sulfato de sodio. Los lubricantes generalmente están presentes en cantidades del 0,25% en peso al 10% en peso y preferiblemente del 0,5% en peso al 3% en peso del comprimido.

Otros ingredientes convencionales incluyen antioxidantes, colorantes, agentes saporíferos, conservantes y agentes enmascarantes del sabor.

Los comprimidos ilustrativos contienen hasta aproximadamente el 80% en peso del fármaco, de aproximadamente el 100% en peso a aproximadamente el 90% en peso de aglutinante, de aproximadamente el 0% en peso a aproximadamente el 85% en peso de diluyente, de aproximadamente el 2% en peso a aproximadamente el 10% en peso de disgregante y de aproximadamente el 0,25% en peso a aproximadamente el 10% en peso de lubricante.

Las mezclas de comprimidos se pueden comprimir directamente o mediante rodillo para formar comprimidos. Las mezclas de comprimidos o partes de las mezclas alternativamente se pueden someter a granulación húmeda, seca o por fusión, coagularse por fusión o extruirse antes de la formación del comprimido. La formulación final puede incluir una o más capas y puede estar revestida o no revestida o encapsulada.

La formulación de comprimidos se describe con detalle en "Pharmaceutical Dosage Forms: Tablets, Vol. 1", por Lieberman y L. Lachman, Marcel Dekker, N. Y., N. Y., 1980 (ISBN 0-8247-6918-X), cuya descripción se incorpora en este

documento como referencia en su totalidad.

Las formulaciones sólidas para administración oral se pueden formular para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil, controlada, dirigida y programada.

Las formulaciones de liberación modificada adecuadas se describen en la Patente de Estados Unidos Nº 6.106.864. Los detalles de otras tecnologías de liberación adecuadas tales como dispersiones de energía alta y partículas osmóticas y revestidas se pueden encontrar en Verma *y col*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). El uso de goma de mascar para conseguir liberación controlada se describe en el documento WO 00/35298. Las descripciones de estas referencias se incorporan en este documento como referencia en sus totalidades.

Administración Parenteral

Los compuestos de la invención también se pueden administrar directamente en el torrente sanguíneo, en el músculo o en un órgano interno. Los medios adecuados para administración parenteral incluyen intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracraneal, intramuscular y subcutánea. Los dispositivos adecuados para administración parenteral incluyen inyectores de aguja (que incluyen microagujas), inyectores sin aguja y técnicas de infusión.

Las formulaciones parenterales típicamente son soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos y agentes tampón (preferiblemente a un pH de 3 a 9), pero, para algunas aplicaciones, las mismas se pueden formular más adecuadamente como una solución estéril no

acuosa o como una forma seca para usarse junto con un vehículo adecuado tal como agua estéril sin pirógenos.

La preparación de formulaciones parenterales en condiciones estériles, por ejemplo, mediante liofilización, se puede conseguir fácilmente usando técnicas farmacéuticas convencionales conocidas por los especialistas en la técnica.

La solubilidad de compuestos de la invención usados en la preparación de soluciones parenterales se puede aumentar mediante el uso de técnicas de formulación apropiadas, tales como la incorporación de agentes potenciadores de solubilidad.

Las formulaciones para administración parenteral se pueden formular para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil, controlada, dirigida y programada. Por tanto, los compuestos de la invención se pueden formular como un sólido, semisólido o líquido tixotrópico para administración como un depósito implantado proporcionando liberación modificada del compuesto activo. Los ejemplos de tales formulaciones incluyen endoprótesis vasculares revestidas con fármaco y microesferas de PGLA.

Administración Tópica

Los compuestos de la invención también se pueden administrar tópicamente a la piel o mucosa, es decir, por vía dérmica o transdérmica. Las formulaciones típicas para este propósito incluyen geles, hidrogeles, lociones, soluciones, cremas, pomadas, polvos de uso externo, apósitos, espumas, películas, parches dérmicos, obleas, implantes, esponjas, fibras, vendas y microemulsiones. También se pueden usar liposomas. Los vehículos típicos

incluyen alcohol, agua, aceite mineral, vaselina líquida, vaselina blanca, glicerina, polietilén glicol y propilen glicol. Se pueden incorporar potenciadores de penetración; véase, por ejemplo, J. Pharm Sci, 88 (10), 955-958 por Finnin y Morgan (octubre de 1999). Otros medios de administración tópica incluyen administración mediante electroporación, iontoferesis, fonoforesis, sonoforesis e inyección con microaguja o sin aguja (por ejemplo, Powderject™, Bioject™, etc). Las descripciones de estas referencias se incorporan en este documento como referencia en sus totalidades.

Las formulaciones para administración tópica se pueden formular para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil, controlada, dirigida y programada.

Administración Inhalada/Intranasal

Los compuestos de la invención también se pueden administrar por vía intranasal o mediante inhalación, típicamente en forma de un polvo seco (solo, como una mezcla, por ejemplo, en una mezcla seca con lactosa o como una partícula de componente mezclado, por ejemplo, mezclado con fosfolípidos, tales como fosfatidilcolina) desde un inhalador de polvo seco o como una pulverización en aerosol a partir de un recipiente, bomba, pulverizador, atomizador (preferiblemente un atomizador que usa electrohidrodinámica para producir una bruma fina) o nebulizador presurizado, con o sin el uso de un propulsor adecuado, tal como 1,1,1,2-tetrafluoroetano o 1,1,1,2,3,3,3-heptafluoropropano. Para uso intranasal, el polvo puede incluir un agente bioadhesivo, por ejemplo, chitosan o ciclodextrina.

El recipiente, bomba, pulverizador, atomizador o nebulizador presurizado

contiene una solución o suspensión del compuesto o los compuestos de la invención que comprende, por ejemplo, etanol, etanol acuoso o un agente alternativo adecuado para dispersar, solubilizar o prolongar la liberación del activo, un propulsor o propulsores como disolvente y un tensioactivo opcional, tal como trioleato de sorbitán, ácido oleico o un ácido oligoláctico.

Antes del uso en una formulación de polvo seco o suspensión, el producto de fármaco se micronizа hasta un tamaño adecuado para administración mediante inhalación (típicamente menos de 5 micrómetros). Esto se puede conseguir mediante cualquier procedimiento triturador apropiado, tal como molienda por chorro en espiral, molienda por chorro en lecho fluido, procesamiento de fluido supercrítico para formar nanopartículas, homogeneización de alta presión o secado por pulverización.

Las cápsulas (hechas, por ejemplo, de gelatina o HPMC), blísteres y cartuchos para uso en un inhalador o insuflador se pueden formular para contener una mezcla en polvo del compuesto de la invención, una base en polvo adecuada tal como lactosa o almidón y un modificador de rendimiento tal como *l*-leucina, manitol o estearato de magnesio. La lactosa puede ser anhidra o en forma del monohidrato, preferiblemente el segundo. Otros excipientes adecuados incluyen dextrano, glucosa, maltosa, sorbitol, xilitol, fructosa, sucrosa y trehalosa.

Una formulación en solución adecuada para uso en un atomizador usando electrohidrodinámica para producir una bruma fina puede contener de 1 μg a 20 mg del compuesto de la invención por accionamiento y el volumen de accionamiento puede variar de 1 μl a 100 μl. Una formulación típica incluye un compuesto de la invención, propilen glicol, agua estéril, etanol y cloruro de

sodio. Los disolventes alternativos que se pueden usar en lugar de propilen glicol incluyen glicerol y polietilén glicol.

Se pueden añadir sabores adecuados, tales como mentol y levomentol o edulcorantes, tales como sacarina o sacarina de sodio, a las formulaciones de la invención pretendidas para administración inhalada/intranasal.

Las formulaciones para administración inhalada/intranasal se pueden formular para ser de liberación inmediata y/o modificada usando, por ejemplo, ácido poli(DL-láctico-coglicólico) y (PGLA). Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil, controlada, dirigida y programada.

En el caso de inhaladores y atomizadores de polvo seco, la unidad de dosificación se determina por medio de una válvula que administra una cantidad medida. Las unidades de acuerdo con la invención típicamente se disponen para administrar una dosis medida o "descarga" que contiene una cantidad deseada del compuesto de la invención. La dosis diaria global se puede administrar en una dosis única o, más habitualmente, como dosis divididas a lo largo del día.

Administración Rectal/Intravaginal

Los compuestos de la invención se pueden administrar por vía rectal o vaginal, por ejemplo, en forma de un supositorio, supositorio vaginal o enema. La manteca de cacao es una base de supositorio tradicional, pero se pueden usar diversas alternativas según sea apropiado.

Las formulaciones para administración rectal/vaginal se pueden formular para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil,

controlada, dirigida y programada.

Administración Ocular

Los compuestos de la invención también se pueden administrar directamente al ojo u oído, típicamente en forma de gotas de una suspensión micronizada o solución en solución salina estéril isotónica de pH ajustado. Otras formulaciones adecuadas para administración ocular y aural incluyen pomadas, implantes biodegradables (por ejemplo, esponjas de gel absorbible, colágeno) y no biodegradables (por ejemplo, silicona), obleas, lentes y sistemas particulados o vesiculares, tales como niosomas o liposomas. Se puede incorporar un polímero tal como ácido poliacrílico reticulado, alcohol polivinílico, ácido hialurónico, un polímero celulósico, por ejemplo, hidroxipropilmetilcelulosa, hidroxietilcelulosa o metil celulosa o un polímero heteropolisacárido, por ejemplo, goma gelan, junto con un conservante, tal como cloruro de benzalconio. Tales formulaciones también se pueden administrar mediante iontoforesis.

Las formulaciones para administración ocular/aural se pueden formular para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, sostenida, pulsátil, controlada, dirigida o programada.

Otras Tecnologías

Los compuestos de la invención se pueden combinar con entidades macromoleculares solubles, tales como ciclodextrina y derivados adecuados de las mismas o polímeros que contienen polietilen glicol, para mejorar su solubilidad, velocidad de disolución, enmascaramiento del sabor, biodisponibilidad y/o estabilidad para uso en cualquiera de los modos de

administración mencionados anteriormente.

Por ejemplo, se observa que los complejos fármaco-ciclodextrina son generalmente útiles para la mayoría de formas farmacéuticas y vías de administración. Se pueden usar complejos tanto de inclusión como de no inclusión. Como una alternativa a la formación de complejos directa con el fármaco, la ciclodextrina se puede usar como un aditivo auxiliar, es decir, como un vehículo, diluyente o solubilizante. Las más comúnmente usadas para estos propósitos son ciclodextrinas alfa, beta y gamma, cuyos ejemplos se pueden encontrar en las Publicaciones PCT Nº WO 91/11172, WO 94/02518 y WO 98/55148, cuyas descripciones se incorporan en este documento como referencia en sus totalidades.

La cantidad del compuesto activo administrado dependerá del sujeto que se esté tratando, la gravedad del trastorno o afección, la cantidad de administración, la disposición del compuesto y la discreción del médico tratante. Sin embargo, una dosis eficaz típicamente está en el intervalo de aproximadamente 0,001 a aproximadamente 100 mg por kg de peso corporal por día, preferiblemente aproximadamente 0,01 a aproximadamente 35 mg/kg/día, en dosis únicas o divididas. Para un ser humano de 70 kg, esto equivaldría a aproximadamente 0,07 a aproximadamente 7000 mg/día, preferiblemente aproximadamente 0,7 a aproximadamente 2500 mg/día. En algunos casos, los niveles de dosis inferiores al límite inferior del intervalo mencionado anteriormente pueden ser más que adecuados, mientras que en otros casos se pueden usar incluso dosis mayores sin causar ningún efecto secundario dañino, dividiendo tales dosis más grandes típicamente en varias dosis más pequeñas para administración a lo largo del día.

Esta invención también se refiere a un procedimiento para el tratamiento de crecimiento celular anormal en un mamífero que comprende administrar a dicho mamífero una cantidad de un compuesto de la presente invención o una sal o solvato del mismo, que sea eficaz para tratar crecimiento celular anormal en combinación con un agente antitumoral seleccionado del grupo constituido por inhibidores mitóticos, agentes alquilantes, antimetabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de respuesta biológica, anticuerpos, citotóxicos, antihormonas y antiandrógenos.

En una realización de la presente invención el agente antitumoral usado junto con un compuesto de la presente invención y composiciones farmacéuticas descritas en este documento es un agente anti-angiogénesis, un inhibidor de quinasa, un inhibidor de pan quinasa o un inhibidor del factor de crecimiento. Los inhibidores de pan quinasa preferidos incluyen Sutent™ (sunitinip), descrito en la Patente de Estados Unidos Nº 6.573.293 (Pfizer, Inc, NY. EE.UU.). Los agentes anti-angiogénesis incluyen, pero sin limitación, los siguientes agentes, tales como inhibidores de EGF, inhibidores de EGFR, inhibidores de VEGF, inhibidores de VEGFR, inhibidores de TIE2, inhibidores de IGF1R inhibidores de COX-II (ciclooxigenasa II), inhibidores de MMP-2 (metaloproteinasa de matriz 2) e inhibidores de MMP-9 (metaloproteinasa de matriz 9).

Los inhibidores de VEGF preferidos, incluyen por ejemplo, Avastin (bevacizumab), un anticuerpo monoclonal anti VEGF de Genentech, Inc. del Sur de San Francisco, California. Los inhibidores de VEGF adicionales incluyen CP-547.632 (Pfizer., N.Y. EE.UU.), AG13736 (Pfizer Inc.), ZD-6474

(AstraZeneca), AEE788 (Novartis), AZD-2171, VEGF Trap (Regeneron/Aventis), Vatalanib (también conocido como PTK-787, ZK-222584: Novartis & Schering AG), Macugen (octasodio de pegaptanib, NX-1838, EYE-001, Pfizer Inc./Gilead/Eyetech), IM862 (Cytran Inc. de Kirkland, Washington, EE.UU.) y angiozima, una ribozima sintética de Ribozyme (Boulder, Colorado) y Chiron (Emeryville, California) y combinaciones de los mismos.

Los inhibidores de VEGF útiles en la práctica de la presente invención se describen en las Patentes de Estados Unidos Nº 6.534.524 y 6.235.764, de las cuales ambas se incorporan en su totalidad para todos los propósitos. Los inhibidores de VEGF adicionales se describen en, por ejemplo, los documentos WO 99/24440, en WO 95/21613, WO 99/61422, la Patente de Estados Unidos Nº 5.834.504, el documento WO 98/50356, la Patente de Estados Unidos Nº 5.883.113, Patente de Estados Unidos Nº 5.886.020, Patente de Estados Unidos Nº 5.792.783, Patente de Estados Unidos Nº 6.653.308, los documentos WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438, WO 99/16755 y WO 98/02437, los cuales se incorporan en este documento como referencia en su totalidad.

Otros compuestos anti-angiogénicos incluyen acitretina, fenretinida, talidomida, ácido zoledrónico, angiostatina, aplidina, cilengtida, combretastina A-4, endostatina, halofuginona, rebimastat, removab, Revlimid, escualamina, ukraina, Vitaxina y combinaciones de los mismos.

Otros agentes antiproliferativos que se pueden usar en combinación con los compuestos de la presente invención incluyen inhibidores de la enzima farnesil protein transferasa e inhibidores del receptor tirosina quinasa PDGFr, incluyendo los compuestos descritos y reivindicados en los siguientes: Patente

de Estados Unidos Nº 6.080.769; Patente de Estados Unidos Nº 6.194.438; Patente de Estados Unidos Nº 6.258.824; Patente de Estados Unidos Nº 6.586.447; Patente de Estados Unidos Nº 6.071.935; Patente de Estados Unidos Nº 6.495.564 y Patente de Estados Unidos Nº 6.150.377; Patente de Estados Unidos Nº 6.596.735; Patente de Estados Unidos Nº 6.479.513; los documentos WO 01/40217 y US 2003-0166675. Cada una de las patentes y solicitudes de patente anteriores se incorporan en este documento como referencia en su totalidad.

Los inhibidores de PDGRr incluyen, pero sin limitación, los que se describen en las publicaciones de solicitud de patente internacional Nº WO 01/40217 y WO 2004/020431, cuyos contenidos se incorporan en su totalidad para todos los propósitos. Los inhibidores de PDGFr preferidos incluyen CP-673.451 y CP-868.596 de Pfizer y sus sales.

Los inhibidores de GARF preferidos incluyen AG-2037 de Pfizer (pelitrexol y sus sales). Los inhibidores útiles de GARF en la práctica de la presente invención se describen en la Patente de Estados Unidos Nº 5.608.082 que se incorpora en su totalidad para todos los propósitos.

Los ejemplos de inhibidores de COX-II útiles que se pueden usar junto con un compuesto de Formula (I) y composiciones farmacéuticas descritas en este documento incluyen CELEBREX™ (celecoxib), parecoxib, deracoxib, ABT-963, MK-663 (etoricoxib), COX-189 (Lumiracoxib), BMS 347070, RS 57067, NS-398, Bextra (valdecoxib), paracoxib, Vioxx (rofecoxib), SD-8381, 4-metil-2-(3,4-dimetilfenil)-1-(4-sulfamoil-fenil)-1H-pirrolo, 2-(4-etoxifenil)-4-metil-1-(4-sulfamoilfenil)-1H-pirrolo, T-614, JTE-522, S-2474, SVT-2016, CT-3, SC-58125 y Arcoxia (etoricoxib). Adicionalmente, se describen inhibidores de COX-II en

las Solicitudes de Patente de Estados Unidos US 2005-0148627 y US 2005-0148777, cuyos contenidos se incorporan es su totalidad para todos los propósitos.

En una realización particular el agente anti-tumoral es celecoxib (Patente de Estados Unidos Nº 5.466.823), valdecoxib (Patente de Estados Unidos Nº 5.633.272), parecoxib (Patente de Estados Unidos Nº 5.932.598), deracoxib (Patente de Estados Unidos Nº 5.521.207), SD-8381 (Patente de Estados Unidos Nº 6.034.256, Ejemplo 175), ABT-963 (documento WO 2002/24719), rofecoxib (CAS Nº 162011-90-7), MK-663 (o etoricoxib) como se describe en el documento WO 1998/03484, COX-189 (Lumiracoxib) como se describe en el documento WO 1999/11605, BMS-347070 (Patente de Estados Unidos Nº 6.180.651), NS-398 (CAS 123653-11-2), RS 57067 (CAS 17932-91-3), 4-metil-2-(3,4-dimetilfenil)-1-(4-sulfamoil-fenil)-1H-pirrolo, 2-(4-etoxifenil)-4-metil-1-(4-sulfamoilfenil)-1H-pirrolo o meloxicam.

Otros inhibidores útiles como agentes antitumorales usados en combinación con un compuesto de la presente invención y composiciones farmacéuticas descritas en este documento incluyen aspirina y fármacos anti-inflamatorios no esteroideos (AINE) que inhiben la enzima que forma las prostaglandinas (ciclooxigenasa I y II), dando como resultado niveles más bajos de prostaglandinas, incluyen pero sin limitación los siguientes, Salsalato (Amigesic), Diflunisal (Dolobid), Ibuprofén (Motrin), Ketoprofén (Orudis), Nabumetona (Relafen), Piroxicam (Feldene), Naproxeno (Aleve, Naprosyn), Diclofenaco (Voltaren), Indometacina (Indocin), Sulindac (Clinoril), Tolmetina (Tolectin), Etodolac (Lodine), Ketorolac (Toradol), Oxaprozina (Daypro) y combinaciones de los mismos.

Los inhibidores de COX-I preferidos incluyen ibuprofén (Motrin), nuprin, naproxeno (Aleve), indometacina (Indocin), nabumetona (Relafen) y combinaciones de los mismos.

Los agentes dirigidos usados en combinación con un compuesto de la presente invención y composiciones farmacéuticas descritas en este documento incluyen inhibidores de EGFr tales como Iressa (gefitinib, AstraZeneca), Tarceva (erlotinib u OSI-774, OSI Pharmaceuticals Inc.), Erbitux (cetuximab, Imclone Pharmaceuticlas, Inc), EMD-7200 (Merck AG), ABX-EGF (Amgen Inc. y Abgenix Inc.), HR3 (Gobierno Cubano), anticuerpos IgA (Universidad de Erlangen-Nuremberg), TP-38 (IVAX) proteína de fusión de EGFR, vacuna de EGF, inmunoliposomas anti-EGFr (Hermes Biosciences Inc) y combinaciones de los mismos. Los inhibidores de EGFr preferidos incluyen Iressa, Erbitux, Tarceva y combinaciones de los mismos.

Otros agentes antitumorales incluyen los seleccionados entre inhibidores de receptor de pan Erb o inhibidores de receptor ErbB2, tales como CP-724.714 (Pfizer, Inc), CI-1033 (canertinib, Pfizer, Inc), Herceptin (trastuzumab, Genentech Inc.), Omitarg (2C4, pertuzumab, Genentech Inc.), TAK-165 (Takeda), GW-572016 (lonafarnib, GlaxoSmithKline), GW-282974 (GlaxoSmith Kline), EKB-569 (Wyeth), PKI-166 (Novartis), dHER2 (Vacuna de HER2, Corixa y GlaxoSmithKline), APC8024 (Vacuna de HER2, Dendreon), anticuerpo biespecífico anti-HER2/neu (Decof Cancer Center), B7.her2.IgG3 (Agensys), AS HER2 (Research Institute for Rad Biology & Medicine), anticuerpos biespecíficos trifuncionales (Universidad de Munich) y mAB AR-209 (Aronex Pharmaceuticals Inc) y mAB 2B-1 (Chiron) y combinaciones de los mismos.

Los agentes anti-tumorales selectivos de erb preferidos incluyen

Herceptin, TAK-165, CP-724.714, ABX-EGF, HER3 y combinaciones de los mismos. Los inhibidores de receptor de pan erbb preferidos incluyen GW572016, CI-1033, EKB-569 y Omitarg y combinaciones de los mismos.

Los inhibidores de erbB2 adicionales incluyen los que se describen en los documentos WO 98/02434, WO 99/35146, WO 99/35132, WO 98/02437, WO 97/13760, WO 95/19970, Patente de Estados Unidos Nº 5.587.458 y Patente de Estados Unidos Nº 5.877.305 cada uno de los cuales se incorpora en este documento como referencia en su totalidad. Los inhibidores de receptor erbB2 útiles en la presente invención también se describen en las Patentes de Estados Unidos Nº 6.465.449 y 6.284.764 y en el documento WO 2001/98277 cada uno de los cuales se incorpora como referencia en este documento en su totalidad.

Adicionalmente, se pueden seleccionar otros agentes anti-tumorales a partir de los agentes siguientes, BAY-43-9006 (Onyx Pharmaceuticals Inc.), Genasense (augmerosen, Genta), Panitumumab (Abgenix/Amgen), Zevalin (Schering), Bexxar (Corixa/GlaxoSmithKline), Abarelix, Alimta, EPO 906 (Novartis), discodermolida (XAA-296), ABT-510 (Abbott), Neovastat (Aeterna), enzastaurina (Eli Lilly), Combrestatina A4P (Oxigene), ZD-6126 (AstraZeneca), flavepiridol (Aventis), CYG-202 (Cyclacel), AVE-8062 (Aventis), DMXAA (Roche/Antisoma), Thymitaq (Eximias), Temodar (temozolomida, Schering Plough) y Revilimd (Celegene) y combinaciones de los mismos.

Otros agentes anti-tumorales se pueden seleccionar entre los agentes siguientes, CyPat (acetato de ciproterona), Histerelin (acetato de histrelina), Plenaixis (abarelix depot), Atrasentan (ABT-627), Satraplatin (JM-216), talomida (Thalidomide), Theratope, Temilifene (DPPE), Abl-007 (paclitaxel),

Evista (raloxifeno), Atamestane (Biomed-777), Xyotax (poliglutamato de paclitaxel), Targetin (bexarotina) y combinaciones de los mismos.

Adicionalmente, se pueden seleccionar otros agentes anti-tumorales entre los agentes siguientes, Trizaone (tirapazamina), Aposyn (exisulind), Nevastat (AE-941), Ceplene (diclorhidrato de histamina), Orathecin (rubitecan), Virulizin, Gastrimmune (G17DT), DX-8951f (mesilato de exatecan), Onconase (ranpirnasa), BEC2 (mitumoab), Xcytrin (motexafin gadolinio) y combinaciones de los mismos.

Se pueden seleccionar agentes anti-tumorales adicionales entre los agentes siguientes, CeaVac (CEA), NeuTrexin (glucuronato de trimetresato) y combinaciones de los mismos. Se pueden seleccionar agentes anti-tumorales adicionales entre los siguientes agentes, OvaRex (oregovomab), Osidem (IDM-1) y combinaciones de los mismos. Se pueden seleccionar agentes anti-tumorales adicionales entre los siguientes agentes, Advexin (ING 201), Tirazona (tirapazamina) y combinaciones de los mismos. Se pueden seleccionar agentes anti-tumorales adicionales entre los siguientes agentes, RSR13 (efaproxiral), Cotara (131I chTNT 1/b), NBI-3001 (IL-4) y combinaciones de los mismos. Se pueden seleccionar agentes anti-tumorales adicionales entre los siguientes agentes, Canvaxina, vacuna de GMK, PEG Intron A, Taxoprexina (DHA/paclitaxel) y combinaciones de los mismos.

Otros agentes anti-tumorales incluyen inhibidor de MEK1/2 de Pfizer PD325901, inhibidor de MEK de Array Biopharm ARRY-142886, inhibidor de CDK2 de Bristol-Myers BMS-387.032, inhibidor de CDK de Pfizer PD0332991 y AXD-5438 de AstraZeneca y combinaciones de los mismos.

Adicionalmente, también se pueden utilizar inhibidores de mTOR tales como

CCI-779 (Wyeth) y derivados de rapamicina RAD001 (Novartis) y AP-23573 (Ariad), inhibidores de HDAC, SAHA (Merck Inc./Aton Pharmaceuticals) y combinaciones de los mismos. Los agentes anti-tumorales adicionales incluyen inhibidor de aurora 2 VX-680 (Vertex) e inhibidor de Chk1/2 XL844 (Exilixis).

Los siguientes agentes citotóxicos, por ejemplo, uno o más seleccionados del grupo constituido por epirubicina (Ellence), docetaxel (Taxotere), paclitaxel, Zinecard (dexrazoxano), rituximab (Rituxan), mesilato de imatinib (Gleevec) y combinaciones de los mismos, se pueden usar en combinación con un compuesto de la presente invención y composiciones farmacéuticas descritas en este documento.

La invención también contempla el uso de los compuestos de la presente invención junto con terapia hormonal, incluyendo pero sin limitación, exemestano (Aromasin, Pfizer Inc.), leuprorelina (Lupron o Leuplin, TAP/Abbott/Takeda), anastrozol (Arimidex,Astrazeneca), gosrelina (Zoladex, AstraZeneca), doxercalciferol, fadrozol, formestano, citrato de tamoxifeno (tamoxifen, Nolvadex, AstraZeneca), Casodex (AstraZeneca), Abarelix (Praecis), Trelstar y combinaciones de los mismos.

La invención también se refiere al uso de compuestos de la presente invención junto con agentes de terapia hormonal tales como anti-estrógenos que incluyen, pero sin limitación, fulvestrant, toremifeno, raloxifeno, lasofoxifeno, letrozol (Femara, Novartis), anti-andrógenos tales como bicalutamida, flutamida, mifepristona, nilutamida, Casodex™ (4'-ciano-3-(4-fluorofenilsulfonil)-2-hidroxi-2-metil-3'-(trifluorometil) propionanilida, bicalutamida) y combinaciones de los mismos.

Además, la invención proporciona un compuesto de la presente invención solo

o en combinación con uno o más productos de cuidados paliativos, por ejemplo, un producto seleccionado del grupo constituido por Filgrastim (Neupogen), ondansetrón (Zofran), Fragmin, Procrit, Aloxi, Emend o combinaciones de los mismos.

Los agentes citotóxicos particularmente preferidos incluyen Camptosar, Erbitux, Iressa, Gleevec, Taxotere y combinaciones de los mismos.

Los siguientes inhibidores de topoisomerasa I se pueden utilizar como agentes anti-tumorales: camptotecina; irinotecán HCl (Camptosar); edotecarina; oratecina (Supergen); exatecan (Daiichi); BN-80915 (Roche) y combinaciones de los mismos. Los inhibidores de topoisomerasa II particularmente preferidos incluyen epirubicina (Ellence).

Los agentes alquilantes incluyen, pero sin limitación, *N*-óxido de nitrógeno mostaza, ciclofosfamida, ifosfamida, melfalán, busulfán, mitobronitol, carbocuona, tiotepa, ranimustina, nimustina, temozolomida, AMD-473, altretamina, AP-5280, apazicuona, brostalicina, bendamustina, carmustina, estramustina, fotemustina, glufosfamida, ifosfamida, KW-2170, mafosfamida y mitolactol; compuestos alquilantes coordinados con platino que incluyen, pero sin limitación, cisplatino, Paraplatin (carboplatino), eptaplatino, lobaplatino, nedaplatino, Eloxatina (oxaliplatino, Sanofi) o satrplatino y combinaciones de los mismos. Los agentes alquilantes particularmente preferidos incluyen Eloxatin (oxaliplatino).

Los antimetabolitos incluyen pero sin limitación, metotrexato, 6-mercaptopurina ribósido, mercaptopurina, 5-fluorouracilo (5-FU) solo o en combinación con leucovorin, tegafur, UFT, doxifluridina, carmofur, citarabina, ocfosfato de citarabina, enocitabina, S-1, Alimta (premetrexed disódico, LY231514, MTA),

Gemzar (gemcitabina, Eli Lilly), fludarabina, 5-azacitidina, capecitabina, cladribina, clofarabina, decitabina, eflornitina, etinilcitidina, arabinósido de citosina, hidroxiurea, TS-1, melfalán, nelarabina, nolatrexed, ocfosfato, premetrexed disódico, pentostatina, pelitrexol, raltitrexed, triapina, trimetrexato, vidarabina, vincristina, vinorelbina o, por ejemplo, uno de los antimetabolitos preferidos descritos en la Solicitud de Patente Europea Nº 239362 tales como ácido *N*-(5-[*N*-(3,4-dihidro-2-metil-4-oxoquinazolin-6-ilmetil)-*N*-metilamino]-2-tenoil)-L-glutámico y combinaciones de los mismos.

Los antibióticos incluyen antibióticos intercalantes e incluyen, pero sin limitación: aclarubicina, actinomicina D, amrubicina, anamicina, adriamicina, bleomicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina, galarubicina, idarubicina, mitomicina C, nemorubicina, neocarzinostatina, peplomicina, pirarubicina, rebecamicina, estimalamer, estreptozocina, valrubicina, zinostatina y combinaciones de los mismos.

Las sustancias anti-tumorales obtenidas de plantas incluyen, por ejemplo, las seleccionadas entre inhibidores mitóticos, por ejemplo vinblastina, docetaxel (Taxotere), paclitaxel y combinaciones de los mismos.

Los agentes citotóxicos que inhiben topoisomerasa incluyen uno o más agentes seleccionados del grupo constituido por aclarubicina, amonafida, belotecan, camptotecina, 10-hidroxicamptotecina, 9-aminocamptotecina, diflomotecan, irinotecán HCl (Camptosar), edotecarina, epirubicina (Ellence), etopósido, exatecan, gimatecan, lurtotecan, mitoxantrona, pirarubicina, pixantrona, rubitecan, sobuzoxano, SN-38, tafluposida, topotecán y combinaciones de los mismos.

Los agentes citotóxicos que inhiben topoisomerasa preferidos incluyen uno o

más agentes seleccionados del grupo constituido por camptotecina, 10-hidroxicamptotecina, 9-aminocamptotecina, irinotecán HCl (Camptosar), edotecarina, epirubicina (Ellence), etopósido, SN-38, topotecán y combinaciones de los mismos.

Los agentes inmunológicos incluyen interferones y muchos otros agentes potenciadores inmunes. Los interferones incluyen interferón alfa, interferón alfa-2a, interferón, alfa-2b, interferón beta, interferón gamma-1a, interferón gamma-1b (Actimmune) o interferón gamma-n1 y combinaciones de los mismos. Otros agentes incluyen filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleuquina, alemtuzumab, BAM-002, dacarbazina, daclizumab, denileuquina, gemtuzumab ozogamicina, ibritumomab, imiquimod, lenograstim, lentinan, vacuna de melanoma (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleuquina, timalfasina, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pemtumomab (Y-muHMFG1), Provenge (Dendreon) y combinaciones de los mismos.

Los modificadores de la respuesta biológica son agentes que modifican los mecanismos de defensa de organismos vivos o respuestas biológicas, tales como supervivencia, crecimiento o diferenciación de células de tejidos para dirigirlos hacia una actividad antitumoral. Tales agentes incluyen krestin, lentinan, sizofiran, picibanil, ubenimex y combinaciones de los mismos.

Otros agentes anticancerígenos que se pueden usar en combinación con un compuesto de la presente invención incluyen alitretinoina, ampligen, atrasentan bexaroteno, bortezomib, Bosentan, calcitriol, exisulind, finasterida, fotemustina, ácido ibandrónico, miltefosina, mitoxantrona, l-asparaginasa, procarbazina, decarbazina, hidroxïcarbamida, pegaspargasa, pentostatina, tazarotne, Telcyta

(TLK-286, Telik Inc.), Velcade (bortemazib, Millenium), tretinoina y combinaciones de los mismos.

Los compuestos coordinados con platino incluyen pero sin limitación, cisplatino, carboplatino, nedaplatino, oxaliplatino y combinaciones de los mismos.

Los derivados de camptotecina incluyen pero sin limitación camptotecina, 10-hidroxicamptotecina, 9-aminocamptotecina, irinotecán, SN-38, edotecarina, topotecán y combinaciones de los mismos.

Otros agentes antitumorales incluyen mitoxantrona, l-asparaginasa, procarbazina, dacarbazina, hidroxicarbamida, pentostatina, tretinoina y combinaciones de los mismos.

También se pueden utilizar agentes antitumorales capaces de potenciar respuestas inmunes antitumorales, tales como anticuerpos CTLA4 (antígeno linfocítico citotóxico 4) y otros agentes capaces de bloquear CTLA4, tales como MDX-010 (Medarex) y compuestos de CTLA4 descritos en la Patente de Estados Unidos Nº 6.682.736 y agentes antiproliferativos tales como otros inhibidores de farnesil proteína transferasa, por ejemplo los inhibidores de farnesil proteína transferasa. Adicionalmente, los anticuerpos específicos de CTLA4 que se pueden usar en combinación con compuestos de la presente invención incluyen los que se describen en las Patentes de Estados Unidos Nº 6.682.736 y 6.682.736 las cuales se incorporan en este documento como referencia en su totalidad.

Los anticuerpos específicos de IGF1R que se pueden usar en los procedimientos de combinación de la presente invención incluyen los que se describen en el documento WO 2002/053596, que se incorpora en este documento como referencia en su totalidad.

Los anticuerpos específicos de CD40 que se pueden usar en la presente invención incluyen los descritos en el documento WO 2003/040170 que se incorpora como referencia en este documento en su totalidad.

También se pueden emplear agentes de terapia génica tales como agentes antitumorales tales como TNFerade (GeneVec), que expresa TNFalfa en respuesta a radioterapia.

En una realización de la presente invención se pueden usar estatinas en combinación con un compuesto de la presente invención y composiciones farmacéuticas de los mismos. Las estatinas (inhibidores de HMG-CoA reductasa) se pueden seleccionar del grupo constituido por Atorvastatina (Lipitor™, Pfizer Inc.), Provastatina (Pravachol™, Bristol-Myers Squibb), Lovastatina (Mevacor™, Merck Inc.), Simvastatina (Zocor™, Merck Inc.), Fluvastatina (Lescol™, Novartis), Cerivastatina (Baycol™, Bayer), Rosuvastatina (Crestor™, AstraZeneca), Lovostatina y Niacina (Advicor™, Kos Pharmaceuticals), derivados y combinaciones de los mismos.

En una realización preferida la estatina se selecciona del grupo constituido por Atorvastatina y Lovastatina, derivados y combinaciones de los mismos. Otros agentes útiles como agentes anti-tumorales incluyen Caduet.

Puesto que puede ser deseable administrar una combinación de compuestos activos, por ejemplo, con el propósito de tratar una enfermedad o afección particular, está dentro del alcance de la presente invención que dos o más composiciones farmacéuticas, al menos una de las cuales contiene un compuesto de acuerdo con la invención, se pueden combinar de forma conveniente en forma de un kit adecuado para co-administración de las composiciones. Por tanto, el kit de la invención incluye dos o más

composiciones farmacéuticas separadas, de las cuales al menos una contiene un compuesto de la invención y medios para conservar dichas composiciones por separado, tales como un recipiente, botella dividida o bolsa de aluminio dividida. Un ejemplo de un kit de este tipo es el paquete de blíster familiar usado para el empaquetamiento de comprimidos, cápsulas y similares.

El kit de la invención es particularmente adecuado para administrar diferentes formas farmacéuticas, por ejemplo, orales y parenterales, para administrar las composiciones separadas a intervalos de dosificación diferentes o para titular las composiciones separadas una frente a otra. Para ayudar al cumplimiento de la terapia por parte del paciente, el kit típicamente incluye direcciones para administración y puede estar provisto de un recordatorio.

Ejemplos

En los siguientes ejemplos las moléculas con un centro quiral único, a menos que se indique otra cosa o se indique por la fórmula estructural o nombre químico, existen en forma de una mezcla racémica. Estas moléculas con dos o más centros quirales, a menos que se indique otra cosa o se indique por la fórmula estructural o nombre químico, existen en forma de una mezcla racémica de diastereómeros. Pueden obtenerse enantiómeros/diastereómeros individuales por procedimientos conocidos por los especialistas en la técnica.

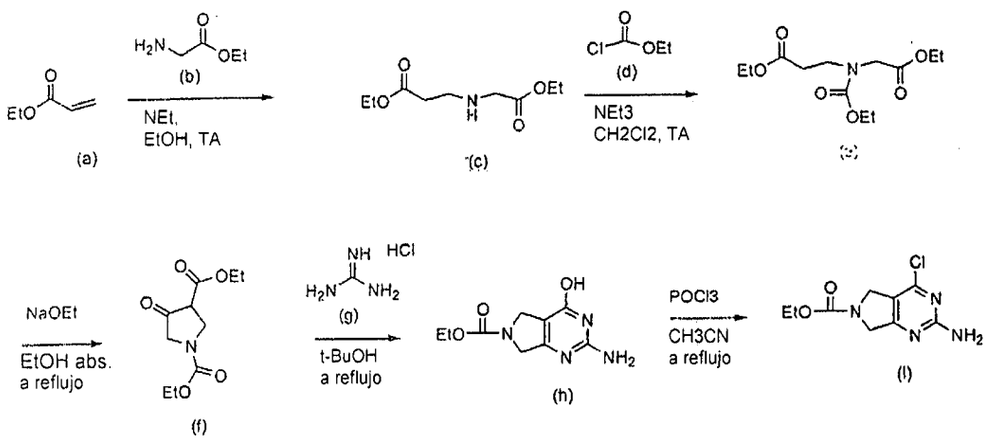
Los espectros de $^{1}H$ RMN se recogieron en un instrumento Bruker que funcionaba a 300 MHz o 400 MHz y los espectros de $^{13}C$ RMN se recogieron funcionando a 75 MHz.

En este documento pueden usarse las siguientes abreviaturas: $Et_2O$ (éter dietílico); DMF (*N,N*-dimetilformamida); THF (tetrahidrofurano); DCM (diclorometano); DMA (dimetil acetal); DBU (1,8-diazabiciclo[5.4.0]undec-7-

eno); LiHMDS o LHMDS (hexametildisilazida de litio); TBME (*terc*-butil metil éter); LDA (diisopropilamida de litio); DMSO (dimetilsulfóxido); MeOH (metanol); EtOH (etanol); BuOH (butanol); EtOAc (acetato de etilo); THF (tetrahidrofurano); Ac (acetilo); Me (metilo); Et (etilo); Ph (fenilo); TMSI (yoduro de trimetilsililo); DSC (carbonato de *N,N'*-disuccinimidilo); CDI (1,1'-carbonildiimidazol); Boc (*terc*-butoxicarbonilo); nBuLi (n-butil litio), EDC (clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida); HOBt (*N*-hidroxibenzitriazol hidrato); DME (1,2-dimetoxietano); $Pd(dba)_2$ (bis(dibencilidenoacetona)paladio (0)); y TA o ta (temperatura ambiente).

**Preparación del Compuesto (i): 2-amino-4-cloro-5,7-dihidro-6*H*-pirrolo[3,4-*d*]pirimidina-6-carboxilato de etilo.**

El Intermedio (f) se preparó en tres etapas usando procedimientos conocidos (véase, por ejemplo Viscontini y Buhler *Helvetica Chimica Acta,* 50 (5): 1289-93; (1967)) y después se convirtió en el compuesto (i) en dos etapas adicionales.




**Etapa 1. *N*-(etoxicarbonil)-*β*-alaninato de etilo (c)**

Se agitaron acrilato de etilo (a) (50 ml, 460 mmol, 1,1 equiv.), clorhidrato del éster etílico de glicina (b) (58,4 g, 418 mmol, 1 equiv.) y trietilamina (58,3 ml,

418 mmol, 1 equiv.) en EtOH absoluto (960 ml) a temperatura ambiente durante aproximadamente 72 h. Después de que se completara la reacción, los componentes volátiles se retiraron al vacío y el intermedio en bruto (c) se llevó a continuación directamente.

**Etapa 2. *N*-(etoxicarbonil)-*N*-(2-etoxi-2-oxoetil)-β-alaninato de etilo (e)**

El intermedio (c) en bruto (418 mmol) se disolvió en $CH_2Cl_2$ (275 ml) y se añadió trietilamina (58,3 ml, 418 mmol) seguido de cloroformiato de etilo (d) (39,8 ml, 418 mmol). La reacción se agitó a temperatura ambiente durante aproximadamente 24 h. Después de que se completara la reacción, los componentes volátiles se retiraron al vacío. Después, el producto en bruto se destiló al vacío (aproximadamente 5 mm Hg) y se disolvió en EtOAc que se lavó con $KHSO_4$ acuoso saturado x 3, con salmuera x 1 y se secó sobre $Na_2SO_4$. Después de la filtración, los componentes volátiles se retiraron al vacío, produciendo el intermedio (e) en forma de un aceite transparente (74,8 g, 272 mmol) con un rendimiento del 65% en dos etapas.

**Etapa 3. 4-oxopirrolidina-1,3-dicarboxilato de dietilo (f)**

Se añadió el Intermedio (e) (18,0 g, 65,2 mmol) a una solución enfriada en un baño de hielo de NaOEt (32,6 ml) (al 21% en peso en EtOH) en EtOH absoluto (41,7 ml) en atmósfera de nitrógeno. El baño de hielo se retiró y la mezcla se calentó a 80°C durante aproximadamente 12 h hasta que la condensación se completo como se observó por TLC. La mezcla se vertió en hielo/agua y se extrajo en EtOAc. El disolvente se secó con $Na_2SO_4$, se filtró y se evaporo, produciendo el intermedio (f) en bruto en forma de un sólido de color blanquecino (14,05 g) que se llevó a continuación sin purificación.

**Etapa 4. 2-amino-4-hidroxi-5,7-dihidro-6*H*-pirrolo[3,4-*d*]pirimidina-6-**

**carboxilato de etilo (h)**

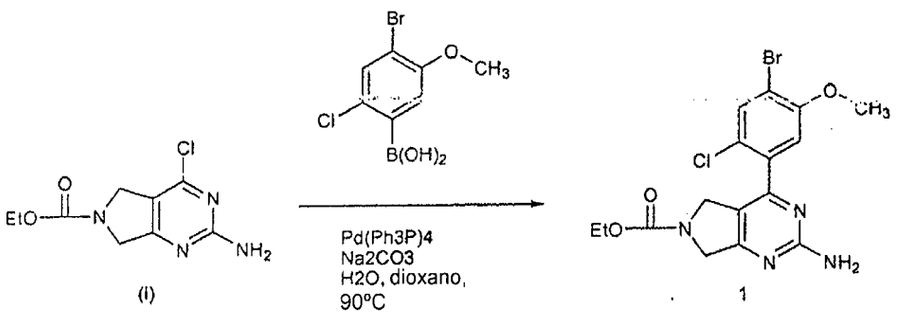
Una suspensión del intermedio (f) (14,05 g) y carbonato de guanidina (g) (16,6 g, 91,9 mmol) se calentó a reflujo en t-butanol (147 ml) durante aproximadamente 6 h. La mezcla se dejó enfriar a temperatura ambiente durante aproximadamente 2 h. Los componentes se retiraron al vacío y se añadió agua. El pH se ajustó a aproximadamente 6-7 usando $KHSO_4$. La suspensión resultante se filtró para recoger los sólidos que se lavaron con agua seguido de EtOAc. Los sólidos se secaron al vacío, produciendo el intermedio (h) en forma de un sólido de color crema (11,9 g, 53,1 mmol) con un rendimiento del 87%. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 11,01 (s, 1H), 6,97 (s, 0,5H, posible tautómero), 6,70 (s, 2H), 4,25 (s, 4H), 4,13-4,03 (m, 2H), 1,22 (t, 3H). LCMS $(M+H)^+$: 225,2.

**Etapa 5. 2-amino-4-cloro-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo (i)**

El Intermedio (h) (11 g, 49 mmol) se destiló azeotrópicamente x 2 con tolueno en el evaporador rotatorio para garantizar la sequedad. Se añadieron acetonitrilo anhidro (250 ml) y $POCl_3$ (25 ml, 270 mmol) y la mezcla se calentó a reflujo durante aproximadamente 2,5 h. Se añadió más cantidad de $POCl_3$ (50 ml) y la mezcla se calentó a reflujo durante 2 h más. Los componentes volátiles se concentraron al vacío a 40°C, dando una solución de color rojo. Se añadió una cantidad mínima de acetonitrilo seco hasta que la solución pudo transferirse fácilmente, después de lo cual se vertió sobre hielo en un vaso de precipitados grande. El matraz se aclaró adicionalmente con una pequeña cantidad de acetonitrilo que se añadió al hielo. Se añadió agua (aproximadamente 50 ml) a la mezcla de hielo para facilitar la agitación. Se

añadió lentamente $NH_4OH$ concentrado (25 ml) con agitación hasta que la mezcla en suspensión de hielo fue fuertemente básica, y después a la suspensión también se le añadió NaOH acuoso al 50% (25 ml) mientras permanecía en agitación con hielo. Se añadió más cantidad de hielo. Después de aproximadamente 5 minutos de agitación en forma de suspensión en hielo, se añadió EtOAc. Después de agitar en el vaso de precipitados durante varios minutos más, se añadió agua para facilitar la fusión del hielo. La mezcla se vertió en un embudo de decantación y las fases se dejaron separar. La fase acuosa se extrajo con EtOAc x 3. Los extractos de EtOAc combinados se lavaron x 2 con $KHSO_4$ acuoso saturado, con $NaHCO_3$ acuoso saturado x 2, con salmuera x 1, se secaron sobre $Na_2SO_4$, se filtraron y se evaporaron, produciendo un polvo de color rosa pálido que se trituró con acetato de etilo, dando el compuesto (i) en forma de sólidos de color rosa pálido (6,8 g, 28 mmol) con un rendimiento del 57%. La pureza de HPLC/LCMS fue mayor del 90%. $^1H$ RMN (400 MHz, DMSO-D6) $\delta$ ppm 7,20 (s, 2H), 4,48 (s, 2H), 4,45 (s, 2H), 4,17-4,08 (m, 2H), 1,24 (t, 3H). LCMS $(M+H)^+$: 243,2, 245,2.

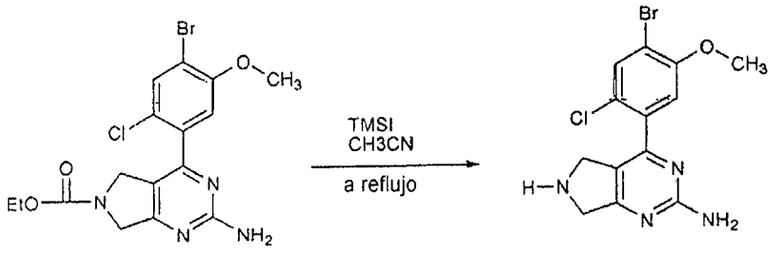
**Ejemplo 1: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




Al compuesto (i) (437 mg, 1,80 mmol), ácido (4-bromo-2-cloro-5-

metoxifenil)borónico (340 mg, 1,28 mmol) y carbonato sódico (382 mg, 3,60 mmol) en un matraz de fondo redondo purgado con Ar se le añadieron 1,4-dioxano (8,6 ml) y agua (5,2 ml). Antes de la adición, se había burbujeado Ar a través de ambos disolventes para producir la desoxigenación. Después, se añadió *tetraquis*(trifenilfosfina)paladio (220 mg, 0,19 mmol) y se burbujeó Ar a través de la mezcla usando una aguja y un tapón de goma durante aproximadamente 3 min, momento en el que la aguja de Ar se retiró y la mezcla se puso en un baño de aceite a 90°C y se calentó durante 2,5 h. Después de enfriar a temperatura ambiente, se añadió agua y el sólido resultante se recogió por filtración. El sólido se lavó con agua x 2 y EtOAc x 2 y se secó a 35°C durante 72 h para producir el compuesto del título **1** (300 mg, 0,70 mmol) en forma de un polvo de color castaño. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 7,88 (s, 1H), 7,16 (s, 1H), 6,98 (s a, 2H), 4,55-4,47 (m, 2H), 4,39-4,32 (m, 2H), 4,17-4,03 (m, 2H), 3,87 (s, 3H), 1,27-1,15 (m, 3H). LCMS $(M+H)^+$: 429,0, 427,2.

**Ejemplo 2: 4-(4-bromo-2-cloro-5-metoxifenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**

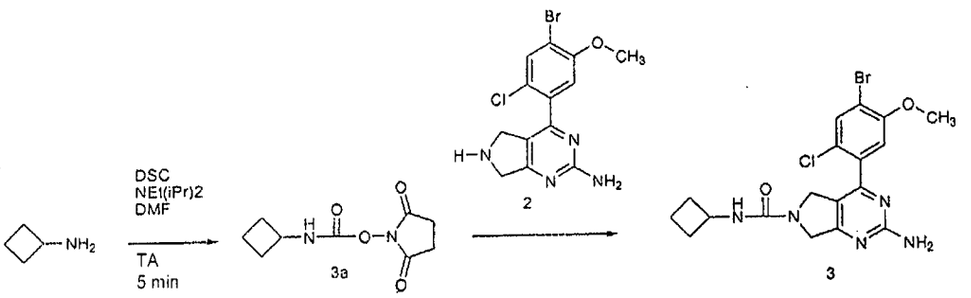



1 2

Al compuesto 1 (300 mg, 0,70 mmol) se le añadió $CH_3CN$ anhidro (4 ml) seguido de yoduro de trimetilsililo (0,5 ml, 4,0 mmol). La mezcla se calentó a reflujo durante aproximadamente 1 h y después se enfrió a temperatura

ambiente, después de lo cual se añadió una pequeña cantidad de metanol para producir la inactivación. Después, los componentes volátiles se redujeron al vacío y se añadió una pequeña cantidad de $CH_3CN$ seguido de $Et_2O$ para precipitar sólidos de color amarillo que se volvieron gradualmente de color naranja. Los sólidos se lavaron con $Et_2O$ y después se secaron al vacío a 30ºC durante una noche. Asumiendo una sal que contenía 2 HI, el compuesto del título **2** (404 mg, 0,66 mmol) se obtuvo en forma de sólidos de color naranja con un rendimiento de aproximadamente el 95% y se llevó a continuación sin purificación adicional. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 3,81-3,90 (m, 3H), 4,30 (s, 2H), 4,39 (s, 2H), 7,12 (s, 1H), 7,16 (s, 2H), 7,89 (s, 1H), 9,40 (s, 1H). LCMS $(M+H)^+$: 357,0, 355,0.

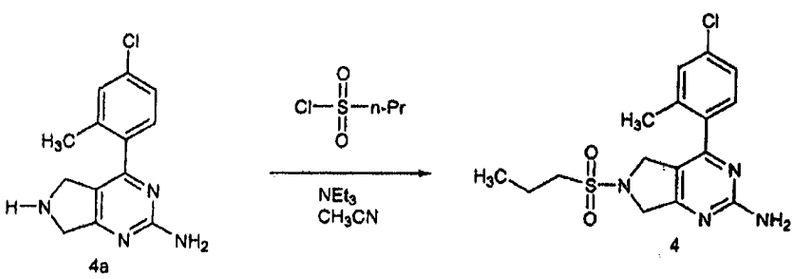
**Ejemplo 3: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-ciclobutil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




A temperatura ambiente, carbonato de *N,N'*-disuccinimidilo en agitación (67 mg, 0,26 mmol) en DMF (1 ml) se le añadió ciclobutilamina (0,022 ml, 0,26 mmol). Después, se añadió diisopropil etilamina (0,152 ml, 0,873 mmol) y la mezcla se dejó en agitación durante aproximadamente 5 min. Con agitación continua, se añadió el compuesto **2** (177 mg, 0,289 mmol) en DMF (2 ml). La mezcla se dejó en agitación durante una noche y después se purificó por HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo

el compuesto del título **3** (57 mg, 0,13 mmol) en forma de un sólido mullido de color blanco con un rendimiento del 48%. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 7,80 (s, 1H), 7,09 (s, 1H), 6,83 (s, 2H), 6,46 (d, 1H), 4,35 (s, 2H), 4,20 (s, 2H), 4,06 (m, 1H), 3,79 (s, 3H), 2,07-1,97 (m, 2H), 1,92-1,79 (m, 2H), 1,53-1,41 (m, 2H). LCMS $(M+H)^+$: 454,2, 452,2.

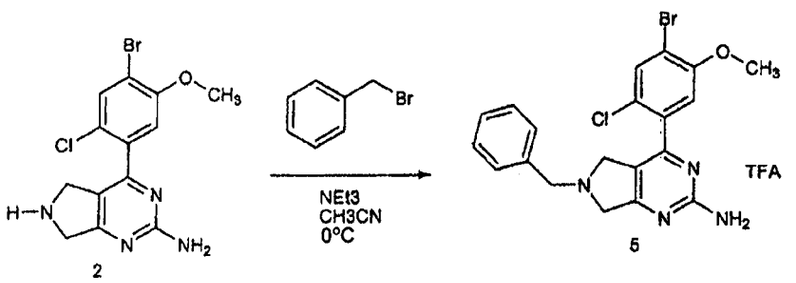
**Ejemplo 4: 4-(4-cloro-2-metilfenil)-6-(propilsulfonil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**




La preparación de 4-(4-cloro-2-metilfenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina **4a** a partir del compuesto (**i**) y ácido 4-cloro-2-metilfenilborónico se realizó en dos etapas de manera análoga a la que se ha descrito para los Ejemplos 1 y 2. A una suspensión de **4a** en bruto (100,7 mg, ~0,200 mmol) en acetonitrilo (4,0 ml) a 0°C se le añadieron trietilamina (0,15 ml, 1,1 mmol) y cloruro de 1-propanosulfonilo (0,025 ml, 0,22 mmol). Después de 30 minutos a 0°C, la mezcla de reacción se concentró al vacío, se disolvió de nuevo en diclorometano (10 ml), se lavó con agua (10 ml) y se concentró. El residuo se purificó por HPLC preparativa y, después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título (16 mg, 0,04 mmol) en forma de un sólido de color blanco con un rendimiento del 22%. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 7,43 (d, J = 1,9 Hz, 1H), 7,38 (d, J = 8,1 Hz, 1H), 7,33 (dd, J = 8,1 y 1,7 Hz, 1H), 6,86 (s a, 2H), 4,49 (s, 2H), 4,36 (s, 2H), 3,22-

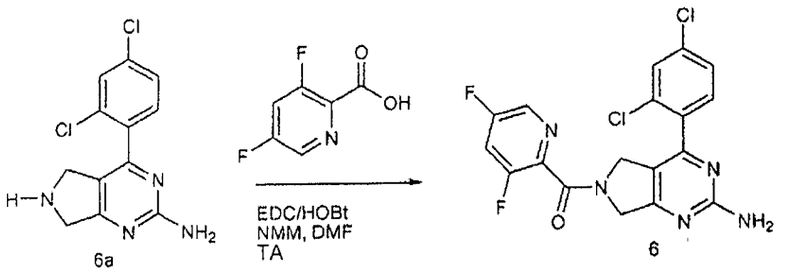
3,17 (m, 2H), 2,26 (s, 3H), 1,75-1,63 (m, 2H), 0,97 (t, J = 7,4 Hz, 3H). LCMS $(M+H)^+$: 367,2.

**Ejemplo 5: trifluoroacetato de 6-bencil-4-(4-bromo-2-cloro-5-metoxifenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**



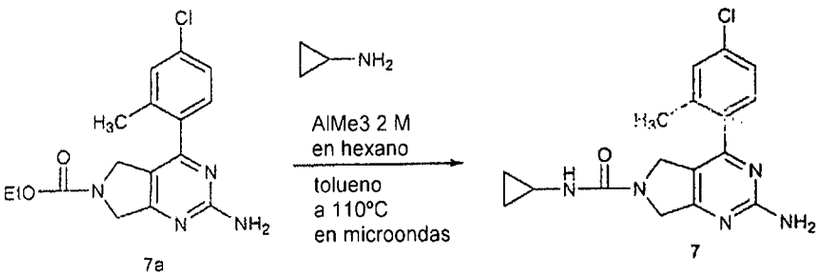

Al compuesto **2** (91 mg, 0,15 mmol) en DMSO (1 ml), enfriado en un baño de hielo, se le añadió *N,N*-diisopropiletilamina (0,078 ml, 0,45 mmol) seguido de bromuro de bencilo (0,016 ml, 0,13 mmol). La mezcla congelada se dejó descongelar y se calentó a temperatura ambiente con agitación. Después de aproximadamente 20 min, la solución de color rojo transparente se analizó por LCMS. Se observó una mezcla aproximadamente 3:2 del producto mono alquilado deseado y la sal cuaternaria. La mezcla se purificó por HPLC preparativa y, después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **5** (29 mg, 0,05 mmol) en forma de una sal THF sólida de color blanco con un rendimiento del 32%. La sal cuaternaria bis-alquilada también se aisló en forma de un subproducto (15 mg). $^1$H RMN (400 MHz, DMSO-D6) δ ppm 7,90 (s, 1H), 7,58-7,39 (m, 5H), 7,29-7,14 (m, 2H), 7,08 (s, 1H), 4,68-4,25 (m, 6H), 3,89 (s, 3H). LCMS $(M+H)^+$: 447,2, 445,2.

**Ejemplo 6: 4-(2,4-diclorofenil)-6-[(35-difluoropiridin-2-il)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**



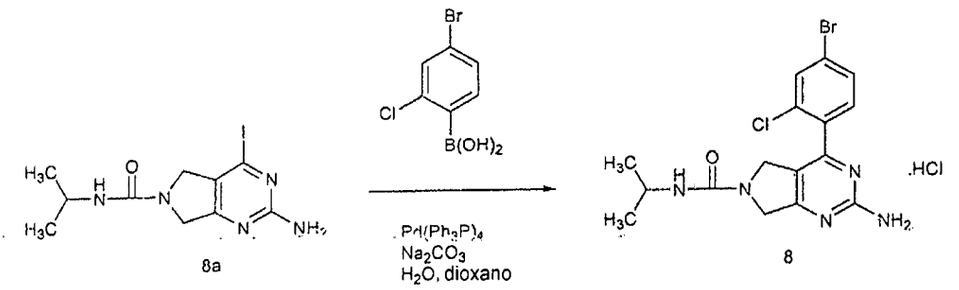

La preparación de 4-(2,4-diclorofenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina **6a** a partir del compuesto (i) y ácido 2,4-diclorofenilborónico se realizó en dos etapas de una forma análoga a la que se ha descrito para los Ejemplos 1 y 2. A una mezcla del compuesto **6a** (54 mg, 0,1 mmol) y ácido 3,5-difluoropiridina-2-carboxílico (24 mg, 0,15 mmol) en DMF (2,0 ml) se le añadieron 4-metilmorfolina (0,1 ml, 1,0 mmol), EDC (58 mg, 0,3 mmol) y HOBt (46 mg, 0,3 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla se repartió entre EtOAc (200 ml) y se lavó con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). La fase orgánica se secó sobre $Na_2SO_4$, se filtró y se concentró al vacío. El residuo se purificó por HPLC preparativa y, después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **6** (25 mg, 0,06 mmol) en forma de un sólido de color blanco (solvatado con 0,4 equivalentes de HOAc) con un rendimiento del 56%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 4,54 (d, J = 32,08 Hz, 2H), 4,70 (d, J = 29,56 Hz, 2H), 6,98 (d, J = 16,93 Hz, 2H), 7,38-7,62 (m, 2H), 7,77 (dd, J = 36,38, 2,02 Hz, 1H), 8,02-8,21 (m, 1H), 8,57 (dd, J = 30,69, 2,15 Hz, 1H). LCMS $(M+H)^+$: 4,24, 422.

**Ejemplo 7: 2-amino-4-(4-cloro-2-metilfenil)-*N*-ciclopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




La preparación de 2-amino-4-(4-cloro-2-metilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo **7a** a partir del compuesto (**i**) y el ácido 4-cloro-2-metilfenilborónico se realizó de manera análoga a la que se ha descrito para el Ejemplo 1. A una solución de ciclopropanamina (0,15 ml, 2,2 mmol) en tolueno (2,5 ml) a 0°C se le añadió gota a gota trimetil aluminio (2,0 M en hexanos, 0,60 ml, 1,2 mmol) y la mezcla de reacción se dejó calentar a temperatura ambiente. Después de 30 minutos, se añadió en una porción el compuesto **7a** (75,0 mg, 0,225 mmol) y la reacción se calentó a 110°C en el microondas durante 30 minutos. Después, la mezcla se enfrió a temperatura ambiente, se inactivó con THF/agua (2,5 ml/0,5 ml) y el precipitado se retiró por filtración. El filtrado se concentró al vacío y se purificó por HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto **7** del título (55 mg, 0,16 mmol) en forma de un sólido de color blanco con un rendimiento del 71%. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 7,43 (d, J = 1,9 Hz, 1H), 7,34 (dd, J = 8,3 y 1,9 Hz, 1H), 7,31 (d, J = 8,1 Hz, 1H), 6,77 (s a, 2H), 6,46 (d, J = 2,8 Hz, 1H), 4,38 (s, 2H), 4,21 (s, 2H), 2,55-2,48 (m, 1H), 2,22 (s, 3H), 0,56-0,50 (m, 2H), 0,41-0,36 (m, 2H). LCMS $(M+H)^+$: 344,2.

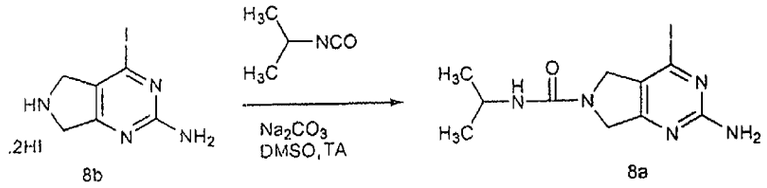
**Ejemplo 8: clorhidrato de 2-amino-4-(4-bromo-2-clorofenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se preparó ácido 4-bromo-2-clorofenilborónico por tratamiento de 1-bromo-3-cloro-4-yodobenceno (1,339 g, 4,219 mmol) en THF (20,0 ml) a -78ºC gota a gota con nBuLi (2,30 ml, 4,60 mmol). Después de 1 h, se añadió gota a gota borato de trimetilo (1,00 ml, 8,97 mmol) y la reacción se dejó calentar a ta. La mezcla de reacción se diluyó con agua (20 ml) y NaOH 3 N (10 ml) y se agitó durante 30 minutos. La mezcla se vertió en $Et_2O$ (50 ml) y las fases se separaron. Después, la fase acuosa se acidificó con $KH_2PO_4$ ac. 1 N (15 ml) y se extrajo ácido borónico en EtOAc. Después del aislamiento, el ácido 4-bromo-2-clorofenilborónico (26,3 mg, 0,112 mmol) se combinó con el compuesto **8a** (43,1 mg, 0,124 mmol) y carbonato sódico acuoso (2,0 M, 0,125 ml, 3,4 mmol) en DME (2,0 ml). Se burbujeó gas nitrógeno en la mezcla durante diez minutos para producir la desoxigenación. Se añadió *tetraquis*(trifenilfosfino)paladio (0) (12,1 mg, 0,0105 mmol) y la reacción se calentó a 85ºC. Después de 4 h, la mezcla de reacción se enfrió a temperatura ambiente, se vertió en EtOAc (50 ml), se lavó con agua (50 ml), se concentró al vacío y se purificó por HPLC preparativa. Las fracciones purificadas se combinaron y se añadió HCl 1 N (aproximadamente 3 equiv.) antes de la liofilización para preparar el clorhidrato. Se obtuvo el compuesto del título **8** (15 mg, 0,11 mmol) con un rendimiento del 30%. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 7,92 (d, J = 1,6 Hz, 1H), 7,69 (dd, J = 8,0 y 1,9 Hz, 1H), 7,41 (d, J = 8,0

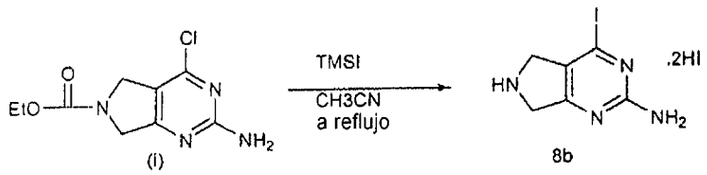
Hz, 1H), 4,41 (s, 2H), 4,24 (s, 2H), 3,82-3,74 (m, 1H), 1,05 (d, J = 6,6 Hz, 6H). LCMS $(M+H)^+$: 412,2, 410,2.

**Preparación del Compuesto 8a, 2-amino-4-yodo-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




A una solución de 4-yodo-6*H*-pirrolo[3,4-d]pirimidin-2-amina **8b** (520 mg, 1,0 mmol) en DMSO a temperatura ambiente se le añadieron carbonato sódico (256 mg, 2,4 mmol) e isocianato de isopropilo (0,13 ml, 1,1 mmol). Después de 3 h, la reacción se completó. La solución de DMSO se filtró y el filtrado se purificó por HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **8a** (204 mg, 0,59 mmol) con un rendimiento del 59%. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 6,96 (s a, 2H), 6,08 (d, J = 7,7 Hz, 1H), 4,34 (s, 2H), 4,20 (s, 2H), 3,78-3,67 (m, 1H), 1,02 (d, J = 6,6 Hz, 6H). LCMS $(M+H)^+$: 348,2.

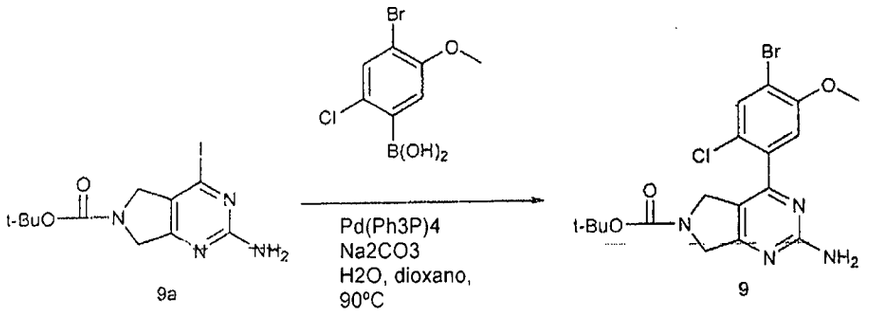
**Preparación del Compuesto 8b, 4-yodo-6*H*-pirrolo[3,4-d]pirimidin-2-amina**




A una suspensión del compuesto (**i**) (1,00 g, 4,12 mmol) en $CH_3CN$ (25,0 ml) se le añadió yodotrimetilsilano TMSI (3,0 ml, 21,1 mmol). La mezcla se calentó a reflujo 5 h y después se enfrió a temperatura ambiente. Se añadió metanol (5 ml) para inactivar el exceso de TMSI y la mezcla se concentró al vacío hasta

alcanzar un volumen de aproximadamente 10 ml. Se añadió éter dietílico (40 ml) y el precipitado resultante se recogió por filtración. Después, los sólidos se agitaron en EtOAc a la temperatura de reflujo (50 ml) durante unos minutos, momento en el que la mezcla se enfrió. Los sólidos de color castaño claro (1,8 g, 3,4 mmol) se recogieron por filtración, produciendo el compuesto del título **8b** con un rendimiento del 83% (dando la sal 2 HI). $^1$H RMN (300 MHz, DMSO-D6) δ ppm 9,47 (s a, 2H), 4,37 (s, 2H), 4,25 (s, 2H). LCMS $(M+H)^+$: 263,2.

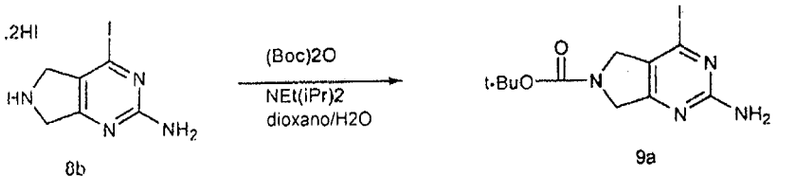
**Ejemplo 9: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo**




El compuesto **9a** impuro (113 mg) en 1,4-dioxano (2 ml) y agua (1,2 ml) se trató con ácido (4-bromo-2-cloro-5-metoxifenil)borónico (385 mg, 0,32 mmol), carbonato sódico (89 mg, 0,84 mmol) y *tetraquis*(trifenilfosfino)paladio (0) (50 mg, 0,04 mmol) y se calentó en condiciones similares a las que se han descrito en el Ejemplo 1. Después de enfriar a temperatura ambiente, se añadieron agua y EtOAc. La fase de agua se extrajo dos veces con EtOAc y los extractos combinados se lavaron con salmuera, se secaron con $Na_2SO_4$, se filtraron y los componentes volátiles se retiraron al vacío. El residuo se purificó por HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **9** protegido con *terc*-butoxicarbonilo (Boc) (33 mg, 0,07 mmol) en forma de un sólido de color blanco

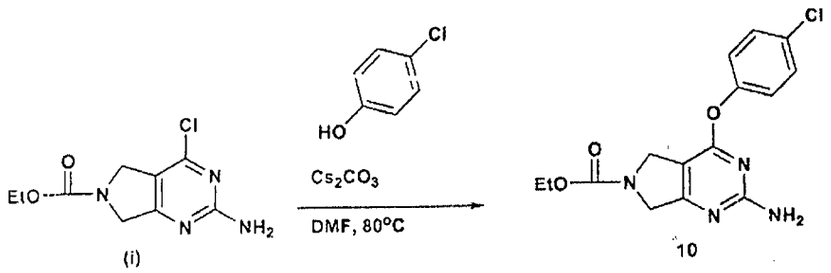
con un rendimiento mayor del 23%. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 7,88 (s, 1H), 7,17 (s, 1H), 5,95 (s, 2H), 4,48-4,42 (m, 2H), 4,33-4,27 (m, 2H), 3,87 (s, 3H), 1,43 (d, 9H). LCMS $(M+H)^+$: 457,2, 455,2.

**Preparación del Compuesto 9a, 2-amino-4-yodo-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo**



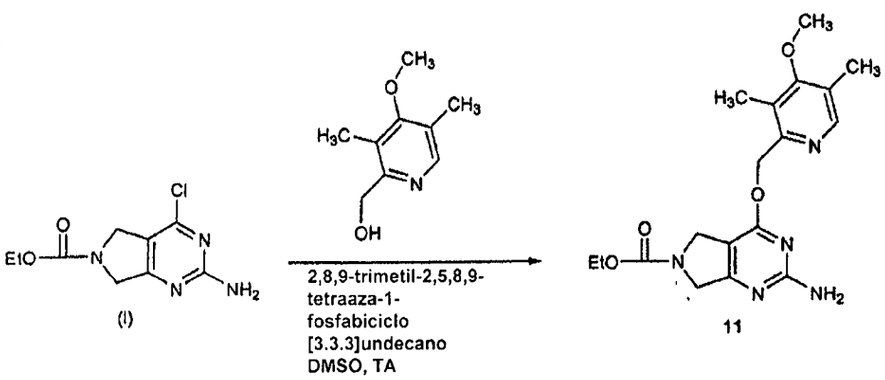

A una mezcla en agitación del compuesto **8b** impuro (113 mg) en 1,4-dioxano (1 ml) y agua (1 ml) se le añadieron dicarbonato de di-*terc*-butilo (0,16 ml, 0,70 mmol) y diisopropiletilamina (0,25 ml, 1,4 mmol). Después de agitar durante una noche, los componentes volátiles se redujeron al vacío y se añadieron EtOAc y $KHSO_4$ acuoso saturado. La mezcla de dos fases resultante se extrajo dos veces con EtOAc y los extractos combinados se lavaron con $KHSO_4$ acuoso saturado x 1, con $NaHCO_3$ acuoso saturado x 2 y con salmuera x 1 y se secaron sobre $Na_2SO_4$. Después de la filtración, los componentes volátiles se retiraron al vacío, produciendo el compuesto del título **9a** en forma de un sólido de color castaño (77 mg) que se combinó con más cantidad de material **9a** (36 mg) de una reacción previa y se llevó a continuación directamente a la siguiente etapa. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 1,44 (d, J = 4,80 Hz, 9H), 4,25 (d, J = 13,14 Hz, 2H), 4,42 (d, J = 8,34 Hz, 2H), 7,06 (s, 2H). LCMS $(M+H)^+$: 348,2.

**Ejemplo 10: 2-amino-4-(4-clorofenoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




Al compuesto (**i**) (99 mg, 0,41 mmol) y p-clorofenol (52 mg, 0,41 mmol) en DMF (2 ml) se le añadió carbonato de cesio (266 mg, 0,82 mmol). La mezcla se calentó a 80ºC durante 1,5 h y se dejó enfriar a temperatura ambiente. La mezcla se filtró a través de un filtro de aguja de teflón de 0,45 μM y el filtrado se sometió a RP-HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título (48 mg, 0,14 mmol) en forma de un sólido de color blanco con un rendimiento del 34%. $^1$H RMN (400 MHz, DMSO-D6) δ ppm 7,49 (d, 2H), 7,26 (d, 2H), 6,75 (s, 2H), 4,50 (s, 1H), 4,46-4,39 (m, 3H), 4,17-4,08 (m, 2H), 1,24 (t, 3H). LCMS $(M+H)^+$: 335,2.

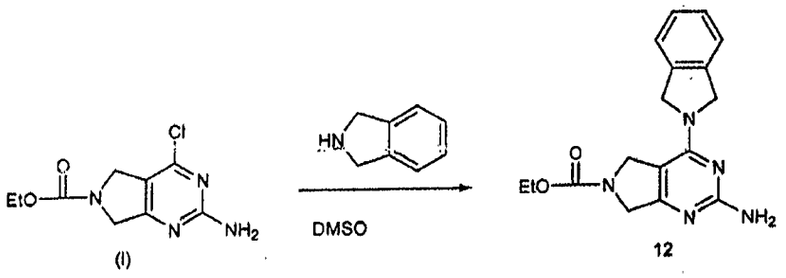
**Ejemplo 11: 2-amino-4-[(4-metoxi-3,5-dimetilpiridin-2-il)metoxi]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




Se agitaron el Compuesto (**i**) (54 mg, 0,22 mmol), 3,5-dimetil-4-metoxi-2-piridinametanol (45 mg, 0,268 mmol) y 2,8,9-trimetil-2,5,8,9-tetraaza-1-fosfabiciclo[3.3.3]undecano (58 mg, 0,27 mmol) en DMSO (1,5 ml) a

temperatura ambiente durante 2 h. Después, la mezcla se purificó por HPLC preparativa y, después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **11** (37 mg, 0,10 mmol) en forma de un sólido de color blanco con un rendimiento del 44%. $^1$H RMN (300 MHz, DMSO-D6) (confórmeros) δ ppm 8,20 (s, 1H), 6,72 (s a, 2H), 5,39 (s, 1H), 5,38 (s, 1H), 4,36-4,29 (m, 4H), 4,11-4,03 (m, 2H), 3,75 (s, 3H), 2,22 (s, 6H), 1,23-1,17 (m, 3H). LCMS $(M+H)^+$: 374,2.

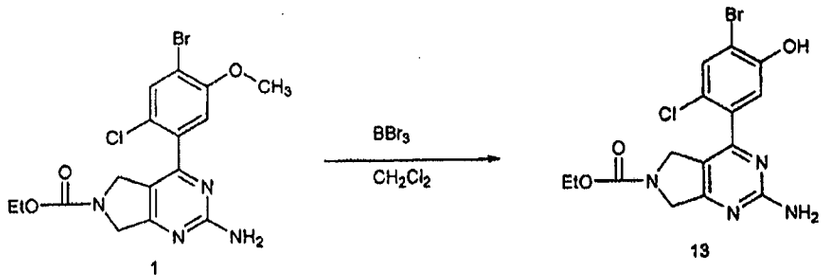
**Ejemplo 12: 2-amino-4-(1,3-dihidro-2*H*-isoindol-2-il)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




Se agitaron el Compuesto (**i**) (74,8 mg, 0,308 mmol) e isoindolina (105 mg, 0,881 mmol) en DMSO (1 ml) y se calentaron a 80ºC durante 20 minutos. Después de un periodo de refrigeración, la mezcla se vertió en agua y se extrajo en $CH_2Cl_2$. Después de la evaporación de los componentes volátiles, el residuo se disolvió en DMSO y se sometió a RP-HPLC preparativa. Después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **12** (68 mg, 0,19 mmol) con un rendimiento del 62%.

$^1$H RMN (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,42-7,39 (m, 2H), 7,32-7,29 (m, 2H), 6,13 (s a, 2H), 4,96-4,87 (m a, 4H), 4,28-4,23 (m, 2H), 4,16-4,10 (m, 2H), 3,31 (s a, parcialmente oscurecido por pico de $H_2O$, 2H), 1,28-1,21 (m, 3H). LCMS $(M+H)^+$: 326,2.

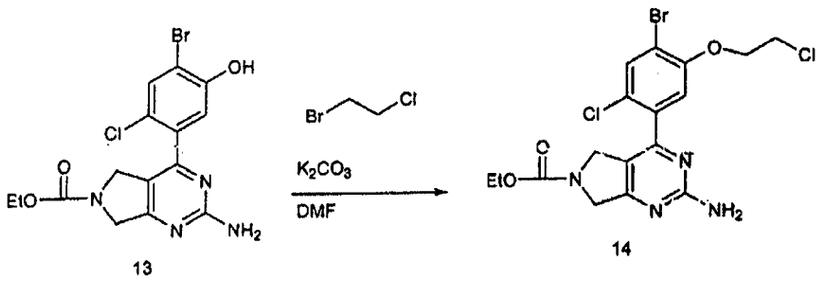
**Ejemplo 13: 2-amino-4-(4-bromo-2-cloro-5-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




1 13

A una suspensión en agitación del compuesto **1** (428 mg, 1,0 mmol) en $CH_2Cl_2$ (10 ml) a 0°C se le añadió $BBr_3$ (0,5 ml, 5,0 mmol). La mezcla se agitó durante una noche y se dejó calentar a temperatura ambiente, después de lo cual se añadieron hielo y agua (10 ml) y el precipitado resultante se recogió por filtración. Después de lavar con agua y $CH_2Cl_2$, el sólido se secó al vacío, dando el compuesto del título **13** (375 mg, 0,91 mmol) en forma de un sólido de color amarillo con un rendimiento del 91%. $^1$H RMN (300 MHz, DMSO-D6) (confórmeros) δ ppm 1,09-1,28 (m, 3H), 3,99-4,16 (m, 2H), 4,33 (d, J = 8,34 Hz, 2H), 4,47 (d, J = 11,12 Hz, 2H), 6,93 (d, J = 1,77 Hz, 1H), 7,74 (s, 1H), 10,89 (s, 1H). LCMS $(M+H)^+$: 417,0, 415,0.

**Ejemplo 14: 2-amino-4-[4-bromo-2-cloro-5-(2-cloroetoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**

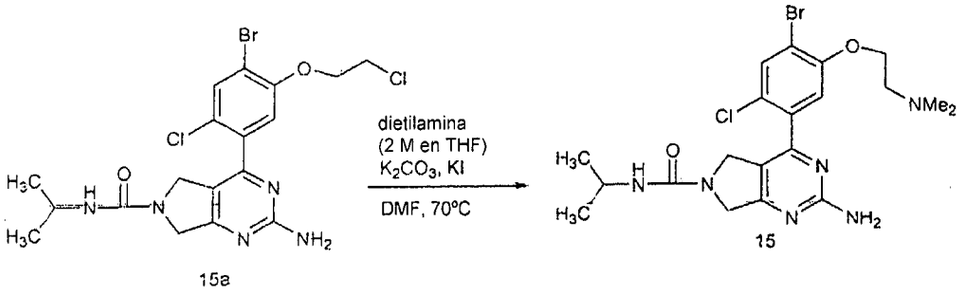



13 14

A una mezcla en agitación del compuesto **13** (360 mg; 0,87 mmol) y carbonato

potásico (361 mg, 2,61 mmol) en DMF anhidra (4 ml) se le añadió 1-bromo-3-cloropropano (0,15 ml, 1,74 mmol). La mezcla se calentó a 50°C durante 12 horas, después de lo cual la mezcla se enfrió y se filtró para retirar los sólidos suspendidos y los sólidos se lavaron bien con EtOAc. Los lavados y el filtrado se combinaron y se añadió más cantidad de EtOAc (200 ml). La fase orgánica combinada se lavó con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml) y después se secó sobre $Na_2SO_4$, se filtró y se concentró al vacío. El residuo amarillo se trató con $CH_2Cl_2$ (30 ml) y los sólidos resultantes se recogieron por filtración. Después de lavar con $CH_2Cl_2$ y hexano, los sólidos se secaron al vacío, dando el compuesto del título **14** (240 mg, 0,5 mmol) en forma de un sólido de color blanco con un rendimiento del 58%. $^1$H RMN (300 MHz, DMSO-D6) $\delta$ ppm 1,11-1,27 (m, 3H), 3,90-4,00 (m, 2H), 4,08 (dd, J = 14,53, 7,20 Hz, 2H), 4,29-4,40 (m, 4H), 4,48 (d, J = 10,61 Hz, 2H), 6,95 (s, 2H), 7,20 (s, 1H), 7,88 (s, 1H). LCMS $(M+H)^+$: 477,0, 475,0.

**Ejemplo 15: 2-amino-4-{4-bromo-2-cloro-5-[2-(dimetilamino)etoxi]fenil}-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

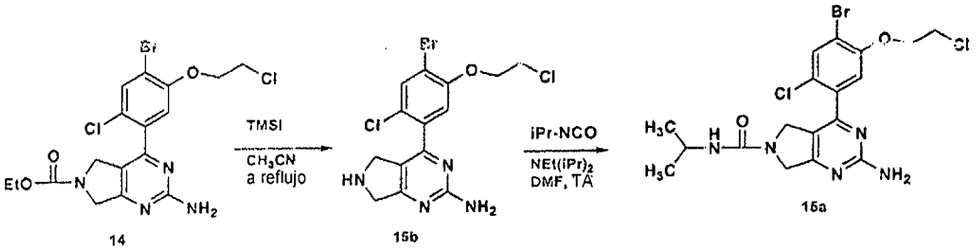



15a 15

A una mezcla del compuesto **15a** (90 mg, 0,18 mmol), $K_2CO_3$ (76 mg, 0,55 mmol) y KI (61 mg, 0,37 mmol) en DMF (2,0 ml) se le añadió una solución de dimetilamina 2 M en THF (0,3 ml, 0,55 mmol). Después de agitar a 70°C durante 12 h, la mezcla se enfrió y se filtró para retirar los sólidos suspendidos.

Los sólidos se lavaron con EtOAc. Los lavados y el filtrado se combinaron y se añadió más cantidad de EtOAc (200 ml). La fase orgánica combinada se lavó con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml) y después se secó sobre $Na_2SO_4$, se filtró y se concentró al vacío. El residuo se purificó por HPLC preparativa y, después de la liofilización de las fracciones purificadas combinadas, se obtuvo el compuesto del título **15** (16 mg, 0,03 mmol) en forma de un sólido de color amarillo con un rendimiento del 17%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,06 (t, J = 7,07 Hz, 6H), 2,22 (s, 6H), 2,65 (t, J = 5,68 Hz, 2H), 3,78 (dd, J = 13,89, 6,82 Hz, 1H), 4,14 (t, J = 5,56 Hz, 2H), 4,25 (s, 2H), 4,42 (s, 2H), 6,08 (d, J = 7,83 Hz, 1H), 6,88 (s, 2H), 7,19 (s, 1H), 7,85 (s, 1H). LCMS $(M+H)^+$: 501,2, 499,2.

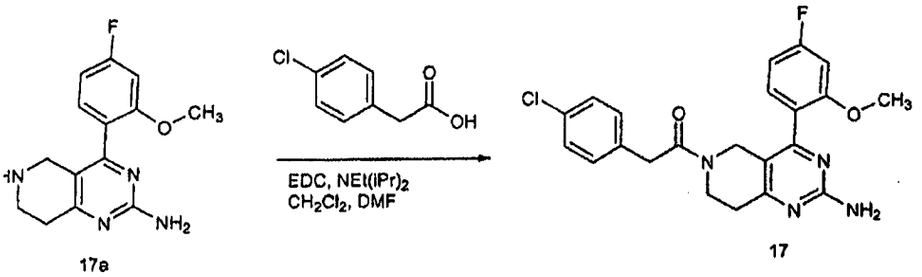
**Preparación del compuesto 15a, 2-amino-4-[4-bromo-2-cloro-5-(2-cloroetoxi)fenil]-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El Compuesto **14** se desprotegió de una manera similar a la que se ha descrito para el Ejemplo 2. El tratamiento extractivo con EtOAc y el $NaHCO_3$ acuoso saturado dio el compuesto **15b**, 4-[4-bromo-2-cloro-5-(2-cloroetoxi)fenil]-6,7-dihidro-5*H*--pirrolo{3,4-d]pirimidin-2-amina, (191 mg, 0,473 mmol) que se disolvió en DMF (2,0 ml) y se trató secuencialmente con diisopropiletilamina (0,4 ml, 2,36 mmol) e isocianato de isopropilo (40 mg, 0,473 mmol) a temperatura ambiente. Después de 3 h, se añadió metanol y la mezcla se

concentró al vacío. El residuo se disolvió en EtOAc y se lavó con $NaHCO_3$ acuoso saturado y salmuera. Las fases orgánicas se secaron sobre $Na_2SO_4$, se filtraron y se concentraron al vacío. El residuo se cromatografió sobre gel de sílice eluyendo con metanol al 10% en $CH_2Cl_2$. Las fracciones más puras se combinaron y los componentes volátiles se retiraron al vacío, dando el compuesto del título **15a** (180 mg, 0,37 mmol) en forma de una espuma de color pardo con un rendimiento del 78%. $^1H$ RMN (400 MHz, DMF-d7) δ ppm 1,04-1,11 (m, 6H), 3,81 (s, 1H), 3,92-4,04 (m, 2H), 4,28 (s, 2H), 4,39 (d, J = 10,11 Hz, 2H), 4,44 (s, 2H), 6,09 (d, J = 8,08 Hz, 1H), 6,91 (s, 2H), 7,24 (s, 1H), 7,91 (s, 1H). LCMS $(M+H)^+$: 488,0, 490,0.

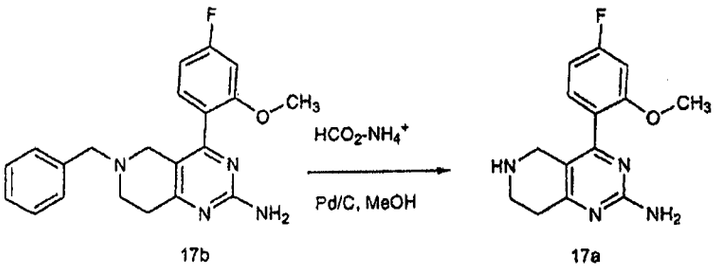
**Ejemplo 17: 6-[(4-clorofenil)acetil]-4-(4-fluoro-2-metoxifenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina**




17a 17

El Compuesto **17a** (32 mg, 0,19 mmol) se acopló a ácido (4-clorofenil)acético (32 mg, 0,19 mmol), usando EDC (40 mg, 0,21 mmol) y $NEt(iPr)_2$ (0,051 ml, 0,29 mmol) en DMF (0,5 ml) y $CH_2Cl_2$ (0,5 ml) de una manera similar a la que se ha descrito para el Ejemplo 6. La purificación sobre gel de sílice (eluyendo con MeOH al 10% en $CH_2Cl_2$) dio, después del aislamiento, el compuesto del título **17** (48 mg, 0,11 mmol) con un rendimiento del 59%. $^1H$ RMN (400 MHz, DMSO-D6) (confórmeros) δ ppm 7,41-6,82 (m, 7H), 6,58-6,47 (m, 2H), 4,17 (s, 2H), 3,85-3,55 (m, 7H), 2,71 (s a, 2H). LCMS $(M+H)^+$: 429,2, 427,2.

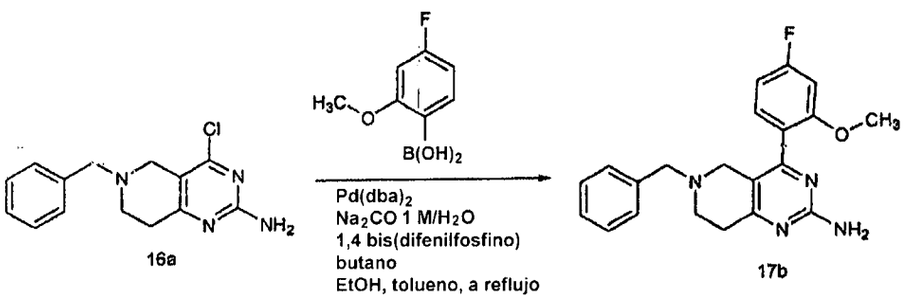
**Preparación del compuesto 17a, 4-(4-fluoro-2-metoxifenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina**




17b 17a

El Compuesto **17b** (971 mg, 2,66 mmol) en metanol se trató con formiato amónico (1,9 g, 29,4 mmol) y paladio al 10% sobre carbono (490 mg). Después de agitar durante varios días, el paladio sobre carbono se retiró mediante dos valoraciones sucesivas - primero a través de papel de filtro y después a través de un filtro de aguja de teflón de 0,45 micrómetros. El filtrado se redujo al vacío y se añadió una pequeña cantidad de agua. El precipitado resultante se recogió por filtración, produciendo el compuesto del título **17a** (438 mg, 1,6 mmol) con un rendimiento del 60% después de secar al vacío. $^1$H RMN (400 MHz, DMSO-D6) (confórmeros) δ ppm 8,26 (s, 1H), 7,19 (m, 1H), 7,03 (m, 1H), 6,87 (m, 1H), 6,41 (s, 2H), 3,78 (s, 3H), 3,53-3,39 (m, 2H, parcialmente oscurecido), 3,12-3,02 (m, 2H), 2,71-2,62 (m, 2H). LCMS $(M+H)^+$: 275,0.

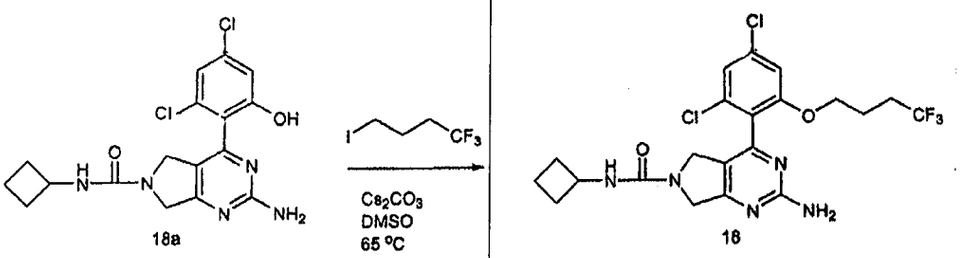
**Preparación del compuesto 17b, 6-bencil-4-(4-fluoro-2-metoxifenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina**




16a 17b

Se burbujeó argón a través de una mezcla del compuesto **16a** (286 mg, 1,04 mmol), ácido 4-fluoro-2-metoxifenil)borónico (194 mg, 1,14 mmol), $Na_2CO_3$ acuoso 1 M (1 ml) en tolueno (2 ml) y etanol (0,5 ml). Se añadieron $Pd(dba)_2$ (30 mg, 0,052 mmol) y 1,4-*bis*(difenilfosfino)butano (44 mg, 0,104 mmol) y se burbujeó más cantidad de argón a través de la mezcla, que después se calentó a reflujo durante aproximadamente 19 h. Después de enfriar a temperatura ambiente, se añadió agua y el producto en bruto se extrajo en EtOAc, se lavó con salmuera, se secó sobre $Na_2SO_4$ y se filtró. Los componentes volátiles se retiraron al vacío y el residuo se purificó sobre sílice eluyendo con EtOAc seguido de acetona. Las fracciones más puras se combinaron y se redujeron a sequedad, después de lo cual los sólidos se disolvieron en THF y se filtraron a través de un filtro de teflón de 0,45 micrómetros. Los componentes volátiles se retiraron de nuevo al vacío, produciendo el compuesto del título **17b** (228 mg, 0,62 mmol) con un rendimiento del 60%. $^1$H RMN (400 MHz, DMSO-D6) (confórmeros) δ ppm 7,32-7,20 (m, 5H), 7,15 (m, 1H), 6,94 (d, 1H), 6,80 (m, 1H), 6,37 (s, 2H), 3,63-3,42 (m, 5H, (contiene 3,63 (s, 3H)), 3,31-2,92 (m, 2H), 2,74-2,59 (m, 4H (contiene 2,66 (s, 2H)). LCMS $(M+H)^+$: 365,0.

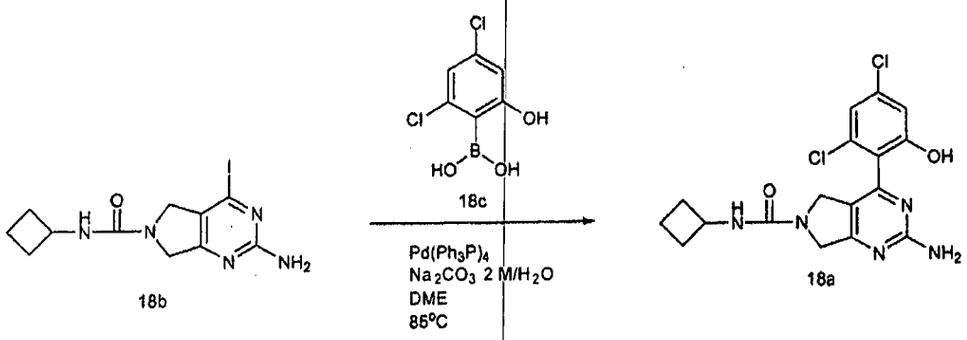
**Ejemplo 18: 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Una solución del compuesto **18a** (91 mg, 0,231 mmol) en DMSO (1,5 ml) se trató con $Cs_2CO_3$ (174 mg, 0,533 mmol) y 1-yodo-4,4,4-trifluorobutano (89,2

mg, 0,375 mmol) y se calentó a 65ºC. Después de 30 minutos, la mezcla de reacción se filtró y la solución de DMSO se sometió a HPLC preparativa. Las fracciones purificadas se combinaron y se liofilizaron. Después, el polvo de color blanco resultante se disolvió en una solución de $CH_3CN$, (2 ml), HCl 1 N (0,45 ml) y agua (5 ml). Después de la liofilización, se obtuvo el compuesto **18** (46 mg, 0,085 mmol) en forma de un polvo de color blanco con un rendimiento del 37%. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 7,32 (d, J = 1,8 Hz, 1H), 7,26 (d, J = 1,8 Hz, 1H), 6,46 (d, J = 7,3 Hz, 1H), 4,40-4,30 (m, 2H), 4,11-4,02 (m, 5H), 2,12-1,99 (m, 4H), 1,91-1,81 (m, 2H), 1,74-1,67 (m, 2H), 1,52-1,43 (m, 2H). LCMS $(M+H)^+$: 504,0, 506,0. Anál. Calc. para $C_{21}H_{22}N_5Cl_2O_2F_3 \cdot HCl$ 0,7 $\cdot H_2O$ 0,6: C, 46,65; H, 4,46; N 12,95; Cl, 17,70. Encontrado: C, 46,75; H, 4,26; N, 12,69; Cl, 17,43.

**Preparación del Compuesto 18a, 2-amino-*N*-ciclobutil-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**



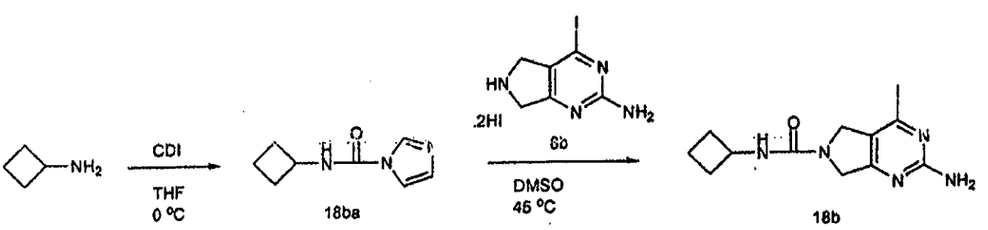

Se burbujeó nitrógeno a través de una solución del compuesto **18b** (1350 mg, 3,75 mmol), el compuesto **18c** ( 775 mg, 3,75 mmol) y carbonato sódico acuoso 2,0 M (0,60 ml, 1,20 mmol) en 1,4-dioxano (7,0 ml) durante 15 minutos. A ésta se le añadió *tetraquis*(trifenilfosfino)paladio (0) (431 mg, 0,373 mmol) y la mezcla se calentó a 85ºC. Después de 5 h, la mezcla se enfrió a temperatura ambiente y se añadieron EtOAc (20 ml) y agua (20 ml). La fase acuosa se

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extrajo con EtOAc y la fase de EtOAc se desechó. El pH de la solución acuosa se ajustó a aproximadamente 5 con $KH_2PO_3$ 1 N y después se extrajo con una mezcla de EtOAc e iPrOH. Los componentes volátiles se retiraron al vacío, dando el compuesto **18a** (869 mg, 2,2 mmol) con un rendimiento del 59% que se llevó a continuación sin purificación adicional. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 10,64 (s, 1H), 7,16 (d, J = 1,7 Hz, 1H), 6,97 (d, J = 1,7 Hz, 1H), 6,79 (a, 2H), 6,52 (d, J = 7,5 Hz, 1H), 4,40 (s a, 2H), 4,15 (s a, 2H), 4,08-3,99 (m, 1H), 2,15-2,03 (m, 2H), 1,97-1,86 (m, 2H), 1,60-1,47 (m, 2H). LCMS $(M+H)^+$: 394,2 y 396,2.

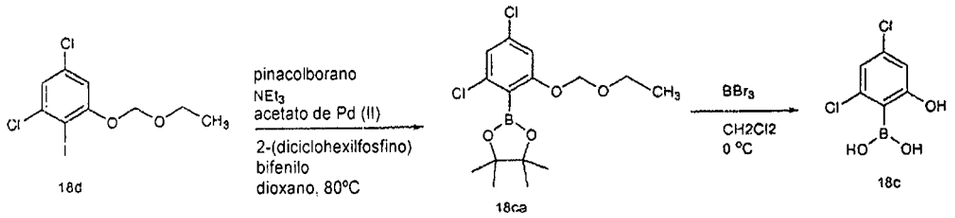
**Preparación del Compuesto 18b: 2-amino-*N*-ciclobutil-4-yodo-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




A una solución de 1,1-carbonildiimidazol (3,54 g, 21,8 mmol) en THF (100 ml) a 0°C se le añadió gota a gota una solución de ciclobutilamina (1,00 g, 14,1 mmol) en THF (9,0 ml) durante 10 minutos. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 2 h. Los componentes volátiles se retiraron al vacío y el aceite resultante se purificó sobre gel de sílice, eluyendo con un gradiente de MeOH al 0-10% en $CH_2Cl_2$. Las fracciones más puras se combinaron y los componentes volátiles se retiraron al vacío, dando el compuesto **18ba**, *N*-ciclobutil-1*H*-imidazol-1-carboxamida (2,2 g, 13,4 mmol) en forma de un aceite transparente. Después, el compuesto **18ba** (1,39 g, 8,41 mmol) y el compuesto **8b** (3,79 g, 7,32 mmol) se disolvieron en DMSO (20 ml) y

se añadió $Cs_2CO_3$ (4,92 g, 15,1 mmol). La mezcla se agitó durante 1 h a temperatura ambiente y después se calentó a 45°C durante 4 h, después de lo cual la mezcla se enfrió a temperatura ambiente y se añadió agua (150 ml). La suspensión acuosa se extrajo con una mezcla de EtOAc y EtOH (200 ml) y los componentes volátiles se retiraron al vacío, dando el compuesto del título **18b** (2 g, 5,6 mmol) con un rendimiento del 66% que se llevó a continuación sin purificación adicional. $^1$H RMN (300 MHz, DMSO-D6) δ ppm 7,02 (s a, 2H), 6,60 (d, J = 7,7 Hz, 1H), 4,41 (s a, 2H), 4,26 (s a, 2H), 4,19-4,07 (m, 1H), 2,18-2,07 (m, 2H), 2,04-1,91 (m, 2H), 1,64-1,50 (m, 2H). LCMS $(M+H)^+$ 360,2.

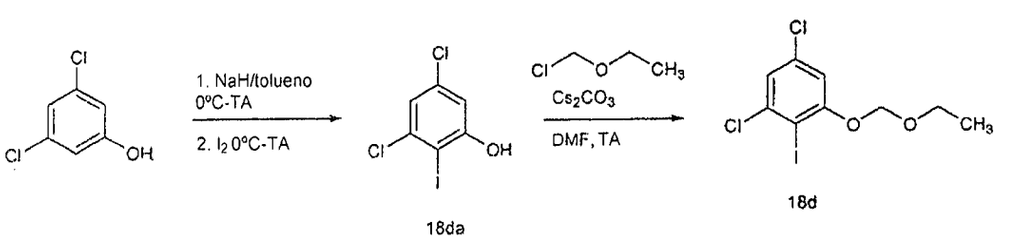
**Preparación del Compuesto 18c, ácido 2,4-dicloro-6-hidroxifenilborónico**




Una solución del compuesto **18d** (4,33 g, 12,5 mmol), pinacolborano (3,80 ml, 26,2 mmol) y trietilamina (5,2 ml, 37 mmol) en 1,4-dioxano (80 ml) se purgó con $N_2$ durante 15 minutos. Se añadieron acetato de paladio (II) (142 mg, 0,632 mmol) y 2-(diciclohexilfosfino)bifenilo (439 mg, 1,25 mmol) y la mezcla se calentó a 80°C durante 1,5 h. Después de enfriar a temperatura ambiente, la mezcla se vertió en EtOAc (200 ml) y se lavó con $NH_4Cl$ acuoso saturado (100 ml) y agua (200 ml). Después de la concentración al vacío, el residuo se purificó sobre gel de sílice, eluyendo con un gradiente de $CH_2Cl_2$ al 10-70% en hexano. Las fracciones más puras se combinaron y los componentes volátiles se retiraron al vacío, dando el compuesto **18ca**, pinacol éster del ácido 2,4-dicloro-6-(etoximetoxo)fenilborónico (1,55 g, 4,47 mmol), que después se

disolvió en diclorometano (50,0 ml) y se enfrió a 0°C. Se añadió lentamente una solución de tribromuro de boro 1,0 M en $CH_2Cl_2$ (10,0 ml, 10,0 mmol) durante 5 minutos. Después de 15 minutos, la mezcla se vertió en agua enfriada con hielo. La mezcla bifásica se agitó vigorosamente y el pH de la fase acuosa se ajustó a aproximadamente 10 con NaOH 3 N. Las fases se separaron y la fase de diclorometano se desechó. Después, el pH de la fase acuosa se ajustó a aproximadamente 3 con HCl 1 N y se extrajo con una mezcla de EtOAc e iPrOH. Después, la fase orgánica se concentró, dando el compuesto del título **18c** (778 mg, 3,8 mmol) en forma de un polvo castaño que se llevó a continuación sin purificación adicional.

**Preparación del Compuesto 18d, 1,5-dicloro-3-(etoximetoxi)-2-yodobenceno**



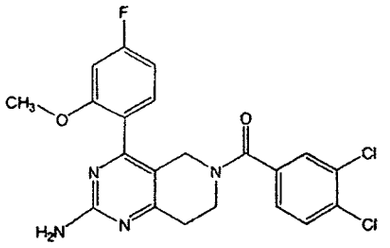
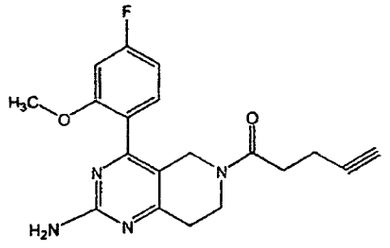

18da

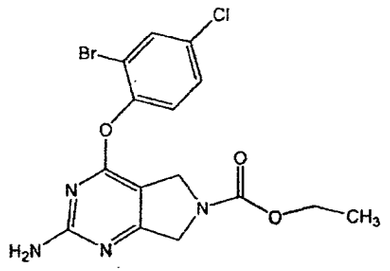
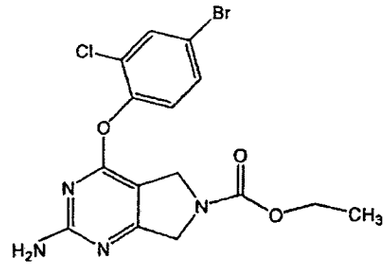
18d

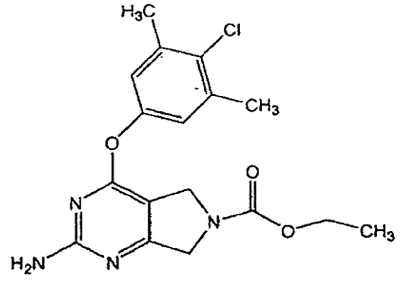
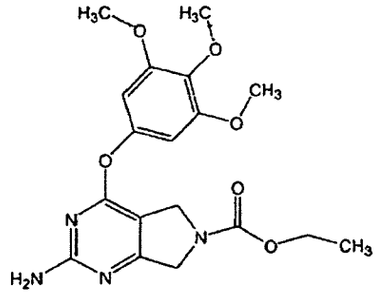
A una solución de 3,5-diclorofenol (5,98 g, 36,7 mmol) en tolueno (200 ml) a 0°C se le añadió en porciones NaH (al 60% en aceite, 4,50 g, 117 mmol). Después, la mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 20 minutos. Después, la suspensión se enfrió de nuevo a 0°C y se añadió lentamente yodo (7,91 g, 31,2 mmol). La mezcla se dejó calentar a temperatura ambiente y se agitó durante una noche. Se añadió HCl acuoso 1 N (200 ml) y la mezcla se extrajo dos veces con $Et_2O$ (300 ml en total). Los extractos orgánicos combinados se concentraron al vacío y el residuo se purificó sobre gel de sílice, eluyendo con un gradiente de $CH_2Cl_2$ al 0-30% en

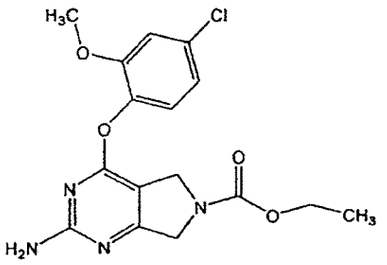
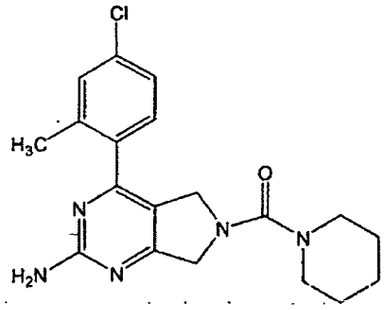
hexano. Las fracciones más puras se combinaron y los componentes volátiles se retiraron al vacío, dando 3,5-dicloro-2-yodofenol, compuesto **18da**, (6,53 g, 22,7 mmol) con un rendimiento del 62%. Después, el compuesto **18da** (3,726 g, 12,90 mmol) en DMF (50 ml) se trató con $CS_2CO_3$ (3,45 g, 10,6 mmol) y clorometiletil éter (1,50 ml, 16,2 mmol). Después de 3 h a temperatura ambiente, se añadió $Et_2O$ (150 ml) y la fase orgánica se lavó con agua (3 x 100 ml). La fase orgánica se concentró al vacío y el residuo se purificó sobre gel de sílice eluyendo con un gradiente de $CH_2Cl_2$ al 0-40% en hexano. Las fracciones más puras se combinaron y los componentes volátiles se retiraron al vacío para dar el compuesto del título **18d** (4,3 g, 12,5 mmol) en forma de un aceite transparente. La pureza estimada (por RMN) fue del 86%. $^1$H RMN (300 MHz, $CDCl_3$) $\delta$ ppm 7,00 (d, J = 1,6 Hz, 1H), 6,98 (d, J = 1,5 Hz, 1H), 5,18 (s, 2H), 3,71 (c, J = 7,2 Hz, 2H), 1,39 (s, 12H), 1,22 (t, J = 7,2 Hz, 3H).

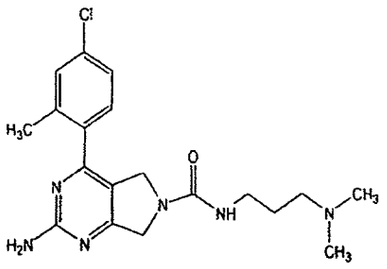
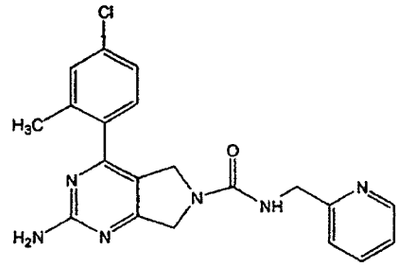
Los compuestos de los Ejemplos 20-98 se prepararon siguiendo los procedimientos de los Ejemplos 1-18, como se muestra en la siguiente Tabla 1.

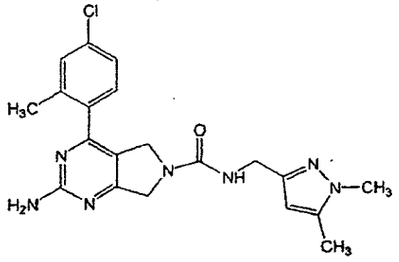
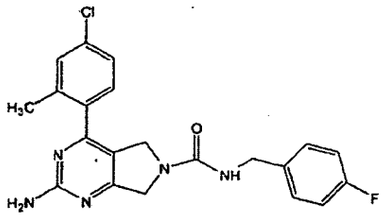
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 20 |  | 6-(3,4-diclorobenzoil)-4-(4-fluoro-2-metoxifenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina | Ejemplo 17 | (400 MHz, DMSO-D6) (confórmeros) δ ppm 7,80-7,57 (m, 2H), 7,46 (m, 1H), 7,27 (m, 1H), 7,11 (m, 1H), 6,89 (m, 1H), 6,59 (s, 2H), 4,29 (s a, 2H), 3,82 (s a, 3H), 3,64-3,37 (m, 2H), 2,85-2,73 (m, 2H). |
| 22 |  | 4-(4-fluoro-2-metoxifenil)-6-pent-4-inoil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina | Ejemplo 17 | (400 MHz, DMSO-D6) (confórmeros) δ ppm 7,22 (m, 1H), 7,08 (m, 1H), 6,90 (m, 1H), 6,52 (m, 2H), 4,15 (s a, 2H), 3,86-3,67 (m, 5H, contiene 3,78 (s)), 2,84-2,49 (m, 5H, parcialmente oscurecido), 2,45-2,27 (m, 2H). |

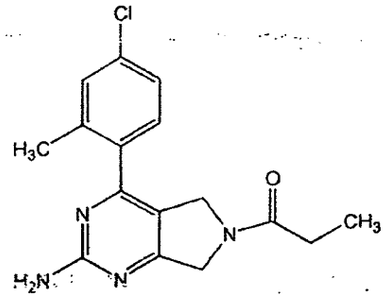
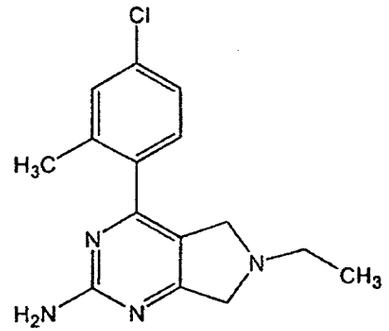
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 23 |  | 2-amino-4-(2-bromo-4-clorofenoxi)-5,7-dihidro-*6H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 10 | (400 MHz, DMSO-D6) δ ppm 7,91 (s, 1H), 7,56 (m, 1H), 7,43 (m, 1H), 6,82 (s a, 2H), 4,55 (s, 1H), 4,52-4,42 (m, 3H), 4,19-4,09 (m, 2H), 1,24 (t, 3H). |
| 24 |  | 2-amino-4-(4-bromo-4-clorofenoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 10 | (400 MHz, DMSO-D6) δ ppm 7,92 (s, 1H), 7,66 (d, 1H), 7,39 (d, 1H), 6,82 (s a, 2H), 4,54 (s, 1H), 4,50 (s, 1H), 4,44 (d, 2H), 4,18-4,09 (m, 2H), 1,25 (t, 3H). |

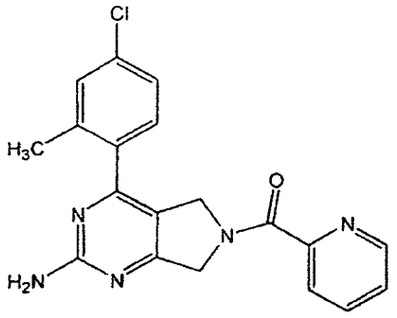
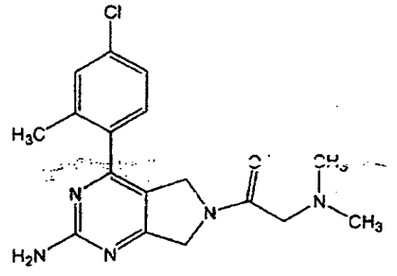
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 25 |  | clorhidrato de 2-amino-4-(4-cloro-3,5-dimetilfenoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 10 | 400 MHz, DMSO-D6) δ ppm 7,09 (s, 2H), 4,50 (s, 1H), 4,46-4,42 (m, 3H), 4,17-4,10 (m, CH2, parcialmente oscurecido), 2,35 (s, 6H), 1,25 (t, 3H). (400 MHz, DMSO-D6) *6* ppm 6,59 (s, 26 |
| 26 |  | 2-amino-4-(3,4,5-trimetoxifenoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 10 | (400 MHz, DMSO-D6) δ ppm 6,59 (s 2H), 4,49-4,40 (m, 4H), 4,17-4,09 (m, 2H, parcialmente oscurecido), 3,78 (s, 6H), 3,67 (s, 3H), 1,28-1,21 (m, 3H). |

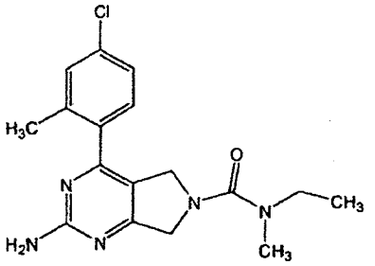
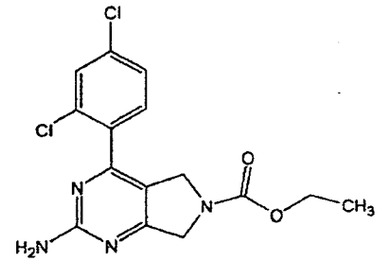
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 27 |  | 2-amino-4-(4-cloro-2-metoxifenoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 10 | (400 MHz, DMSO-D6) δ ppm 7,30-7,18 (m, 2H), 7,05 (m, 1H), 6,71 (s, 2H), 4,49 (s, 1H), 4,43-4,38 (m, 3H), 4,17-4,08 (m, 2H), 3,77 (s, 3H), 1,23 (t, 3H) |
| 29 |  | 4-(4-cloro-2-metilfenil)-6-(piperidin-1-ilcarbonil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s a, 1H), 7,35-7,33 (m, 2H), 6,75 (s a, 2H), 4,52 (s, 2H), 4,39 (s, 2H), 3,18-3,15 (m, 4H), 2,24 (s, 3H), 1,56-1,39 (m, *6H*). |

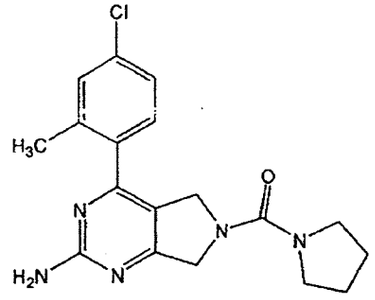
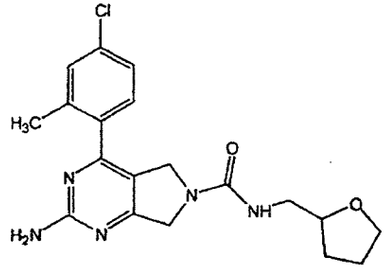
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 30 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-[3-(dimetilamino)propil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,43 (s a, 1H), 7,35-7,32 (m, 2H), 6,77 (s a, 2H), 6,44 (t, J = 5,5 Hz, 1H), 4,40 (s, 2H), 4,24 (s, 2H), 3,07-3,00 (m, 2H), 2,23 (s, 3H), 2,18 (t, J = 7,1 Hz, 2H), 2,09 (s, 6H), 1,57-1,48 (m, 2H). |
| 31 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-(piridin-2-ilmetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 8,48-8,44 (m 1H) 7, 72 (dt, J = 7,7 y 1,9 Hz, 1H), 7,43 (s a, 1H) 7,36-7,33 (m, 2H), 7,31 (d, J = 7,9 Hz, 1H), 7,25-7,18 (m, 1H), 7,07 (t, J = 5,9 Hz, 1H), 6,79 (s a, 2H), 4,48 (s, 2H), 4,36-4,31 (m, 4H), 2,24 (s, 3H). |

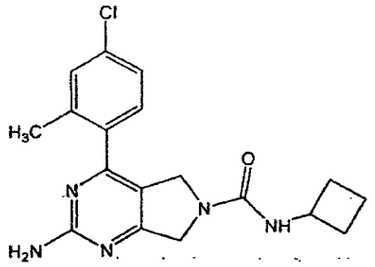
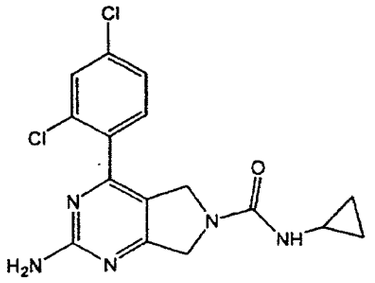
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 32 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-[(15-dimetil-1*H*-pirazol-3-il)metil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s a, 1H), 7,34-7,32 (m, 2H), 6,77 (s a, 2H), 6,73 (t, J = 5,8 Hz, 1H), 5,88 (s, 1H), 4,42 (s, 2H), 4,26 (s, 2H), 4,08 (d, J - 5,7 Hz, 2H), 3,62 (s, 3H), 2,23 (s, 3H), 2,17 (s, 3H). |
| 33 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-(4-fluorobencil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s a, 1H), 7,34-7,27 (m, 4H), 7,14-7,06 (m, 2H), 6,99 (t, J = 5,8 Hz, 1H), 6,78 (s a, 2H), 4,45 (s, 2H), 4,30 (s, 2H), 4,22 (d, J = 5,7 Hz, 2H), 2,23 (s, 3H). |

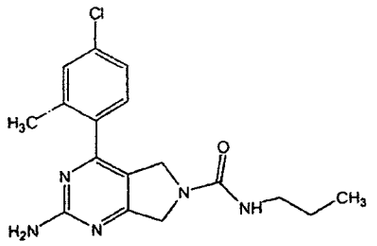
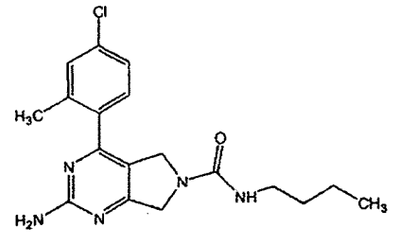
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 34 |  | 4-(4-cloro-2-metilfenil)-6-propionil-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (300 MHz, DMSO D6) δ ppm 7,43 (s a, 1H), 7,35-7,32 (m, 2H), 6,79 (s a, 2H), 4,67 (s, 1H), 4,52 (s, 1H), 4,45 (s, 1H), 4,29 (s, 1H), 2,36-2,23 (m, 5H), 1,03-0,95 (m, 3H) 4,52 (s, 1H), 4,45 (s, 1H), 4,29 (s, 1H), 2,36-2,23 (m, 5H), 1,03-0,95 (m, 3H). |
| 35 |  | 4-{4-cloro-2-metilfenil)-6-etil-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 5 | (300 MHz, DMSO-D6) δ ppm 7,40 (d, J = 2,1 Hz, 1H), 7,31 (dd, J = 8,3 y 2,1 Hz, 1H), 7,25 (d, J = 8,3 Hz, 1H), 6,58 (s a, 2H), 3,70 (s, 2H), 3,58 (s, 2H), 2,65 (c, J = 7,2 Hz, 2H), 2,24 (s, 3H), 1,04 (t, J = 7,2 Hz, 3H). |

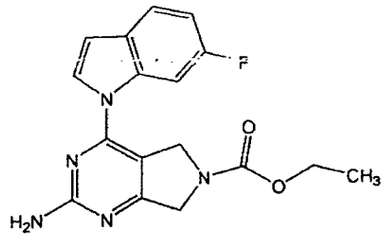
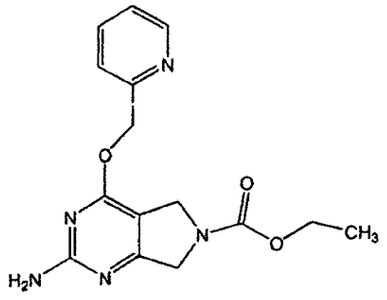
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 36 |  | 4-(4-cloro-2-metilfenil)-6-(piridin-2-ilcarbonil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 8,68 (d, J = 4,3 Hz, 0,5H), 8,57 (d, J = 4,3 Hz, 0,5H), 8,01-7,91 (m, 1H), 7,88-7,78 (m, 1H), 7,58-7,37 (m, 3H), 7,29 (s, 1H), 6,82 (s a, 1H), 6,79 (s a, 1H), 4,99 (s, 1H), 4,80 (s, 1H), 4,74 (s, 1H), 4,60 (s, 1H), 2,27 (s, 1,5H), 2,22 (s, 1,5H). |
| 37 |  | 4-(4-cloro-2-metilfenil)-6-[(dimetilamino)acetil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,43 (m, 1H), 7,35-7,32 (m, 2H), 6,80 y 6,78 (2 solapamiento, s a, 2 H). 4,75 (s, 1H), 4,58 (s, 1H), 4,46 (s, 1H), 4,32 (s, 1H), 3,12 (s, |

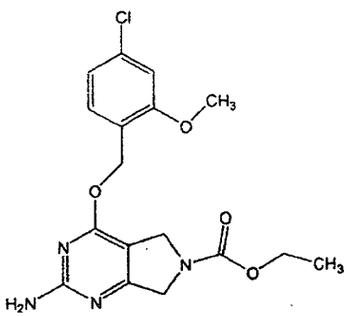
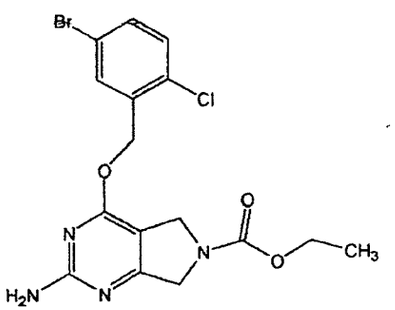
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| | | | | 1H), 3,08 (s, 1H), 2,25 (s, 1,5H), 2,24 (s, 1,5H), 2,23 (s, 3H), 2,18 (s, 3H) |
| 38 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-etil-*N*-metil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s, 1H), 7,35-7,32 (m, 2H), 6,73 (s a, 2H), 4,51 (s, 2H), 4,38 (s, 2H), 3,15 (c, J = 7,0 Hz, 2 H), 2,76 (s, 3H), 2,25 (s, 3H), 1,05 (t, J = 7,0 Hz, 3H) |
| 39 |  | 2-amino-4-(2,4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 1 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,78 (d, J = 1,9 Hz, 1H), 7,56 (dd, J = 8,3 y 1,9 Hz, 1H), 7,48 (d, J = 8,3 Hz, 1H), 6,92 (s a, 2H), 4,49 (s, 1H), 4,47 (s, 1H), 4,34 (s, 1H), 4,31 (s, 1H), 4,13-4,03 (m, 2H), |

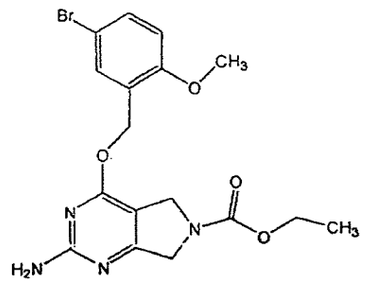
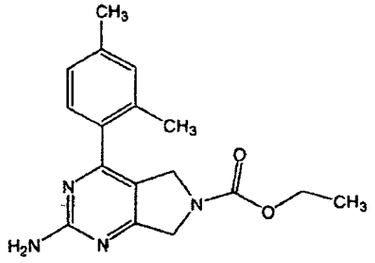
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| | | | | 1,24-1,15 (m, 3H). |
| 40 |  | 4-(4-cloro-2-metilfenil)-6-(pirrolidin-1-ilcarbonil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s, 1H), 7,35-7,32 (m, 2H), 6,73 (s a, 2H), 4,53 (s, 2H), 4,39 (s, 2H), 3,32-3,27 (m, 4H), 2,24 (s, 3H), 1,79-1,73 (m, 4H) |
| 41 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-(tetrahidrofuran-2-ilmetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,43 (s a, 1H), 7,35-7,32 (m, 2H), 6,75 (s a, 2H), 6,41 (t, J = 5,8 Hz, 1H), 4,41 (s, 2H), 4,26 (s, 2H), 3,87-3,80 (m, 1H), 3,76-3,69 (m, 1H), 3,62-3,54 (m, 1H), 3,07 (dt, J = 5,8 y 2,3 Hz, 2H), 2,23 (s, 3H), 1,88-1,72 (m, 3H), 1,58-1,50 (m, 1H) |

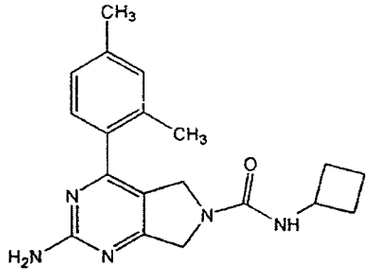
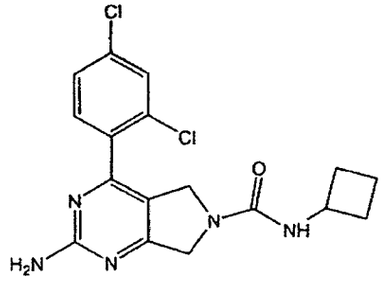
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 42 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-ciclobutil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (00 MHz, DMSO-D6) δ ppm 7,43 (s a, 1H), 7,35-7,32 (m, H), 6,75 (s a, 2H), 6,50 (d, J = 8,1 Hz, 1H), 4,40 (s, 2H), 4,24 (s, 2H), 4,18-4,08 (m, 1H), 2,22 (s, 3H), 2,14-2,03 (m, 2H), 1,96-1,89 (m, 2H), 1,59-1,50 (m, 2H). |
| 43 |  | 2-amino-*N*-ciclopropil-4-(24-diclorofenil)-5,7-dihidro-*6H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,79 (d, J = 1,9 Hz, 1H), 7,55 (dd, J = 8,3 y 2,0 Hz, 1H), 7,47 (d, J = 8,3 Hz, 1H), 6,87 (s a, 2H), 6,46 (d, J = 2,6 Hz, 1H), 4,40 (s, 2H), 4,22 (s, 2H), 0,57-0,50 (m, 2H), 0,41-0,36 (m, 2H). |

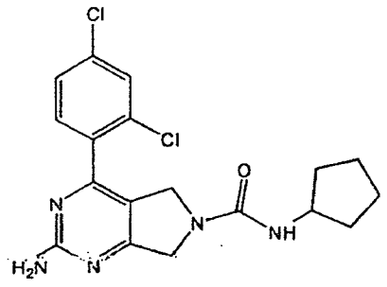
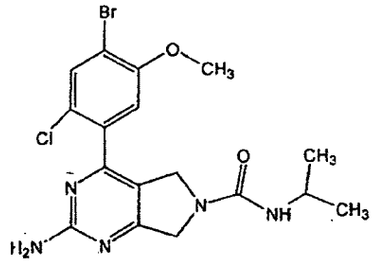
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 44 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-propil-5,7-dihidro-*6H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,43 (s a, 1H), 7,34-7,32 (m, 2H), 6,77 (s a, 2H), 6,36 (t, J = 6,4 Hz, 1H), 4,40 (s, 2H), 4,24 (s, 2H), 2,98 (m, 2H), 2,23 (s, 3H), 1,47-1,34 (m, 2H), 0,82 (t, J = 7,4 Hz, 3H). |
| 45 |  | 2-amino-*N*-butil-4-(4-cloro-2-metilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,42 (s a, 1H), 7,34-7,32 (m, 2H), 6,77 (s a, 2H), 6,32 (t, J = 5,5 Hz, 1H), 4,39 (s, 2H), 4,23 (s, 2H), 3,01 (m, 2H), 2,22 (s, 3H), 1,45-1,36 (m, 2H), 1,33-1,24 (m, 2H), 0,88 (t, J = 7,4 Hz, 3H) |

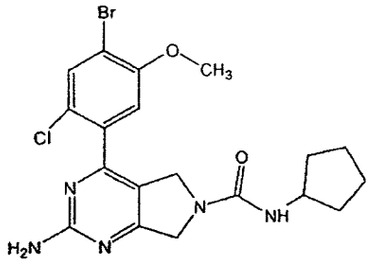
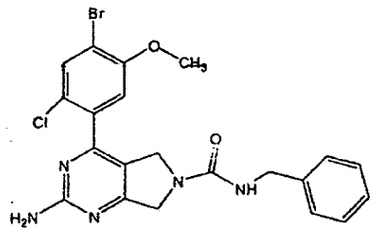
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 46 |  | 2-amino-4-(6-fluoro-1*H*-indol-1-il)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 12 | (300 MHz, DMSO-D6) δ ppm 8,50-8,44 (m, 1H), 7,70-7,63 (m 2H), 7,14-7,07 (m, 3H), 6,84 (d, J = 3,6 Hz, 1H), 4,82 (s, 1H), 4,79 (s, 1H), 4,47 (s, 1H), 4,44 (s, 1H), 4,13 (c, J = 7,2 Hz, 2H), 1,24 (t, J = 7,2 Hz, 3H) |
| 47 |  | 2-amino-4-(piridin-2-ilmetoxi)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 11 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 8,56 (m, 1H), 7,82 (dt, J = 7,7 y 1,7 Hz, 1H), 7,47 (d, J = 7,9 Hz, 1H), 7,36-7,32 (m, 1H), 6,72 (s a, 2H), 5,46 (s, 1H), 5,45 (s, 1H), 4,46-4,34 (m, 4H), 4,14-4,05 (m, 2H), 1,25-1,18 (m, 3H). |

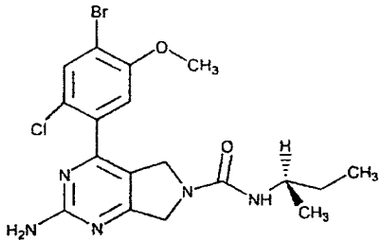
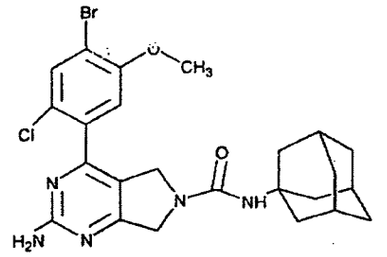
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 48 |  | 2-amino-4-[(4-cloro-2-metoxibencil)oxi]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 11 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,41 (d, J = 8,1 Hz, 1H), 7,13 (d, J =2,0 Hz, 1H), 7,03 (dd, J = 8,1 y 1,8 Hz, 1H), 6,73 (s a, 2H), 5,32 (s, 1H), 5,31 (s, 1H), 4,40-4,32 (m, 4H), 4,12-4,05 (m, 2H), 3,84 (s, 3H), 1,23-1,19 (m, 3H). |
| 49 |  | 2-amino-4[(5-bromo-2-clorobencil)oxi]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 11 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,78-7,76 (m, 1H), 7,62-7,59 (m, 1H), 7,49 (d, J = 8,6, 1H), 6,79 (s a, 2H), 5,42 (s, 1H), 5,41 (s, 1H), 4,42-4,33 (m, 4H), 4,12-4,06 (m, 2H), 1,23-1,19 (m, 3H). |

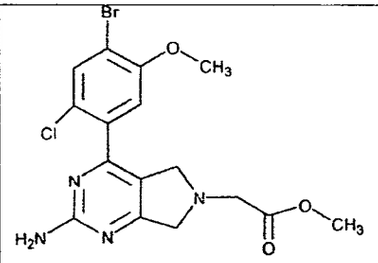
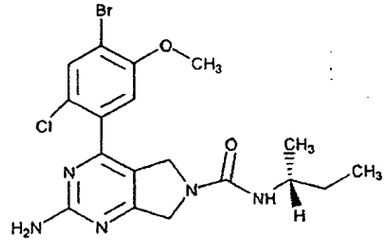
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 50 |  | 2-amino-4-[(5-bromo-2-metoxibencil)oxi]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 11 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,53-7,48 (m, 2H), 7,05-7,00 (m, 1H), 6,75 (s a, 2H), 5,33 (s, 1H), 5,32 (s, 1H), 4,41-4,32 (m, 4H), 4,13-4,05 (m, 2H), 3,81 (s, 3H), 1,24-1,19 (m, 3H).) |
| 51 |  | 2-amino-4-(2,4-dimetilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 11 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,21-7,07 (m, 3H), 4,48 y 4,45 (2 solapamiento s a, 2H), 4,32 y 4,29 (2 solapamiento s a, 2H), 4,12-4,01 (m, 2H), 2,31 (s, 3H), 2,21 y 2,20 (2 solapamiento s, 3H), 1,23-1,14 (m, 3H) |

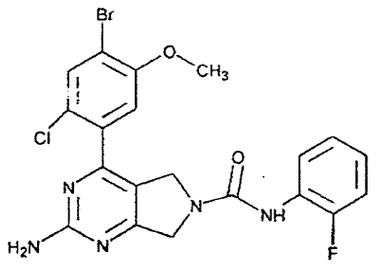
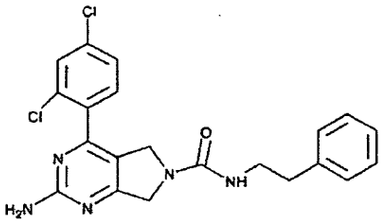
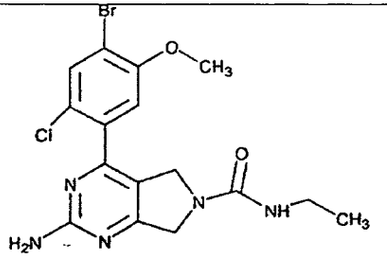
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 52 |  | 2-amino-*N*-ciclobutil-4-(2,4-dimetilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,17-7,06 (m, 3H), 6,67 (s a, 2H), 6,50 (d, J = 7,5 Hz, 1H), 4,38 (s a, 2H), 4,24 (s a, 2H), 4,16-4,08 (m, 1H), 2,31 (s, 3H), 2,19 (s, 3H), 2,13-2,04 (m, 2H), 1,99-1,85 (m, 2H), 1,58-1,48 (m, 2H). |
| 53 |  | 2-amino-*N*-ciclobutil-4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | (300 MHz, DMSO-D6) δ ppm 7,80 (d, J = 2,0 Hz, 1H), 7,56 (dd, J = 8,1 y 2,0 Hz, 1H), 7,48 (d, J = 8,3 Hz, 1H), 6,89 (s a, 2H), 6,53 (d, J -7,8 Hz, 1H), 4,40 (s a, 2H), 4,24 (s a, 2H), 4,17-4,07 (m, 1H), 2,12-2,05 (m, 2H), 1,97-1,86 (m, 2H), 1,58- |

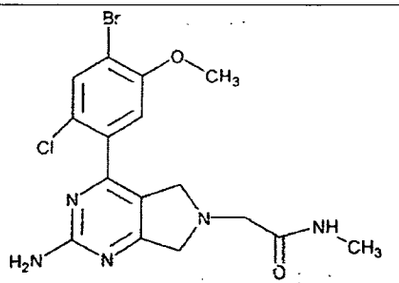
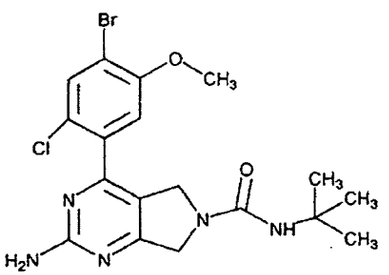
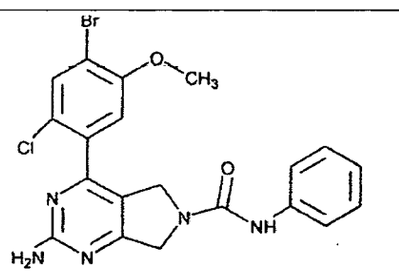
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| | | | | 1,48 (m, 2H) |
| 54 |  | 2-amino-*N*-ciclopentil-4-(2,4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,80 (d, J = 2,0 Hz, 1H), 7,56 (dd, J = 8,3 y 2,0 Hz, 1H), 7,48 (d, J = 8,3 Hz, 1H), 6,88 (s a, 2H), 6,13 (d, J = 7,3 Hz, 1H), 4,42 (s a, 2H), 4,25 (s a, 2H), 3,97-3,88 (m, 1H), 1,81-1,73 (m, 2H), 1,65-1,67 (m, 2H), 1,50-1,34 (m, 4H) |
| 55 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,16 (s, 1H), 6,89 (s a, 2H), 6,07 (d, J = 7,7 Hz, 1H), 4,42 (s a, 2H), 4,25 (s a, 2H), 3,86 (s, 3H), 3,82-3,75 (m, 1H), 1,05 (d, J = 6,4 Hz, 6H) |

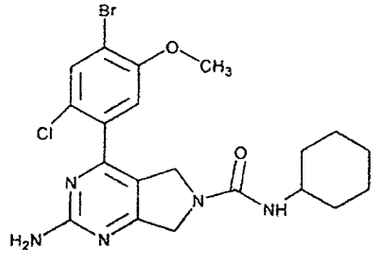
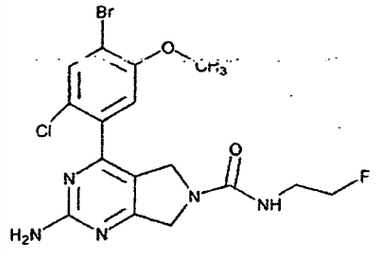
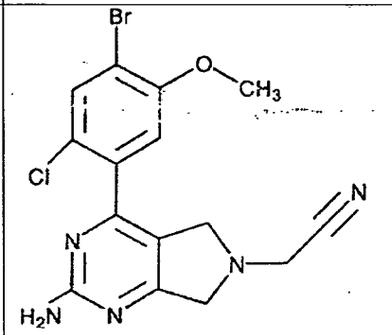
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN |
|---|---|---|---|---|
| 56 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-ciclopentil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,16 (s, 1H), 6,90 (s a, 2H), 6,13 (d, J = 7,5 Hz, 1H), 4,42 (s, 2H), 4,26 (s, 2H), 3,97-3,87 (m, 1H), 3,86 (s, 3H), 1,84-1,71 (m, 2H), 1,67-1,56 (m, 2H), 1,52-1,32 (m, 4H) |
| 57 |  | 2-amino-*N*-bencil-4-(4-bromo-2-cloro-2-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,31-7,24 (m, 4H), 7,22-7,17 (m, 1H), 7,17 (s, 1H), 7,00 (t, J = 5,7 Hz, 1H), 6,19 (s a, 2H), 4,47 (s, 2H), 4,33 (s, 2H), 4,25 (d, J = 5,7 Hz, 2H), 3,86 (s, 3H) |

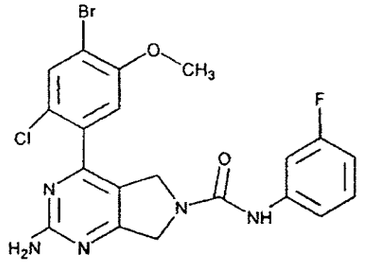
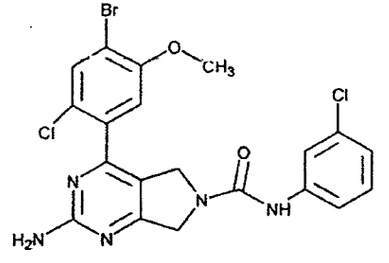
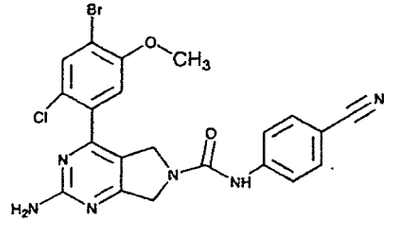
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| 58 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-[(1*R*)-1-metilpropil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,17 (s, 1H), 6,90 (s a, 2H), 6,00 (d, J = 7,8 Hz, 1H), 4,43 (s, 2H), 4,27 (s, 2H), 3,86 (s, 3H), 3,62-3,49 (m, solapa con pico de H2O, 1H), 1,46-1,31 (m, 2H), 1,02 (d, J - 6,6 Hz, 3H), 0,81 (t, J a 7,3 Hz, 3H) | 454,2, 456,2 |
| 59 |  | *N*-1-adamantil-2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,16 (s, 1H), 6,97 (s a, 2H), 5,45 (s, 1H), 4,41 (s, 2H), 4,26 (s, 2H), 3,86 (s, 3H), 1,99 (s a, 3 H), 1,94 (s a, 6H), 1,60 (s a, 6H) | 532,2, 534,2 |

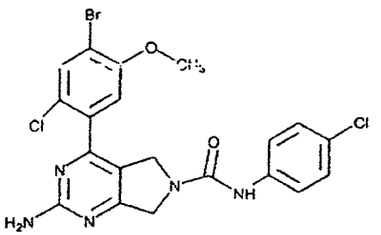
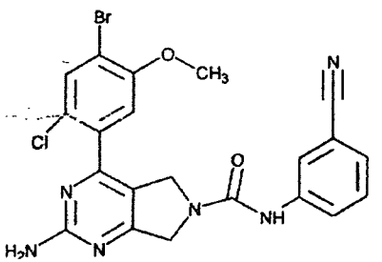
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| 60 |  | [2-amino-4-(4-bromo-2-cloro-5-metoxifenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]acetato de metilo | Ejemplo 5 | (300 MHz, CDCl3) δ ppm 7,66 (s, 1H), 6,98 (s, 1H), 5,76 (s a, 2H), 4,45 (s a, 2H), 4,33 (s a, 2H), 3,97 (s, 3H), 3,88 (s, 2H), 3,82 (s, 3 H) | 472,2, 429,2 |
| 61 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-[(1*S*)-1-metilpropil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | 300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,17 (s, 1H), 6,89 (s a, 2H), 6,00 (d, J = 8,3 Hz, 1H), 4,42 (s, 2H), 4,26 (s, 2H), 3,86 (s, 3H), 3,64-3,51 (m, solapa con pico de H2O, 1H), 1,47-1,30 (m, 2H), 1,02 (d, J = 6,4 Hz, 3H), 0,80 (t, J = 7,3 Hz, 3H). | 454,2, 456,2 |

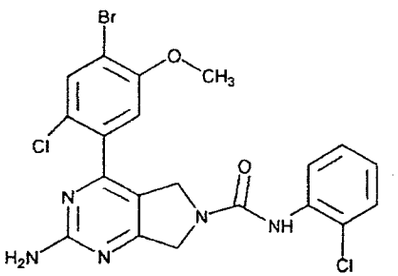
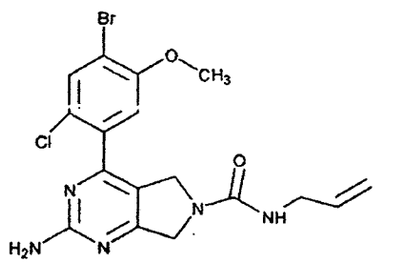
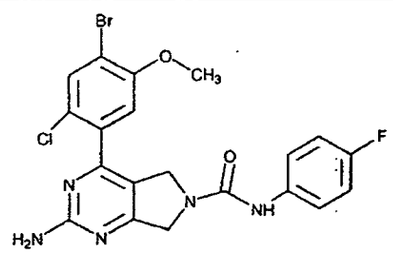
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| 62 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(2-fluorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,18 (s, 1H), 7,88 (s, 1H), 7,50-7,44 (m, 1H), 7,23-7,10 (m, 4H), 6,95 (s a, 2H), 4,61 (s a, 2H), 4,48 (s a, 2H), 3,88 (s, 3H). | 492,2, 494,2 |
| 63 |  | 2-amino-4-(2,4-diclorofenil)-*N*-(2-feniletil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,80 (s, 1H), 7,57 (d, J = 8,3 Hz, 1H), 7,49 (d, J = 8,1 Hz, 1H), 7,32-7,26 (m, 2H), 7,23-7,15 (m, 3H), 6,90 (s a, 2H), 6,52 (m, 1H), 4,42 (s a, 2H), 4,25 (s a, 2H), 3,32-3,19 (m, solapa con pico de H2O, 2H), 2 72 (t, J = 7,3 Hz, 2H). | 428,2, 430,2 |
| 64 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-etil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,17 (s, 1H), 6,90 (s a, 2H), 6,36 (t, J - 5,2 Hz, 1H), 4,42 (s a, 2H), 4,26 (s a, 2H), 3,86 (s, 3H), 3,10-3,01 (m, | 426,2, 428,2 |

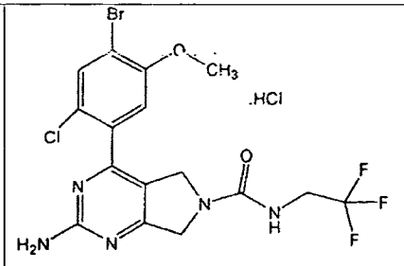
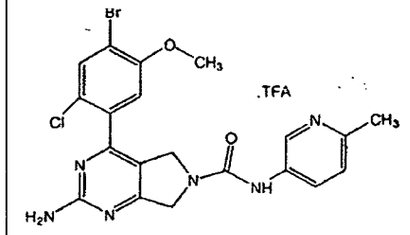
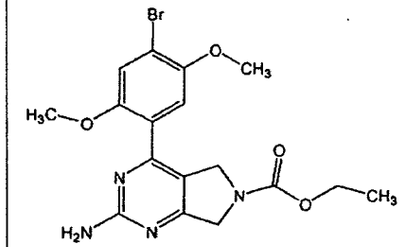
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| | | | | 2H), 1,01 (t, J = 7,2 Hz, 3H). | |
| 65 |  | 2-[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]-*N*-metilacetamida | Ejemplo 5 | (300 MHz, DMSO-D6) δ ppm 7,82 (s, 1H), 7,81-7,75 (m, 1H), 7,07 (s, 1H), 6,76 (s a, 2H), 3,85 (s, 5H), 3,73 (s, 2H), 3,28 (s, 2H), 2,57 (d, J = 4,7 Hz, 3H). | 426,2, 428,2 |
| 66 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(*terc*-butil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO- D6) δ ppm 7,86 (s, 1H), 7,16 (s, 1H), 6,88 (s a, 2H), 5,58 (s, 1H), 4,42 (s, 2H), 4,26 (s, 2H), 3,86 (s, 3H), 1,26 (s, 9H) | 454,2, 456,2 |
| 67 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-fenil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO- D6) δ ppm 8,34 (s, 1H), 7,89 (s, 1H), 7,51 (d, J = 7,9 Hz, 2H), 7,26-7,19 (m, 3H), 6,98-6,91 (m, 3H), 4,60 (s, 2H), 4,48 (s, 2H), 3,88 (s, 3H) | 474,2, 476,2 |

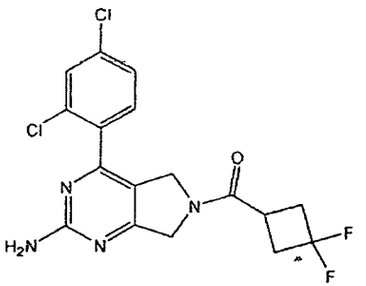
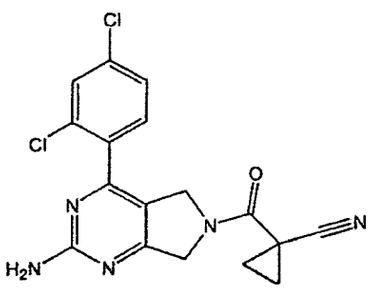
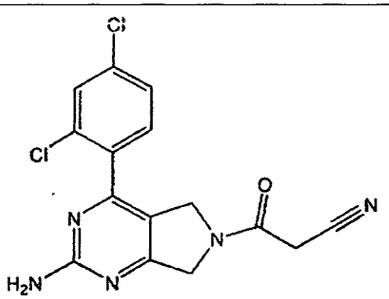
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| 68 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-ciclohexil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,16 (s, 1H), 6,89 (s a, 2H), 6,07 (d, J = 7,9 Hz, 1H), 4,42 (s, 2H), 4,25 (s, 2H), 3,49-3,44 (m, bajo pico de H2O, 1H), 3,86 (s, 3H), 1,78-1,00 (M, 10H). | 480,2, 482,2 |
| 69 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(2-fluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | (300 MHz, DMSO-D6) δ ppm 7,87 (s, 1H), 7,17 (s, 1H), 6,91 *(s a,* 2H) 6,65 (t, J = 5,4 Hz, 1H), 4,50-4,43 (m, 3H), 4,35-4,28 (m, 3H), 3,86 (s, 3H), 3,36-3,25 (m, bajo pico de H2O, 2H). | 444,2, 446,2 |
| 70 |  | [2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]acetonitrilo | Ejemplo 5 | (300 MHz, DMSO-D6) δ ppm 7,84 (s, 1H), 7,14 (s, 1H), 6,87 (s a, 2H), 3,96 (s, 2H), 3,86 (s, 3H), 3,85 (s, 2H), 3,74 (s, 2H). | 394,2, 396,2 |

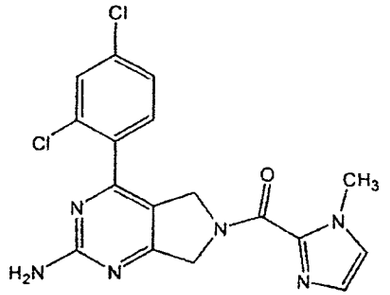
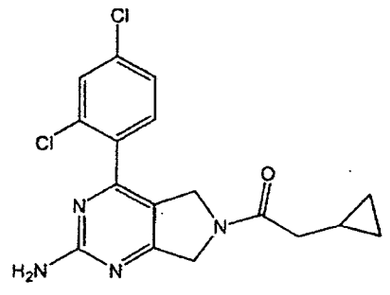
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| 71 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(3-fluorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,54 (s, 1H), 7,88 (s, 1H), 7,50 (dt, J = 12,2 y 1,9 Hz, 1H), 7,33-7,21 (m, 2H), 7,19 (s, 1H), 6,95 (s a, 2H), 6,78-6,72 (m, 1H), 4,60 (s, 2H), 4,48 (s, 2H), 3,87 (s, 3H). | 492,2, 494,2 |
| 72 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(3-clorofenil)-5,7-dihidro-6*H*-pirrolo[3,5-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,52 (s, 1H), 7,88 (s, 1H), 7,70 (t, J = 1,8 Hz, 1H), 7,48 (d, J = 7,5 Hz, 1H), 7,25 (t. J = 8,10 Hz, 1H), 7,19 (s, 1H), 7,01-6,94 (m, 3H), 4,60 (s, 2H), 4,47 (s, 2H), 3,87 (s, 3H) | 508,0, 510,2, 512,0 |
| 73 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(4-cianofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,80 (s, 1H), 7,89 (s, 1H), 7,76 (d, J = 8,9 Hz, 2H), 7,69 (d, J = 8,9 Hz, 2H), 7,19 (s, 1H), 6,97 (s a, 2H), 4,63 (s, 2H), 4,51 (s, 2H), 3,87 (s, 3H). | 499,2, 501,2 |

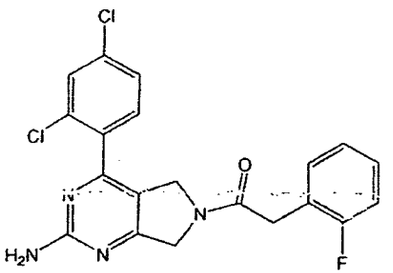
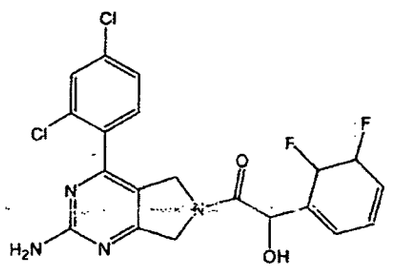
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| 74 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(4-clorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,48 (s, 1H), 7,89 (s, 1H), 7 56 (d, J = 8,9 Hz. 2H), 7,29 (d, J = 8,9 Hz, 2H), 7,19 (s, 1H), 6,95 (s a, 2H), 4,60 (s, 2H), 4,47 (s, 2H), 3,87 (s, 3H). | 508,0, 510,0, 512,0 |
| 75 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(3-cianofenil)-5,7-dihidro-*6H*-pirrolo[3,4-d]pirimidina-6-carboxamida | (300 MHz, DMSO-D6) δ ppm 8,69 (s, 1H), 8,01-7,99 (m, 1H), 7,89 (s, 1H), 7,85-7,80 (m, 1H), 7,49-7,38 (m 2H), 7,20 (s, 1H), 6,97 (s a, 2H), 4,61 (s, 2H), 4,49 (s, 2H), 3,88 (s, 3H). | Ejemplo 15a | 499,2, 501,2 |

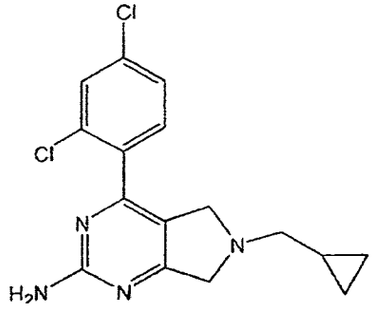
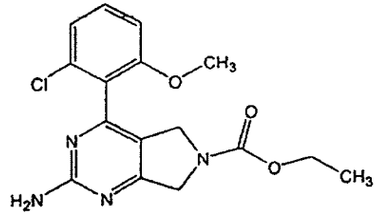
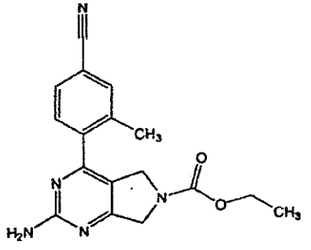
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| 76 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(2-clorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO D6) δ ppm 8,07 (s, 1H), 7,87 (s, 1H), 7,55 (d, J = 7,5 Hz, 1H), 7,46 (d, J = 7,4 Hz, 1H), 7,29 (t, J = 7,3 Hz, 1H), 7,20 (s, 1H), 7,15 (t, J = 7,5 Hz, 1H), 6,95 (s a, 2H), 4,61 (s, 2H), 4,49 (s, 2H), 3,87 (s, 3H). | 508,0, 510,0, 512,0 |
| 77 |  | *N*-alil-2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 7,86 (s, -1H), 7,17 (s, 1H), 6,92 (s a, 2H), 6,59 (t, J = 5,4 Hz, 1H), 5,87-5,74 (m, 1H), 5,12-4,97 (m, 2H), 4,45 (s, 2H), 4,30 (s, 2H), 3,86 (s, 3H), 3,67 (m, 2H). | 438,2, 440,2 |
| 78 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(4-fluorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (300 MHz, DMSO-D6) δ ppm 8,40 (s, 1H), 7,88 (s, 1H), 7,54-7,47 (M, 2H), 7,19 (s, 1H), 7,07 (t, J = 8,7 Hz, 2H), 6,95 (s a, 2H), 4,59 (s, 2H), 4,46 (s, 2H), 3,87 (s, 3H). | 492,2, 494,2 |

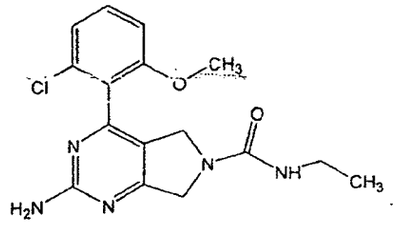
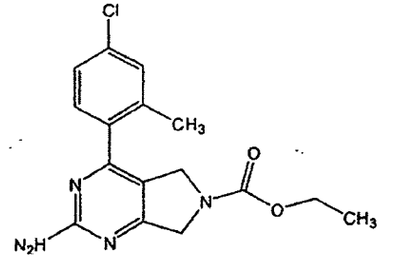
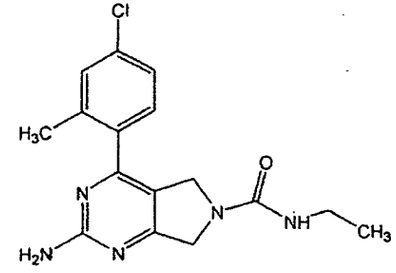
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| 79 |  | clorhidrato de 2-amino-4-(4-bromo-2-cloro-2-metoxifenil)-*N*-(2,2,2-trifluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | (300 MHz, DMSO-D6) δ ppm 7,86 (s, 1H), 7,17 (s, 1H), 7,09 (t, J = 6,0 Hz, 1H), 6,93 (s a, 2H), 4,47 (s, 2H), 4,32 (s, 2H), 3,86 (s, 3H), 3,86-3,76 (m, 2H). | 480,2, 482,2 |
| 80 |  | trifluoroacetato de 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(6-metilpiridin-3-il)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 3 | (300 MHz, DMSO-D6) δ ppm 8,98 (s, 1H), 8,84 (s, 1H), S.23 (d, J = 8,5 Hz, 1H), 7,90 (s, 1H), 7,61 (d, J = 8,3 Hz, 1H), 7,20 (s, 1H), 6,99 (s a, 2H), 4,63 (s, 2H), 4,51 (s, 2H), 3,88 (s, 3H), 2,55 (s, 3H). | 489,2, 491,2 |
| 81 |  | 2-amino-4-(4-bromo-2,5-dimetoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 1 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,39 (s, 1H), 7,05 (s, 1H), 6,82 (s a, 2H), 4,45 (s a, 1H), 4,43 (s a, 1H), 4,31 (s a, 1H), 4,29 (s a, 1H), 4,12-4,02 (m, 2H), 3,79 (s, 3H), 3,77 (s, 3H), 1,23-1,15 (m, 3H). | 423,2, 425,2 |

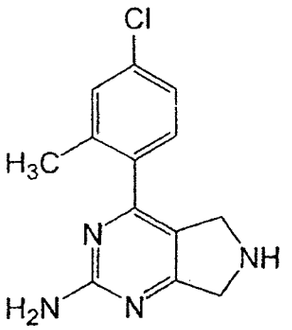
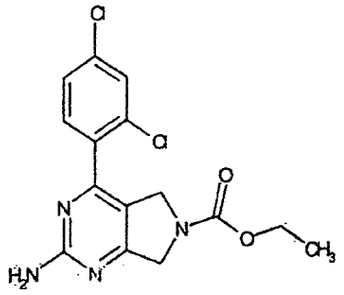
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| 82 |  | 4-(2,4-diclorofenil)-6-[(3,3-difluorociclobutil)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 2,68 - 2,88 (m, 4H), 3,14 - 3,28 (m, 1H) 4,35 (s, 1H) 4,52 (d, J = 14,40 Hz, 2H) 4,69 (s. 1H) 6,95 (s, 2H) 7,44 - 7,52 (m, 1H) 7,53 - 7,61 (m, 1H) 7,80 (d, J = 1,77 Hz, 1H). | 399, 401 |
| 83 |  | 1-{[2-amino-4-(2,4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]carbonil}ciclopropano carbonitrilo | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 1,47 - 1,67 (m, 4H). 4,49 (d, J = 58,86 Hz, 2 H) 4,94 (d, J = 43,96 Hz, 2H) 7,00 (s, 2H) 7,42 -7,63 (m, 2H) 7,81 (dd, J = 17,94, 2,02 Hz, 1H). | 374, 376 |
| 84 |  | 3-[2-amino-4-(2,4-diclorofenilo)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]-3-oxo propanonitrilo | Ejemplo 6 | 400 MHz, DMSO-d6) δ ppm. 4,03 (d, J = 27,79 Hz, 2H) 4,35 (s, 1H) 4,51 (d, J = 3,54 Hz, 2H) 4,68 (s, 1H) 6,99 (s, 2H) 7,48 (dd, J = 8,34, 6,32 Hz, 1H) 7,52 - 7,61 (m, 1H) 7,80 (dd, J = 7,33, 2,02 Hz, 1H). | 348, 350 |

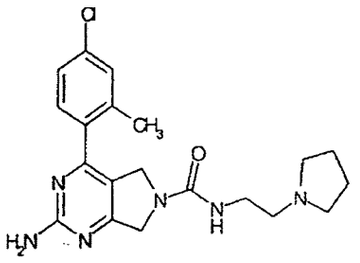
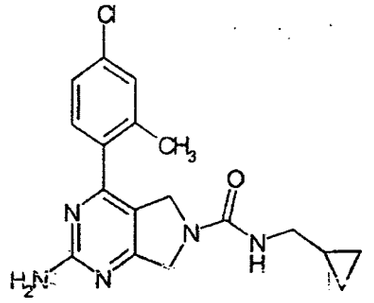
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| 85 |  | 4-(2,4-diclorofenil)-6-[(1-metil-1*H*-imidazol-2-il)carbonil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 3,86 (d, J = 1,77 Hz, 3H) 4,62 (d, J = 61,39 Hz, 2H) 5,04 (d, J = 61,64 Hz, 2H) 6,94 (s, 2H) 7,03 (dd, J = 34,61, 1,01 Hz, 1H) 7,35 (d, J = 14,91 Hz, 1H) 7,44 - 7,52 (m, 1H) 7,54 - 7,62 (m, 1H) 7,80 (d, J = 1,77 Hz, 1H). | 389, 391 |
| 86 |  | 6-(ciclopropilacetil)-4-(2,4-diclorofenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 0,01 - 0,18 (m, 2H) 0,36 - 0,52 (m, 2H) 0,99 (dd, J = 7,33, 4,80 Hz, 1H) 2,25 (dd, J = 30,06, 6,57 Hz, 2H) 4,31 (s, 1H) 4,48 (d, J = 9,85 Hz, 2H) 4,67 (s, 1H) 6,93 (s, 2H) 7,43 -7,51 (m, 1H) 7,52 - 7,61 (m, 1H) 7,79 (d, J = 1,26 Hz, 1H). | 386, 365 |

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| 87 |  | 4-(2,4-diclorofenil)-6-[(2-fluorofenil)acetil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 3,77 (d, J = 32,34 Hz, 2H) 4,35 (s, 1H) 4,51 (s, 1H) 4,70 (s, 1H) 4,86 (s, 1H) 6,97 (s, 2H) 7,08 - 7,21 (m, 2H) 7,24 - 7,37 (m, 2H) 7,46 -7,63 (m, 2H) 7,80 (dd, J = 9,85, 1,77 Hz, 1H). | 417, 419 |
| 88 |  | 2-[2-amino-4-(2,4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]-1-(2,3-difluorofenil)-2-oxoetanol | Ejemplo 6 | (400 MHz, DMSO-d6) δ ppm 4,44 - 4,60 (m, 2H) 4,75 - 5,02 (m, 2H) 5,59 (dd, J = 26,02, 7,07 Hz, 1H) 6,18 (dd, J = 6,82, 2,27 Hz, 1H) 6,96 (d, J = 8,59 Hz, 2H), 7,16 - 7,33 (m, 2H) 7,33 - 7,44 (m, 1H) 7,44 - 7,54 (m, 1H) 7,53 - 7,61 (m, 1 H) 7,79 (dd, J = 3,03, 2,02 Hz, 1H). | 451, 453 |

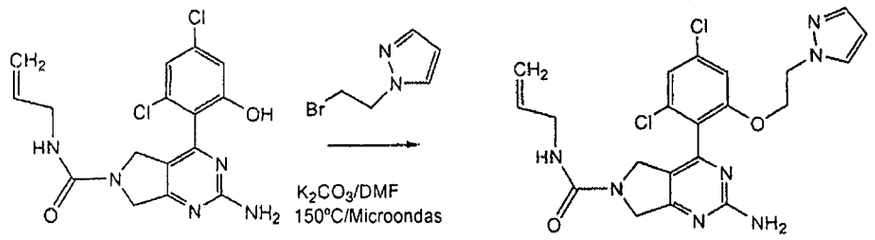
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| 89 |  | 6-(ciclopropilmetil)-4-(2,4-diclorofenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 5 | (400 MHz, MeOH-d4) δ ppm 0,29 (d, J = 6,06 Hz, 2H) 0,55 - 0,69 (m, 2H) 0,93 -1,10 (m, 1H) 2,84 (d, J = 7,07 Hz, 2H) 4,04 (s, 2H) 4,14 (s, 2H) 7,35-7,54 (m, 2H) 7,64 (d, J = 1,77 Hz, 1H). | 335, 337 |
| 90 |  | 2-amino-4-(2-cloro-6-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 1 | (400 MHz, DMSO-D6) δ 7,45 (dd, 1H, J = 8,4, 8,3 Hz), 7,16-7,12 (m, 2H), 6,84 (s a, 2H), 4,55-4,45 (m, 2H), 4,20-3,98 (m, 4H), 3,74 (s, 3H), 1,27-1,12 (m, 3H) | 349,2 351,2 |
| 91 |  | 2-amino-4-(4-ciano-2-metilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 1 | (400 MHz, DMSO-D6) δ ppm 7,84 (s, 1H), 7,76 (d, 1H, J = 7,9 Hz), 7,68-7,48 (m, 1H), 6,89 (s a, 2H), 4,55-4,40 (m, 2H), 4,35-4,20 (m, 2H), 4,15-3,95 (m, 2H), 2,26 (s, 3H), 1,27-1,12 (m, 3H) | 324 |

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|---|---|---|---|---|---|
| 92 |  | 2-amino-4-(2-cloro-6-metoxifenil)-*N*-etil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (400 MHz, DMSO-D6) δ ppm 7,44 (dd, 1H, J = 8,4, 8,3 Hz), 7,16-7,12 (m, 2H), 6,79 (s a, 2H), 6,36 (t, 1H), 4,42 (s a, 2H), 4,10 (s a, 2H), 3,74 (s, 3H), 3,08-2,95 (m, 2H), 1,00 (t, 3H) | 348,2, 350,2 |
| 93 |  | 2-amino-4-(4-cloro-2-metilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato | Ejemplo 1 | (400 MHz, DMSO-D6) δ ppm 7,43 (s, 1H), 7,34 (s, 2H), 6,82 (s a, 2H), 4,47 (d, 2H, J = 8), 4,32 (d, 2H, J = 12 Hz), 4,07 (m, 2H), 2,24 (s, 3H), 1,22 (t, 3H, J = 7,1 Hz). | 333,2, 335,2 |
| 94 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-etil-57-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 15a | (400 MHz, CD3OD) δ ppm 7,27 (s, 1H), 7,20 (s, 2H), 4,44 (s, 2H), 4,27 (s, 2H), 3,11 (m, 2H), 2,17 (s, 3H), 1,01 (t, 3H, 8 Hz) | 332,4, 334,2 |

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| 95 |  | 4-(4-cloro-2-metilfenil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina | Ejemplo 2 | (400 MHz, DMSO-D6) δ ppm 7,41 (s, 1H) 7,32 (3, 1H, J= 8 Hz), 7,26 (d, 1H, J = 8 Hz), 6,56 (s a, 2H), 3,88 (s, 2H), 3,80 (s, 2H), 2,24 (s, 3H) | 261 |
| 96 |  | 2-amino-4-(2,4-diclorofenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ejemplo 1 | (300 MHz, DMSO-D6) (confórmeros) δ ppm 7,78 (d, J = 1,9 Hz, 1H), 7,56 (dd, J = 8,3 y 1,9 Hz, 1H), 7,48 (d, J = 8,3 Hz, 1H), 6,92 (s a, 2H), 4,49 (s, 1H), 4,47 (s, 1H), 4,34 (s, 1H), 4,31 (s, 1H), 4-13-4,03 (m, 2H), 1,24-1,15 (m, 3H). | 355,2, 353,2 |

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| 97 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-(2-pirrolidin-1-iletil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,43-7,42 (m, 1H), 7,36-7,30 (m, 2H), 6,77 (s a, 2H), 6,35 (t, J = 5,8 Hz, 1H), 4,40 (s, 2H), 4,24 (s, 2H), 3,17-3,10 (m, 2H), 2,46-2,39 (m, 6H), 2,22 (s, 3H), 1,66-1,62 (m, 4H), | 401,2 |
| 98 |  | 2-amino-4-(4-cloro-2-metilfenil)-*N*-(ciclopropilmetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ejemplo 7 | (300 MHz, DMSO-D6) δ ppm 7,43-7,42 (m, 1H), 7,35-7,33 (m, 2H), 6,77 (s a, 2H), 6,46 (t, J = 5,6 Hz, 1H), 4,41 (s, 2H), 4,25 (s, 2H), 2,90 (dd, J = 6,0 y 6,0 Hz, 2H), 2,23 (s, 3H), 0,97-0,87 (m, 1H), 0,38-0,32 (m, 2H), 0,16-011 (m, 2H) | 358,2 |

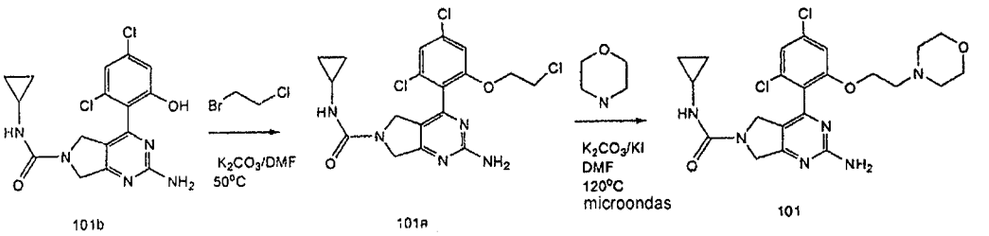
**Ejemplo 100: *N*-alil-2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




100a 100

El compuesto **100a**, *N*-alil-2-amino-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida, se preparó de una manera similar al Ejemplo **18a** con la excepción de que se sustituyó ciclobutilamina y CDI por isocianato de alilo en el Ejemplo **18b.** El compuesto **100a** (60 mg, 0,16 mmol), carbonato potásico (131 mg, 0,95 mmol), 1-(2-bromoetil)-1*H*-pirazol (56 mg, 0,316 mmol) y DMF (2,0 ml) se sometieron a microondas a 120°C durante 30 min. El aislamiento por HPLC preparativa dio el compuesto **100** (39 mg, 0,08 mmol) en forma de un sólido de color blanco con un rendimiento del 52%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,60 (d, J = 12,88 Hz, 2H), 3,67 (t, J = 5,05 Hz, 2H), 3,94 (d, J = 13,14 Hz, 2H), 4,27-4,37 (m, 4H), 4,41 (d, J = 5,81 Hz, 2H), 5,74-5,90 (m, 1H), 6,00 (t, J = 2,02 Hz, 1H), 6,45 (s a, 1H), 6,78 (s, 2H), 7,18 (d, J = 2,02 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,29 (d, J = 1,52 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). LCMS $(M+H)^+$ 474,0, 476,0.

**Ejemplo 101: 2-amino-*N*-ciclopropil-4-[2,4-dicloro-6-(2-morfolin-4-4-iletoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**



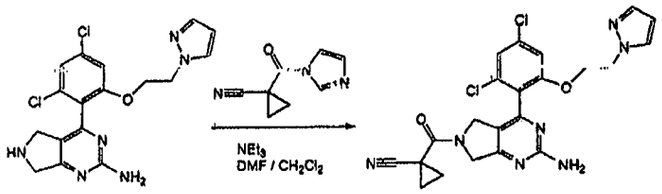

101b 101a 101

El compuesto **101b,** 2-amino-*N*-ciclopropil-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida, se preparó de una manera similar al Ejemplo **18a** con la excepción de que se sustituyó ciclobutilamina por ciclopropilamina en el Ejemplo **18b.** El compuesto **101b** (800 mg, 2,1 mmol), carbonato potásico (872 mg, 6,31 mmol) y 1-bromo-2-cloroetano (0,4 ml, 4,2 mmol) en DMF (8,0 ml) se calentaron a 50°C durante 12 h y la mezcla se filtró. El material insoluble recogido se lavó con EtOAc. Los lavados/filtrado combinados adicionales de EtOAc (200 ml) se lavaron con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml), se secaron ($Na_2SO_4$), se filtraron y se concentraron. El aislamiento por cromatografía sobre gel de sílice (gradiente de MeOH al 0-10% en $CH_2Cl_2$) dio el compuesto **101a**, 2-amino-*N*-ciclopropil-4-[2,4-dicloro-6-(2-cloroetoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida (786 mg, 1,79 mmol) en forma de una grasa de color pardo con un rendimiento del 85%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,43 (m, 2H), 0,47-0,58 (m, 2H), 3,69-3,86 (m, 1H), 4,00-4,12 (m, 2H), 4,19 (d, J = 13,14 Hz, 2H), 4,23-4,31 (m, 2H), 4,32-4,45 (m, 2H), 6,42 (d, J = 2,78 Hz, 1H), 6,80 (s, 2H), 7,38 (d, J = 1,77 Hz, 1H), 7,96 (s, 1H). LCMS $(M+H)^+$ 444,0, 446,0.

Después, el compuesto **101a** (50 mg, 0,11 mmol), $K_2CO_3$ (94 mg, 0,68 mmol), KI (38 mg, 0,23 mmol), morfolina (30 mg, 0,34 mmol) y DMF (2,0 ml) se

sometieron a microondas a 130°C durante 45 min. El aislamiento por HPLC preparativa dio el compuesto **101** (32 mg, 0,063 mmol) en forma de un sólido de color blanco con un rendimiento del 57%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,45 (m, 2H), 0,48-0,58 (m, 2H), 2,07-2,37 (m, 4H), 2,52-2,58 (m, 1H), 3,39 (s a, 4H), 4,02-4,22 (m, 5H), 4,34-4,46 (m, 3H), 6,46 (d, J = 2,27 Hz, 1H), 6,81 (s a, 2H), 7,32 (d, J = 15,66 Hz, 2H). LCMS $(M+H)^+$ 493,1, 495,1.

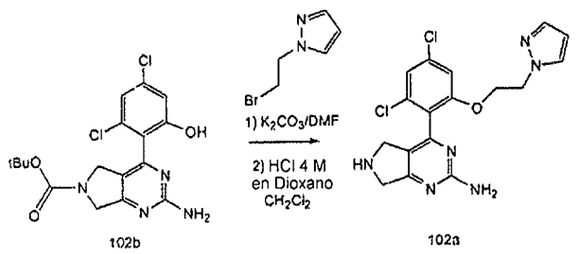
**Ejemplo 102: 2-amino-*N*-(1-cianociclopropil)-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




102a 102

El compuesto **102a**·HCl (45 mg, 0,12 mmol) se trató con el aducto preformado de clorhidrato de 1-amino-ciclopropanocarbonitrilo (59 mg, 0,5 mmol) y CDI (126 mg, 0,775 mmol) de una manera similar a la que se ha descrito para el Ejemplo **18b.** Después del tratamiento extractivo en EtOAc lavando con $NaHCO_3$ acuoso saturado, el producto se aisló por HPLC preparativa, dando el compuesto **102** (38 mg, 0,08 mmol) en forma de un sólido de color blanco con un rendimiento del 66%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,12 (d, J = 7,33 Hz, 2H), 1,41 (s a, 2H), 3,57 (s, 2H), 3,87 (d, J = 12,63 Hz, 1H), 4,33 (s, 4H), 4,41 (d, J = 7,33 Hz, 2H), 6,02 (t, J = 1,89 Hz, 1H), 6,82 (s, 2H), 7,21 (d, J = 2,02 Hz, 1H), 7,26 (d, J = 1,52 Hz, 1H), 7,32 (dd, J = 3,66, 1,64 Hz, 2H). LCMS $(M+H)^+$ 499,2.

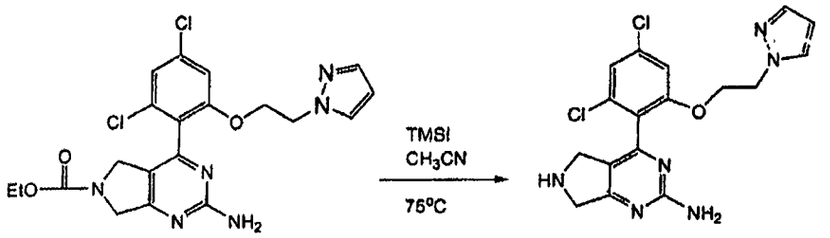
**Preparación del Compuesto 102a, 4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**




El compuesto **102b,** 2-amino-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo, se preparó a partir del compuesto **9a** (1090 mg, 3,0 mmol), el compuesto **18c** (682 mg, 3,3 mmol), $Pd(PPh_3)_4$ (347 mg, 0,3 mmol) y $Na_2CO_3$ 2 M (4,5 ml, 9,0 mmol) en 1,4-dioxano (25 ml) de una manera similar a la que se ha descrito para el Ejemplo **1**. $^1H$ RMN (400 MHz, DMSO-d6) δ ppm 1,37-1,47 (m, J = 12,88 Hz, 9H), 4,07-4,24 (m, 2H), 4,42 (d, J = 7,58 Hz, 2H), 6,82 (s, 2H), 6,95 (d, J = 1,77 Hz, 1H), 7,08-7,21 (m, 1H), 10,67 (s, 1H). LCMS $(M+H)^+$ 397,1 399,1. El compuesto **102b** (1,627 g, 4,1 mmol) se O-alquiló usando carbonato potásico (3,4 g, 24,6 mmol) y 1-(2-bromoetil)-1*H*-pirazol (1,43 g, 8,19 mmol) en DMF (10 ml) de una manera similar a la que se ha descrito para el Ejemplo **100**. La desprotección de Boc se realizó usando HCl 4 M en 1,4-dioxano (10 ml) y MeOH (20 ml) con agitación a temperatura ambiente durante aproximadamente 16 h. Después del tratamiento extractivo con EtOAc lavando con $NaHCO_3$ acuoso saturado, el producto en bruto se aisló por HPLC preparativa, dando el compuesto **102a,** 4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina (405 mg, 0,95 mmol) en forma de una sal HCl de color blanco con un rendimiento del 26%. $^1H$ RMN (400 MHz, DMSO-d6) δ ppm 3,51 (d, J = 13,39

Hz, 2H), 3,93-4,07 (m, 2H), 4,24-4,44 (m, 4H), 6,14 (s a, 1H), 6,65 (s a, 2H), 7,19 (s a, 1H), 7,24 (s a, 1H), 7,29 (s a, 1H), 7,40 (s, 1H), 8,24 (s, 1H). LCMS $(M+H)^+$ 391,2, 393,2.

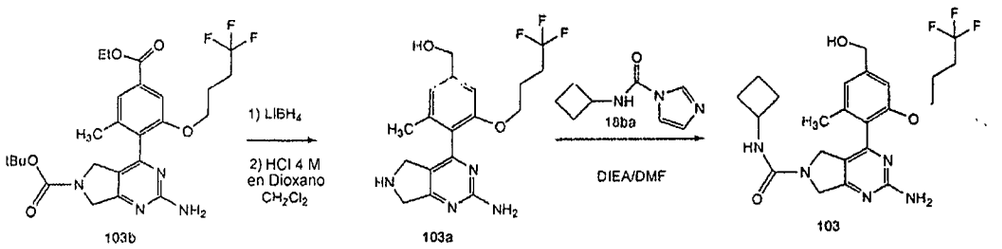
**Preparación Alternativa del Compuesto 102a, 4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**




108 102a

La desprotección del carbamato de etilo del compuesto **108** (5,06 g, 10,3 mmol) usando yodotrimetilsilano (8,0 ml, 56 mmol) en $CH_3CN$ (80,0 ml) se realizó de una manera similar al Ejemplo 2. El compuesto **102a** (8,46 g) se obtuvo en forma de una sal HCl en bruto. LCMS $(M+H)^+$: 393,2, 391,3.

**Ejemplo 103: 2-amino-*N*-ciclobutil-4-[4-(hidroximetil)-2-metil-6-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

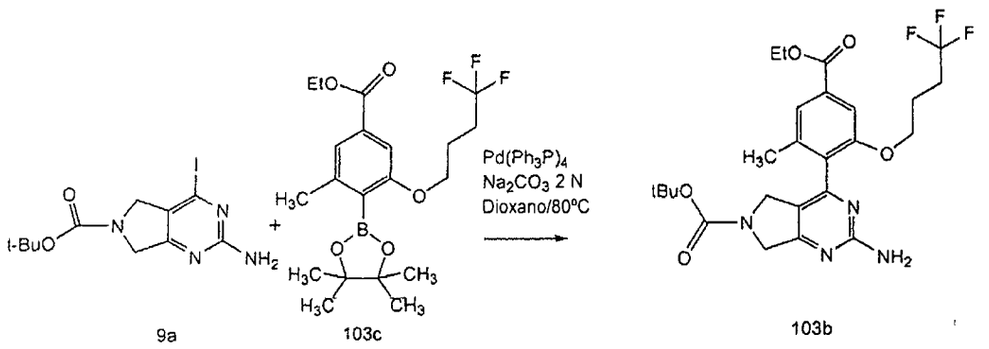



103b 103a 103

Al compuesto **103b** (205 mg, 0,39 mmol) en THF (4 ml) a 0°C se le añadieron $LiBH_4$ 2 M en THF (0,6 ml, 1,17 mmol) y MeOH (0,5 ml). La mezcla se agitó a 0°C y se dejó calentar a temperatura ambiente durante una noche.

Después del tratamiento extractivo con EtOAc (300 ml) lavando con $NaHCO_3$ acuoso saturado (50 ml) y después con salmuera (50 ml), la solución de EtOAc se secó ($Na_2SO_4$), se filtró y los componentes volátiles se retiraron, dando el alcohol (185 mg) en forma de una grasa transparente que se llevó a continuación directamente. LCMS $(M+H)^+$ 483,2, 484,2. Para la desprotección de Boc, se añadió $CH_2Cl_2$ (5 ml) seguido de HCl 4 M en dioxano (1,0 ml, 3,83 mmol). Después de agitar durante 12 h, la mezcla se concentró y se añadieron éter y hexano. Los componentes volátiles se retiraron, dando el compuesto **103a**, ácido 4-(2-amino-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-4-il)-3-metil-5-(4,4,4-trifluorobutoxi)benzoico (189 mg) en forma de un clorhidrato de color amarillo que se llevó a continuación sin purificación. LCMS $(M+H)^+$ 383,2, 384,2. El compuesto **103a** en DMF (2,0 ml) se hizo reaccionar con el compuesto **18ba** (76 mg, 0,46 mmol) y DIEA (0,4 ml, 6,0 mmol) de una manera similar al Ejemplo **18b.** El aislamiento por HPLC preparativa dio el compuesto **103** (33 mg, 0,083 mmol) en forma de un sólido de color blanco con un rendimiento del 21%. $^1H$ RMN (400 MHz, DMSO-d6) $\delta$ ppm 1,44-1,61 (m, 2H), 1,69-1,81 (m, 2H), 1,84-1,98 (m, 2H), 2,00-2,16 (m, 7H), 3,92-4,05 (m, 3H), 4,06-4,20 (m, 2H), 4,37 (d, J = 5,31 Hz, 2H), 4,49 (d, J = 5,56 Hz, 2H), 5,25 (t, J = 5,68 Hz, 1H), 6,51 (d, J = 7,83 Hz, 1H), 6,65 (s, 2H), 6,85 (s, 1H), 6,89 (s, 1H). LCMS $(M+H)^+$ 480,4, 481,4.

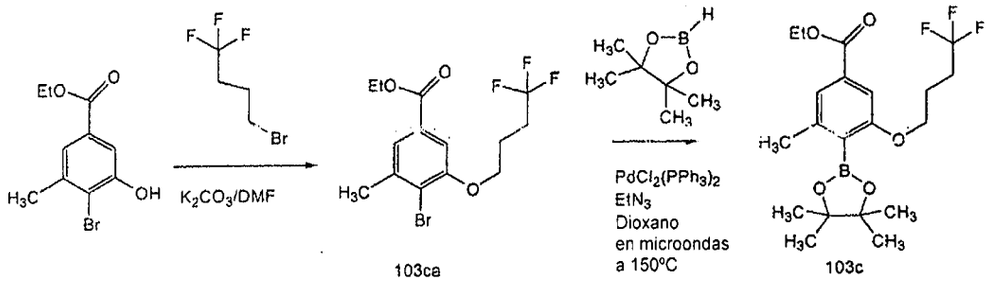
**Preparación del Compuesto 103b, 2-amino-*N*-ciclobutil-4-[4-(hidroximetil)-2-metil-6-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




9a 103c 103b

El compuesto **9a** (200 mg, 0,552 mmol) y el compuesto **103c** (253 mg, 0,61 mmol), $Pd(PPh_3)_4$ (32 mg, 0,028 mmol) y una solución de $Na_2CO_3$ 2 M (0,8 ml, 1,66 mmol) en 1,4-dioxano (6 ml) se hicieron reaccionar durante 48 h de una manera similar al Ejemplo **1**. El control (LCMS) indicó que la reacción no se había completado, así que la mezcla se sometió a microondas a 160°C durante 1 h, después de lo cual la suspensión se filtró y los sólidos se lavaron con MeOH. El filtrado/lavados combinados se concentraron y se sometieron a tratamiento extractivo con EtOAc (300 ml) lavado con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). El aislamiento por cromatografía sobre gel de sílice (gradiente de EtOAc al 0-60% en $CH_2Cl_2$) dio el compuesto **103b** (205 mg, 0,433 mmol) en forma de una grasa transparente con un rendimiento del 71%. $^1H$ RMN (400 MHz, CLOROFORMO-d) $\delta$ ppm 1,21-1,28 (m, 9H), 1,38-1,54 (m, 4H), 1,85-1,98 (m, 2H), 1,98-2,12, (m, 2H), 2,20 (d, J = 4,55 Hz, 3H), 3,98-4,13 (m, 2H), 4,41 (c, J = 7,07 Hz, 2H), 4,60 (d, J = 22,48 Hz, 2H), 7,39-7,52 (m, 2H), 7,59-7,73 (m, 1H). LCMS $(M+H)^+$ 524,2, 526,2.

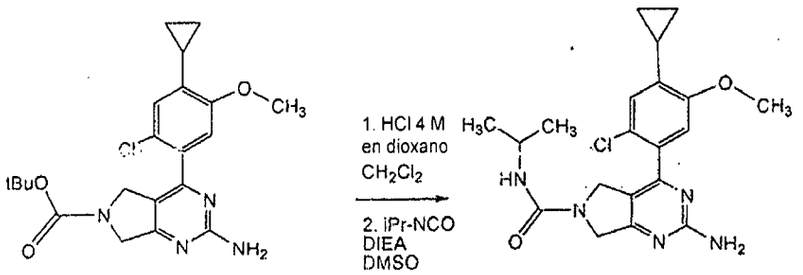
**Preparación del Compuesto 103c, 3-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5-(4,4,4-trifluorobutoxi)benzoato de etilo**




Se O-alquiló 4-bromo-3-hidroxi-5-metilbenzoato de etilo (650 mg, 2,5 mmol) con 4-bromo-1,1,1-trifluorobutano (950 mg; 5,0 mmol) usando carbonato potásico (1040 mg, 7,5 mmol) en DMF (5,0 ml) de una manera similar a la que se ha descrito para el Ejemplo **100**. El aislamiento usando cromatografía sobre gel de sílice (gradiente de EtOAc al 0-20% en hexano) dio el compuesto **103ca**, 4-bromo-3-metil-5-(4,4,4-trifluorobutoxi)benzoato de etilo (858 mg, 2,33 mmol) en forma de un sólido de color blanco con un rendimiento del 93%. $^1$H RMN (400 MHz, CLOROFORMO-d) δ ppm 1,41 (t, J = 7,20 Hz, 3H), 2,04-2,21 (m, 2H), 2,32-2,44 (m, 2H), 2,44-2,50 (m, 3H), 4,15 (t, J = 5,94 Hz, 2H), 4,38 (c, J = 7,07 Hz, 2H), 7,35 (d, J = 1,77 Hz, 1H), 7,57 (d, J = 1,01 Hz, 1H). Se purgaron el compuesto **103ca** (561 mg, 1,52 mmol), pinacolborano (0,7 ml, 4,6 mmol) y $Et_3N$ (0,9 ml, 6,1 mmol) en 1,4-dioxano (6,0 ml) con $N_2$ durante 15 min y después se añadió $Pd(II)Cl_2(PPh_3)_2$ (107 mg, 0,1 mmol). La mezcla se sometió a microondas a 150°C durante 1 h, se enfrió y se filtró a través de celite lavando con EtOAc. El filtrado/lavados combinados se lavaron con agua (50 ml) y salmuera (50 ml), se secaron ($Na_2SO_4$), se filtraron y se concentraron. El aislamiento usando cromatografía sobre gel de sílice (gradiente de EtOAc al 0-20% en hexano) dio el compuesto **103c** (252 mg, 0,61 mmol) con un rendimiento del 40%. $^1$H RMN (400 MHz, CLOROFORMO-d) δ ppm 1,37-1,41 (m, 15H), 2,05 (dd, J = 10,74, 5,68 Hz, 2H), 2,31-2,39 (m, 2H), 2,39-2,41 (m,

3H), 4,06 (t, J = 5,81 Hz, 2H), 4,36 (c, J = 7,24 Hz, 2H), 7,25 (s, 1H), 7,46 (s, 1H).

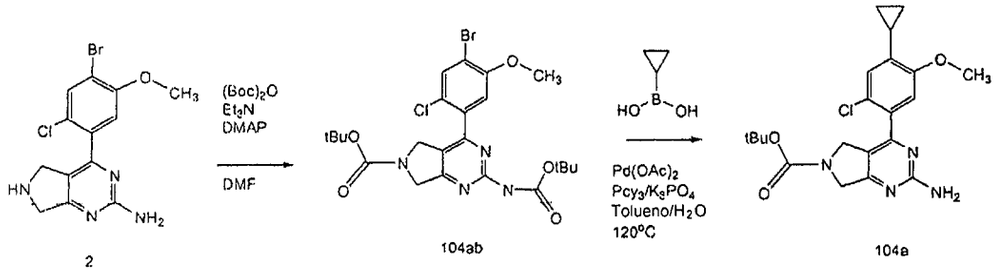
**Ejemplo 104: 2-amino-4-(2-cloro-4-ciclopropil-5-metoxifenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




104a 104

Al compuesto **104a** (67 mg, 0,16 mmol) en $CH_2Cl_2$ (4,0 ml) se le añadió HCl 4 M en 1,4-dioxano (0,2 ml, 0,804 mmol). Después de agitar a temperatura ambiente durante 12 h, la mezcla se concentró y se trató con éter y hexano. La retirada de los componentes volátiles dio el intermedio desprotegido con Boc (65 mg) en forma de un clorhidrato de color amarillo que se llevó a continuación directamente. LCMS $(M+H)^+$ 317,2, 319,2. Se añadieron dimetilformamida (2,0 ml) y diisopropiletilamina (0,14, 0,8 mmol) seguido de isocianato de isopropilo (14,0 mg, 0,16 mmol) para formar la urea de una forma similar al Ejemplo **15a**. El aislamiento por HPLC preparativa dio el compuesto **104** (13 mg, 0,032 mmol) en forma de una espuma de color pardo con un rendimiento del 20%. $^1H$ RMN (400 MHz, DMSO-d6) δ ppm 0,69-0,78 (m, 2H), 0,90-0,98 (m, 2H), 1,05 (d, J = 6,57 Hz, 6H), 2,04-2,18 (m, 1H),3,77 (t, J = 6,95 Hz, 1H), 3,81 (s, 3H), 4,25 (s, 2H), 4,40 (s, 2H), 6,09 (d, J = 7,83 Hz, 1H), 6,82 (s, 2H), 6,95 (s, 2H). LCMS $(M+H)^+$ 402,2, 404,2.

**Preparación del Compuesto 104a, 2-amino-4-(2-cloro-4-ciclopropil-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo**

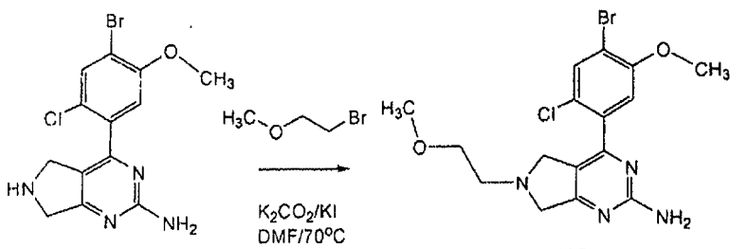



2 104ab 104a

Al compuesto **2** (612 mg, 1,0 mmol) y dicarbonato de di-*terc*-butilo (655 mg, 3,0 mmol) en DMF (5,0 ml) se le añadieron trietilamina (0,84 ml, 6,0 mmol) y DMAP (25 mg, 0,2 mmol). Después de agitar 4 h a temperatura ambiente, la mezcla se sometió a tratamiento extractivo con EtOAc (200 ml) lavando con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). Después del secado ($Na_2SO_4$), el filtrado y la concentración, el aislamiento usando cromatografía sobre gel de sílice (gradiente de EtOAc al 0-50% en $CH_2Cl_2$) dio el compuesto **104ab**, 4-(4-bromo-2-cloro-5-metoxifenil)-2-[(*terc*-butoxicarbonil)amino]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo (320 mg, 0,58 mmol) en forma de espuma de color amarillento con un rendimiento del 58%. $^1H$ RMN (400 MHz, DMF-d7) δ ppm 1,34-1,50 (m, 18H), 3,84-3,90 (m, 3H), 4,30 (d, J = 7,33 Hz, 2H), 4,45 (d, J = 6,06 Hz, 2H), 7,16 (d, J = 3,79 Hz, 1H), 7,88 (d, J = 3,54 Hz, 1H), 7,97 (s, 1H). LCMS $(M+H)^+$ 556,4, 566,4. Se purgaron con $N_2$ durante 15 min el compuesto **104ab** (167 mg, 0,3 mmol), ácido ciclopropilborónico (52 mg, 0,6 mmol), $K_3PO_4$ (255 mg, 1,20 mmol) y triciclohexilfosfina (9,0 mg, 0,03 mmol) en tolueno (4,0 ml) con $H_2O$ (0,1 ml) y después se añadió $Pd(OAc)_2$ (4,0 mg, 0,02 mmol). Después de calentar a

120ºC durante 6 h, la mezcla se filtró a través de celite lavado con EtOAc. El filtrado/lavados se sometieron a tratamiento extractivo con EtOAc (500 ml) lavado con $NaHCO_3$ acuoso saturado (100 ml) y salmuera (100 ml). Después del secado ($Na_2SO_4$), la filtración y la concentración, el aislamiento usando cromatografía sobre gel de sílice (gradiente EtOAc al 0-50% en $CH_2Cl_2$) dio el compuesto **104a** (67 mg, 0,324 mmol) en forma de una espuma de color amarillento con un rendimiento del 54%. $^1$H RMN (400 MHz, CLOROFORMO-d) δ ppm 0,79-0,94 (m, 2H), 0,94-1,06 (m, 2H), 1,43-1,54 (m, 9H), 2,08-2,25 (m, 1H), 3,84-3,93 (m, 3H), 4,48 (d, J = 19,70 Hz, 2H), 4,58 (d, J = 23,75 Hz, 2H), 5,28 (s, 2H), 6,77 (d, J = 10,11 Hz, 1H), 6,87 (d, J = 11,12 Hz, 1H). LCMS $(M+H)^+$ 417,2, 419,2.

**Ejemplo 105: 4-(4-bromo-2-cloro-5-metoxifenil)-6-(2-metoxietil)-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-2-amina**

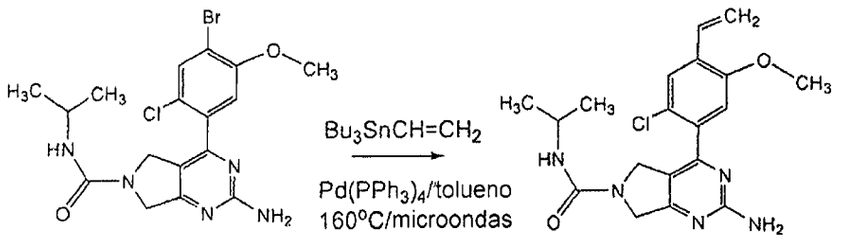



2 105

El clorhidrato del compuesto **2** (70 mg, 0,16 mmol), $K_2CO_3$ (225 mg, 1,63 mmol) y 2-bromoetilmetil éter (113 mg, 0,85 mmol) en DMF (3 ml) se sometieron a microondas a 100ºC durante 2 h. El aislamiento por HPLC preparativa dio el compuesto **105** (13 mg, 0,03 mmol) en forma de un sólido de color blanco con un rendimiento del 19%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,27-3,32 (m, 3H), 3,47-3,60 (m, 2H), 3,66 (s a, 2H), 3,84-3,93 (m, 3H), 4,35-

4,62 (m, 4H), 7,05-7,12 (m, 1H), 7,14-7,25 (m, 2H), 7,91 (s, 1H). LCMS $(M+H)^+$ 415,0, 417,0.

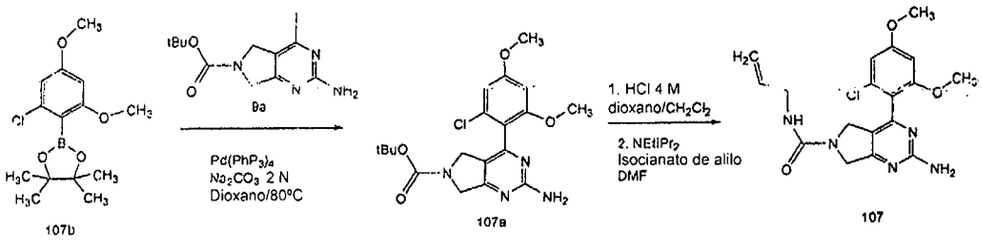
**Ejemplo 106: 2-amino-4-(2-cloro-4-etenil-5-metoxifenil)-*N*-(1-metiletil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




55 106

El compuesto **55** (66 mg, 0,15 mmol) y eteniltributilestanano (62 mg, 0,2 mmol) en tolueno (1 ml) y dioxano (1 ml) se purgaron con $N_2$, se añadió $Pd(PPh_3)_4$ (9 mg, 0,008 mmol) y la mezcla se sometió a microondas a 160°C durante 30 min. La mezcla se filtró a través de celite y se lavó con MeOH. El filtrado se concentró y se sometió a tratamiento extractivo con EtOAc (200 ml) lavando con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). Después del secado ($Na_2SO_4$) y la concentración, el aislamiento por HPLC preparativa dio el compuesto **106** (11 mg, 0,029 mmol) en forma de un sólido de color blanco con un rendimiento del 19%. $^1H$ RMN (400 MHz, DMSO-d6) δ ppm 1,02-1,10 (m, 6H), 3,74-3,80 (m, 1H), 3,79-3,86 (m, 3H), 4,28 (s, 2H), 4,43 (s, 2H), 5,40 (d, J = 12,38 Hz, 1H), 5,98 (dd, J = 17,94, 1,01 Hz, 1H), 6,09 (d, J = 6,82 Hz, 2H), 6,93 (dd, J = 17,68, 11,37 Hz, 1H), 7,06 (s, 1H), 7,70 (s, 1H). LCMS $(M+H)^+$ 386,2, 386,2.

**Ejemplo 107: 2-amino-4-(2-cloro-4,6-dimetoxifenil)-*N*-prop-2-en-1-il-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

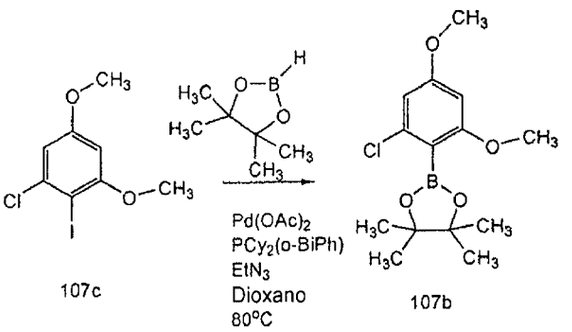



107b 107a 107

Se hicieron reaccionar el compuesto **9a** (199 mg, 0,549 mmol), el compuesto **107b** (164 mg, 0,549 mmol), $Pd(PPh_3)_4$ (32 mg, 0,027 mmol) y $Na_2CO_3$ acuoso 2 M (0,8 ml, 1,65 mmol) en 1,4-dioxano (4 ml) de una manera similar al Ejemplo **9**. El aislamiento usando cromatografía sobre gel de sílice (gradiente de MeOH al 0-10% en $CH_2Cl_2$) dio el compuesto **107a**, 2-amino-4-(2-cloro-4,6-dimetoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de *terc*-butilo (204 mg, 0,52 mmol) en forma de un sólido de color amarillento. LCMS $(M+H)^+$ 407,4, 409,4. Para la desprotección de Boc, el tratamiento del compuesto **107a** (204 mg, 0,5 mmol) en $CH_2Cl_2$ (5 ml) con HCl 4 M en 1,4-dioxano (1,3 ml) de una manera similar al Ejemplo **102a** dio el clorhidrato (200 mg) en forma de una grasa de color amarillo que se llevó a continuación sin purificación. LCMS $(M+H)^+$ 307,2, 309,2. Una porción del clorhidrato protegido con Boc (95 mg, 0,25 mmol) en DMF (2,0 ml) se trató con diisopropiietilamina (0,3 ml, 1,5 mmol) e isocianato de alilo (21 mg, 0,25 mmol) de una manera similar al Ejemplo **15a.** El aislamiento por HPLC preparativa dio el compuesto **107** (15 mg, 0,038 mmol) en forma de un sólido de color blanco con un rendimiento del 15%. $^1H$ RMN (400 MHz, DMSO-d6) $\delta$ ppm 3,62-3,70 (m, 2H), 3,73 (s, 3H), 3,83 (s, 3H), 4,09-4,18 (m, 2H), 4,43 (s, 2H), 5,00 (dd, J = 10,36, 1,52 Hz, 1H), 5,10 (dd, J = 17,18, 1,52 Hz, 1H), 5,72-5,88 (m, 1H), 6,57 (t, J =

5,56 Hz, 1H), 6,67 (d, J = 2,27 Hz, 1H), 6,72-6,78 (m, 2H). LCMS $(M+H)^+$ 390,1, 392.

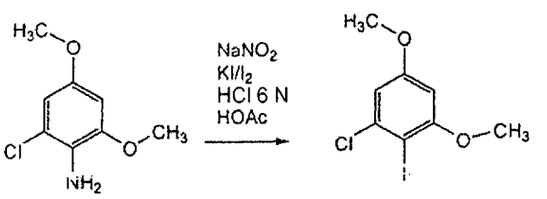
**Preparación del Compuesto 107b, 2-(2-cloro-4,6-dimetoxifenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano**




107c 107b

Se hicieron reaccionar el compuesto **107c** (1,45 g, 4,86 mmol), pinacolborano (1,4 ml, 9,72 mmol) y $Et_3N$ (2,0 ml, 14,6,0 mmol), acetato de paladio (II) (55 mg, 0,243 mmol) y 2-(diciclohexiifosfino)bifenilo (170 mg, 0,7 mmol) en 1,4-dioxano (25 ml) de una manera similar al Ejemplo **18ca**. El aislamiento usando cromatografía sobre gel de sílice (gradiente de EtOAc al 0-20% en hexano) dio el compuesto **107b** (1,104 g, 3,74 mmol) en forma de un sólido de color amarillento con un rendimiento del 77%. Datos de RMN: $^1H$ RMN (400 MHz, CLOROFORMO-D) δ ppm 1,37 (s, 12H), 3,73 (s, 3H), 3,76 (s, 3H), 6,25 (s, 1H), 6,44 (s, 1H).

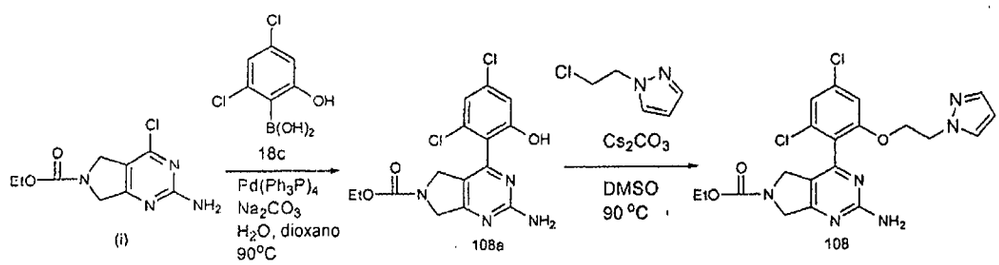
**Preparación del Compuesto 107c, 1-cloro-2-yodo-3,5-dimetoxibenceno**




107c

A (2-cloro-4,6-dimetoxifenil)amina (1,9 g, 10,0 mmol) en ácido acético (40 ml) se le añadió HCl 6 M (10 ml). Con agitación y refrigeración en un baño de hielo y sal, se añadió lentamente nitrito sódico (828 mg, 12,0 mmol) en agua (6 ml) manteniendo la temperatura de reacción a 5°C. Después de la adición, la mezcla se agitó durante aproximadamente 30 min y se añadió gota a gota una solución de yoduro potásico (3320 mg, 20,6 mmol) y yodo (761 mg, 3,0 mmol) en agua (35 ml). La mezcla se dejó calentar a temperatura ambiente durante aproximadamente 90 min y se añadió agua (120 ml). La mezcla se sometió a tratamiento extractivo con EtOAc (2 x 300 ml) y los extractos combinados se lavaron con una solución acuosa de $Na_2S_2O_3$ al 10% (2 x 100 ml) y salmuera (100 ml). Después del secado ($Na_2SO_4$), el filtrado y la concentración, el aislamiento usando cromatografía sobre gel de sílice (gradiente de EtOAc al 0-30% en hexano) dio el compuesto **107c** (1,45 g, 4,9 mmol) en forma de un sólido de color amarillento con un rendimiento del 49%. $^1$H RMN (400 MHz, CLOROFORMO-D) δ ppm 3,79 (s, 3H), 3,84 (s, 3H), 6,30 (d, J = 2,53 Hz, 1H), 6,68 (d, J = 2,53 Hz, 1H).

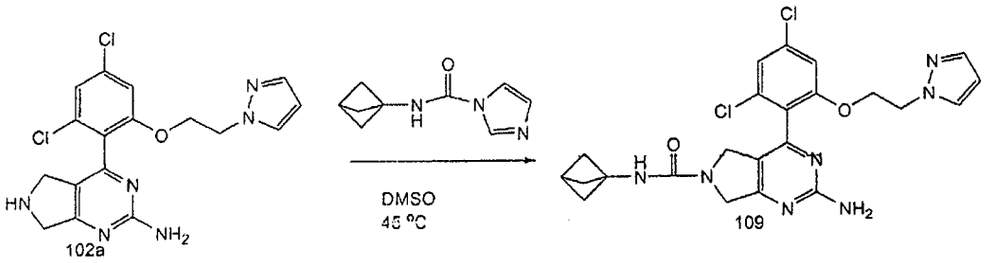
**Ejemplo 108: 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




Se hicieron reaccionar el compuesto (i) (4,04 g, 16,6 mmol), el compuesto **18c** (4,82 g, 23,3 mmol), carbonato sódico acuoso 2 M (21 ml, 42

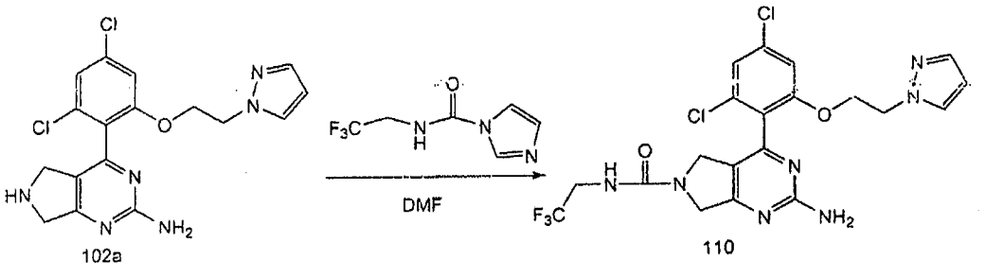
mmol) y *tetraquis*(trifenilfosfino)paladio (0) (1,82 g, 1,58 mmol) en 1,4-dioxano (200 ml) de una manera similar al Ejemplo 1. El tratamiento extractivo con EtOAc se realizó de una manera similar al Ejemplo **18a** usando primero NaOH ac. 0,5 N (300 ml) para extraer el producto de fenol de la fase acuosa seguido de acidificación a pH 5 con $KH_2PO_4$ 1 N (75 ml) y extracción del producto de fenol en EtOAc (400 ml). La fase de EtOAc se concentró, dando el compuesto **108a**, 2-amino-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo (6,15 g) que se llevó a continuación sin purificación. 1H RMN (400 MHz, DMSO-d6) δ ppm 1,07-1,34 (m, 3H) 3,99-4,26 (m, 4H) 4,48 (d, J = 11,87 Hz, 2H) 6,84 (s, 2H) 7,14 (d, J = 1,77 Hz, 1H) 7,48-7,79 (m, 1H) 10,71 (s, 1H). LCMS $(M+H)^+$: 369,0 371,0. Se hicieron reaccionar el compuesto **108a** (5,11 g, 13,8 mmol), 1-(2-cloro-etil)-1*H*-pirazol (5,02 g, 38,4 mmol) y carbonato de cesio (15,8 g, 48,4 mmol) en DMSO (50,0 ml) a 90°C de una manera similar al Ejemplo **18**. Después del tratamiento extractivo con EtOAc (500 ml) lavando con agua (200 ml), el producto se aisló usando cromatografía sobre gel de sílice (EtOAc al 100% seguido de un gradiente de MeOH al 0-13% en diclorometano) dando el compuesto **108** (5,06 g, 13,8 mmol) en forma de un polvo de color castaño con un rendimiento del 77%. $^1$H RMN (300 MHz, DMSO-$d_6$) $\delta$ ppm 1,13-1,29 (m, 3H) 3,49-3,64 (m, 1H), 3,91 (d, J = 13,19 Hz, 1H) 4,02-4,19 (m, 2H) 4,34 (s, 4H) 4,40-4,48 (m, 2H) 5,99-6,04 (m, 1H) 6,83 (s, 2H) 7,23-7,28 (m, 2H) 7,28-7,33 (m, 2H). LCMS $(M+H)^+$: 465,2, 463,2.

**Ejemplo 109: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**



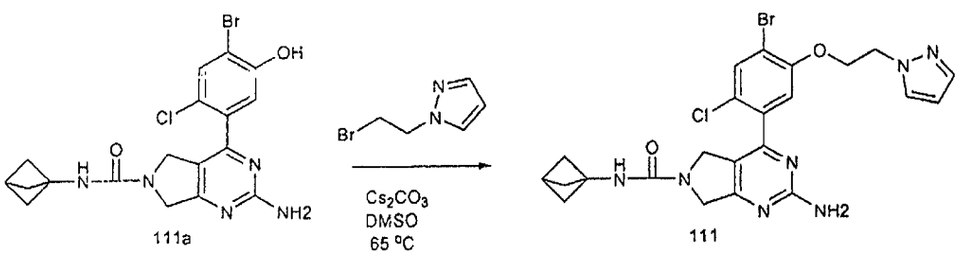

Se añadió biciclo[1.1.1]pentan-1-amina-HCl (637 mg, 5,33 mmol) seguido de trietilamina (4,00 ml, 28,7 mmol) a 1,1-carbonildiimidazol (870 mg, 5,37 mmol) en DMF (50 ml) a 0°C. La mezcla se agitó a temperatura ambiente durante 1 h y se añadió el compuesto **102a** · sal HI (4,650 g, 5,150 mmol). La mezcla se calentó a 45°C durante 0,5 h. Después del tratamiento extractivo con EtOAc, lavando con agua, el producto en bruto se sometió a cromatografía sobre gel de sílice (gradiente de MeOH al 10-15% en diclorometano). Después del aislamiento, se añadió $CH_3CN$ al 10% en agua. Después de la liofilización, se obtuvo el compuesto **109** (1,54 g, 3,08 mmol) en forma de un polvo de color blanco con un rendimiento del 58%. $^1H$ RMN (300 MHz, DMSO-d6) δ ppm 1,95 (s, 6H), 2,36 (s, 1H), 3,53 (d, J = 13,19 Hz, 1H), 3,89 (d, J = 13,00 Hz, -1-H), 4,33 (s, 6H), 5,99-6,02 (m, 1H), 6,77 (s a, 2H), 6,85 (s a, 1H), 7,19 (d, J = 2,07 Hz, 1H), 7,25 (d, J = 1,51 Hz, 1H), 7,30 (d, J = 1,70 Hz, 1H), 7,32 (d, J = 1,70 Hz, 1H). LCMS $(M+H)^+$: 502,2, 500,2.

**Ejemplo 110: 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-(2,2,2-trifluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se hicieron reaccionar 2,2,2-trifluoroetilamina (19,8 mg, 0,200 mmol), 1,1-carbonildiimidazol (32,4 mg, 0,200 mmol), el compuesto **102a** · HCl (89,9 mg, 0,180 mmol) y trietilamina (0,080 ml, 0,57 mmol) en DMF (2 ml) de una manera similar al Ejemplo **18b**. El aislamiento usando HPLC preparativa dio el compuesto **110** (37 mg, 0,72 mmol) en forma de un polvo de color blanco con un rendimiento del 40%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,54 (d, J = 12,38 Hz, 1H), 3,77-3,92 (m, 2H), 3,94 (d, J = 12,88 Hz, 1H), 4,42-4,50 (m, 2H), 5,98 (t, J = 2,15 Hz, 1H), 6,82 (s, 2H), 7,21 (d, J = 2,02 Hz, 1H), 7,27 (s, 2H), 7,33 (d, J = 1,77 Hz, 1H). LCMS $(M+H)^+$: 518,0, 516,0.

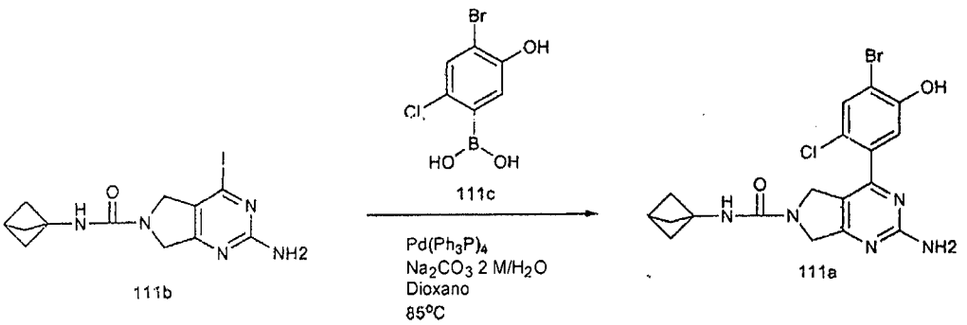
**Ejemplo 111: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{4-bromo-2-cloro-5-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El compuesto **111a** (44,0 mg, 0,0976 mmol) se alquiló con 1-(2-bromo-etil)-1*H*-pirazol (32,4 mg, 0,185 mmol) y carbonato de cesio (122 mg, 0,374 mmol) en DMSO (1,5 ml) de una manera similar a la que se ha descrito en el

Ejemplo **18**. El aislamiento usando HPLC preparativa dio el compuesto **111** (29 mg, 0,053 mmol) en forma de un polvo de color blanco con un rendimiento del 55%. $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,92 (s, 6H), 2,34 (s, 1H), 4,21 (s, 2H), 4,36-4,42 (m, 4H), 4,52 (t, J = 4,71 Hz, 2H), 6,24 (t, J = 1,98 Hz, 1H), 6,88 (s, 2H), 6,99 (s, 1H), 7,15 (s, 1H), 7,44 (d, J = 1,76 Hz, 1H), 7,78 (d, J = 2,26 Hz, 1H), 7,84 (s, 1H). LCMS $(M+H)^+$: 546,2, 544,2.

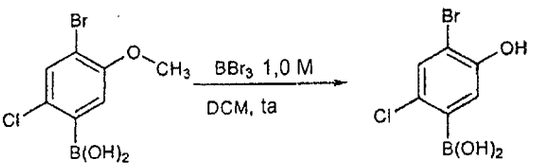
**Preparación del Compuesto 111a, 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-(4-bromo-2-cloro-5-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El compuesto **111b**, 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-yodo-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida, se preparó a partir del compuesto **8b** de una manera similar al Ejemplo **18b** con la excepción de que la ciclobutilamina se sustituyó por biciclo[1.1.1]pentan-1-amina-HCl. El acoplamiento del compuesto **111b** (0,2995 g, 0,8070 mmol) con el compuesto **111c** (0,201 g, 0,800 mmol) se realizó usando *tetraquis*(trifenilfosfino)paladio (0) (0,065 g, 0,070 mmol) y carbonato sódico acuoso 2 M (0,80 ml, 1,6 mmol) en 1,4-dioxano (5,0 ml) de una manera similar a la que se ha descrito para el Ejemplo **1**. El tratamiento extractivo implicó la extracción de la base acuosa seguido de acidificación y extracción de EtOAc de una manera similar al

Ejemplo **108a**. El aislamiento dio el compuesto **11a** (0,316 g) en forma de un sólido de color castaño que se llevó a continuación sin purificación. $^1$H RMN (300 MHz, DMSO-$d_6$) $\delta$ ppm 1,93 (s, 6H), 2,34 (s, 1H), 4,22 (s, 2H), 4,38 (s, 2H), 6,87 (s a, 2H), 6,91 (s, 1H), 7,01 (s, 1H), 7,74 (s, 1H), 10,83 (s a, 1H). LCMS $(M+H)^+$: 452,0, 450,0.

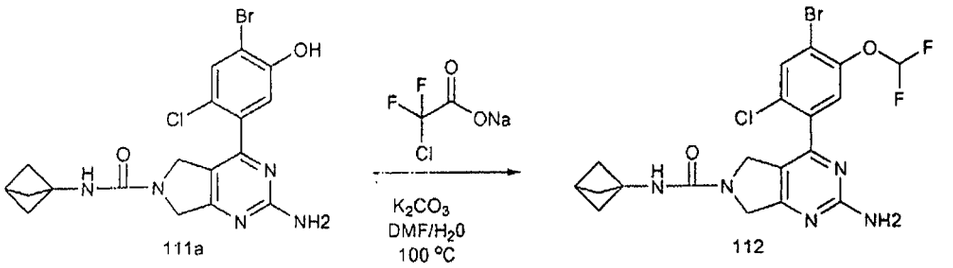
**Preparación del Compuesto 111c, ácido (4-bromo-2-cloro-5-hidroxifenil)borónico**




111c

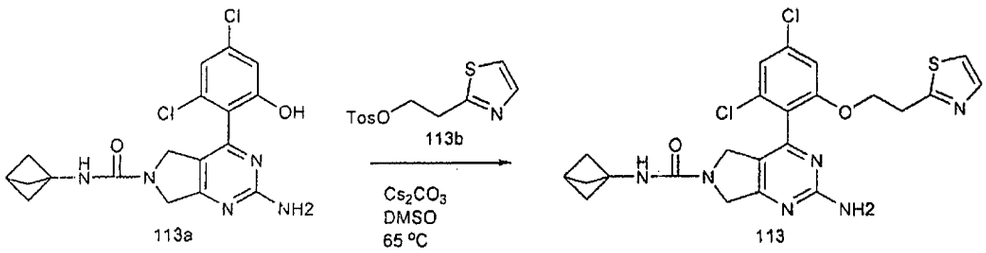
A una suspensión de ácido (4-bromo-2-cloro-5-metoxifenil)borónico (4,96 g, 18,7 mmol) en diclorometano (125 ml) a 0ºC se le añadió tribromuro de boro 1 M (52 ml, 52 mmol) en diclorometano. La mezcla de reacción se dejó calentar a temperatura ambiente y en agitación durante 48 h. Después, la mezcla de reacción se vertió sobre hielo, se añadió NaOH 3 N (52 ml) y la mezcla se agitó vigorosamente durante 30 minutos. Las fases se separaron y la fase de diclorometano se desechó. La fase acuosa, una suspensión, se acidificó a pH 5 con HCl concentrado y el tratamiento extractivo con EtOAc dio el compuesto **111c** (4,614 g, 18,36 mmol) en forma de un polvo de color blanco que se llevó a continuación sin purificación.

**Ejemplo 112: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-[4-bromo-2-cloro-5-(difluorometoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se burbujeó nitrógeno a través de una solución del compuesto **111a** (53 mg, 0,12 mmol) en DMF (1,0 ml) y $H_2O$ (0,13 ml) durante 10 minutos. Se añadieron carbonato de potasio (0,092 g, 0,67 mmol) y clorodifluoroacetato de sodio (0,067 g, 0,44 mmol). La mezcla de reacción se calentó a 100°C durante 4 h. El aislamiento usando HPLC preparativa dio el compuesto **112** (0,019 g, 0,038 mmol) en forma de un polvo de color blanco con un rendimiento del 32%. $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,93 (s, 6H), 2,35 (s, 1H), 4,23 (s, 2H), 4,39 (s, 2H), 6,94 (s, 1H), 6,99-7,03 (m, 1H), 7,36 (t, J = 72,90 Hz, 1H), 7,43 (s, 1H), 8,10 (s, 1H). LCMS $(M+H)^+$: 502,2, 500,0.

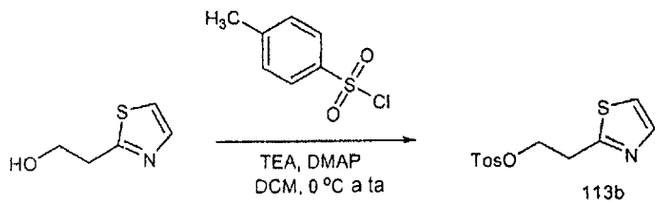
**Ejemplo 113: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{2,-dicloro-6-[2-(1,3-tiazol-2-il)etoxi]fenil}5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El compuesto **113a**, 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-(2,4-dicloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida, se preparó de una manera similar al Ejemplo **18a** con la excepción de que se sustituyó ciclobutilamina por biciclo[1.1.1]pentan-1-amina-HCl. Se calentaron el

compuesto **113a** (65 mg, 0,16 mmol), carbonato de cesio (201 mg, 0,617 mmol) y el compuesto **113b** (73 mg, 0,26 mmol) en DMSO (1,5 ml) a 65ºC. Después de 0,5 h, se añadió en porciones más cantidad del compuesto **113b** (196 mg 0,629 mmol) durante 5 h con calentamiento continuado. El tratamiento extractivo con EtOAc, lavando con agua, seguido de aislamiento usando HPLC preparativa dio el compuesto **113** (0,0101 g, 0,0195 mmol) en forma de un sólido de color blanco con un rendimiento del 12%. $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,95 (s, 6H), 2,36 (s, 1H), 3,26 (t, J = 5,81 Hz, 2H), 3,57 (d, J = 12,63 Hz, 1H), 3,90 (d, J = 13,14 Hz, 1H), 4,31-4,39 (m, 4H), 6,75 (s, 2H), 6,87 (s, 1H), 7,31 (d, J = 1,77 Hz, 1H), 7,33 (d, J = 1,77 Hz, 1H), 7,35 (d, J = 3,28 Hz, 1H), 7,58 (d, J = 3,28 Hz, 1H). LCMS $(M+H)^+$: 519,2, 517,2.

**Preparación del Compuesto 113b, 4-metilbencenosulfonato de 2-(1,3-tiazol-2-il)etilo**

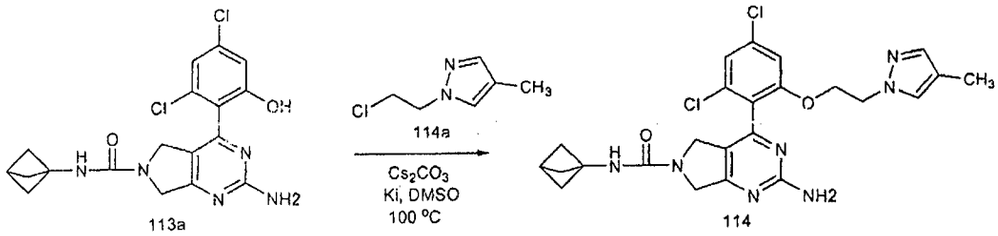



113b

A 2-(1,3-tiazol-2-il)etanol (123 mg, 0,952 mmol) (Young et al. *Eur. J. Med. Chem.*, 28: 201-211; (1993)) y trietilamina (0,15 ml, 1,1 mmol) en diclorometano (5,0 ml) a 0ºC se le añadieron cloruro de 4-toluenosulfonilo (189 mg, 0,991 mmol) y una cantidad sin medir de DMAP catalítico. La mezcla se agitó durante una noche y se dejó calentar a temperatura ambiente. El tratamiento extractivo con diclorometano (30 ml), lavando con $NH_4Cl$ acuoso saturado, dio el compuesto **113b** (0,255 g, 0,901 mmol) con un rendimiento del 95% en bruto. $^1$H RMN (300 MHz, DMSO-d6) δ ppm 2,42 (s, 3H) 3,34 (t, J =

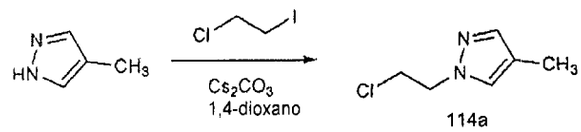
6,03 Hz, 2H), 4,36 (t, J = 6,03 Hz, 2H), 7,46 (d, J = 8,48 Hz, 2H), 7,60 (d, J = 3,39 Hz, 1H), 7,69 (d, J = 3,39 Hz, 1H), 7,72 (d, J = 8,10 Hz, 2H). LCMS $(M+H)^+$: 284,1.

**Ejemplo 114: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{2,4-dicloro-6-[2-(4-metil-1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**



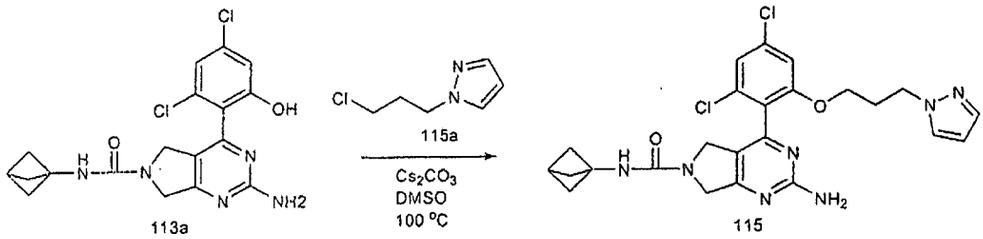

Se calentaron el compuesto **113a** (59 mg, 0,15 mmol), el compuesto **114a** (49 mg, 0,34 mmol), carbonato de cesio (177 mg, 0,543 mmol) y yoduro potásico (7 mg) en DMSO (1,5 ml) a 100°C durante 6 h. El aislamiento por HPLC preparativa dio el compuesto **114** (0,0258 g, 0,0501 mmol) en forma de un sólido de color blanco con un rendimiento del 35%. $^1$H RMN (300 MHz, DMSO-d6) $\delta$ ppm 1,90 (s, 3H), 1,94 (s, 6H), 2,35 (s, 1H), 3,69 (d, J = 13,38 Hz, 1H), 3,95 (d, J = 12,24 Hz; 1H), 4,20-4,39 (m, 6H), 6,80 (s, 2H), 6,89-6,93 (m, 1H), 6,97 (s, 1H), 7,10 (s, 1H), 7,25 (d, J = 1,51 Hz, 1H), 7,33 (d, J = 1,13 Hz, 1H). LCMS $(M+H)^+$: 516,2, 514,2.

**Preparación del Compuesto 114a, 1-(2-cloroetil)-4-metil-1*H*-pirazol**



Se calentaron 4-metil pirazol (0,177 g, 2,16 mmol), 1-cloro-2-yodoetano (1,20 g, 6,30 mmol) y carbonato de cesio (1,10 g, 3,38 mmol) en 1,4-dioxano (5,0 ml) a 95°C durante 24 h. Después de enfriar a temperatura ambiente, se añadió diclorometano (10 ml). Después de la filtración para retirar los sólidos, el filtrado se redujo y se sometió a cromatografía sobre gel de sílice (gradiente de EtOAc al 0-70% en hexano), dando el compuesto **114a** (0,049 g, 0,34 mmol) en forma de un aceite transparente con un rendimiento del 16%. $^1$H RMN (300 MHz, CLOROFORMO-d) δ ppm 2,12 (s, 3H), 3,92 (t, J = 5,84 Hz, 2H), 4,49 (t, J = 5,93 Hz, 2H), 7,33 (s, 1H), 7,46 (s, 1H).

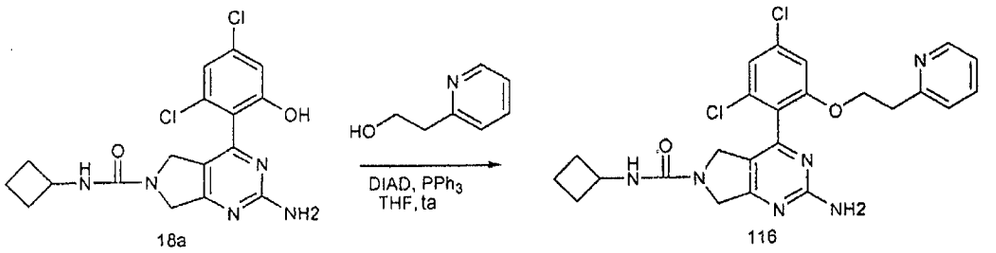
**Ejemplo 115: 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{2,4-dicloro-6-[3-(1*H*-pirazol-1-il)propoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El compuesto **115a,** 1-(3-cloropropil)-1*H*-pirazol, se preparó de una manera similar al compuesto **114a** con la excepción de que se sustituyó 4-metilpirazol por pirazol y se sustituyó 1-cloro-2-yodoetano por 1-bromo-3-cloropropano. $^1$H RMN (300 MHz, CLOROFORMO-d) δ ppm 2,33-2,42 (m, 2H), 3,47 (t, J = 6,03 Hz, 2H), 4,41 (t, J = 6,40 Hz, 2H), 6,31 (t, J = 2,17 Hz, 1H), 7,49 (d, J = 2,07 Hz, 1H), 7,61 (d, J = 1,51 Hz, 1H). Después, el compuesto **113a** (0,0442 g, 0,109 mmol) se O-alquiló con el compuesto **115a** (0,054 g, 0,37 mmol) y carbonato de cesio (0,122 g, 0,374 mmol) en DMSO (1,5 ml) a

100ºC de una manera similar al Ejemplo **18.** El aislamiento usando HPLC preparativa dio el compuesto **115** (0,0234, 0,0372 mmol) en forma de una sal TFA con un rendimiento del 34%. $^1$H RMN (300 MHz, METANOL-d4) δ ppm 2,03 (s, 6H), 2,12-2,22 (m, J = 2,45 Hz, 2H), 2,37 (s, 1H), 3,86-3,94 (m, 1H), 3,98-4,07 (m, 1H), 4,12 (t, J = 6,59 Hz, 2H), 4,31 (s, 2H), 4,57 (s, 2H), 6,23-6,25 (m, 1H), 7,14 (d, J = 1,70 Hz, 1H), 7,25 (d, J = 1,70 Hz, 1H), 7,45 (d, J = 1,51 Hz, 1H), 7,53 (d, J = 2,07 Hz, 1H), LCMS $(M+H)^+$: 516,2, 514,2.

**Ejemplo 116: 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(2-piridin-2-iletoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

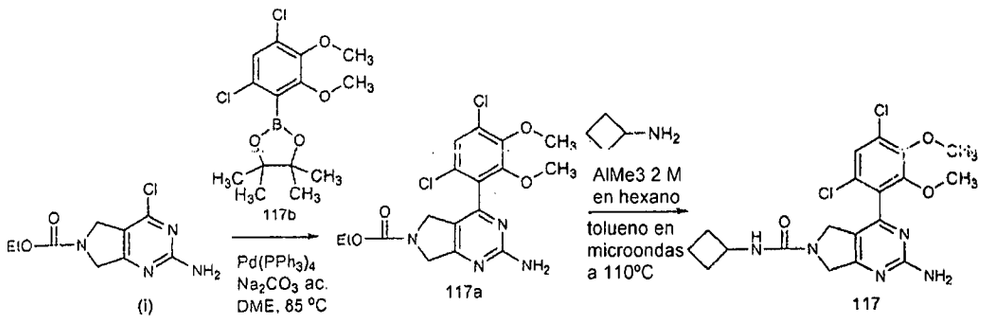



18a 116

Al compuesto **18a** (0,032 g, 0,081 mmol), 2-(2-hidroxietil)piridina y trifenilfosfina (0,053 g, 0,20 mmol) en THF (1,5 ml) se le añadió azodicarboxilato de diisopropilo (40 µl, 0,207 mmol). Después de 3 h, se añadió DMSO (1,5 ml) y los componentes volátiles se retiraron al vacío. El aislamiento usando HPLC preparativa dio el compuesto **116** (0,0208 g, 0,0416 mmol) en forma de un polvo de color castaño con un rendimiento del 51%. $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,49-1,63 (m, 2H), 1,88-2,00 (m, 2H), 2,05-2,21 (m, 2H), 2,93-3,02 (m, 2H), 3,38 (d, 1H, solapa con pico de agua), 3,86 (d, J = 13,00 Hz, 1H), 4,08-4,23 (m, 1H), 4,28-4,45 (m, 4H), 6,37 (d, J = 8,10 Hz, 1H), 6,77 (s, 2H), 6,91 (d, J = 7,72 Hz, 1H), 6,99-7,06 (m, 1H), 7,28-7,32 (m, 2H),

7,50 (dt, J = 7,58, 1,79 Hz, 1H), 8,36 (d, J = 4,14 Hz, 1H). LCMS $(M+H)^+$: 501,2, 499,2.

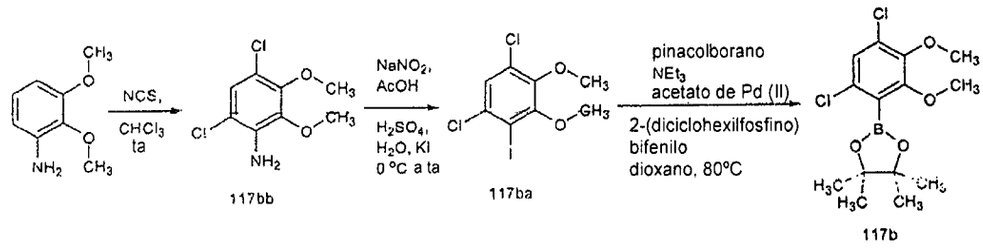
**Ejemplo 117: 2-amino-*N*-ciclobutil-4-(4,6-dicloro-2,3-dimetoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se hicieron reaccionar el compuesto **(i)** (0,263 g, 1,08 mmol), el compuesto **117b** (0,525 g, 1,58 mmol), carbonato sódico acuoso 2 M (0,80 ml, 1,6 mmol) y *tetraquis*(trifenilfosfino)paladio (0) (0,075 g, 0,065 mmol) en DME (10 ml) de una manera similar al Ejemplo **1**. El tratamiento extractivo con EtOAc (30 ml), lavando con agua (30 ml) seguido de aislamiento usando cromatografía sobre gel de sílice (gradiente de MeOH al 0-25% en diclorometano) dio el compuesto **117a,** 2-amino-4-(4,6-dicloro-2,3-dimetoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo, (0,034 mg, 0,082 mmol) con un rendimiento del 8%. Se hicieron reaccionar el compuesto **117a** (0,034 g, 0,082 mmol), ciclobutilamina (0,040 g, 0,60 mmol) y trimetil aluminio 2 M en hexano (0,25 ml, 0,50 mmol) de una manera similar al Ejemplo **7.** El aislamiento usando HPLC preparativa dio el compuesto **117** (0,010 g, 0,023 mmol) con un rendimiento del 28%. $^1$H RMN (300 MHz, DMSO-d6) $\delta$ ppm 1,49-1,61 (m, 2H), 1,85-2,00 (m, 2H), 2,03-2,15 (m, 2H), 3,69 (s, 3H),

3,85 (s, 3H), 4,07-4,24 (m, 3H), 4,43 (s, 2H), 6,51 (d, J = 7,91 Hz, 1H), 6,89 (s a, 2H), 7,60 (s, 1H). LCMS $(M+H)^+$: 440,2, 438,2.

**Preparación del Compuesto 117b, 2-(4,6-dicloro-2,3-dimetoxifenil)-4,4,5,5-tetrametil-1,3,2-dioxaborolano**

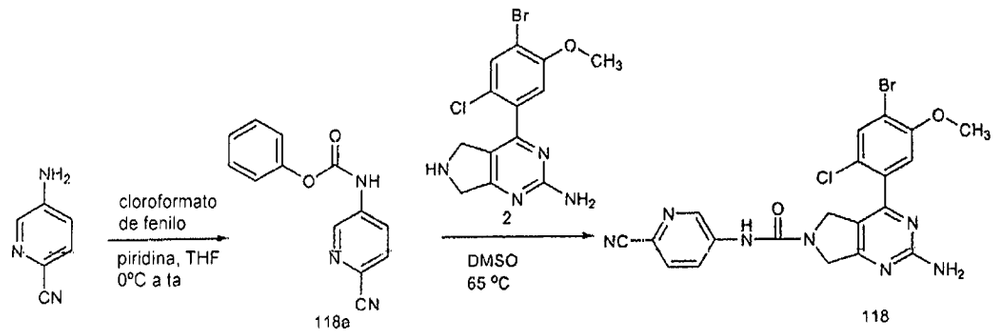



117bb 117ba 117b

Se añadió *N*-clorosuccinimida (6,87 g, 50,4 mmol) a 2,3-dimetoxianilina (3,86 g, 25,2 mmol) en cloroformo (100 ml) a 0°C. Después de dejar calentar a temperatura ambiente y de un periodo de agitación adicional de 4 h, el aislamiento por cromatografía sobre gel de sílice (diclorometano) dio el compuesto **117bb,** 4,6-dicloro-2,3-dimetoxianilina (1,97 g, 8,87 mmol) en forma de un aceite de color naranja con un rendimiento del 35%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 3,74 (s, 3H), 3,77 (s, 3H), 5,27 (s a, 2H), 7,12 (s, 1H). Con agitación, se añadió gota a gota nitrito sódico (799 mg, 11,6 mmol) en $H_2O$ (4,0 ml) al compuesto **117bb** (1,97 g, 8,87 mmol) en ácido acético (20,0 ml), $H_2O$ (6,0 ml) y $H_2SO_4$ concentrado (6,0 ml) a 0°C. Después de 3 h a 0°C, la mezcla se vertió en una solución de yoduro potásico (10,4 g, 62,7 mmol) en $H_2O$ (20,0 ml) a 0°C aclarando con más cantidad de $H_2O$ (20 ml). La mezcla se dejó calentar lentamente a temperatura ambiente y se agitó durante 16 h más. Después, la mezcla se extrajo con éter dietílico (100 ml) y la fase de $Et_2O$ se lavó con $Na_2S_2O_3$ acuoso saturado (100 ml), NaOH 3 N (100 ml) y agua (100 ml). El aislamiento usando cromatografía sobre gel de sílice (gradiente de

diclorometano al 0-20% en hexano) dio el compuesto **117ba,** 1,5-dicloro-2-yodo-3,4-dimetoxibenceno (2,46 g, 7,39 mmol) con un rendimiento del 83%. $^1$H RMN (300 MHz,-DMSO-$d_6$) δ ppm 3,81 (s, 3H), 3,82 (s, 3H), 7,62 (s, 1H). El compuesto **117ba** (2,45 g, 7,36 mmol), pinacolborano (2,1 ml, 14,5 mmol) y trietil amina (3,00 ml, 21,5 mmol) en 1,4-dioxano (40 ml) se purgaron con $N_2$ durante 15 min y se añadieron acetato de paladio (II) (86 mg, 0,38 mmol) y 2-(diciclohexilfosfino)bifenilo (263 mg, 0,750 mmol). La mezcla se calentó a 80°C durante 2,5 h, se enfrió y se sometió a tratamiento extractivo con EtOAc, lavando con $NH_4Cl$ acuoso saturado. El aislamiento usando cromatografía sobre gel de sílice (gradiente de diclorometano al 0-50% en hexano) dio el compuesto **117b** (1,155 g, 3,468 mmol) con un rendimiento del 47%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,32 (s, 12H), 3,79 (s, 6H), 7,36 (s, 1H).

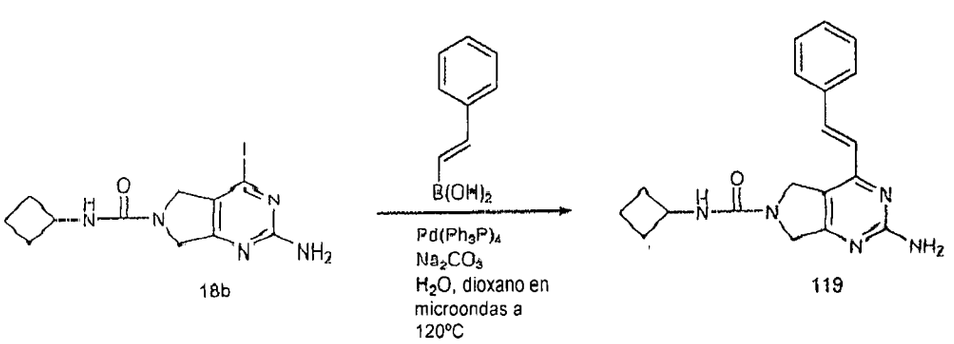
**Ejemplo 118: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(6-cianopiridin-3-il)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se añadió gota a gota cloroformiato de fenilo (0,70 ml, 5,6 mmol) en THF (10 ml) a 5-amino-2-cianopiridina (655 mg, 5,50 mmol) y piridina (0,50 ml, 6,2 mmol) en THF (10,0 ml) a 0°C. Después de dejar calentar a temperatura ambiente y de un periodo de agitación de 1 h, la mezcla se enfrió de nuevo a 0°C y el precipitado se retiró por filtración. La retirada de los componentes

volátiles del filtrado dio el compuesto **118a,** (6-cianopiridin-3-il)carbamato de fenilo (0,921, 3,85 mmol) en forma de un sólido de color naranja pálido con un rendimiento en bruto del 70%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 7,24-7,33 (m, 3H), 7,45 (t, J = 7,82 Hz, 2H), 8,01 (d, J = 8,48 Hz, 1H), 8,13 (dd, J = 8,48, 2,55 Hz, 1H), 8,81 (d, J = 2,45 Hz, 1H), 11,01 (s, 1H). Se calentaron el compuesto **2** (0,093 g, 0,152 mmol), el compuesto **118a** (0,038 g, 0,160 mmol) y el carbonato de cesio (0,154 g, 0,473 mmol) en DMSO (1,5 ml) a 65°C durante 20 min. El aislamiento usando HPLC preparativa dio el compuesto **118** (0,013 g, 0,026 mmol) en forma de un sólido de color naranja con un rendimiento del 17%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 3,87 (s, 3H), 4,52 (s a, 2H), 4,64 (s a, 2H), 6,97 (s a, 2H), 7,19 (s, 1H), 7,87-7,94 (m, 2H), 8,20 (dd, J = 8,57, 2,17 Hz, 1H), 8,87 (d, J = 2,45 Hz, 1H), 9,04 (s a, 1H). LCMS $(M+H)^+$: 502,2, 500,2.

**Ejemplo 119: 2-amino-*N*-ciclobutil-4-[(E)-2-fenilvinil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

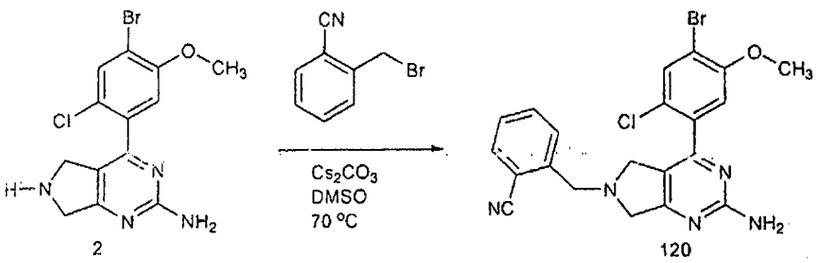



18b 119

El compuesto **18b** (0,103 g, 0,287 mmol), ácido trans-2-fenilvinilborónico (0,0602 mg, 0,407 mmol) y carbonato sódico acuoso 2 M (0,30 ml, 0,60 mmol) en 1,4-dioxano (3,0 ml) se purgaron con $N_2$. Se añadió *tetraquis*(trifenilfosfino)paladio (0) (0,024 g, 0,021 mmol) y la mezcla se sometió

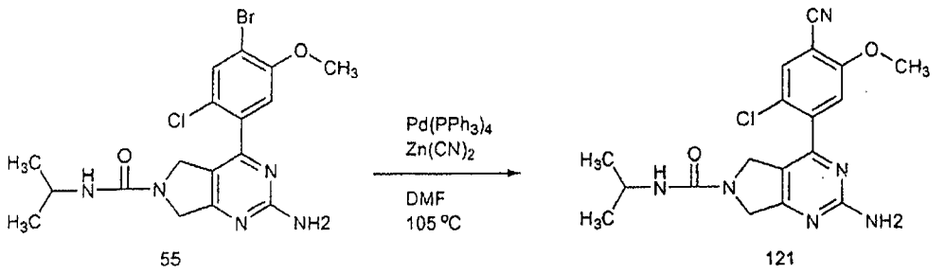
a microondas a 120°C durante 1,5 h. Después del tratamiento extractivo con EtOAc, lavando con agua (20 ml), el aislamiento usando HPLC preparativa dio el compuesto **119** (0,022 g, 0,066 mmol) con un rendimiento del 23%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,52-1,68 (m, 2H), 1,92-2,07 (m, 2H), 2,09-2,23 (m, 2H), 4,11-4,28 (m, 1H), 4,37 (s, 2H), 4,60 (s, 2H), 6,52 (d, J = 7,72 Hz, 1H), 6,59 (s a, 2H), 7,02 (d, J = 16,01 Hz, 1H), 7,34-7,48 (m, 3H), 7,63-7,77 (m, 3H). LCMS $(M+H)^+$: 336,4.

**Ejemplo 120: 2-{[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]metil}benzonitrilo**




Se calentaron el compuesto **2** (0,067 g, 0,110 mmol), 2-(bromometil)-benzonitrilo (0,0215 mg, 0,110 mmol) y carbonato de cesio (0,1189 g, 0,365 mmol) en DMSO (1,5 ml) a 70°C durante 10 min. El aislamiento usando HPLC preparativa dio el compuesto **120** (0,007 g, 0,01 mmol) con un rendimiento del 10%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 3,67 (s, 2H), 3,83 (s, 2H), 3,34 (s, 3H), 4,03 (s, 2H), 6,79 (s a, 2H), 7,10 (s, 1H), 7,47 (t, J = 7,44 Hz, 1H), 7,60-7,71 (m, 2H), 7,79-7,84 (m, 2H). LCMS $(M+H)^+$: 472,2, 470,2.

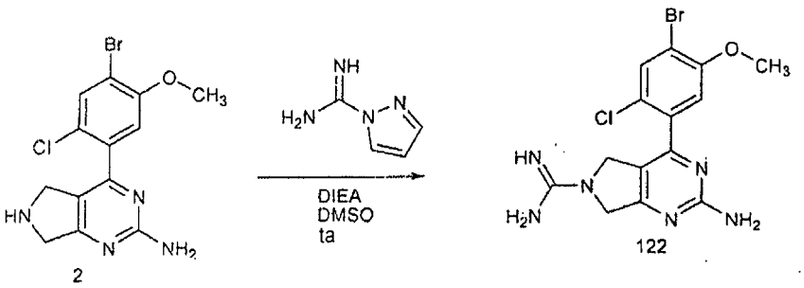
**Ejemplo 121: 2-amino-4-(2-cloro-4-ciano-5-metoxifenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




55 121

El compuesto **55** (0,0247 g, 0,056 mmol) y cianuro de cinc (0,0212 g, 0,181 mmol) en DMF (1,5 ml) se calentaron con $N_2$. Se añadió *tetraquis*(trifenilfosfino)paladio (0) (0,0102 mg, 0,00883 mmol) y la mezcla se calentó a 105°C durante 5 h. El tratamiento extractivo con acetato etilo (50 ml), lavando con agua (50 ml) seguido del aislamiento usando HPLC preparativa dio el compuesto **121** (0,008 g) en forma del clorhidrato con un rendimiento del 30%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,06 (d, J = 6,59 Hz, 6H), 3,71-3,85 (m, 1H), 3,93 (s, 3H), 4,25 (s, 2H), 4,43 (s, 2H), 6,07 (d, J = 7,54 Hz, 1H), 6,95 (s a, 2H), 7,34 (s, 1H), 8,12 (s, 1H). LCMS $(M+H)^+$: 387,2.

**Ejemplo 122: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboximidamida**

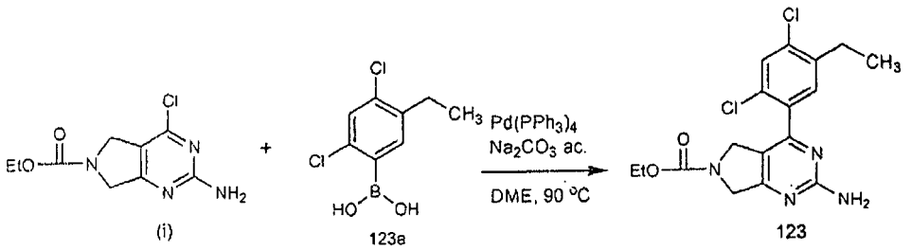



2 122

Al compuesto **2** (0,0779 g, 0,105 mmol) en DMSO (1,0 ml) a temperatura ambiente se le añadieron diisopropil etilamina (0,10 ml, 0,57 mmol) y clorhidrato de (1H)-pirazol-1-carboxamida (0,0201 g, 0,137 mmol). Después de

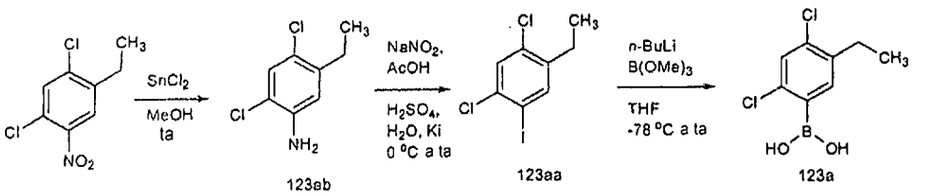
agitar durante 16 h, el aislamiento usando HPLC preparativa dio el compuesto **122** (0,016 g, 0,040 mmol) en forma de un sólido de color blanco con un rendimiento del 38%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 3,88 (s, 3H), 4,45 (s, 2H), 4,60 (s, 2H), 7,07 (s a, 2H), 7,17 (s, 1H), 7,31-7,47 (m a, 3H), 7,90 (s, 1H). LCMS $(M+H)^+$: 399,0, 397,2.

**Ejemplo 123: 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se hicieron reaccionar el compuesto (**i**) (0,0953 g, 0,393 mmol), el compuesto **123a** (0,086 mg, 0,39 mmol), carbonato sódico acuoso 2 M (0,4 ml, 0,8 mmol) y *tetraquis*(trifenilfosfino)paladio (0) (0,0227 mg, 0,0196 mmol) en DME (4 ml) de una manera similar al Ejemplo **1**. El aislamiento usando HPLC preparativa dio el compuesto **123** (0,047 g, 0,12 mmol) en forma de un polvo de color blanco con un rendimiento del 31%. 1H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,13-1,24 (m, 6H), 2,73 (c, J = 7,41 Hz, 2H), 4,01-1,14 (m, 2H), 4,30-4,36 (m, 2H), 4,44-4,51 (m, 2H), 6,94 (s a, 2H), 7,42 (s, 1H), 7,73 (s, 1H). LCMS $(M+H)^+$: 383,2, 381,2.

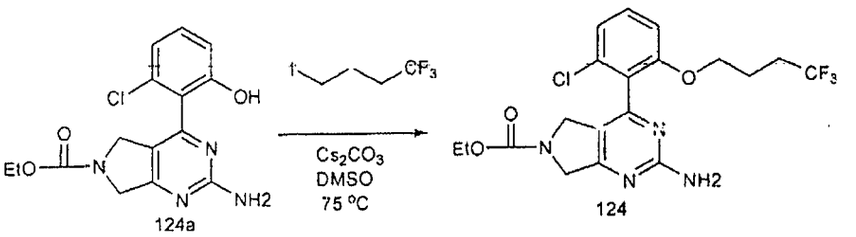
**Preparación del Compuesto 123a, ácido (2,4-dicloro-5-etilfenil)borónico**




Se calentaron a reflujo 1,5-dicloro-2-etil-4-nitrobenceno (2,1 g, 9,5 mmol) y $SnCl_2$ (8,1 g, 42,8 mmol) en metanol anhidro hasta que la reducción se completó. Se añadieron NaOH acuoso al 10% y EtOAc, se dejó que se posaran los sólidos resultantes y la mayor parte del EtOAc se decantó. Este procedimiento se repitió varias veces y las extracciones de EtOAc se combinaron y se filtraron a través de celite, se secaron ($Na_2SO_4$), se filtraron y los componentes volátiles se retiraron. El residuo se disolvió en $Et_2O$ y se añadió HCl 4 M en exceso en 1,4-dioxano. La evaporación de los componentes volátiles dio el compuesto **123ab**, 2,4-dicloro-5-etilanilina (2,1 g, 9,27 mmol) en forma de un clorhidrato de color amarillo con un rendimiento del 97%. El compuesto **123ab** se convirtió en el compuesto **123aa**, 1,5-dicloro-2-etil-4-yodobenceno (0,577 g, 1,92 mmol) con un rendimiento del 36% de una manera similar al Ejemplo **117ba** con la excepción de que el compuesto **117bb** se sustituyó por el compuesto **123ab**. $^1$H RMN (300 MHz, CLOROFORMO-*d*) δ ppm 1,22 (t, J = 7,54 Hz, 3H), 2,69 (c, J = 7,54 Hz, 2H), 7,44 (s, 1H), 7,70 (s, 1H). Al compuesto **123aa** (0,576 g, 1,91 mmol) en THF (15,0 ml) a -78ºC se le añadió gota a gota n-BuLi 2 M en ciclohexano (1,00 ml, 2,00 mmol). Después de 1 h, se añadió gota a gota borato de trimetilo (0,30 ml, 2,7 mmol) y la reacción se dejó calentar a temperatura ambiente. Se añadió agua (50 ml) seguido de éter/hexanos (25 ml/25 ml) y las fases se separaron. Después, la fase orgánica se extrajo con NaOH 0,5 N (30 ml) y la extracción acuosa se

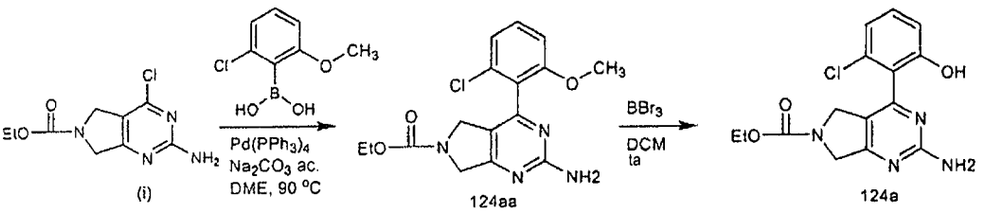
llevó a pH 6 con $KH_2PO_4$ 1 N (15 ml) y se extrajo con EtOAc (50 ml). La retirada de los componentes volátiles de la fase de EtOAc dio el compuesto **123a** (0,088 g) en forma de un sólido ceroso de color blanco que se llevó a continuación sin purificación.

**Ejemplo 124: 2-amino-4-[2-cloro-6-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**



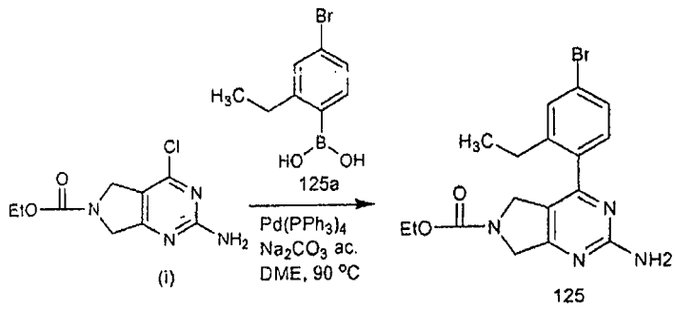

El compuesto **124a** (0,0763 g, 0,228 mmol) se O-alquiló con 1-yodo-4,4,4-trifluorobutano (0,0801 g, 0,337 mmol) y carbonato de cesio (0,0992 mg, 0,304 mmol) en DMSO (1,0 ml) de una manera similar a la que se ha descrito para el Ejemplo 18. El aislamiento usando HPLC preparativa dio el compuesto **124** (0,0353 g, 0,0794 mmol) en forma de un polvo de color blanco con un rendimiento del 35%. $^1$H RMN (300 MHz, DMSO-$d_6$) $\delta$ ppm 1,11-1,25 (m, 3H), 1,70-1,82 (m, 2H), 2,03-2,23 (m, 2H), 3,99-4,21 (m, 6H), 4,37-4,57 (m, 2H), 6,83 (s a, 2H), 7,11-7,20 (m, 2H), 7,44 (t, J = 8,19 Hz, 1H). LCMS $(M+H)^+$: 445,2.

**Preparación del Compuesto 124a, 2-amino-4-(2-cloro-6-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**



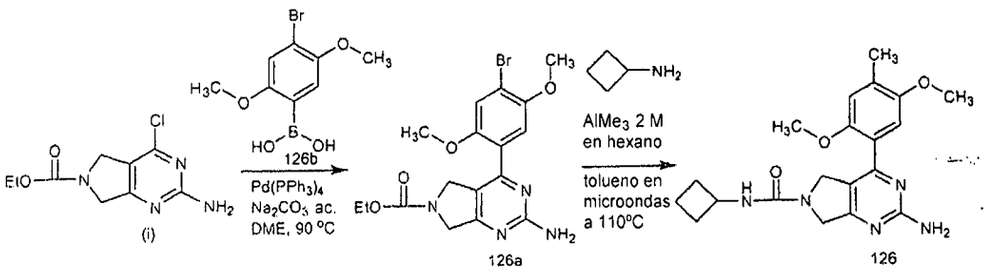

Se hicieron reaccionar el compuesto (**i**) (0,300 g, 1,24 mmol), ácido 2-cloro-6-metoxifenilborónico (0,351 g, 1,88 mmol), carbonato sódico acuoso 2 M (1,85 ml, 3,70 mmol) y *tetraquis*(tifenilfosfino)paladio (0) (0,0789 g, 0,0683 mmol) en DME (10,0 ml) de una manera similar a la que se ha descrito para el Ejemplo **1** dando el compuesto en bruto **124aa**, 2-amino-4-(2-cloro-6-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo (0,481 g) que se llevó a continuación sin purificación. LCMS $(M+H)^+$: 349,2. Al compuesto **124aa** (0,407 g) en diclorometano (10,0 ml) a 0ºC se le añadió gota a gota bromuro de boro 1 M (0,20 ml, 2,1 mmol) en diclorometano. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 2 h. Se añadió más cantidad de tribromuro de boro (0,20 ml, 2,1 mmol) en diclorometano y la mezcla se agitó durante 4 h más. Después, la mezcla se vertió en $NaHCO_3$ acuoso saturado frío y se extrajo con diclorometano/MeOH. La retirada de los componentes volátiles dio el compuesto **124a** (0,249 g) en forma de un residuo de color naranja que se llevó a continuación sin purificación. LCMS $(M+H)^+$: 335,2.

**Ejemplo 125: 2-amino-4-(4-bromo-2-etilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo**




El compuesto **125a**, ácido 4-bromo-2-etilfenilborónico, se preparó de una manera al Ejemplo **123a** con la excepción de que se sustituyó el compuesto **123aa** por 4-bromo-2-etil-1-yodobenceno. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,19 (t, J = 7,35 Hz, 3H), 3,02 (c, J = 7,41 Hz, 2H), 7,33-7,41 (m, 2H), 7,74 (d, J = 7,91 Hz, 1H). Se hicieron reaccionar el compuesto (**i**) (0,114 g, 0,470 mmol), el compuesto **125a** (0,0852 g, 0,372 mmol), carbonato sódico acuoso 2 M (0,50 ml, 1,0 mmol) y *tetraquis*(trifenilfosfino)paladio (0) (0,031 g, 0,027 mmol) en DME (3,5 ml) de una manera similar a la que se ha descrito para el Ejemplo 1. El aislamiento usando HPLC preparativa dio el compuesto **125** (0,029 g, 0,074 mmol) con un rendimiento del 15%. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,02 (t, J = 7,54 Hz, 3H), 1,13-1,25 (m, 3H), 2,55-2,63 (m, 2H), 4,00-4,13 (m, 2H), 4,26-4,32 (m, 2H), 4,44-4,50 (m, 2H), 6,82 (s a, 2H), 7,24 (d, J = 7,91 Hz, 1H), 7,48 (dd, J = 8,01, 1,60 Hz, 1H), 7,57 (d, J = 1,70 Hz, 1H). LCMS $(M+H)^+$: 393,2, 391,2.

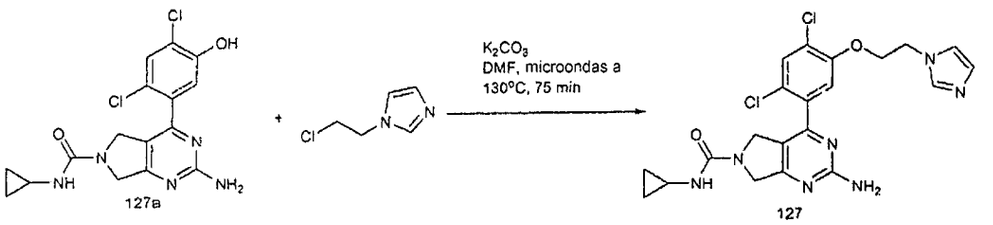
**Ejemplo 126: 2-amino-*N*-ciclobutil-4-(2,5-dimetoxi-4-metilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




El compuesto **126b, ácido** 4-dibromo-2,5-dimetoxifenilborónico, se preparó de una manera similar al Ejemplo **123a** con la excepción de que se sustituyó el compuesto **123aa** por 1,4-dibromo-2,5-dimetoxibenceno. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 3,77 (s, 3H), 3,78 (s, 3H), 7,20 (s, 1H), 7,22 (s, 1H), 7,83 (s, 2H). Se hicieron reaccionar el compuesto (**i**) (0,114 g, 0,470 mmol), el compuesto **126b** (0,112 g, 0,429 mmol), carbonato sódico acuoso 2 M (0,50 ml, 1,0 mmol) y *tetraquis*(trifenilfosfino)paladio (0) (0,030 g, 0,026 mmol) en DME (3,5 ml) de una manera similar al Ejemplo 1 dando el compuesto **126a,** 2-amino-4-(4-bromo-2,5-dimetoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo (0,065 g, 0,154 mmol), con un rendimiento del 36% que se llevó a continuación sin purificación. $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,14-1,25 (m, 3H), 3,78 (s, 3H), 3,80 (s, 3H), 4,02-4,14 (m, 2H), 4,27-4,33 (m, 2H), 4,42-4,48 (m, 2H), 6,82 (s a, 2H), 7,05 (s, 1H), 7,39 (s, 1H). LCMS $(M+H)^+$: 425,2, 423,2. Se sometieron a microondas ciclobutilamina (0,10 ml, 1,2 mmol), trimetilaluminio 2,0 M (0,30 ml, 0,6 mmol) en hexano y el compuesto **126a** (49,2 mg, 0,116 mmol) en tolueno (2,0 ml) durante 1 h de una manera similar al Ejemplo 7. El tratamiento, también de una manera similar, y el aislamiento usando HPLC preparativa, dieron el compuesto **126** (0,0174 g, 0,0454 mmol) con un rendimiento del 30% en forma de una sal TFA (no se anticipó la conversión del bromo del compuesto **126a** en el grupo

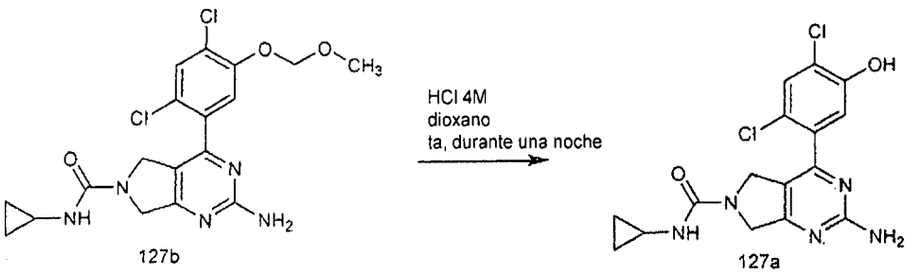
metilo del compuesto **126**). $^1$H RMN (300 MHz, DMSO-$d_6$) δ ppm 1,50-1,63 (m, 2H), 1,88-2,03 (m, 2H), 2,06-2,17 (m, 2H), 2,24 (s, 3H), 3,77 (s, 6H), 4,10-4,20 (m, 1H), 4,28 (s, 2H), 4,42 (s, 2H), 6,53 (d, J = 7,72 Hz, 1H), 6,91 (s, 1H), 7,04 (s, 1H). LCMS $(M+H)^+$: 384,4.

**Ejemplo 127: 2-amino-*N*-ciclopropil-4-{2,4-dicloro-5-[2-(1*H*-imidazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




Se hicieron reaccionar el compuesto **127a** (70 mg, 0,184 mmol), HCl 1-(2-cloroetil)-1*H*-imidazol (84 mg, 0,55 mmol) y carbonato potásico (127 mg, 0,92 mmol) en DMF (2 ml) de una manera similar al Ejemplo **100**. El aislamiento usando HPLC preparativa dio el compuesto 127 (9,0 mg, 0,02 mmol) en forma de un polvo con un rendimiento del 11%. $^1$H RMN (DMSO-$d_6$, 300 MHz): δ 7,71 (s, 1H), 7,63 (s, 1H), 7,19 (s, 1H), 7,16 (s, 1H), 6,85 (m, 3H), 6,43 (s, 1H) 4,37 (s, 4H), 4,31 (m, 2H), 4,18 (s, 2H), 2,69 (s a, 1H), 0,50 (m, 2H), 0,36 (m, 2H).

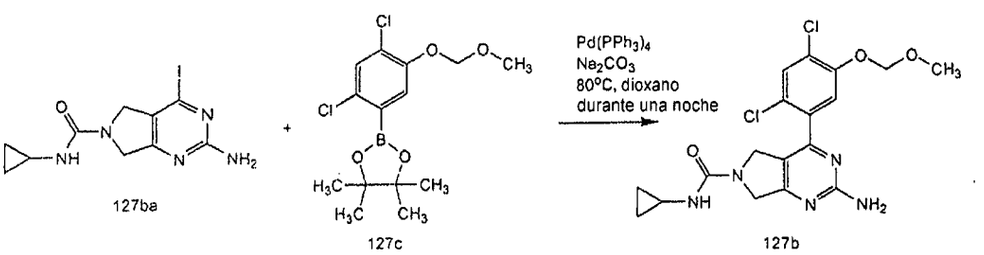
**Preparación del Compuesto 127a, 2-amino-*N*-ciclopropil-4-(2,4-dicloro-5-hidroxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




127b 127a

A una suspensión del compuesto **127b** (640 mg, 1,51 mmol) en MeOH (4 ml) se le añadió HCl en 1,4-dioxano (4 ml, 16,0 mmol). Después de agitar durante una noche, los componentes volátiles se retiraron y el residuo se sometió a tratamiento extractivo con EtOAc, lavando con $NaHCO_3$ acuoso saturado. El secado ($Na_2SO_4$), la filtración y la evaporación de los componentes volátiles dieron el compuesto **127a** (426 mg, 1,12 mmol) en forma de un polvo con un rendimiento del 74% que se llevó a continuación sin purificación. $^1H$ RMN (400 MHz, DMSO-$d_6$) $\delta$ ppm: 10,77 (s, 1H), 7,62 (s, 1H), 6,94 (s, 1H), 6,87 (s, 2H), 6,47 (d, J = 2,78 Hz, 1H), 4,39 (s, 2H), 4,23 (s, 2H), 2,51-2,56 (m, 1H), 0,50-0,57 (m, 2H), 0,36-0,43 (m, 2H). LCMS $(M+H)^+$: 380,2, 382,2.

**Preparación del Compuesto 127b, 2-amino-*N*-ciclopropil-4-[2,4-dicloro-5-(metoximetoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**

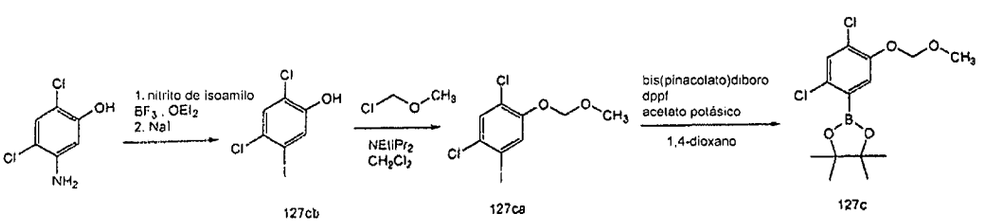



127ba 127c 127b

El compuesto **127ba**, 2-amino-*N*-ciclopropil-4-yodo-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida, se preparó a partir del compuesto **8b** de una forma similar al Ejemplo **18b** con la excepción de que se sustituyó

ciclobutilamina por ciclopropilamina. Se hicieron reaccionar el compuesto **127ba** (825 mg, 2,39 mmol), el compuesto **127c** (876 mg, 2,63 mmol), carbonato sódico acuoso 2 M (3,6 ml, 7,18 mmol) y *tetraquis*(trifenilfosfina)paladio (0) (276 mg, 0,239 mmol) en 30 ml de 1,4-dioxano de una manera similar al Ejemplo **18a**. Después de filtrar y lavar el material insoluble recogido con EtOAc, El filtrado/lavados combinados se concentraron y se sometieron a tratamiento extractivo con EtOAc (100 ml), lavando con agua (200 ml) y salmuera (2 x 100 ml) y se secó ($Na_2SO_4$). El aislamiento usando cromatografía sobre gel de sílice (gradiente de MeOH al 0-5% en EtOAc) dio el compuesto **127b** (656 mg, 1,55 mmol) en forma de un sólido con un rendimiento del 65%. $^1$H RMN (400 MHz, DMSO-$d_6$) δ ppm: 7,78 (s, 1H), 7,28 (s, 1H), 6,90 (s, 2H), 6,46 (d, J = 2,78 Hz, 1H), 5,32 (s, 2H), 4,40 (s, 2H), 4,23 (s, 2H), 3,41 (s, 3H), 0,49-0,60 (m, 2H), 0,36-0,44 (m, 2H). LCMS $(M+H)^+$: 424,2, 426,2.

**Preparación del Compuesto 127c, 2-(2,4-dicloro-5-metoximetoxi-fenil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano**

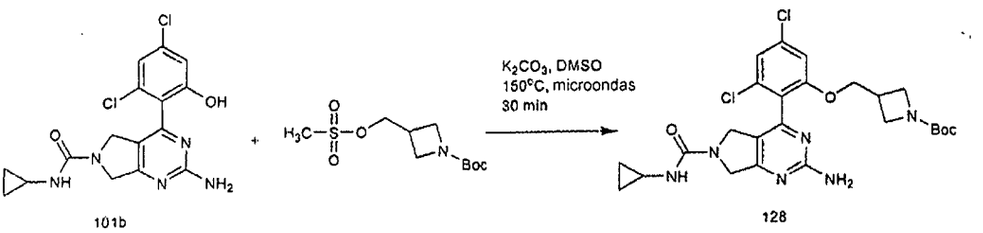



Se enfrió $BF_3OEt_2$ (70,6 ml, 560 mmol) a 0ºC y se añadió 5-amino-2,4-diclorofenol (50,0 g, 280 mmol) en THF (700 ml) durante 45 min. Después, se añadió nitrito de isoamilo (48,8 ml, 365 mmol) en THF (150 ml) durante 15 min. Después de agitar durante 30 min a 0ºC, se formó un precipitado de color amarillo, se añadió más cantidad de $Et_2O$ y el sólido de color amarillo se

recogió por filtración, se lavó con $Et_2O$ y se secó al aire. El sólido recogido se añadió en porciones a una solución de NaI (54,7 g, 365 mmol) en acetona (1,2 l) y se agitó a temperatura ambiente durante una noche. Los componentes volátiles se redujeron, se añadió agua y la mezcla se sometió a tratamiento extractivo con EtOAc, lavando con $NaHSO_3$ acuoso saturado, y se secó ($Na_2SO_4$). El asilamiento después de la cromatografía sobre un lecho de gel de sílice ($CH_2Cl_2$) dio una mezcla contaminada por la impureza de des-yodo. La recristalización en hexanos (3 extracciones) dio el compuesto **127cb**, 2,4-dicloro-5-yodofenol (43,4 g, 150 mmol), en forma de un sólido de color amarillo con un rendimiento del 54%. $^1H$ RMN (400 MHz, CLOROFORMO-*d*) $\delta$ ppm 3,77 (c, J = 7,07 Hz, 3H), 5,27 (s, 2H), 7,45 (s, 1H), 7,66 (s, 1H). Se enfrió el compuesto **127cb** en $CH_2Cl_2$ (400 ml) a 0ºC y se añadió cloruro de metoximetilo (13,7 ml, 180 mmol) seguido de diisopropiletil amina (31,5 ml, 23,3 g, 180 mmol). Después de calentar a temperatura ambiente durante una noche, la solución de $CH_2Cl_2$ se lavó con $NaHCO_3$ acuoso saturado y se secó sobre $Na_2SO_4$. La filtración y la evaporación de los componentes volátiles dio el compuesto **127ca**, 1,5-dicloro-2-yodo-4-(metoximetoxi)benceno (46,8 g, 141 mmol) en forma de un sólido de color amarillo con un rendimiento del 94%. El compuesto **127ca** (41,8 g, 125 mmol), bis(pinacolato)diboro (35,1 g, 138 mmol), acetato potásico (24,6 g, 250 mmol), aducto de diclorometano de bis(difenilfosfino)ferroceno-dicloropaladio (6,15 g, 7,5 mmol) y 1,4-dioxano seco (375 ml) se purgaron con $N_2$ durante 1 h y se calentaron a 90ºC. Después de 5 días, la mezcla se enfrió a temperatura ambiente, se filtró y el sólido recogido se lavó con $Et_2O$. El filtrado/lavados combinados se sometieron a cromatografía sobre gel de sílice (gradiente por etapas de EtOAc al 0 a 17% en hexano) y el

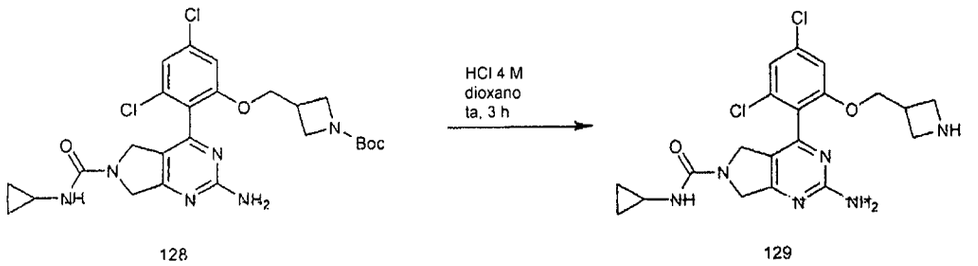
aislamiento dio el compuesto **127c** (30,2 g, 91 mmol) en forma de un sólido de color amarillo con un rendimiento del 73% (pureza >94% por CGEM).

**Ejemplo 128: 3-[(2-{2-amino-6-[(ciclopropilamino)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-4-il}-3,5-diclorofenoxi)metil]azetidina-1-carboxilato de *terc*-butilo**




Se sometieron a microondas el compuesto **101b** (300 mg, 0,789 mmol), 3-{[(metilsulfonil)oxi]metil}azetidina-1-carboxilato de *terc*-butilo (419 mg, 1,58 mmol) y carbonato potásico (327 mg, 2,37 mmol) en DMF (10 ml) a 150ºC durante 30 min. Después del tratamiento extractivo con EtOAc, lavando con agua y salmuera, y del secado ($Na_2SO_4$), el aislamiento usando cromatografía sobre gel de sílice (MeOH al 10% en EtOAc) dio el compuesto **128** (272 mg, 0,495 mmol) con un rendimiento del 63%. $^1$H RMN (400 MHz, CLOROFORMO-*d*) δ ppm: 7,15 (d, J = 1,77 Hz, 1H), 6,00 (d, J = 1,77 Hz, 1H), 5,15 (s, 2H), 4,55 (s, 3H), 4,35-4,42 (m, 1H), 4,21-4,29 (m, 1H), 4,01-4,13 (m, 2H), 3,86-3,96 (m, 2H), 3,53-3,62 (m, 2H), 2,74-2,86 (m, 1H), 2,64-2,74 (m, 1H), 1,43 (s, 9H), 0,71-0,79 (m, 2H), 0,48-0,56 (m, 2H). LCMS $(M+H)^+$: 549,2, 550,2.

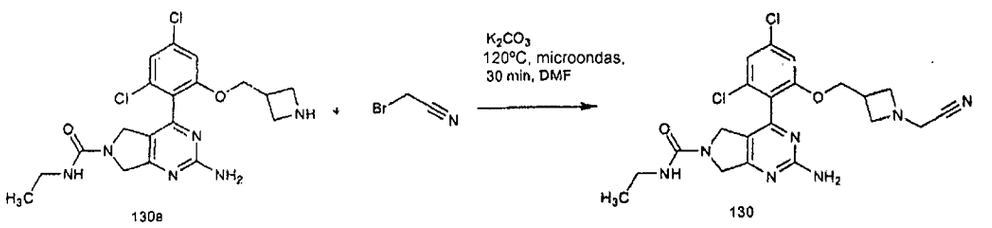
**Ejemplo 129: 2-amino-4-[2-(azetidin-3-ilmetoxi)-4,6-diclorofenil]-*N*-ciclopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**




128 129

Al compuesto **128** (490 mg, 0,892 mmol, 1,0 equiv.) en 1,4-dioxano (5 ml) se le añadió HCl 4 M en 1,4-dioxano (5 ml). Después de agitar 3 h, el aislamiento por HPLC preparativa dio el compuesto **129** (25 mg, 0,056 mmol) en forma de un sólido con un rendimiento del 6%. $^1$H RMN (400 MHz, *MeOD*) ppm 8,55 (s, 1H), 7,15-7,35 (m, 2H), 4,44-4,62 (m, 2H), 4,15-4,40 (m, 4H), 3,85-4,03 (m, 2H), 3,66-3,83(m, 2H), 3,13-3,27 (m, 1H), 2,47-2,63 (m, 1H), 0,58-0,75 (m, 2H), 0,49 (d, J = 2,02 Hz, 2H). LCMS $(M+H)^+$: 449,2, 450,2.

**Ejemplo 130: 2-amino-4-(2,4-dicloro-6-{[1-(cianometil)azetidin-3-il]metoxi}fenil)-*N*-etil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida**



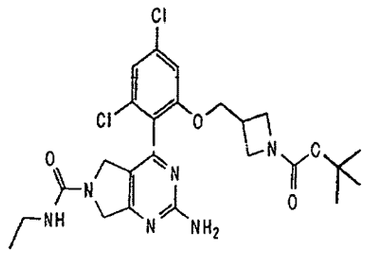

130a 130

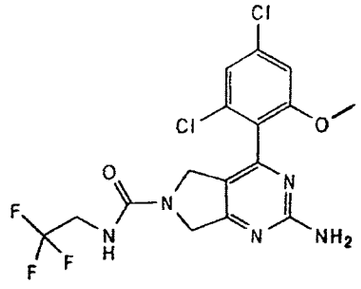
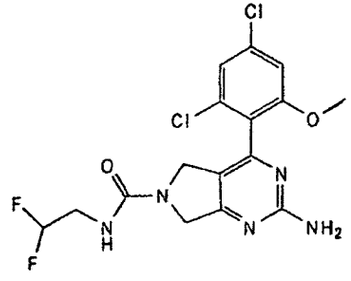
El compuesto **130a**, 2-amino-4-[2-(azetidin-3-ilmetoxi)-4,6-diclorofenil]-*N*-etil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida se preparó a partir del compuesto **131** de una manera similar al Ejemplo **129**. Una mezcla del compuesto **130a** (78 mg, 0,180 mmol), bromoacetonitrilo (26 mg, 0,216 mmol) y carbonato potásico (124 mg, 0,899 mmol) en DMF (2,5 ml) se sometió a

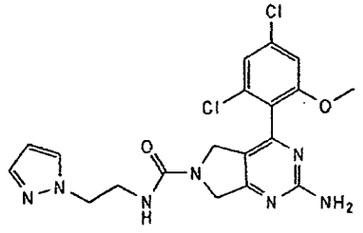
microondas a 120°C durante 30 min. El aislamiento por HPLC preparativa dio el compuesto **130** (20,0 mg, 0,042 mmol) en forma de un polvo con un rendimiento del 23%. $^1$H RMN (400 MHz, DMSO-$d_6$) $\delta$ ppm: 7,35 (d, J = 1,26 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H), 6,81 (s a, 2H), 6,34 (t, J = 5,31 Hz, 1H), 4,42 (s, 2H), 4,04-4,20 (m, 4H), 3,43-3,48 (m, 2H), 3,25-3,34 (m, 2H), 3,00-3,10 (m, 2H), 2,87-2,99 (m, 2H), 2,62-2,75 (m, 1H), 1,01 (t, J = 7,07 Hz, 3H). LCMS $(M+H)^+$: 476,0, 478,0.

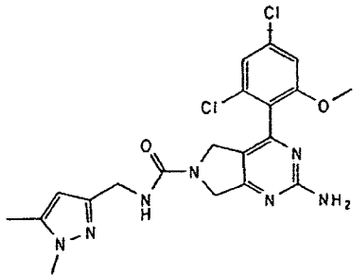
Los compuestos de los Ejemplos 131-2xx se prepararon siguiendo los procedimientos de los Ejemplos 1-18 y 100-130 como se muestra en la siguiente Tabla 2.

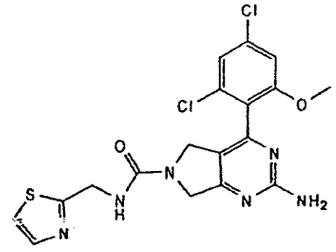
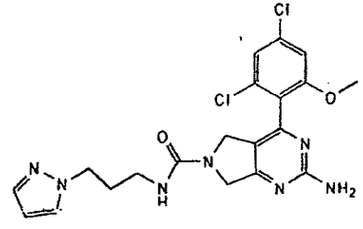
**Tabla 2**

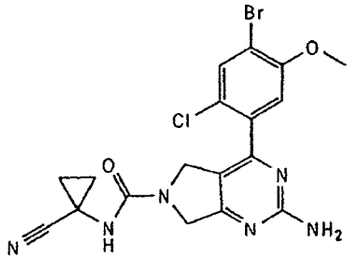
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 131 |  | 3-[(2-{2-amino-6-[(etilamino)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-4-il}-3,5-diclorofenoxi)metil]azetidina-1-carboxilato de *terc*-butilo | Ej. 128 | $^1$H RMN (400 MHz, CLOROFORMO-d) δ ppm: 7,15 (d, J = 1,77 Hz, 1H), 6,90 (d, J = 1,77 Hz, 1H), 5,17 (s, 2H), 4,58 (s, 2H), 4,37-4,45 (m, 1H), 4,20-4,32 (m, 2H), 4,01-4,13 (m, 2H), 3,87-3,96 (m, 2H), 3,53-3,62 (m, 2H), 3,27-3,38 (m, 2H), 2,73-2,87 (m, 1H), 1,42 (s, 9H), 1,17 (t, J = 7,20 Hz, 3H). | 537,1, 539,1 |

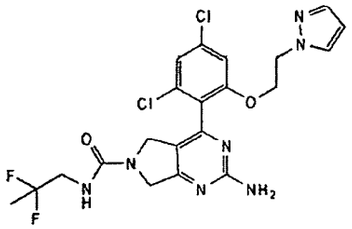
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 132 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-(2,2,2-trifluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,78 (s, 3H), 3,82 (dd, J = 9,60, 6,57 Hz, 2H), 4,16 (s, 2H), 4,48 (s, 2H), 6,87 (s, 2H), 7,07 (s a, 1H), 7,28 (d, J = 1,52 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H). | 436,0, 438,0 |
| 133 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-(2,2-difluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) d ppm 3,38 - 3,48 (m, 2H), 3,72-3,82 (m, 3H), 4,11-4,18 (m, 2H), 4,46 (s, 2H), 5,74-6,15 (m, 1H), 6,82 (t, J = 5,68 Hz, 1H), 6,86 (s, 2H), | 418,0, 420,0 |

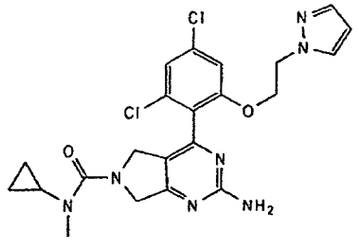
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| | | | | 7,28 (d, J = 1,77 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H). | |
| 134 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-[2-(1*H*-pirazol-1-il)etil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,35-3,40 (m, 2H), 3,78 (s, 3H), 4,09 (s, 2H), 4,15 (t, J = 6,57 Hz, 2H), 4,41 (s, 2H), 6,20 (t, J = 2,02 Hz, 1H), 6,54 (t, J = 5,05 Hz, 1H), 6,86 (s a, 2H), 7,28 (d, J = 1,52 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H), 7,42 (d, J = 1,26 Hz, 1H), 7,67 (d, J = 2,02 Hz, 1H). | 448,2, 450,2 |

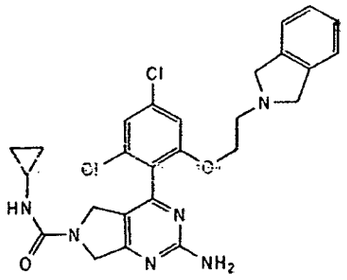
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 135 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-[(1,5-dimetil-1*H*-pirazol-3-il)metil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,17 (s, 3H), 3,62 (s, 3H), 3,77 (s, 3H), 4,08 (d, J = 5,31 Hz, 2H), 4,12 (s, 2H), 4,44 (s, 2H), 5,88 (s, 1H), 6,73 (t, J = 5,68 Hz, 1H), 6,84 (s, 2H), 7,28 (d, J = 1,52 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H). | 462,2, 464,2 |

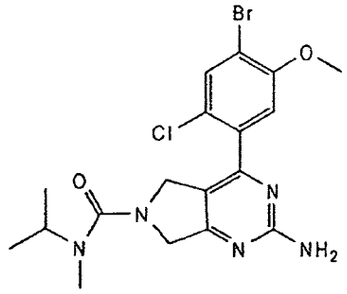
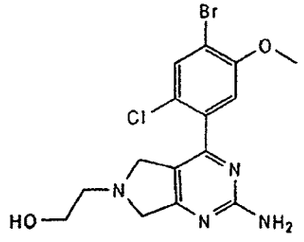
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 136 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-(1,3-tiazol-2-ilmetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,78 (s, 3H), 4,18 (s, 2H), 4,43-4,56 (m, 4H), 6,87 (s, 2H), 7,28 (s, 1H), 7,35 (s, 1H), 7,36-7,42 (m, 1H), 7,55-7,60 (m, 1H), 7,66-7,71 (m, 1H). | 451,0, 453,0 |
| 137 |  | 2-amino-4-(2,4-dicloro-6-metoxifenil)-*N*-[3-(1*H*-pirazol-1-il)propil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,89 (t, J = 6,95 Hz, 2H), 3,02 (c, J = 6,40 Hz, 2H), 3,77 (s, 3H), 4,06-4,15 (m, 4H), 4,42 (s, 2H), 6,19 (t, J = 2,02 Hz, 1H), 6,40 (t, J = | 462,2, 464,2 |

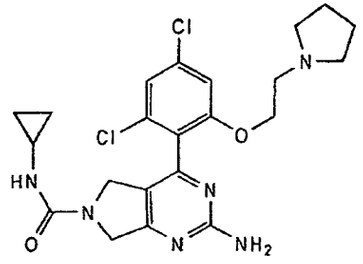
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| | | | | 5,43 Hz, 1H), 6,84 (s, 2H), 7,28 (d, J = 2,02 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H), 7,39 (d, J = 1,26 Hz, 1H), 7,72 (d, J = 2,27 Hz, 1H). | |
| 138 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(1-cianociclopropil)-5,7-dihidro-*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,06-1,17 (m, 2H), 1,35-1,47 (m, 2H), 3,86 (s, 3H), 4,27 (s a, 2H), 4,45 (s, 2H), 6,93 (s, 2H), 7,15 (s, 1H), 7,46 (s a, 1H), 7,87 (s, 1H). | 463,0, 465,0 |

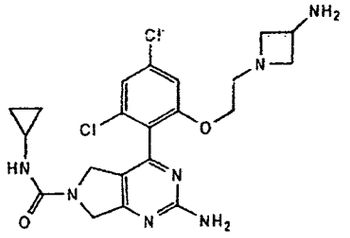
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 139 |  | 2-amino-4-(2,4-dicloro-6-[2-1*H*-pirazol-1-il)etoxi]fenil}-*N*-(2,2-difluoropropil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,54-1,66 (m, 3H), 3,48 (td, J = 13,89, 8,08 Hz, 2H), 3,58 ,'d. J = 12,88 Hz, 2H), 3,97 (d, J = 12,88 Hz, 1H), 4,33 (s, 4H), 4,44 (s a, 2H), 6,00 (t, J = 2,02 Hz, 1H), 6,66 (s a, 1H), 6,80 (s, 2H), 7,20 (d, J = 2,02 Hz, 1H), 7,26 (d, J = 1,52 Hz, 1H), 7,29 (d, J = 1,52 Hz, 0 H), 7,33 (d, J = 1,52 Hz, 1H). | 512,0, 514,0 |

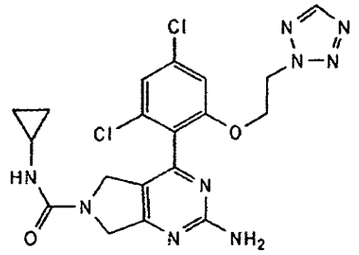
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 140 |  | 2-amino-*N*-ciclopropil-4-2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-metil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6,carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,50-0,63 (m, 2H), 0,68 (dd, J = 6,57, 2,27 Hz, 2H), 2,63 (ddd, J = 6,82, 3,28, 3,03 Hz, 1H), 2,74 (s, 3H), 3,82 (d, J = 13,39 Hz, 1H), 4,18 (dd, J = 13,39, 1,52 Hz, 1H), 4,33 (s, 4H), 4,49-4,69 (m, 2H), 6,06 (t, J = 2,02 Hz, 1H), 6,76 (s, 2H), 7,19 (d, J = 2,02 Hz, 1H), 7,23 (d, J = 1,77 Hz, 1H). 7,31 (d, J = 1,77 Hz, 1H), 7,33 (d, J = 1,52 Hz, 1H). | 489,0, 491,0 |

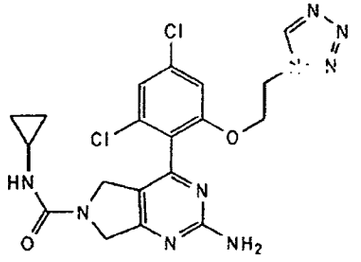
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 141 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(1,3-dihidro-2*H*-isoindol-2-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,41 (m, 2H), 0,45-0,57 (m, 2H), 1,91 (s, 1H), 2,92 (s a, 2H), 3,69 (s a, 4H), 4,10-4,25 (m, 4H), 4,26-4,36 m, 1H), 4,38-4,48 (m, 1H), 6,45 (d, J = 2,78 Hz, 1H), 6,90 (s, 2H), 7,15 (s, 4H), 7,31 (d, J = 1,77 Hz, 1H), 7,35 (d, J = 1,52 Hz, 1H). | 525,2, 527,2 |

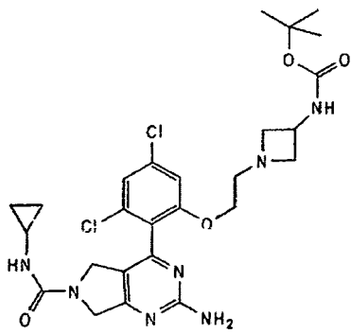
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 142 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil}-*N*-isopropil-*N*-metil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,07 (d, J = 6,57 Hz, 6H), 2,64 (s, 3H), 3,82-3,89 (m, 3H), 3,94-4,08 (m, 1H), 4,40 (s, 2H), 4,53 (s, 2H), 6,87 (s, 2H), 7,16 (s, 1H), 7,85 (s, 1H) | 456,0, 458,0 |
| 143 |  | 2-[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]etanol | Ej. 105 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,44 (d, J = 10,36 Hz, 2H), 3,71-3,79 (m, 2H), 3,85-3,91 (m, 3H), 4,46 (s a, 2H), 4,59 (s, 2H), 5,36 (s a, 1H), 7,09 (s, 1H), 7,17- | 401,0, 403,0 |

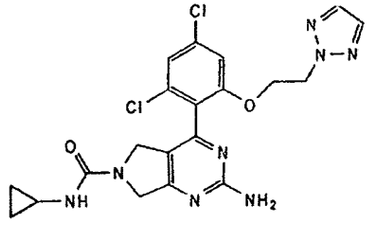
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| | | | | 7,24 (m, 2H), 7,91 (s, 1H). | |
| 144 |  | 2-amino-*N*-ciclopropil-4-[2,4-dicloro-6-(2-pirrolidin-1-iletoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,43 (m, 2H), 0,46-0,58 (m, 2H), 1,59 (s a, 4H), 2,25-2,45 (m, 3H), 2,54 (s, 1H), 2,62-2,84 (m, 2H), 4,03-4,20 (m, 5H), 4,29-4,48 (m, 2H), 6,54 (s, 1H), 6,80 (s, 2H), 7,29 (s, 1H), 7,34 (d, J = 1,52 Hz, 1H). | 477,2, 479,2 |

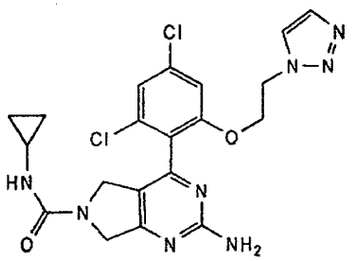
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 145 |  | 2-amino-4-{2-[2-(3-aminoazetidin-1-il)etoxi]4,6-diclorofenil}-*N*-ciclopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,46 (m, 2H), 0,47-0,60 (m, 2H), 1,91 (s, 2H), 2,59 (dd, J = 4,93, 3,16 Hz, 2H), 2,62-2,75 (m, 4H), 3,98 (t, J = 5,05 Hz, 2H), 4,03-4,14 (m, 2H), 4,14-4,25 (m, 2H), 4,41 (s, 2H), 6,46 (d, J = 2,53 Hz, 1H), 6,77 (s, 2H), 7,25 (d, J = 1,77 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | 478,2, 780,2 |

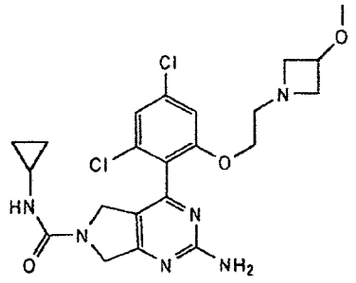
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 146 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(2*H*-tetrazol-2-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,48 (m, 2H), 0,47-0,59 (m, 2H), 2,51-2,57 (m, 1H), 3,62 (d, J = 13,14 Hz, 1H), 3,95 (dd, J = 13,01, 1,89 Hz, 1H), 4,28-4,45 (m, 3H), 4,44-4,57 (m, 1H), 4,75 (t, J = 5,05 Hz, 2H), 6,34 (s a, 1H), 6,77 (s a, 2H), 7,33 (d, J = 1,77 Hz, 1H), 7,36 (d, J = 1,77 Hz, 1H), 8,82 (s, 1H). | 476,1, 478,1 |

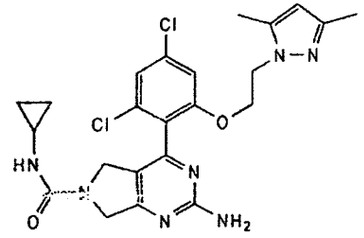
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 147 |  | 2-amino-*N*-ciclopropil-4-2,4-dicloro-6-[2-(1*H*-tetrazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) d ppm 0,36-0,48 (m, 2H), 0,50-0,61 (m, 2H), 2,53-2,58 (m, 1H), 3,36-3,42 (m, 1H), 3,83 (dd, J = 13,01, 2,15 Hz, 1H), 4,25-4,47 (m, 2H), 4,46-4,63 (m, 2H), 4,91-5,04 (m, 2H), 6,34 (s a, 1H), 6,72 (s, 2H), 7,34 (s, 2H), 8,61 (s, 1H). | 476,1, 477,1 |

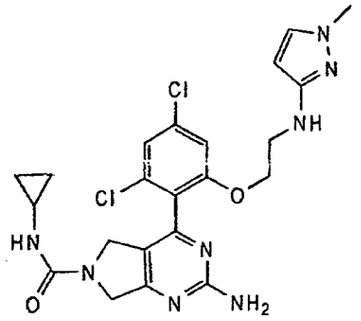
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 148 |  | {1-[2-(2-{2-amino-6-[(ciclopropilamino)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-4-il}-3,5-diclorofenoxi)etil]azetidin-3-il}carbamato de *terc*-butilo | Ej. 101 | $^1$H RMN (400 MHz, CLOROFORMO-d) δ ppm 1,44 (s, 9H), 1,66 (s a, 3H), 2,70 (s a, 4H), 2,75-2,89 (m, 2H), 3,37-3,47 (m, 1H), 3,50 (s, 1H), 3,86-4,03 (m, 2H), 4,19 (s a, 1H), 4,34 (s a, 2,H), 4-57 (s, 2H), 4,62 (s, 1H), 5,08 (s a, 1H), 5,30 (s a, 2H), 6,85 (d, J = 1,52 Hz, 1H), 7,12 (d, J = 1,77 Hz, 1H). | 578,2, 580,2 |

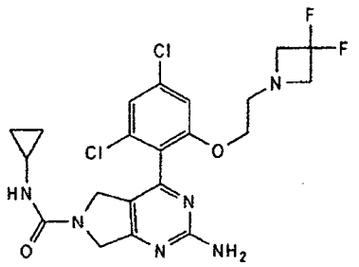
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 149 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(2*H*-1,2,3-triazol-2-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,35-0,47 (m, 2H), 0,56 (d, J = 7,07 Hz, 2H), 2,52-2,60 (m, 1H), 3,38-3,47 (m, 1H), 3,84 (d, J = 13,14 Hz, 1H), 4,35 (d, J = 4,80 Hz, 2H), 4,42-4,56 (m, 2H), 4,65 (t, J = 4,93 Hz, 2H), 6,33 (s a, 1H), 6,53 (s, 1H), 6,71 (s, 2H), 7,26-7,37 (m, 1H), 7,53 (s, 2H). | 475,1, 477,1 |

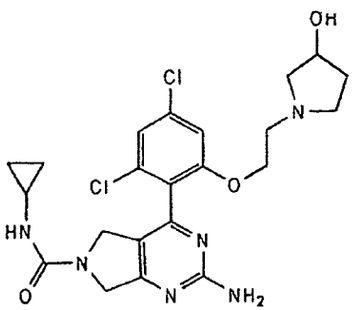
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 150 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(1*H*-1,2,3-triazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,35-0,48 (m, 2H), 0,49-0,60 (m, 2H), 2,52-2,58 (m, 1H), 3,60 (d, J = 13,14 Hz, 1H), 3,94 (dd, J = 12,88, 2,02 Hz, 1H), 4,30-4,51 (m, 4H), 4,59-4,71 (m, 2H), 6,35 (s a, 1H), 6,79 (s a, 2H), 7,29 (d, J = 1,77 Hz, 1H), 7,35 (d, J = 1,52 Hz, 1H), 7,48 (s, 1H), 7,56 (s, 1H). | 475,1, 477,1 |

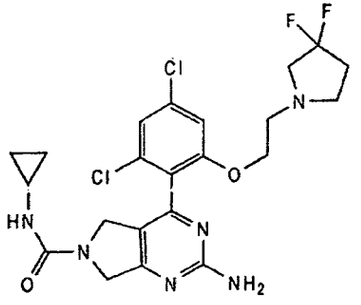
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 151 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3-metoxiazetidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,46 (m, 2H), 0,49-0,59 (m, 2H), 2,52-2,57 (m, 1H), 2,59-2,75 (m, 4H), 3,07 (s, 3H), 3,23-3,28 (m, 2H), 3,79 (t, J = 5,68 Hz, 1H), 3,93-4,05 (m, 2H), 4,04-4,23 (m, 2H), 4,29-4,48 (m, 2H), 6,46 (d, J = 2,78 Hz, 1H), 6,82 (s, 2H), 7,23 (d, J = 1,52 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | 493,1, 495,1 |

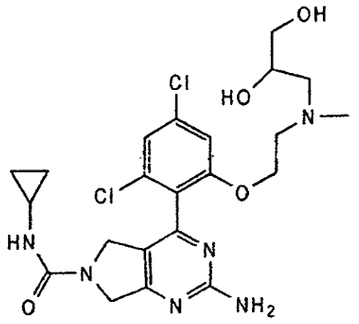
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 152 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3,5-dimetil-1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,47 (m, 2H), 0,54 (dd, J = 7,07, 2,27 Hz, 2H), 1,66 (s, 3H) 2,00 (s, 3H), 2,54-2,58 (m, 1H), 3,84 (d, J = 12,88 Hz, 1H), 4,00-4,17 (m, 2H), 4,16-4,27 (m, 2H), 4,31-4,43 (m, 2H), 5,49 (s, 1H), 6,33 (s a, 1H), 6,53 (s, 1H), 6,78 (s, 2H), 7,25 (d, J = 1,77 Hz, 1H), 7,31 (d, J = 1,77 Hz, 1H). | 502,1, 504,1 |

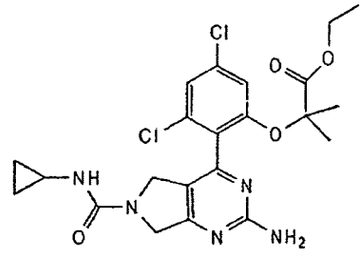
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 153 |  | 2-amino-*N*-ciclopropil-4-(2,4-dicloro-6-{2-[(1-metil-1*H*-pirazol-3-il)amino]etoxi}fenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,35-0,45 (m, 2H), 0,49-0,61 (m, 2H), 2,53-2,58 (m, 1H), 3,25 (t, J = 5,81 Hz, 2H), 3,60-3,67 (m, 3H), 4,04-4,12 (m, 2H), 4,12-4,23 (m, 3H), 4,40 (s, 2H), 5,39 (d, J = 2,27 Hz, 1 H), 6,41 (s a, 1H), 6,62-7,04 (m, 2H), 7,34 (d, J = 1,77 Hz, 1H), 7,38 (d, J = 2,02 Hz, 1H), 7,45 (d, J = 1,77 Hz, 1H). | 503,1, 505,1 |

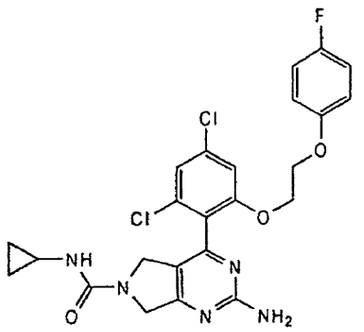
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 154 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3,3-difluoroazetidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,44 (m, 2H), 0,47-0,59 (m, 2H), 2,74 (d, J = 3,54 Hz, 2H), 3,22-3,35 (m, 4H), 3,57 (s, 1H), 3,97-4,09 (m, 2H), 4,08-4,17 (m, 2H), 4,26-4,51 (m, 2H), 6,46 (d, J = 2,53 Hz, 1H), 6,85 (s, 2H), 7,25 (d, J = 1,77 Hz, 1H), 7,30-7,38 (m, 1H). | 499,1, 500,1 |

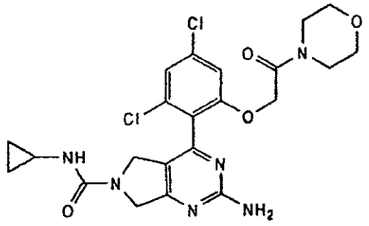
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 155 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3-hidroxipirrolidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,45 (m, 2H), 0,47-0,58 (m, 2H), 1,34-1,49 (m, 2H), 1,74-1,88 (m, 0 H), 2,17-2,34 (m, 2H), 2,34-2,45 (m, 1H), 2,55-2,73 (m, 3H), 3,17 (d, J = 4,80 Hz, 2H), 3,99-4,20 (m, 4H), 4,38 (s a, 2H), 4,59 (s a, 1H), 6,38-6,48 (m, 1H), 6,78 (s, 2H), 7,27 (s, 1H), 7,32 (d, J = 1,52 Hz, 1H). | 493,1, 495,1 |

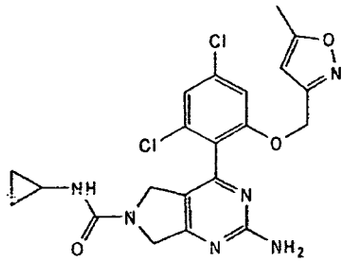
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 156 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3,3-difluoropirrolidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,33-0,43 (m, 2H), 0,47-0,57 (m, 2H), 2,09-2,32 (m, 2H), 2,52-2,58 (m, 1H), 3,00 (d, J = 3,79 Hz, 3H), 3,13-3,21 (m, 2H), 4,11 (s, 2H), 4,46-4,26 (m, 2H), 4,29-4,47 (m, 3H), 6,44 (d, J = 2,27 Hz, 1H), 6,82 (s a, 2H), 7,32 (s, 1H), 7,37 (s, 1H). | 516,1, 514,1 |

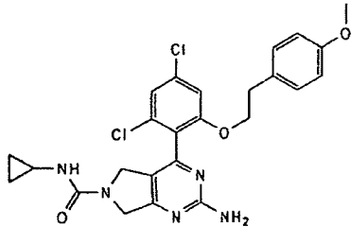
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 157 |  | 2-amino-*N*-ciclopropil-4-(2,4-dicloro-6-{2-[(2,3-dihidroxipropil)(metil)(amino]etoxi}fenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,90 (s, 1H), 2,06-2,12 (m, 3H), 2,11-2,14 (m, 2H), 2,20 (dd, J = 12,88, 7,07 Hz, 2H), 2,29-2,40 (m, 2H), 2,56-2,63 (m, 2H), 3,17-3,27 (m, 2H), 3,39-3,49 (m, 2H), 4,02-4,13 (m, 3H), 4,13-4,30 (m, 2H), 4,39 (s, 2H), 6,43 (d, J = 2,53 Hz, 1H), 6,77 (s, 2H), 7,28 (d, J = 1,77 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | 512,2, 513,2 |

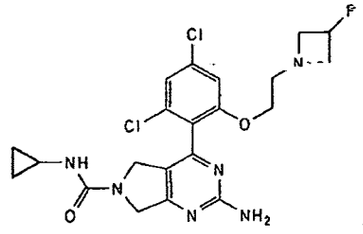
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 158 |  | 2-(2-{2-amino-6-[(ciclopropilamino)carbonil]-6,7-dihidro-5*H*-pirrolo[3,4-d]pirimidin-4-il}-3,5-diclorofenoxi)-2-metilpropanoato de etilo | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,45 (m, 2H), 0,48-0,58 (m, 2H), 1,17 (t, J = 7,07 Hz, 3H), 1,24 (s, 1H), 1,35 (s, 3H), 1,43 (s, 3H), 4,10-4,23 (m, 4H), 4,40 (s, 2H), 6,45 (d, J = 2,78 Hz, 1H), 6,79-6,88 (m, 3H), 7,45 (d, J = 2,02 Hz, 1H). | 494,1, 496,1 |

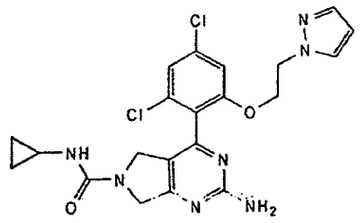
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 159 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(4-fluorofenoxi)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,43 (m, 2H), 0,49-0,61 (m, 2H), 1,23 (s, 1H), 3,96-4,28 (m, 5H), 4,29-4,42 (m, 3H), 6,41 (d, J = 2,02 Hz, 1H), 6,70-6,83 (m, 3H), 6,95-7,06 (m, 2H), 7,31-7,41 (m, 2H), 7,50-7,68 (m, 1H). | 518,1, 520,1 |

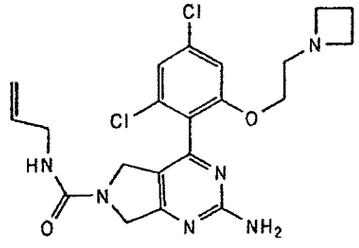
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 160 |  | 2-amino-*N*-ciclopropil-4-[2,4-dicloro-6-(2-morfolin-4-il-2-oxoetoxi)fenil-]5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,44 (m, 2H), 0,47-0,59 (m, 2H), 2,54 (s, 1H), 3,46 (s, 4H), 3,47-3,60 (m, 4H), 4,10 (d, J = 13,39 Hz, 1H), 4,19-4,32 (m, 1H), 4,39 (s, 2H), 4,81-4,96 (m, 1H), 4,96-5,09 (m, 1H), 6,45 (d, J = 2,53 Hz, 1H), 6,79 (s a, 2H), 7,18 (d, J = 1,26 Hz, 1H), 7,31 (d, J = 1,52 Hz, 1H). | 507,1, 509,1 |

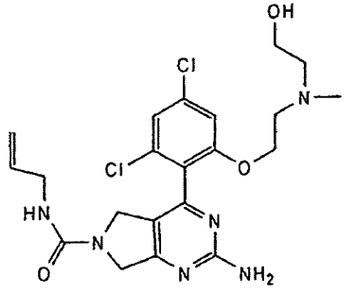
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 161 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[(5-metilisoxazol-3-il)metoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,45 (m, 2H), 0,48-0,59 (m, 2H), 2,33-2,41 (m, 3H), 2,52-2,56 (m, 1H), 3,96-4,16 (m, 2H), 4,40 (s, 2H), 5,19-5,33 (m, 2H), 6,04 (s, 1H), 6,44 (d, J = 2,53 Hz, 1H), 6,84 (s, 2H), 7,39 (d, J = 1,77 Hz, 1H), 7,42 (d, J = 1,77 Hz, 1H). | 475,1, 477,1 |

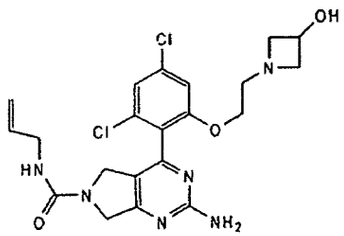
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 162 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(4-metoxifenil)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,44 (m, 2H), 0,47-0,58 (m, 2H), 2,65-2,84 (m, 2H), 3,69 (s, 3H), 3,74 (d, J = 13,14 Hz, 1H), 3,97 (d, J = 12,88 Hz, 1H), 4,06-4,23 (m, 3H), 4,41 (s, 2H), 6,36 (s a, 1H), 6,69 (d, J = 8,59 Hz, 2H), 6,83 (s, 2H), 6,86 (s, 1H), 6,88 (s, 1H), 7,24 (d, J = 1,77 Hz, 1H), 7,29 (d, J = 1,77 Hz, 1H). | 514,1, 515,1 |

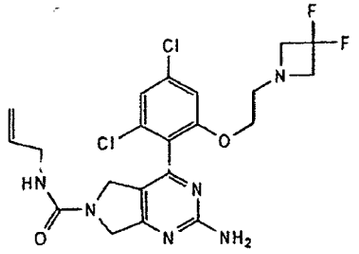
| Ej Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 163 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(3-fluoroazetidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,44 (m, 2H), 0,47-0,59 (m, 2H), 2,52-2,57 (m, 1H), 2,66 (s a, 2H), 2,90 (d, J = 7,83 Hz, 2H), 4,00 (t, J = 4,93 Hz, 2H), 4,07-4,20 (m, 4H), 4,33-4,46 (m, 2H), 4,84-5,11 (m, 1H), 6,46 (d, J = 2,53 Hz, 1H), 6,81 (s, 2H), 7,24 (d, J = 1,52 Hz, 1H), 7,29-7,36 (m, 1H). | 481,1, 483,1 |

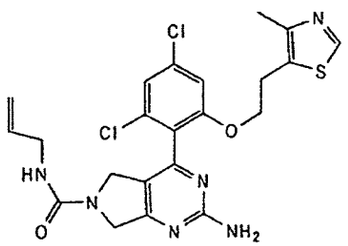
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 164 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,32-0,45 (m, 2H), 0,50-0,59 (m, 2H), 2,52-2,57 (m, 1H), 3,55 (d, J = 12,88 Hz, 1H), 3,82-3,97 (m, 1H), 4,32 (s, 4H), 4,35-4,42 (m, 2H), 6,00 (t, J = 2,02 Hz, 1H), 6,33 (s a, 1H), 6,78 (s, 2H), 7,18 (d, J = 2,02 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,29 (d, J = 1,77 Hz, 1H), 7,32 (d, J = 1,52 Hz, 1H). | 474,1, 476,1 |

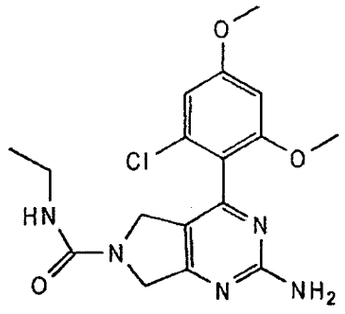
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 165 |  | *N*-alil-2-amino-4-[2-(2-azetidin-1-iletoxi)-4,6-diclorofenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,85 (t, J = 7,07 Hz, 2H), 2,60 (t, 2H), 3,01 (s a, 2H), 3,67 (t, J = 5,31 Hz, 2H), 3,98 (t, J = 4,93 Hz, 2H), 4,08-4,28 (m, 4H), 4,37-4,48 (m, 2H), 5,00 (dd, J = 10,23, 1,64 Hz, 1H), 5,10 (dd, J = 17,18, 1,77 Hz, 1H), 5,68-5,90 (m, 1H), 6,57 (t, J = 5,68 Hz, 1H), 6,81 (s, 2H), 7,24 (d, J = 1,77 Hz, 1H), 7,29-7,36 (m, 1H). | 463,2, 646,2 |

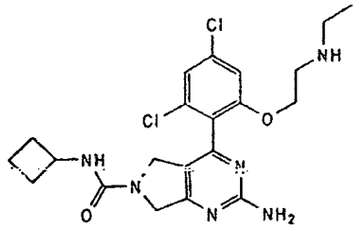
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 166 |  | *N*-alil-2-amino-4-(2,4-dicloro-6-{2-[(2-hidroxietil){metil)amino]etoxi}fenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | 1H RMN (400 MHz, DMSO-d6) d ppm 2,08 (s, 3H), 2,33 (t, J = 6,19 Hz, 2H), 2,56-2,63 (m, 2H), 3,67 (t, J = 5,31 Hz, 3H), 3,97 - 4,17 (m, 4H), 4,25 (d, J = 13,14 Hz, 2H), 4,43 (s a, 2H), 5,00 (dd, J = 10,23, 1,64 Hz, 1H), 5,10 (dd, J = 17,31, 1,64 Hz, 1H), 5,73-5,88 (m, 1H), 6,55 (t, J = 5,56 Hz, 1H), 6,79 (s, 2H), 7,29 (d, J = 1,77 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | 481,2, 483,2 |

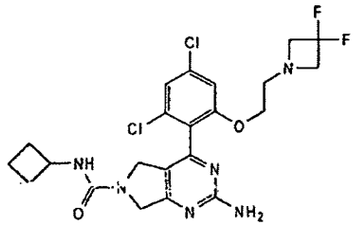
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 167 |  | *N*-alil-2-amino-4-{2,4-dicloro-6-[2-(3-hidroxiazetidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) d ppm 2,56 (d, J = 6,57 Hz, 2H), 3,63-3,72 (m, 2H), 3,93-4,04 (m, 4H), 4,06-4,18 (m, 2H), 4,18-4,29 (m, 2H), 4,39-4,49 (m, 2H), 5,01 (dd, J = 10,23, 1,64 Hz, 1H), 5,06-5,16 (m, 1H), 5,20 (s a, 1H), 5,73-5,89 (m, 1H), 6,51-6,61 (m, 2H), 6,81 (s, 2H), 7,25 (d, J = 1,77 Hz, 1H), 7,31-7,36 (m, 1H). | 479,2, 481,2 |

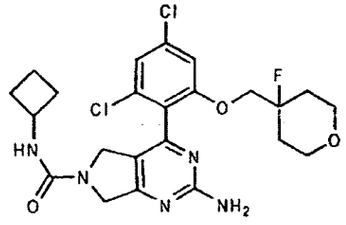
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 168 |  | *N*-alil-2-amino-4-{2,4-dicloro-6-[2-(3,3-difluoroazetidin-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 101 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,73 (d, J = 4,04 Hz, 2H), 3,20-3,29 (m, 2H), 3,66 (t, J = 5,31 Hz, 2H), 3,99-4,09 (m, 2H), 4,15 (s, 2H), 4,29,-4,51 (m, 4H), 4,99 (dd, J = 10,23, 1,64 Hz, 1H), 5,09 (dd, J = 17,43, 1,77 Hz, 1H), 5,73-5,85 (m, 1H), 6,56 (t, J = 5,56 Hz, 1H), 6,85 (s, 2H), 7,24 (d, J = 1,77 Hz, 1H), 7,33 (d, J = 1,77 Hz, 1H). | 499,0, 501,0 |

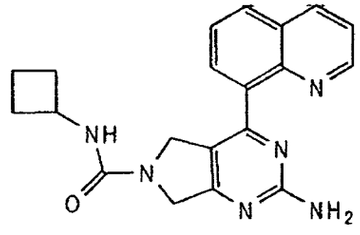
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 169 |  | *N*-alil-2-amino-4-{2,4-dicloro-6-[2-(4-metil-1,3-tiazol-5-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,02 (s, 3H), 2,99-3,12 (m, 2H), 3,55-3,65 (m, 1H), 3,68 (t, J = 5,18 Hz, 2H), 3,87-4,00 (m, 1H), 4,01-4,12 (m, 1H), 4,23-4,34 (m, 1H), 4,33-4,54 (m, 2H), 5,02 (dd, J = 10,36, 1,52 Hz, 1H), 5,13 (dd, J = 17,18, 1,52 Hz, 1H), 5,74-5,93 (m, 1H), 6,46 (s a, 1H), 6,80 (s, 2H), 7,26 (d, J = 1,52 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H), 8,56 (s, | 505,0, 507,0 |

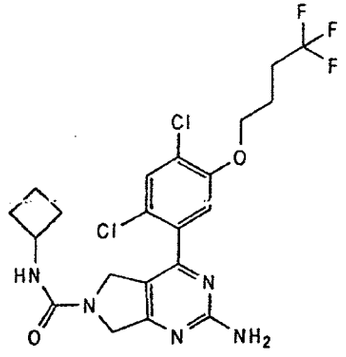
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| | | | | 1H). | |
| 170 |  | 2-amino-4-(2-cloro-4,6-dimetoxifenil)-*N*-etil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 107 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,01 (t, J = 7,20 Hz, 3H), 2,97-3,12 (m, 2H), 3,73 (s, 3H), 3,80-3,87 (m, 3H), 4,05-4,17 (m, 2H), 4,37-4,53 (m, 2H), 6,35 (t, J = 5,43 Hz, 1H), 6,68 (d, J = 2,27 Hz, 1H), 6,75 (d, J = 2,27 Hz, 2H), 7,21 (s, 1H). | 378,1, 380,1 |

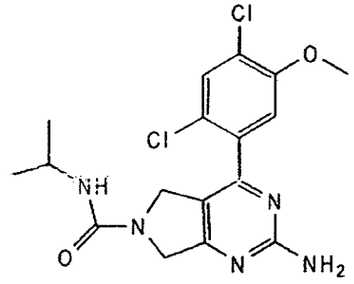
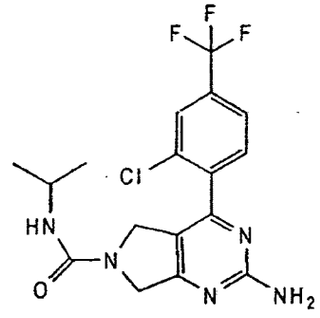
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 171 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[2-(etilamino)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,87 (t, J = 7,07 Hz, 3H), 1,44-1,61 (m, 2H), 1,83-1,96 (m, 4H), 2,02-2,14 (m, 2H), 2,38-2,45 (m, 2H), 2,73 (t, J = 4,93 Hz, 2H), 4,01-4,19 (m, 4H), 4,40 (s a, 2H), 6,51 (d, J = 7,83 Hz, 1H), 6,82 (s, 2H), 7,31 (s, 1H), 7,34 (s, 1H). | 465,1, 467,1 |

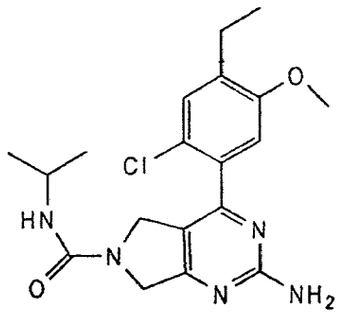
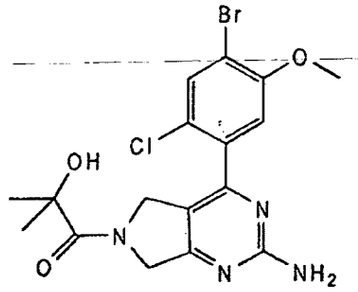
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 172 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[2-(3,3-difluoroazetidin-1-il)etoxi]fenil}-6,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,54 (dd, J = 9,85, 7,33 Hz, 2H), 1,85-1,97 (m, 2H), 2,08 (dd, J = 6,82, 3,54 Hz, 2H), 2,74 (s a, 2H), 3,36-3,47 (m, 2H), 3,98-4,08 (m, 2H), 4,09-4,17 (m, 3H), 4,26-4,48 (m, 2H), 6,47-6,57 (m, 2H), 6,85 (s, 2H), 7,25 (d, J = 1,77 Hz, 1H), 7,34 (d, J = 1,52 Hz, 1H). | 513,1, 515,1 |

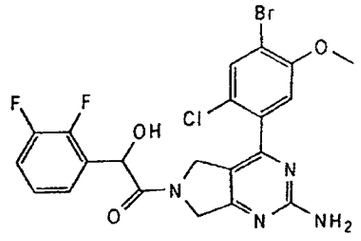
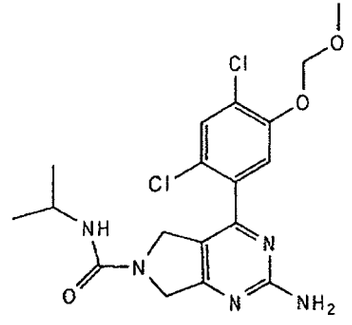
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 173 |  | amino-ciclobutil-4-{2,4-dicloro-6-[(4-fluorotetrahidro-2*H*-piran-4-il)metoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,46-1,60 (m, 4H), 1,91 (s a, 2H), 2,09 (dd, J = 6,82, 3,28 Hz, 2H), 3,28-3,40 (m, 4H), 3,42-3,52 (m, 2H), 3,56-3,68 (m, 2H), 4,09-4,16 (m, 3H), 4,36-4,44 (m, 2H), 6,52-6,59 (m, 2H), 6,82 (s, 1H), 7,37 (dd, J = 8,08, 1,77 Hz, 2H). | |

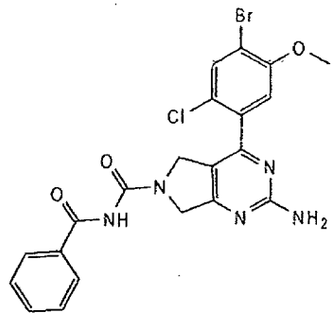
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 174 |  | 2-amino-*N*-ciclobutil-4-quinolin-8-il-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18a | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,44-1,62 (m, 2H), 1,81-1,94 (m, 2H), 1,99-2,18 (m, 2H), 3,95-4,19 (m, 3H), 4,42 (d, J = 18,44 Hz, 2H), 6,42 (d, J = 7,83 Hz, 1H), 6,75 (s, 2H), 7,59-7,66 (m, 1H), 7,69-7,77 (m, 1H), 7,78-7,84 (m, 1H), 8,08-8,17 (m, 1H), 8,43-8,55 (m, 1H), 8,93 (dd, J = 4,17, 1,64 Hz, 1H). | 361,4 |

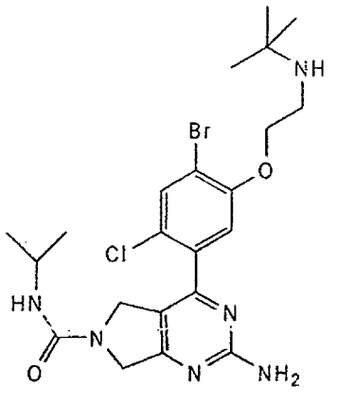
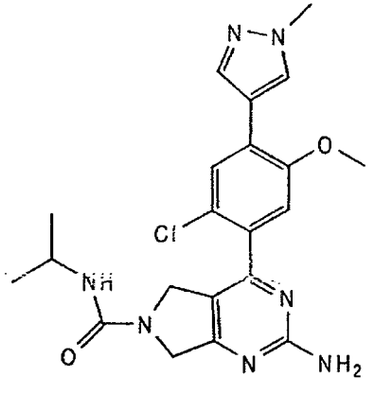
| Ej. Nº | Estructura | Nombre | Procedimiento Sintético | $^1$H RMN | EM |
|---|---|---|---|---|---|
| 175 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-5-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,45-1,65 (m, 2H) 1,86-2,01 (m, 4H) 2,03-2,15 (m, 2H) 2,37-2,46 (m, 2H) 4,06-4,21 (m, 3H) 4,26 (s, 2H) 4,41 (s, 2H) 6,53 (d, J = 8,08 Hz, 1H), 6,89 (s, 2H), 7,23 (s, 1H) 7,77 (s, 1H). | 504,2, 506,2 |

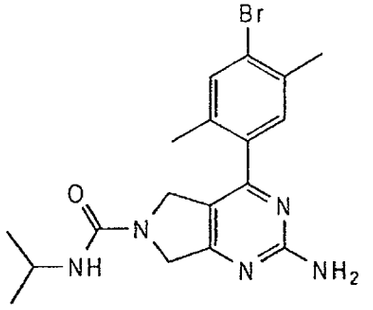
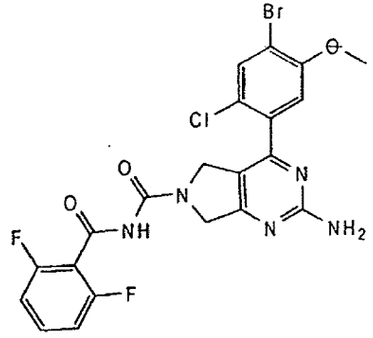
| | | | | | |
|---|---|---|---|---|---|
| 177 |  | 2-amino-4-(2,4-dicloro-5-metoxifenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,05 (d, J = 6,57 Hz, 6H), 3,77 (d, J = 7,07 Hz, 1H), 3,87 (s, 3H), 4,25 (s, 2H), 4,41 (S, 2H), 6,07 (d, J = 7,58 Hz, 1H), 6,89 (s, 2H), 7,20 (s, 1H), 7,74 (s, 1H). | 396,0, 397,0 |
| 178 |  | 2-amino-4-[2-cloro-4-(trifluorometil)fenil]-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18a | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,05 (d, J = 6,32 Hz, 6H) 3,77 (d, J = 6,82 Hz, 1H) 4,25 (s, 2H) 4,43 (s, 2H) 6,08 (d, J = 7,83 Hz, 1H) 6,93 (s, 2H) 7,70 (d, J = 7,83 Hz, 1H) 7,86 (d, J = 7,83 Hz, 1H), 8,06 (s, 1H). | 400,1, 402,1 |

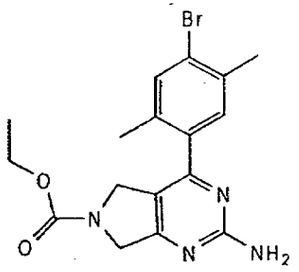
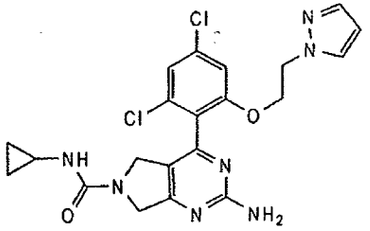
| | | | | | |
|---|---|---|---|---|---|
| 179 |  | 2-amino-4-(2-cloro-4-etil-5-metoxifenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 104 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,00-1,11 (m, 6H), 1,10-1,21 (m, 3H), 2,54-2,67 (m, 2H), 3,76-3,83 (m, 3H) 4,27 (s, 2H) 4,37-4,44 (m, 2H) 6,10 (d, J = 7,83 Hz, 1H) 6,82 (s, 2H) 6,96 (s, 1H) 7,27-7,35 (m, 1H). | 390,4, 392,4 |
| 180 |  | 1-[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]-2-metil-1-oxopropan-2-ol | Ej. 6 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,31 (d, J = 13,89 Hz, 6H), 3,85 (s, 3H), 4,44 (d, J = 61,39 Hz, 2H), 4,91 (d, J = 48,25 Hz, 2H), 5,35 (d, J = 25,52 Hz, 1H), 6,92 (s, 2H), 7,16 (d, J = 14,65 Hz, 1H), 7,87 (d, J = 5,05 Hz, 1H). | |

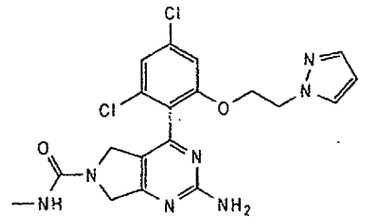
| | | | | | |
|---|---|---|---|---|---|
| 181 |  | 2-[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidin-6-il]-1-(2,3-difluorofenil)-2-oxoetanol | Ej. 6 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,82-3,89 (m, 3H), 4,40 (d, J = 6,06 Hz, 2H), 4,49-4,58 (m, 2H), 4,76-5,02 (m, 1H), 5,60 (d, J = 24,25 Hz, 1H), 6,86-7,05 (m, 2H), 7,11-7,21 (m, 1H), 7,22-7,31 (m, 2H), 7,33-7,44 (m, 1H), 7,86 (d, J = 1,01 Hz, 1H). | |
| 182 |  | 2-amino-4-[2,4-dicloro-5-(metoximetoxi)fenil]-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,06 (d, J = 6,57 Hz, 6H), 3,39-3,45 (m, 3H), 3,78 (dd, J = 14,15, 6,57 Hz, 1H), 4,25 (s, 2H), 4,42 (s, 2H), 5,33 (s, 2H), 6,08 (d, J = 7,58 | 427,2, 429,2 |

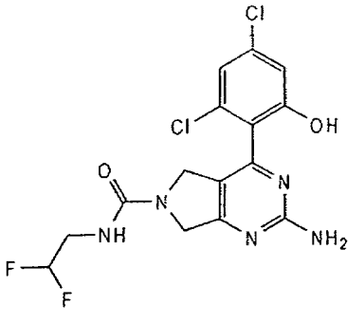
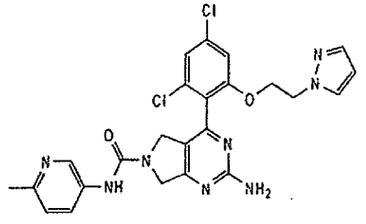
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| | | | | Hz, 1H), 6,92 (s, 2H), 7,29 (s, 1H), 7,80 (s, 1H). | |
| 183 |  | 2-amino-*N*-benzoil-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15a | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,85 (d, J = 10,61 Hz, 3H), 4,45 (s, 2H), 4,60 (s, 2H), 4,75 (s, 1H), 6,97 (s, 2H), 7,16 (s, 1H), 7,44-7,57 (m, 2H), 7,61 (s, 1H), 7,78-7,85 (m, 1H), 7,85-7,93 (m, 2H). | 505,2, 506,2 |

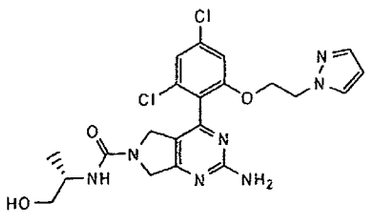
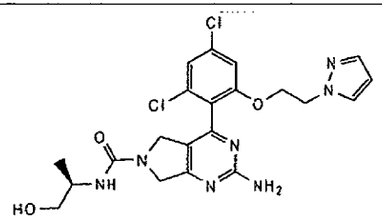
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| 184 |  | 2-amino-4-{4-bromo-5-[2-(*terc*-butilamino)etoxi]-2-clorofenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,05 (t, J = 3,16 Hz, 15H), 1,90 (s, 1H), 2,87 (t, J = 5,43 Hz, 2H), 3,78 (dd, J = 14,02, 6,69 Hz, 1H), 4,09 (t, J = 5,68 Hz, 2H), 4,25 (s, 2H), 4,41 (s, 2H), 6,07 (d, J = 7,58 Hz, 1H), 6,88 (s, 2H), 7,19 (s, 1H), 7,86 (s, 1H). | 527,1, 528,1 |
| 185 |  | 2-amino-4-[2-cloro-5-metoxi-4-(1-metil-1*H*-pirazol-4-il)fenil]-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 104 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,05 (t, J = 5,81 Hz, 6H), 3,78 (s, 1H), 3,86-3,92 (m, 6H), 4,30 (s, 2H), 4,43 (s, 2H), 6,05-6,16 (m, 1H), 6,85 (s, 2H), 7,08 (s, 1H), 7,80 (s, 1H), 8,03 (s, 1H), 8,25 (s, | 442,2, 444,2 |

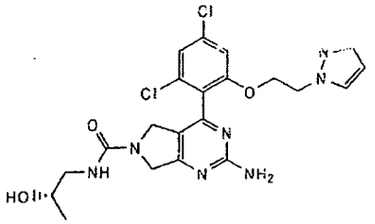
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| | | | | 1H). | |
| 186 |  | 2-amino-4-(4-bromo-2,5-dimetilfenil)-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15a | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,05 (d, J = 6,57 Hz, 6H), 2,17 (s, 3H), 2,33 (s, 3H), 3,72-3,84 (m, 1H), 4,24 ($, 2H), 4,41 (s, 2H), 6,06 (d, J = 7,33 Hz, 1H), 7,28 (s, 1H), 7,56 (s, 1H). | 405,1, 406,1 |
| 187 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(2,6-difluorobenzoil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15a | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,86 (d, J = 10,86 Hz, 3H), 4,34 (s, 1H), 4,48 (s, 1H), 4,59 (s, 1H), 4,74 (s, 1H), 6,97 (s, 2H), 7,03-7,11 (m, 1H), 7,11-7,23 (m, 2H), 7,46-7,59 (m, 1H), 7,58-7,68 (m, 1H), 7,86 (d, J = 13,64 | 540,2, 542,2 |

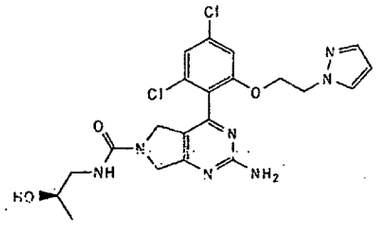
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| | | | | Hz, 1H). | |
| 188 |  | 2-amino-4-(4-bromo-2,5-dimetilfenil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 1 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,09-1,30 (m, 3H), 2,18 (d, J = 7,83 Hz, 3H), 2,33 (s, 3H), 4,08 (dd, J = 14,02, 6,95 Hz, 2H), 4,32 (d, J = 5,05 Hz, 2H), 4,46 (d, J = 10,36 Hz, 2H), 6,81 (s, 2H), 7,29 (d, J = 5,05 Hz-1H).7,55 (s, 1H). | 391,1, 392,1 |
| 189 |  | 2-amino-*N*-ciclopropil-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 100 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,33-0,44 (m, 2H), 0,49-0,58 (m, 2H), 2,51-2,56 (m, 1H), 3,55 (d, J = 12,88 Hz, 1H), 3,82-3,94 (m, 1H), 4,29-4,35 (m, 4H), 4,36- | 474,2, 476,2 |

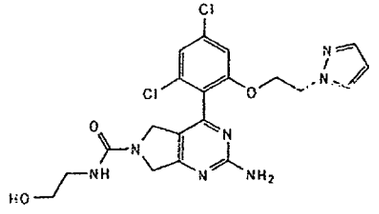
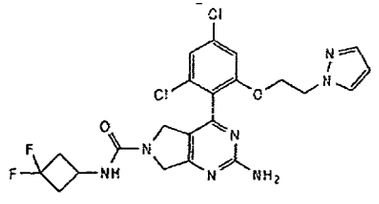
| | | | | | |
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| | | | | 4,42 (m, 2H), 6,00 (t, J = 2,02 Hz, 1H), 6,32 (s a, 1H), 6,77 (s a, 2H), 7,18 (d, J = 2,27 Hz, 1H), 7,24 (d, J = 1,77 Hz, 1H), 7,29 (d, J = 1,52 Hz, 1H), 7,31 (d, J = 1,52 Hz, 1H). | |
| 190 |  | 2-amino-4-{2,4-dicloro-6-[2-1*H*-pirazol-1-il)etoxi]fenil}-*N*-metil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 106 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,59 (d, J = 4,29 Hz, 3H), 3,60 (d, J = 12,63 Hz, 1H), 3,92 (dd, 1H), 4,29-4,36 (m, 4H), 4,36-4,46 (m, 2H), 6,00 (t, J = 2,02 Hz, 1H), 6,18 (d, J = 4,29 Hz, 1H), 6,78 (s, 2H), 7,19 (d, J = 2,02 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,29 (d, J = | 450,2, 448,2 |

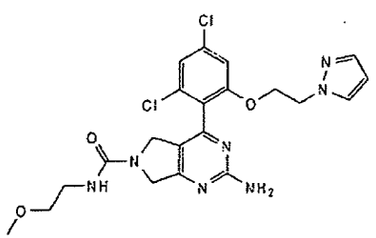
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| | | | | 1,52 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | |
| 191 |  | 2-amino-4-(2,4-dicloro-6-hidroxifenil-*N*-(2,2-difluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 3,35-3,49 (m, 2H), 4,19 (s, 2H), 4,45 (s, 2H), 5,96 (tt, 1H), 6,76-6,89 (m, 3H), 6,96 (d, J = 1,77 Hz, 1H), 7,15 (d, J = 2,02 Hz, 1H), 10,66 (s, 1H). | 406,0, 404,2 |
| 192 |  | 2-amino-4-{2,4-dicloro-6-[2-1*H*-pirazol-1-il)etoxi]fenil}-*N*-(6-metilpiridin-3-il)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 109 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,42 (s, 3H), 3,69 (d, J = 12,63 Hz, 1H), 4,13 (d, J = 12,63 Hz, 1H), 4,31-4,40 (m, 4H), 4,49-4,63 (m, 2H), 6,01 (t, J = 1,89 Hz, 1H), 6,84 (s, 2H), 7,22-7,27 (m, 3H), | 527,2, 525,2 |

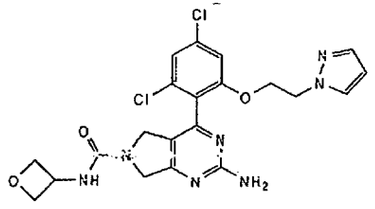
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| | | | | 7,29 (d, J = 1,52 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H), 7,91 (dd, J = 8,46, 2,40 Hz, 1H), 8,43 (s, 1H), 8,61 (s, 1H). | |
| 193 |  | 2-amino-4-{2,4-dicloro-6-[2-1*H*-pirazol-1-il)etoxi]fenil}-*N*-[(1S)-2-hidroxi-1-metiletil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | | 494,2, 492,2 |
| 194 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-[(1R)-2-hidroxi-1-metiletil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | | 494,2, 492,2 |

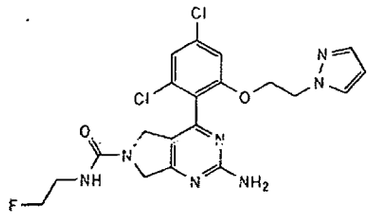
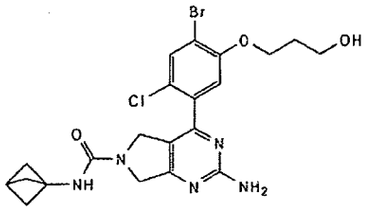
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| 195 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-[(2S)-2-hidroxipropil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,01 (dd, J = 6,19, 1,39 Hz, 3H), 2,96-3,03 (m, J = 5,56, 5,56 Hz, 2H), 3,58-3,70 (m, 2H), 3,95 (d, J = 12,63 Hz, 1H), 4,30-4,37 (m, 4H), 4,39-4,47 (m, 2H), 6,01 (c, J = 1,94 Hz, 1H), 6,21-6,30 (m, 1H), 6,78 (s, 2H), 7,19 (d, J = 2,27 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,30-7,32 (m, 1H), 7,32 (d, J = 1,77 Hz, 1H). | 494,2, 492,2 |

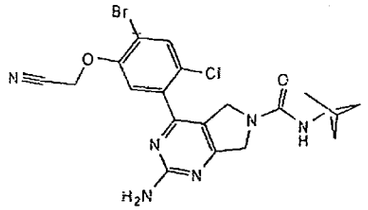
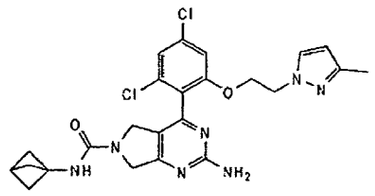
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| 196 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il}etoxi]fenil}-*N*-[(2R)-2-hidroxipropil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,01 (dd, J = 6,32, 1,26 Hz, 3H), 2,95-3,02 (m, J = 5,56, 5,56 Hz, 2H), 3,58-3,70 *(m, 2H)*, 3,95 (d, J = 12,63 Hz, 1 H), 4,30-4,38 (m, 4H), 4,39-4,47 (m, 2H), 6,01 (c, J = 1,85 Hz, 1H), 6,22-6,30 (m, 1H), 6,78 (s, 2H), 7,19 (d, J = 2,27 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,29-7,31 (m, 1H), 7,32 (d, J = 1,52 Hz, 1H). | 494,2, 492,2 |

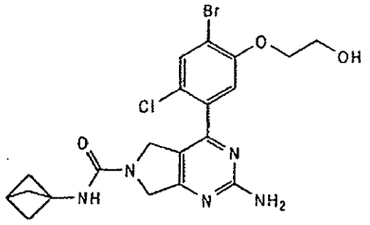
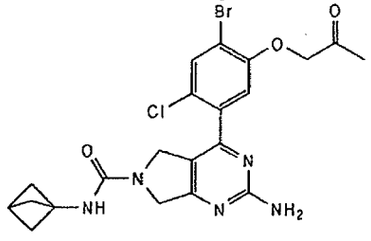
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| 197 |  | 2-amino-4-(2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-(2-hidroxietil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 3,06-3,15 (m, 2H), 3,37-3,43 (m, 2H), 3,59 (d, J = 13,00 Hz, 1H), 3,93 (d, J = 12,62 Hz, 1H), 4,33 (s, 4H), 4,38-4,48 (m, 2H), 6,01 (t, J = 1,98 Hz, 1H), 6,22-6,28 (m, 1H), 6,79 (s, 2H), 7,19 (d, J = 2,26 Hz, 1H), 7,25 (d, J = 1,70 Hz, 1H), 7,30-7,33 (m, 1,70 Hz, 2H). | 480,2, 478,2 |
| 198 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazoil-1-il)etoxi]fenil}-*N*-(3,3-difluorociclobutil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 2,57-2,70 (m, 2H), 2,77-2,90 (m, 2H), 3,60 (d, J = 12,88 Hz, 1H), 3,95 (d, J = 12,88 | 526,0, 524,0 |

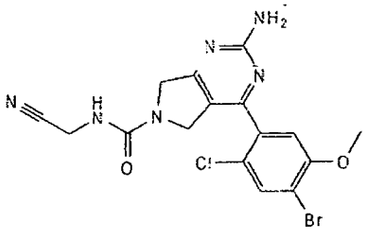
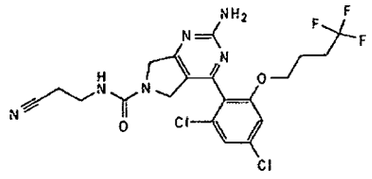
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| | | | | Hz, 1H), 3,99-4,08 (m, 1H), 4,31-4,37 (m, 4 H), 4,39-4,47 (m, 2H), 6,00 (t, J = 2,02 Hz, 1H), 6,60 (d, J = 6,32 Hz, 1H), 6,77 (s, 2H), 7,20 (d, J = 2,02 Hz, 1H), 7,26 (d, J = 1,52 Hz, 1H), 7,29 (d, J = 1,52 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | |
| 199 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-(2-metoxietil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 3,16-3,22 (m, 2H), 3,24 (s, 3 H), 3,31-3,37 (m, 2H), 3,57 (d, J = 12,88 Hz, 1H), 3,92 (d, J = 13,14 Hz, 1H), 4,30-4,36 (m, 4 H), 4,37-4,45 (m, 2H), 6,00 (t, J = | 494,2, 492,2 |

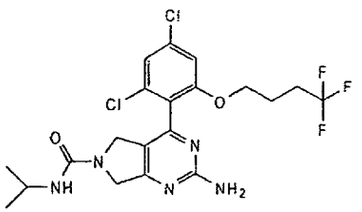
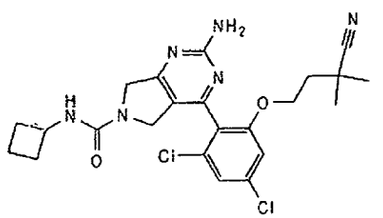
| | | | | | |
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| | | | | 1,89 Hz, 1H), 6,28-6,35 (m, 1H), 6,79 (s, 2H), 7,19 (d, J = 1,77 Hz, 1H), 7,25 (d, J = 1,77 Hz, 1H), 7,30 (d, J = 1,26 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | |
| 200 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 3,60 (d, J = 13,00 Hz, 1H), 3,97 (d, J = 12,81 Hz, 1H), 4,33 (s, 4 H), 4,38-4,52 (m, 4H), 4,61-4,81,-(m, 3 H), 5,97-6,02 (m, 1H), 6,80 (s, 2H), 6,89 (d, J = 5,65 Hz, 1H), 7,20 (d, J = 1,88 Hz, 1H), 7,25-7,30 (m, 2H), 7,33 (d, J = 1,51 Hz, 1H). | 492,2, 490,2 |

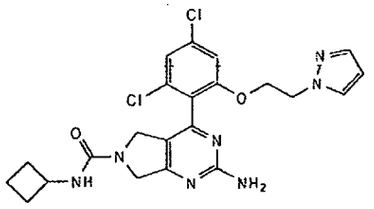
| | | | | | |
|---|---|---|---|---|---|
| 201 |  | 2-amino-4-{2,4-dicloro-6-[2-(1*H*-pirazol-1-il)etoxi]fenil}-*N*-(22-fluoroetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 3,26-3,41 (m, 2H), 3,57 (d, J = 13,00 Hz, 1H), 3,93 (d, J = 12,81 Hz, 1H), 4,30-4,54 (m, 8H), 6,00 (t, J = 1,88 Hz, 1H), 6,50 (s, 1 H), 6,79 (s, 2H), 7,20 (d, J = 2,07 Hz, 1H), 7,25 (d, J = 1,70 Hz, 1H), 7,30 (d, J = 1,51 Hz, 1H), 7,32 (d, J = 1,51 Hz, 1H). | 482,2, 480,2 |
| 202 |  | 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-[4-bromo-2-cloro-5-(3-hidroxipropoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,82-1,90 (m, 2H), 1,93 (s, 6H), 2,34 (s, 1H), 3,57 (t, J = 6,22 Hz, 2H), 4,12 (t, J = 6,12 Hz, 2H), 4,23 (s, 2H), | 510,2, 508,2 |

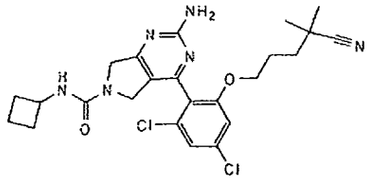
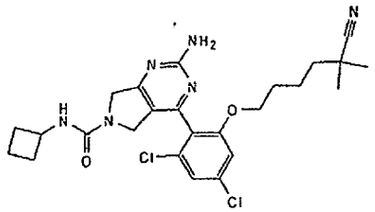
| | | | | | |
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| | | | | 4,39 (s, 2H), 6,90 (s, 2H), 7,01 (s, 1H), 7,15 (s, 1H), 7,85 (s, 1H). | |
| 203 |  | 2-amino-*N*-biciclo[1.1.1]pent-1-il-4[4-bromo-2-cloro-5-(cianometoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,93 (s, 6H), 2,34 (s, 1H), 4,23 (s, 2H), 4,40 (s, 2H), 5,31 (s, 2H), 6,93 (s, 2H), 6,98 (s, 1H), 7,36 (s, 1H), 7,98 (s, 1H) | 491,2, 489,2 |
| 204 |  | 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-{2,4-dicloro-6-[2-(3-metil-1*H*-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, METANOL-d4) δ ppm 2,05 (s, 6H). 2,19 (s, 3H), 2,38 (s, 1H), 3,65 (d, J = 12,81 Hz, 1H), 4,06 (d, J = 12,81 Hz, 1H), 4,32 (s, 4H), 4,53 (s, 2H), 5,89 (d, J = 2,07 Hz, 1H), 7,08 (d, J = 2,26 | 516,2, 514,2 |

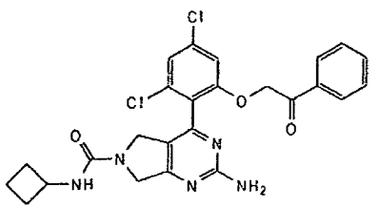
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| | | | | Hz, 1H), 7,18 (d, J = 1,70 Hz, 1H), 7,24 (d, J = 1,70 Hz, 1H). | |
| 205 |  | 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-[4-bromo-2-cloro-5-(2-hidroxietoxi)fenil]-5,7-dihidro-*6H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,93 (s, 6H), 2,34 (s, 1H), 3,72 (t, J = 4,71 Hz, 2H), 4,09 (t, J = 4,80 Hz, 2H), 4,23 (s, 2H), 4,39 (s, 2H), 6,89 (s, 2H), 7,01 (s, 1H), 7,18 (s, 1H), 7,85 (s, 1H). | 496,2, 494,2 |
| 206 |  | 2-amino-*N*-biciclo[1.1.1]pent-1-il-4-[4-bromo-2-cloro-5-(2-oxopropoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,93 (s, 6H), 2,14 (s, 3H), 2,34 (s, 1H), 4,18 (s, 2H), 4,38 (s, 2H), 4,99 (s, 2H), 6,88 (s, 2H), 7,00 (s, 1H), 7,07 (s, 1H), 7,87 (s, 1H). | |

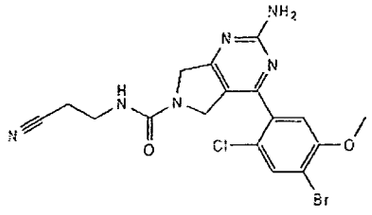
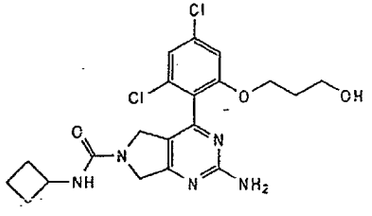
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| 207 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-(cianometil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 2<br>Ej. 109 | 1H RMN (300 MHz, DMSO-d6) δ ppm 3,87 (s, 3H), 4,06 (d, J = 5,09 Hz, 2H), 4,31 (s, 2H), 4,47 (s, 2H), 6,93 (s, 2H), 7,17 (s, 1H), 7,18 (t, J = 5,36 Hz, 1H), 7,87 (s, 1H). | |
| 208 |  | 2-amino-*N*-(2-cianoetil)-4-[2,4-dicloro-6-(4,4,4-trifluorobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,70-1,82 (m, 2H), 2,02-2,20 (m, 2H), 2,62 (t, J = 6,31 Hz, 2H), 3,25 (c, J = 6,09 Hz, 2H), 4,04-4,20 (m, 4H), 4,35-4,50 (m, 2H), 6,81 (t, J = 5,46 Hz, 1H), 6,85 (s, 2H), 7,31 (d, J = 1,51 Hz, 1H), 7,36 (d, J = 1,32 Hz, 1H). | |

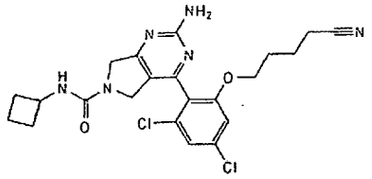
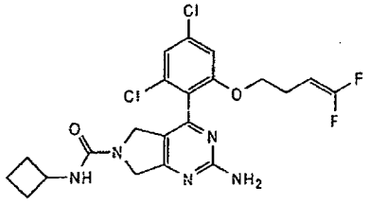
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| 209 |  | 2-amino-4-[2,4-dicloro-6-(4,4,4-trifluorobutoxi)fenil]-*N*-isopropil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 8a, Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,05 (d, J = 5,27 Hz, 6H), 1,69-1,83 (m, 2H), 2,01-2,20 (m, 2H), 3,70-3,85 (m, 1H), 4,04-4,18 (m, J = 7,54 Hz, 4H), 4,37-4,44 (m, 2H), 6,04 (d, J = 7,72 Hz, 1H), 6,81 (s a, 2H), 7,31 (d, J = 1,32 Hz, 1H), 7,36 (d, J = 1,51 Hz, 1H). | |
| 210 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(3-ciano-3-metilbutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,19 (d, J = 3,01 Hz, 6H), 1,46-1,60 (m, 2H), 1,81-1,99 (m, 4H), 2,02-2,15 (m, 2H), 4,07-4,23 (m, 5H), 4,30-4,45 (m, 2H), 6,51 (d, | |

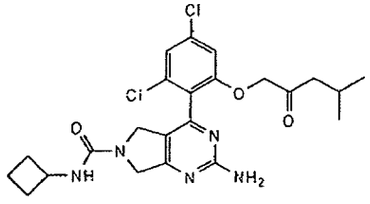
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| | | | | J = 7,72 Hz, 1H), 6,80 (s, 2H), 7,36-7,39 (m, J = 3,20 Hz, 2H). | |
| 211 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,62 (m, 2H), 1,85-2,01 (m, 1H), 2,04-2,18 (m, 2H), 3,57 (d, J = 13,00 Hz, 1H), 3,93 (d, J = 12,24 Hz, 1H), 4,08-4,20 (m, 1H), 4,29-4,46 (m, 6H), 5,98-6,00 (m, 1H), 6,40 (d, J = 7,72 Hz, 1H), 6,79 (s, 2H), 7,19 (d, J = 2,26 Hz, 1H), 7,26 (d, J = 1,32 Hz, 1H), 7,28 (d, J = 1,51 Hz, 1H), 7,33 (d, J = 1,32 Hz, 1H). | |

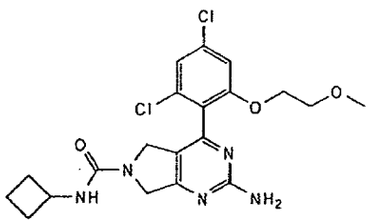
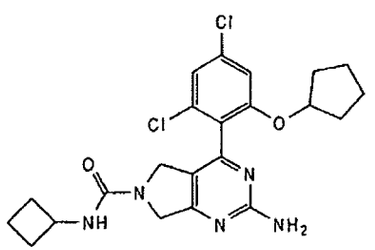
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| 212 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[(4-ciano-4-metilpenil)oxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,17 (s, 6H), 1,32-1,42 (m, 2H), 1,48-1,72 (m, 4H), 1,83-1,99 (m, 2H), 2,02-2,15 (m, 2H), 4,02-4,20 (m, 5H), 4,33-4,47 (m, 2H), 6,52 (d, J = 7,72 Hz, 1H), 6,83 (s, 2H), 7,29 (d, J = 1,32 Hz, 1H), 7,34 (d, J = 1,70 Hz, 1H). | |
| 213 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[(5-ciano-5-metilhexil)oxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,18 (d, J = 2,07 Hz, 6H), 1,25-1,64 (m, 8H), 1,83-1,99 (m, 2H), 2,02-2,15 (m, 2H), 4,00-4,18 (m, 5H), 4,40 (s, 2H), 6,50 (d, J = | |

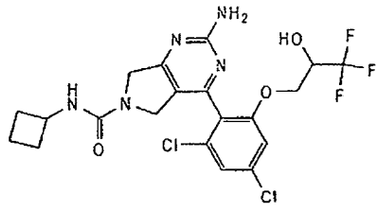
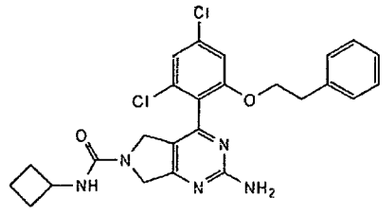
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| | | | | 7,72 Hz, 1H), 6,81 (s, 2H), 7,29 (d, J = 1,51 Hz, 1H), 7,33 (d, J = 1,70 Hz, 1H). | |
| 214 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(2-oxo-2-feniletoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 1,47-1,61 (m, 2H), 1,87-1,99 (m, 2H), 2,05-2,14 (m, 2H), 4,07-4,21 (m, 2H), 4,29 (d, J = 13,14 Hz, 1H), 4,41 (s, 2H), 5,66 (d, J = 17,94 Hz, 1H), 5,79 (d, J = 17,68 Hz, 1H), 6,54 (d, J = 7,83 Hz, 1H), 6,83 (s, 2H), 7,29 (d, J = 1,77 Hz, 1H), 7,34 (d, J = 1,77 Hz, 1H), 7,54 (t, J = 7,71 Hz, 2H), 7,67 (t, J = 7,45 Hz, 1H), 7,93 (d, J = 7,33 Hz, 2H). | |

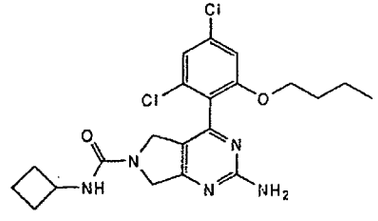
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| 215 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-*N*-2-cianoetil)-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 2, Ej. 109 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 2,63 (t, J = 6,40 Hz, 2H), 3,21-3,30 (m, 2H), 3,86 (s, 3H), 4,28 (s, 2H), 4,44 (s, 2H), 6,83 (t, J = 4,52 Hz, 1H), 6,93 (s, 2H), 7,18 (s, 1H), 7,87 (s, 1H). | |
| 216 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(3-hidroxipropoxi)fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,47-1,60 (m, 2H), 1,62-1,73 (m, 2H), 1,84-1,99 (m, 2H), 2,02-2,15 (m, 2H), 3,31 (t, J = 5,56 Hz, 2H), 4,04-4,18 (m, 5H), 4,41 (s, 2H), 6,51 (d, J = 7,54 Hz, 1H), 6,82 (s, 2H), 7,28 (s, 1H), 7,32 (s, 1H). | |

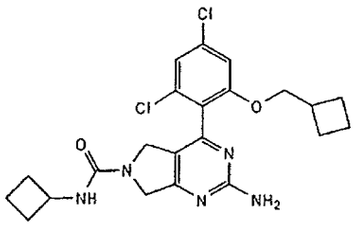
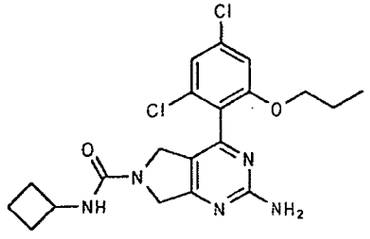
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| 217 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(4-cianobutoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,43-1,72 (m, 6H), 1,84-2,00 (m, 2H), 2,03-2,17 (m, 2H), 2,40 (t, J = 7,06 Hz, 2H), 4,02-4,21 (m, 5H), 4,41 (s, 2H), 6,50 (d, J = 7,91 Hz, 1H), 6,81 (s, 2H), 7,29 (d, J = 1,70 Hz, 1H), 7,34 (d, J = 1,51 Hz, 1H). | |
| 218 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[(4,4-difluorobut-3-en-1-il)oxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,46-1,61 (m, 2H), 1,82-1,99 (m, 2H), 2,02-2,14 (m, 2H), 2,15-2,28 (m, 2H), 3,94-4,46 (m, 8H), 6,48 (d, J = 8,48 Hz, 1H), 6,79 (s, 2H), 7,28 (d, J = 1,32 Hz, | |

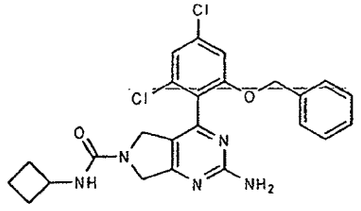
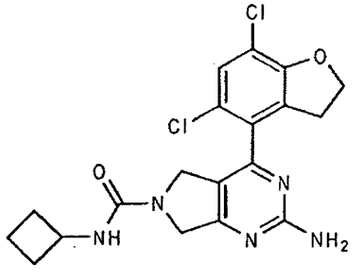
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| | | | | 1H), 7,34 (d, 1H). | |
| 219 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-[(4-metil-2-oxopentil)oxi]fenil}-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 0,80 (dd, J = 6,59, 2,45 Hz, 6H), 1,48-1,60 (m, 2H), 1,86-2,15 (m, 5H), 2,24 (dd, J = 6,78, 2,07 Hz, 2H), 4,06-4,29 (m, 3H), 4,41 (s, 2H), 4,81 (d, J = 17,52 Hz, 1H), 4,93 (d, J = 17,33 Hz, 1H), 6,52 (d, J = 7,72 Hz, 1H), 6,83 (s, 2H), 7,13 (d, J = 1,32 Hz, 1H), 7,35 (d, J = 1,70 Hz, 1H). | |

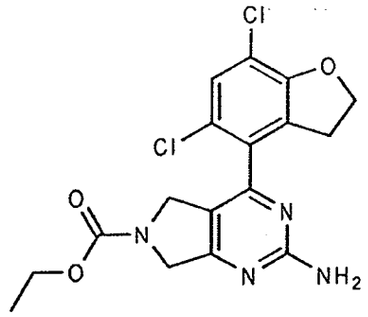
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| 220 |  | 2-amino-*N*-ciclobutil-4-{2,4-dicloro-6-(2-metoxietoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,60 (m, 2H), 1,83-1,99 (m, 2H), 2,02-2,14 (m, 2H), 3,12 (s, 3H), 3,45-3,52 (m, 2H), 4,06-4,22 (m, 5H), 4,40 (s a, 2H), 6,49 (d, J = 8,10 Hz, 1H), 5,81 (s a, 2H), 7,31 (d, J = 1,51 Hz, 1H), 7,34 (d, J = 1,70 Hz, 1H). | |
| 221 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(ciclopentiloxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,39-1,98 (m, 12H), 2,02-2,15 (m, 2H), 4,03-4,18 (m, 3H), 4,40 (s, 2H), 4,89-4,97 (m, 1H), 6,52 (d, J = 7,91 Hz, 1H), 6,80 (s, 2H), | |

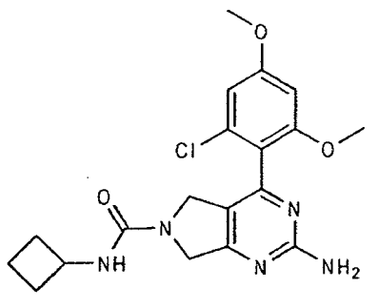
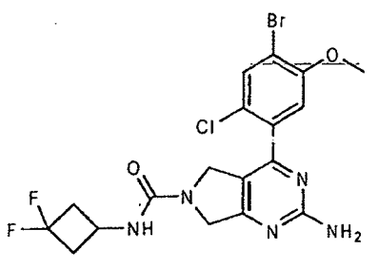
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|---|---|---|---|---|---|
| | | | | 7,26 (d, J = 1,70 Hz, 1H), 7,30 (d, J = 1,70 Hz, 1H). | |
| 222 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(3,3,3-trifluoro-2-hidroxipropoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,59 (m, 2H), 1,84-1,99 (m, 2H), 2,03-2,14 (m, 2H), 4,04-4,25 (m, 6H), 4,39 (s, 2H), 6,48 (d, J = 7,35 Hz, 1H), 6,63 (s a, 1H), 6,78 (s, 2H), 7,38 (s, 1H), 7,41 (s, 1H). | |
| 223 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(2-feniletoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,62 (m, 2H), 1,84-2,01 (m, 2H), 2,04-2,19 (m, 2H), 2,70-2,92 (m, 2H), 3,60 (d, J = 12,62 Hz, 1H), 3,94 (d, J = 13,19 Hz, 1H), | |

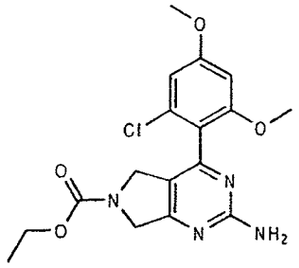
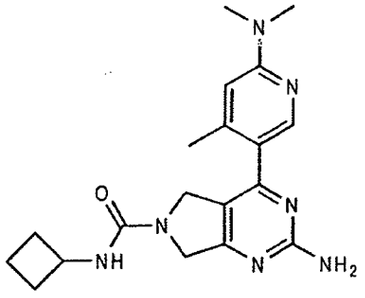
| | | | | | |
|---|---|---|---|---|---|
| | | | | 4,07-4,46 (m, 5H), 6,39 (d, J = 7,72 Hz, 1H), 6,83 (s a, 2H), 6,98 (d, J = 6,41 Hz, 2H), 7,04-7,19 (m, 3H), 7,26 (s, 1H), 7,30 (s, 1H). | |
| 224 |  | 2-amino-4-{2-butoxi-4,6-diclorofenil)-*N*-ciclobutil-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (400 MHz, DMSO-d6) δ ppm 0,78 (t, J = 7,45 Hz, 3H), 1,14-1,25 (m, 2H), 1,46-1,58 (m, 4H), 1,86-1,97 (m, 2H), 2,04-2,13 (m, 2H), 3,98-4,05 (m, 2H), 4,08-4,16 (m, 3 H), 4,40 (s, 2H), 6,52 (d, J = 7,83 Hz, 1H), 6,82 (s, 2H), 7,28 (d, J = 1,77 Hz, 1H), 7,32 (d, J = 1,77 Hz, 1H). | |

| | | | | | |
|---|---|---|---|---|---|
| 225 |  | 2-amino-*N*-ciclobutil-4-[2,4-dicloro-6-(ciclobutilmetoxi)fenil]-5,7-dihidro-6*H*-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | $^1$H RMN (300 MHz, DMSO-d6) δ ppm 1,45-2,00 (m, 11H), 2,02-2,16 (m, 2H), 3,98 (d, J = 5,84 Hz, 2H), 4,08-4,20 (m, 3H), 4,36-4,48 (m, 2H), 6,51 (d, J = 7,91 Hz, 1H), 6,81 (s, 2H), 7,28 (s, 1H), 7,33 (s, 1H). | |
| 226 |  | 2-amino-N-ciclobutil-4-(2,4-dicloro-6-propoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (300 MHz, DMSO-d6) δ ppm 0,76 (t, J = 7,35 Hz, 3 H) 1,47-1,62 (m, 4 H) 1,83-2,01 (m, 2 H) 2,02-2,15 (m, 2 H) 3,93-4,05 (m, 2 H) 4,07-4,17 (m, 3 H) 4,40 (s, 2 H) 6,51 (d, J = 8,29 Hz, 1 H) 6,82 (s a, 2 H) 7,27 | 438,2, 436,2 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | (d, J = 1,32 Hz, 1 H) 7,32 (d, J = 1,32 Hz, 1 H) | |
| 227 |  | 2-amino-4-[2-(benciloxi)-4,6-diclorofenil]-N-ciclobutil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,60 (m, 2 H) 1,84-2,01 (m, 2 H), 2,03-2,15 (m, 2 H), 4,07-4,20 (m, 3 H) 4,40 (s, 2 H) 5,20 (s, 2 H) 6,51 (d, J = 7,91 Hz, 1 H) 6,85 (s a, 2 H) 7,19-7,25 (m, 2 H) 7,26-7,34 (m, 3 H) 7,36 (s, 2 H) | 486,2, 484,2 |
| 228 |  | 2-amino-N-ciclobutil-4-(5,7-dicloro-2,3-dihidro-1-benzofuran-4-il)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 7 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,47-1,61 (m, 2 H) 1,87-1,99 (m, 2 H) 2,05-2,13 (m, 2 H) 2,99-3,21 (m, 2 H) 4,07-4,21 (m, 2 H) 4,27 (d, | 422,2, 420,2 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | J = 13,14 Hz, 1 H), 4,36-4,48 (m, 2 H) 4,61-4,74 (m, 2 H) 6,54 (d, J = 7,83 Hz, 1 H) 6,90 (s a, 2 H) 7,53 (s, 1 H) | |
| 229 |  | 2-amino-4-(5,7-dicloro-2,3-dihidro-1-benzofuran-4-il)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 1 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,13-1,27 (m, 3 H) 2,95-3,26 (m, 2 H) 3,98-4,16 (m, 2 H) 4,22-4,39 (m, 2 H) 4,41-4,58 (m, 2 H) 4,61-4,76 (m, 2 H) 6,94 (s a, 2 H) 7,51 (s, 1 H) | 397,2, 395,2 |

| | | | | | |
|---|---|---|---|---|---|
| 230 |  | 2-amino-4-(2-cloro-4,6-dimetoxifenil)-N-ciclobutil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 117 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,60 (m, 2 H) 1,84-2,00 (m, 2 H) 2,03-2,15 (m, 2 H) 3,72 (s, 3 H) 3,83 (s, 3 H) 4,04-4,19 (m, 3 H) 4,40 (s, 2 H) 6,51 (d, J = 7,91 Hz, 1 H) 6,67 (d, J = 2,07 Hz, 1 H) 6,71-6,77 (m, 3 H) | 406,0, 404,0 |
| 231 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-N-{3,3-difluorociclobutil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 2, Ej. 109 | 1H RMN (300 MHz, DMSO-d6) δ ppm 2,53-2,89 (m, 4H), 3,87 (s, 3H), 3,95-4,08 (m, 1 H) 4,28 (s, 2 H) 4,44 (s, 2 H) 6,75 (d, J = 6,78 Hz, 1 H) 6,91 (s a, 2 H) 7,17 (s, 1 H) 7,87 (s, 1 H) | 489,8, 487,8 |

| | | | | | |
|---|---|---|---|---|---|
| 232 |  | 2-amino-4-(2-cloro-4,6-dimetoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 117a | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,13-1,24 (m, 3 H) 3,72 (s, 3 H) 3,83 (s, 3 H) 4,00-4,19 (m, 4 H) 4,47 (d, J = 8,48 Hz, 2 H) 6,66 (d, J = 2,26 Hz, 1 H) 6,74 (d, J = 2,07 Hz, 1 H) 6,79 (s a, 2 H) | 379,2 |
| 233 |  | 2-amino-N-ciclobutil-4-[6-(dimetilamino)-4-metilpiridin-3-il]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 117 | 1H RMN (300 MHz, DMSO) δ ppm 1,48-1,63 (m, 2 H) 1,87-2,02 (m, 2 H) 2,04-2,17 (m, 2 H) 2,28 (s, 3 H) 3,06 (s, 6 H) 4,06-4,22 (m, 1 H) 4,34-4,48 (m, 4 H) 6,52-6,69 (m, 4 H) 8,05 (s, 1 H) | 343,4 |

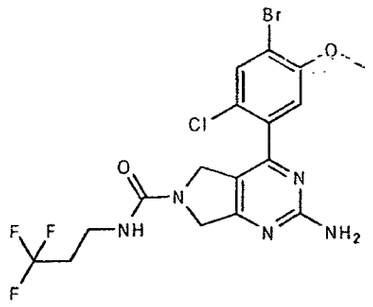
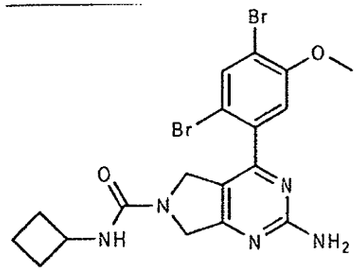
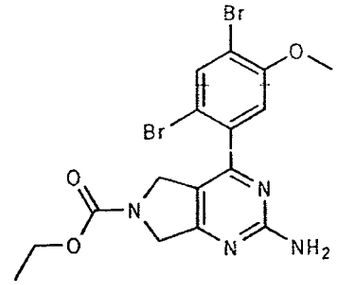
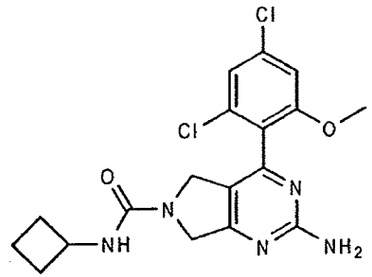
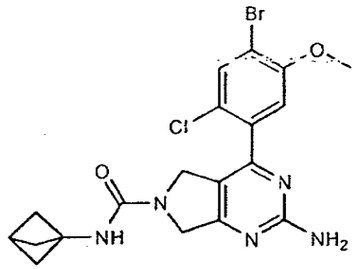
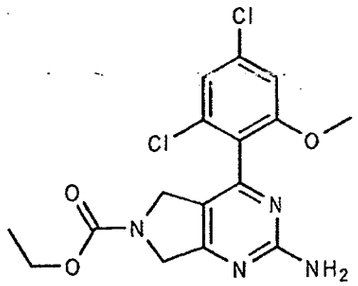
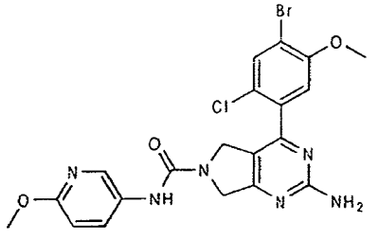
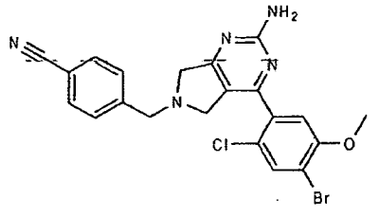
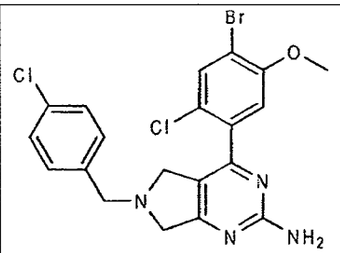
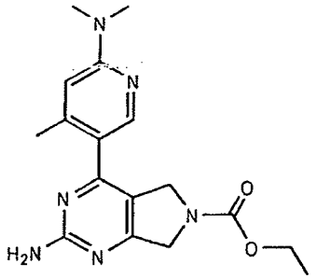
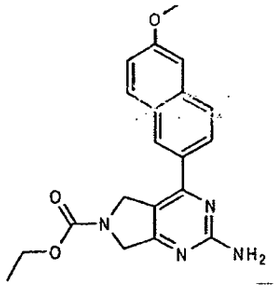
| | | | | | |
|---|---|---|---|---|---|
| 234 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-N-(3,3,3-trifluoropropil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 2, Ej. 109 | 1H RMN (300 MHz, DMSO-d6) δ ppm 2,32-2,47 (m, 2 H) 3,22-3,30 (m, 2 H) 3,86 (s 3 H) 4,27 (s, 2 H) 4,42 (s 2 H) 6,63 (t, J = 5,27 Hz, 1 H) 6,90 (s a, 2 H) 7,17 (s, 1 H) 7,86 (s, 1 H) | 496,0, 493,9 |
| 235 |  | 2-amino-N-ciclobutil-4-(2,4-dibromo-5-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 117 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,47-1,63 (m, 2 H) 1,84-2,01 (m, 2 H) 2,02-2,16 (m, 2 H) 3,85 (s, 3 H) 4,05-4,20 (m, 1 H) 4,24 (s, 2 H) 4,41 (s, 2 H) 6,52 (d, J = 7,91 Hz, 1 H) 6,88 (s a, 2 H) 7,15 (s, 1 H) 7,96 (s, 1 H) | 498,2 |

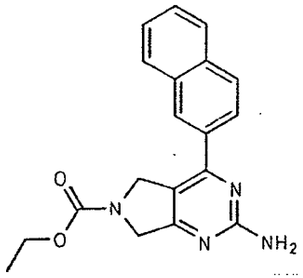
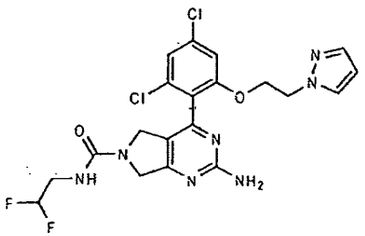
**Tabla 2**

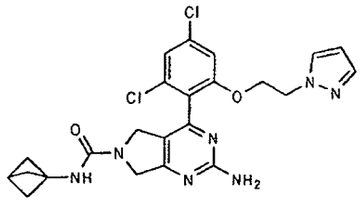
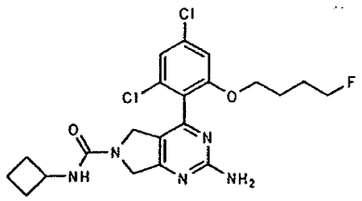
| | | | | | |
|---|---|---|---|---|---|
| 236 |  | 2-amino-4-(2,4-dibromo-5-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 117a | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,13-1,27 (m, 3 H) 3,85 (s, 3 H) 4,02-4,16 (m, 2H), 4,29-4,35 (m, 2 H) 4,45-4,52 (m, 2 H) 6,94 (s a, 2 H) 7,12 (s, 1 H) 7,96 (s, 1 H) | 473,2 |
| 237 |  | 2-amino-N-ciclobutil-4-(2,4-dicloro-6-metoxifenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 117 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,48-1,61 (m, 2 H) 1,85-2,00 (m, 2 H) 2,03-2,15 (m, 2 H) 3,77 (s, 3 H) 4,04-4,19 (m, 3 H) 4,41 (s, 2 H) 6,50 (d, J = 7,91 Hz, 1 H) 6,82 (s a, 2 H) 7,28 (d, J = 1,70 Hz, 1 H) 7,34 (d, J = 1,70 Hz, 1 H) | 408,2 |

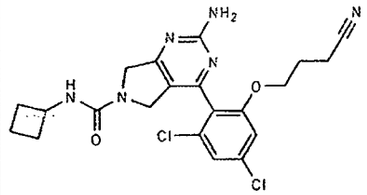
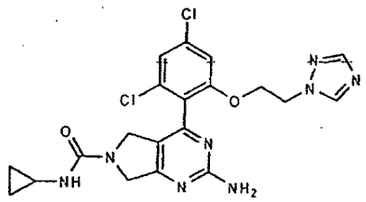
| | | | | | |
|---|---|---|---|---|---|
| 238 |  | 2-amino-N-biciclo[1.1.1]pent-1-il-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 2, Ej. 109 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,93 (s, 6H) 2,34 (s, 1 H) 3,86 (s, 3 H) 4,23 (s, 2 H) 4,39 (s, 2 H) 6,87 (s a, 2 H) 6,99 (s, 1 H) 7,15 (s, 1 H) 7,85 (s, 1 H) | 466,0, 464,0 |
| 239 |  | 2-amino-4-(2,4-dicloro-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 117a | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,13-1,24 (m, 3 H) 3,77 (s, 3 H) 4,00-4,12 (m, 2 H) 4,14 (s, 1 H) 4,17 (s, 1 H) 4,47 (s, 1 H) 4,49 (s, 1 H) 6,87 (s a, 2 H) 7,25 (d, J = 1,51 Hz, 1 H) 7,32 (d, J = 1,51 Hz, 1 H) | 385,2, 383,2 |

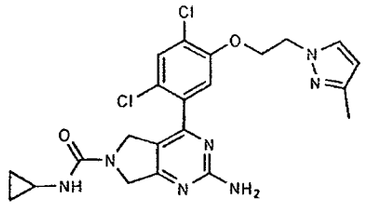
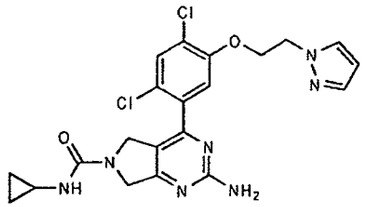
| | | | | | |
|---|---|---|---|---|---|
| 240 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-N-(6-metoxipiridin-3-il)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 118 | 1H RMN (300 MHz, DMSO-d6) δ ppm 3,79 (s, 3 H) 3,87 (s, 3 H) 4,46 (s, 2 H) 4,58 (s, 2 H) 6,73 (d, J = 8,85 Hz, 1 H) 6,94 (s, 2 H) 7,19 (s, 1 H) 7,79 (dd, J = 8,95, 2,54 Hz, 1 H) 7,88 (s, 1 H) 8,21 (d, J = 2,64 Hz, 1 H) 8,37 (s, 1 H) | 507,2, 505,2 |
| 241 |  | 4-{[2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidin-6-il]metil}benzonitrilo | Ej. 120 | 1H RMN (300 MHz, DMSO-d6) δ ppm 3,63 (s, 2H) 3,78 (s, 2H) 3,84 (s, 3H), 3,94 (s, 2 H) 6,76 (s a, 2 H) 7,09 (s, 1 H) 7,54 (d, J = 8,10 Hz, 2 H) 7,76-7,83 (m, 3 H) | 472,2, 470,2 |

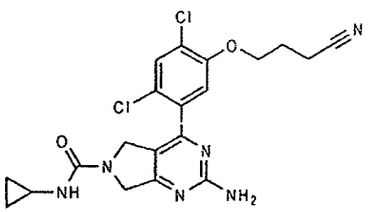
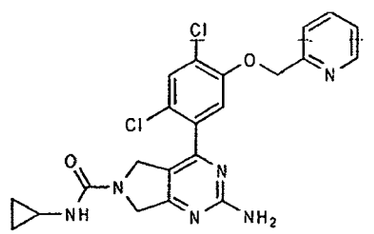
| | | | | | |
|---|---|---|---|---|---|
| 242 |  | 4-(4-bromo-2-cloro-5-metoxifenil)-6-(4-clorobencil}-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-amina | Ej. 120 | 1H RMN (300 MHz, DMSO-d6) δ ppm 3,59 (s, 2 H) 3,75 (s, 2 H) 3,82-3,86 (m, 5 H) 6,77 (s a, 2 H) 7,09 (s, 1 H) 7,35-7,39 (m, 4 H) 7,79 (s, 1 H) | 481,0, 479,0 |
| 243 |  | 2-amino-4-[6-(dimetilamino)-4-metilpiridin-3-il]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 117a | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,15-1,26 (m, 3 H) 2,28 (s, 3H) 3,03 (s, 6 H) 4,02-4,15 (m, 2 H) 4,40-4,50 (m, 4 H) 6,56 (s, 1 H) 6,67 (s, 2 H) 8,06 (d, J = 3,58 Hz, 1 H) | 343,4 |
| 244 |  | 2-ameno-4-(6-metoxi-2-naftil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 1 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,24 (t, J = 7,06 Hz, 3 H) 3,91 (s, 3 H) 4,14 (c, J = 6,78 Hz, 2 H) 4,44-4,51 (m, 2 H) 4,86 (s, 2 H) 7,24 (dd, J = 8,95, 2,35 Hz, 1 H) 7,40 (d, J = 1,88 Hz, 1 H) 7,93- | 365,4 |

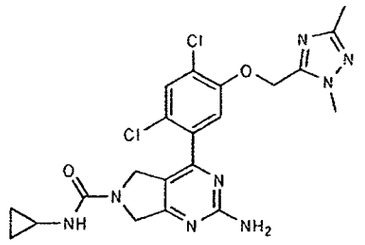
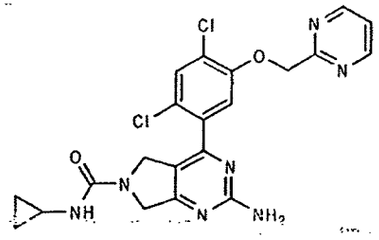
| | | | | | |
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| | | | | 8,04 (m, 3 H) 8,32 (d, J = 3,20 Hz, 1 H) | |
| 245 |  | 2-amino-4-(2-naftil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 1 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,20-1,28 (m, 3 H) 4,14 (c, J = 7,16 Hz, 2 H) 4,45-4,51 (m, 2 H) 4,37 (s, 2 H) 6,86 (s a, 2 H) 7,57-7,67 (m, 2 H) 7,95-8,14 (m, 4 H) 8,38 (d, J = 3,58 Hz, 1 H) | 335,2 |
| 246 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-Pirazol-1-il)etoxi]fenil}-N-(2,2-difluoroetil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | 1H RMN (300 MHz, DMSO-d6) δ ppm 3,33-3,51 (m, 2 H) 3,56 (d, J = 12,81 Hz, 1 H) 3,94 (d, J = 12,62 Hz, 1 H) 4,29-4,38 (m, 4 H) 4,40-4,50 (m, 2 H) 5,77-6,20 (m, 2 H) 6,70 (s a, 1 H) 6,80 (s a, 2 H) 7,20 (d, J = 2,07 Hz, 1 H) 7,26 (d, J = 1,51 Hz, 1 H) 7,30 (d, J = 1,51 Hz, 1 H) | 500,2, 498,2 |

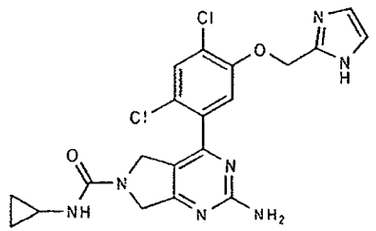
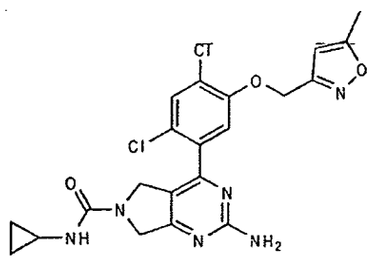
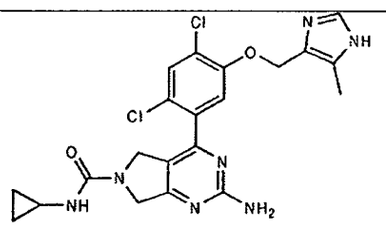
| | | | | | |
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| | | | | 7,32 (d, J = 1,70 Hz, 1 H) | |
| 247 |  | 2-amino-N-biciclo[1.1.1]pent-1-il-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 110 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,95 (s, 6 H) 2,36 (s, 1 H) 3,53 (d, J = 13,19 Hz, 1 H) 3,89 (d, J = 13,00 Hz, 1 H) 4,33 (s, 6 H) 5,99-6,02 (m, 1 H) 6,77 (s a, 2 H) 6,85 (s a, 1 H) 7,19 (d, J = 2,07 Hz, 1 H) 7,25 (d, J = 1,51 Hz, 1 H) 7,30 (d, J = 1,70 Hz, 1 H) 7,32 (d, J = 1,70 Hz, 1 H) | 502,2, 500,2 |
| 248 |  | 2-amino-N-ciclobutil-4-[2,4-dicloro-6-(4-fluorobutoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,61 (d, J = 5,27 Hz, 6 H) 1,84-1,98 (m, 2 H) 2,03-2,15 (m, 2 H) 4,03-4,28 (m, 6 H) 4,37-4,43 (m, 3 H) 6,51 (d, J = 7,91 Hz, 1 H) 6,82 (s a, 2 H) 7,29 (d, J = 1,32 | 470,2, 468,2 |

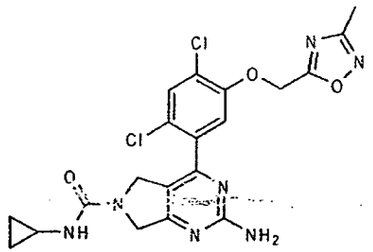
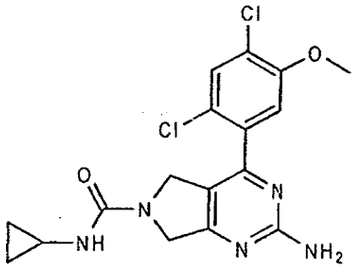
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| | | | | Hz, 1 H) 7,34 (d, J = 1,13 Hz, 1 H) | |
| 249 |  | 2-amino-N-ciclobutil-4-[2,4-dicloro-6-(3-cianopropoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,47-1,59 (m, 2 H) 1,82-1,98 (m, 4H) 2,04-2,13 (m, 2 H) 2,38 (t, J = 7,20 Hz, 2 H) 4,06-4,18 (m, 5 H) 4,40 (s a, 2 H) 6,50 (d, J = 7,83 Hz, 1 H) 6,82 (s a, 2 H) 7,33 (d, J = 1,77 Hz, 1 H) 7,37 (d, J = 1,77 Hz, 1 H) | 463,2, 461,2 |
| 250 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-6-[2-{1H-1,2,4-triazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,96 (s, 1 H), 7,73 (s, 1 H), 7,33 (d, J = 1,77 Hz, 1 H), 7,29 (d, J = 1,77 Hz, 1 H), 6,75 (s, 2 H), 6,35 (s a, 1 H), 4,37-4,51 (m, 4H), 4,25-4,36 (m, 2 H), 3,87 (dd, J = 13,01, 2,15 Hz, 1 H), | 475,0, 477,0 |

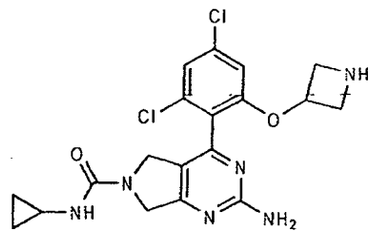
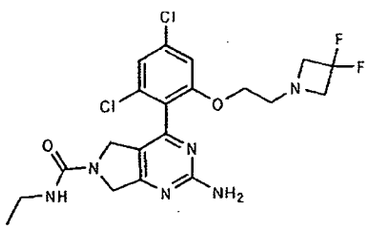
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| | | | | 3,44-3,52 (m, 1 H), 2,52-2,57 (m, 1 H), 0,50-0,58 (m, 2 H), 0,42 (d, J = 3,28 Hz, 2 H). | |
| 251 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[2-(3-metil-1H-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,46 (s, 2 H), 6,72 (s, 1H), 5,97 (s, 1H), 5,19 (s, 2 H), 4,52 (s, 2 H), 4,51 (s, 1H), 4,46 (t, 2H, J = 5 Hz), 4,38 (s, 2 H), 4,31 (t, 2H, J = 5 Hz), 2,67 (s a, 1H), 2,20 (s, 3H), 0,70 (c, 2H, J = 5 Hz), 0,51 (m, 2 H). | 488,0, 490,0 |
| 252 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[2-(1H-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,60 (s, 1H), 7,49 (s, 1H), 7,44 (s, 1H), 6,72 (s, 1H), 6,24 (s, 1H), 5,18 (s, 2 H), 4,54 (m, 5H), 4,38 (s, 2 H), 4,32 (t, 2H, J = 5 Hz), 2,66 (s a, 1H), | 474,0, 476,0 |

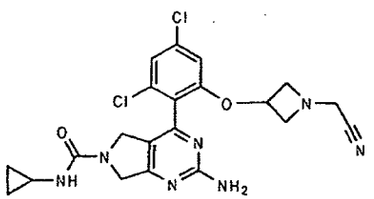
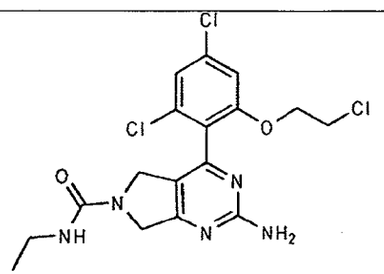
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| | | | | 0,73 (c, 2H, J = 6 Hz), 0,51 (m, 2 H). | |
| 253 |  | 2-amino-N-ciclopropil-4-[2,4-dicloro-5-(3-cianopropoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,48 (s, 1H), 6,87 (s, 1H), 5,18 (s, 2 H), 4,56 (s, 3H), 4,48 (s, 2 H), 4,12 (t, 2H, J = 6 Hz), 2,68 (s a, 2 H), 2,65 (t, 2H, J = 6 Hz), 2,19 (c, 2H, J = 6 Hz), 0,72 (m, 2 H), 0,50 (m, 2 H). | 446,0, 448,0 |
| 254 |  | 2-amino-N-ciclopropil-4-[2,4-dicloro-5-(piridin-2-ilmetoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 8,55 (d, 1H, J = 6 Hz), 7,72 (t, 1H, J = 6 Hz), 7,60 (d, 1H, J = 6 Hz), 7,51 (s, 1H), 7,25 (m, 1H), 6,95 (s, 1H), 5,24 (s, 2 H), 5,14 (s, 2 H), 4,55 (s, 2H), 4,49 (s, 1H), 4,32 (s, 2 H), 2,68 (s a, 1H), 0,73 (c, 2H, J = 6 Hz), 0,50 (m, 2 H). | 471,0, 473,0 |

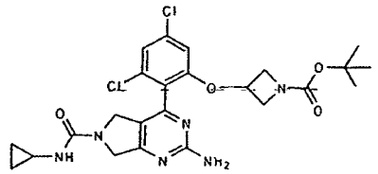
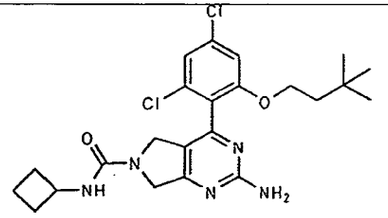
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| 255 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[(1,3-dimetil-1H-1,2,4-triazol-5-il)metoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-.d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,49 (s, 1H), 7,16 (s, 1H), 5,23 (s, 2 H), 5,20 (s, 2 H), 4,57 (s, 1H), 4,56 (s, 2 H), 4,38 (s, 2 H), 3,93 (s, 3H), 2,69 (s a, 1H), 2,33 (s, 3H), 0,74 (c, 2H, J = 6 Hz), 0,51 (m, 2 H). | 489,0, 491,0 |
| 256 |  | 2-amino-N-ciclopropil-4-[2,4-dicloro-5-(pirimidin-2-ilmetoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 8,79 (d, 2H, J = 6 Hz), 7,51 (s, 1H), 7,27 (t, 1H), 6,97 (s, 1H, J = 6 Hz), 5,37 (s, 2H), 5,17 (s, 2 H), 4,52 (s, 2H), 5,41 (s, 1H), 4,32 (s, 2 H), 2,68 (s a, 1H), 0,73 (m, 2 H), 0,50 (s, 2 H). | 473,0, 475,0 |

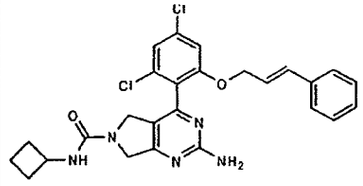
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| 257 |  | 2-amino-N-ciclopropil-4-[2,4-dicloro-5-(1H-imidazol-2-ilmetoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (DMSO-d6, 300 MHz): δ 7,59 (s, 1H), 7,46 (s, 1H), 6,85 (s a, 2 H), 6,77 (s, 1H), 6,44 (s, 1H), 4,50 (d, 1H, J = 3 Hz), 4,39 (m, 4H), 4,14 (s, 1H), 2,06 (2H), 0,50 (m, 2H), 0,39 (m, 2H). | 460,0, 462,0 |
| 258 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[(5-metilisoxazol-3-il)metoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,50 (s, 1H), 7,01 (s, 1H), 6,16 (s, 1H), 5,21 (s.2H\ 5,16 (s, 2H), 4,66 (s, 1H), 4,59 (s, 2 H), 4,42 (s, 2 H), 2,70 (s a, 1H), 2,44 (s, 3H), 0,76 (m, 2 H), 0,54 (m, 2 H). | 477,0, 479,0 |
| 259 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[(5-metil-1H-imidazol-4-il)metoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (DMSO-d6, 300 MHz); δ 7,42 (s, 1H), 7,36 (s, 1H), 6,77 (s, 1H), 6,42 (s, 1H),4,68 (s, 2H), 4,30 (d, 2H, J = 3 Hz), 4,21 (s, | 476,0, 478,0 |

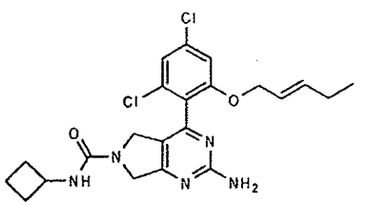
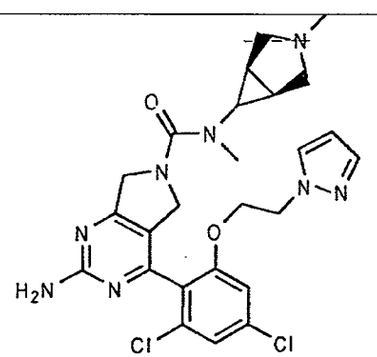
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| | | | | 2 H), 2,10 (s a, 2 H) 2,06 (s, 3H) 0,51 (m, 2 H), 0,39 (m, 2 H). | |
| 260 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-5-[(3-metil-1,2,4-oxadiazol-5-il)metoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (CDCl3, 300 MHz): δ 7,56 (s, 1H), 7,01 (s, 1H), 5,34 (s, 2 H), 5,16 (s, 1H), 4,59 (s, 2 H), 4,42 (s, 2 H), 2,65 (s a, 1H), 2,44 (s, 3H), 0,74 (m, 2 H), 0,52 (m, 2 H). | 475,0, 477,0 |
| 261 |  | 2-amino-N-ciclopropil-4-(2,4-dicloro-5-metoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 14 | 1H RMN {400 MHz, DMSO-d6) δ ppm: 7,74 (s, 1 H), 7,20 (s, 1 H), 6,89 (s, 2 H), 6,47 (d, J = 2,70 Hz, 1 H), 4,41 (s, 2 H), 4,24 (s, 2 H), 3,87 (s, 3 H), 2,52-2,55 (m, 1 H), 0,50-0,57 (m, 2 H), 0,35-0,42 (m, 2 H). | 394,1, 396,1 |

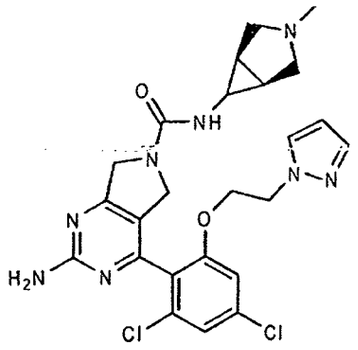
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| 262 |  | 2-amino-4-[2-(azetidin-3-iloxi)-4,6-diclorofenil]-N-Ciclopropil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 129 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,39 (d, J = 1,77 Hz, 1 H), 7,01 (d, J = 1,77 Hz, 1H), 6,84 (s, 2H) (s, 2 H), 6,45 (d, J = 2,53 Hz, 1 H), 5,02-5,13 (m, 1 H), 4,42 (s, 2 H), 4,05-4,19 (m, 2 H), 3,89-4,04 (m, 2 H), 3,45-3,55 (m, 2 H), 3,17-3,45 (m, 2 H), 0,47-0,58 (m, 2 H), 0,33-0,44 (m, 2 H). | 435,2, 437,2 |
| 263 |  | 2-amino-4-{2,4-dicloro-6-[2-(3,3-difluoroazetidin-1-il)etoxi]fenil}-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 15 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,34 (d, J = 1,77 Hz, 1 H), 7,25 (d, J = 1,77 Hz, 1 H), 6,85 (s, 2 H), 6,35 (t, J = 5,31 Hz, 1 H), 4,30-4,47 (m, 2 H), 4,13 (s, 2 H), 4,00-4,08 (m, 2 H), 3,36-3,42 (m, 2 H), 3,21-3,29 (m, 2 H), | 487,0, 489,0 |

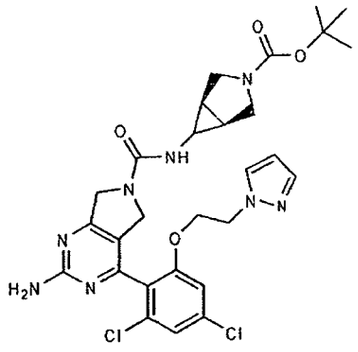
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| | | | | 3,01-3,10 (m, 2H), 2,70-2,77 (m, 2 H), 1,01 (t, J = 7,20 Hz, 3 H). | |
| 264 |  | 2-amino-N-ciclopropil-4-(2,4-dicloro-6-{[1-(cianometil)azetidin-3-il]oxi}fenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 130 | 1H RMN (400 MHz, CLOROFORMO-d) δ ppm: 7,16 (d, J = 1,77 Hz, 1 H), 6,59 (d, J = 1,77 Hz, 1 H), 5,24 (s, 2 H), 4,75-4,84 (m, 1 H), 4,53-4,66 (m, 3 H), 4,33-4,43 (m, 2 H), 3,76 - 3,90 (m, 2 H), 3,51 (s, 2 H), 3,27-3,38 (m, 2 H), 2,64-2,75 (m, 1 H), 0,67-0,80 (m, 2 H), 0,46-0,56 (m, 2 H). | 474,0, 476,0 |
| 265 |  | 2-amino-4-[2,4-dicloro-6-{2-cloroetoxi)fenil]-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 14 | 1H RMN (400 MHz, CLOROFORMO-d) δ ppm: 7,17 (d, J = 1,77 Hz, 1 H), 6,89 (d, J = 1,77 Hz, 1 H), 5,18 (s, 2 H), 4,61 (s, 2 H), 4,31-4,43 (m, 2 H), 4,16- | 430,0, 432,0 |

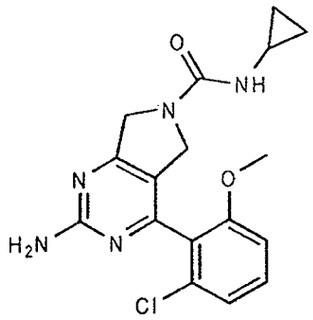
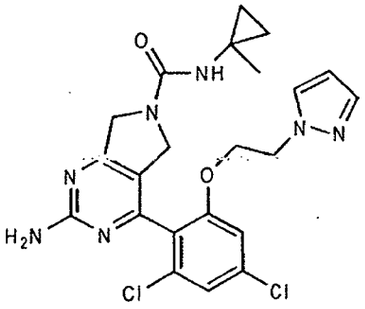
| | | | | | |
|---|---|---|---|---|---|
| | | | | 4,26 (m, 3 H), 3,62-3,69 (m, 2 H), 3,27-3,37 (m, 2 H), 1,17 (t, J = 7,20 Hz, 3 H). | |
| 266 |  | 3-(2-{2-amino-6-[(ciclopropilamino)carbonil]-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-4-il}-3,5-diclorofenoxi)azetidina-1-carboxilato de terc-butilo | Ej. 128 | 1H RMN (400 MHz, CLOROFORMO-d) δ ppm: 7,15 (d, J = 1,26 Hz, 1 H), 6,52 (s, 1 H), 5,24-5,38 (m, 2H), 4,78-4,90 (m, 1 H), 4,65 (s a, 1 H), 4,56 (s a, 2 H), 4,32-4,43 (m, 1 H), 4,19-4,32 (m, 3 H), 3,76-3,93 (m, 2 H), 2,60-2,75 (m, 1 H), 1,42 (s, 9 H), 0,74 (t, J = 5,94 Hz, 2 H), 0,46-0,59 (m, 2 H). | 534,1, 536,1 |
| 267 |  | 2-amino-N-ciclobutil-4-[2,4-dicloro-6-(3,3-dimetilbutoxi)fenil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,32 (s, 2 H), 6,80 (s a, 2 H), 6,52 (d, J = 7,83 Hz, 1 H), 4,39 (d, J = 4,04 Hz, 2 H), 4,09- | 478,0, 480,0 |

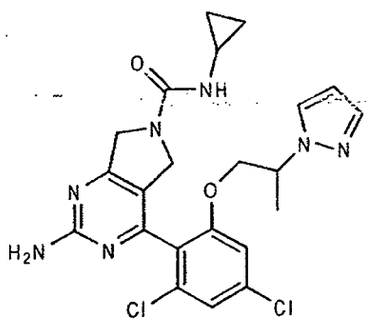
| | | | | | |
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| | | | | 4,17 (m, 3 H), 4,00-4,08 (m, 2 H), 2,03-2,15 (m, 2 H), 1,84-1,99 (m, 2 H), 1,49-1,62 (m, 2 H), 1,45 (t, J = 6,69 Hz, 2 H) 0 80 (s, 9 H). | |
| 268 |  | 2-amino-N-ciclobutil-4-(2,4-dicloro-6-{[(2E)-3-fenilprop-2-en-1-il]oxi}fenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,22-7,42 (m, 7 H), 6,87 (s, 2 H), 6,46-6,57 (m, 2 H), 6,28-6,40 (m, 1 H), 4,81 (d, J = 4,80 Hz, 2 H), 4,42 (s, 2 H), 4,17 (s, 2 H), 4,06-4,15 (m, 1 H), 2,02-2,14 (m, 2 H), 1,82-1,98 (m, 2 H), 1,46-1,60 (m, 2 H). | 510,0, 512,0 |

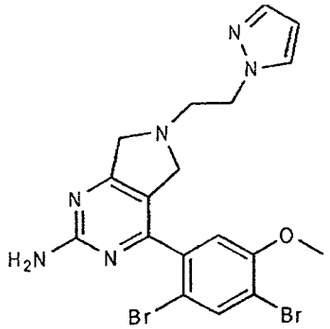
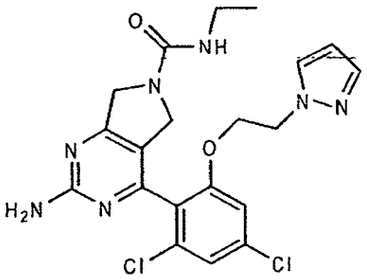
| | | | | | |
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| 269 |  | 2-amino-N-ciclobutil-4-{2,4-dicloro-6-[(2E)-pent-2-en-1-iloxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 127 | 1H RMN (400 MHz, DMSO-d6) δ ppm: 7,33 (d, J = 1,77 Hz, 1 H), 7,28 (d, J = 1,52 Hz, 1 H), 6,83 (s a, 2 H), 6,48-6,55 (m, 1 H), 5,64-5,76 (m, 1 H), 5,42-5,53 (m, 1 H), 4,57 (d, J = 5,56 Hz, 2 H), 4,40 (s, 2 H), 4,07-4,17 (m, 3 H), 2,04-2,13 (m, 2 H), 1,85-2,02 (m, 4 H), 1,46-1,59 (m. 2 H), 0,88 (t, J = 7,45 Hz, 3 H). | 462,0, 464,0 |
| 270 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-N-metil-N-[(1R,5S)-3-metil-3-azabiciclo[3.1.0]hex-6-il]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,66 (s, 1 H) 1,85 (s, 1 H) 2,19 (s, 3 H) 2,26-2,35 (m, 2 H) 2,85-2,91 (m, 1 H) 2,97-3,12 (m, 2 H) 3,56-3,65 (m, 2 H) 4,04-4,11 (m, 2 H) 4,28-4,42 (m, 4 H) | 543,2, 544,2 |

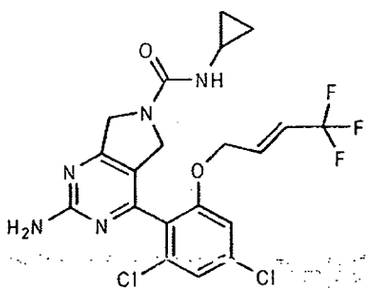
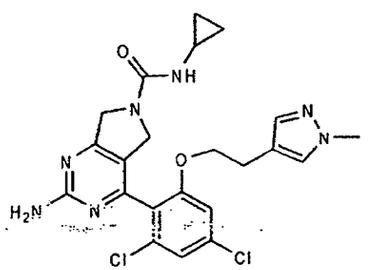
| | | | | | |
|---|---|---|---|---|---|
| | | | | 5,86-5,91 (m, 1 H) 7,17 (d, J = 2,02 Hz, 1 H) 7,19 (d, J = 1,52 Hz, 1 H) 7,29 (s, 1 H) 7,35 (s, 1 H) | |
| 271 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-N-[(1R,5S)-3-metil-3-azabiciclo[3.1.0]hex-6-il]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,81-1,97 (m, 2 H) 2,54 (s, 3 H) 2,60-2,72 (m, J = 1,52 Hz, 2 H) 3,03 (s, 2 H) 3,11-3,20 (m, 1 H) 3,60-3,70 (m, J = 19,45 Hz, 1 H) 3,85 (d, J = 12,63 Hz, 2 H) 4,29-4,33 (m, 4 H) 4,37 (d, J = 7,58 Hz, 2 H) 5,94-6,02 (m, 1 H) 7,17 (d, J = 1,77 Hz, 1 H) 7,23 (d, J = 1,52 Hz, 1 H) 7,29 (d, J = 1,52 Hz, 1 H) 7,30 (d, J = 1,52 Hz, 1 H) | 464,0, 466,0 |

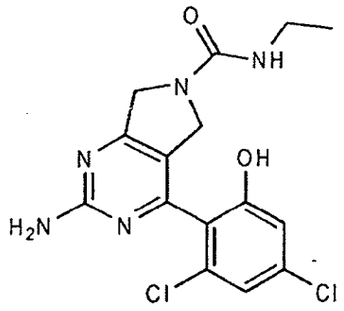
| | | | | | |
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| 272 |  | (1R,5S)-6-{[(2-amino-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidin-6-il)carbonil]amino}-3-azabiciclo[3.1.0]hexano-3-carboxilato de terc-butilo | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,20-1,26 (m, 2 H) 1,54-1,67 (m, J = 23,49 Hz, 2 H) 2,13-2,23 (m, J = 2,02 Hz, 1 H) 2,82-2,94 (m, 2 H) 3,30-3,36 (m, 1 H) 3,45 (dd, J = 10,74, 4,17 Hz, 2 H) 3,52-3,59 (m, 1 H) 3,84-3,96 (m, 1 H) 4,32 (s, 2 H) 4,38 (d, J = 6,82 Hz, 1 H) 6,00 (t, J = 1,89 Hz, 1 H) 6,42 (s, 1 H) 6,79 (s, 1 H) 7,22 (dd, J = 26,78, 1,77 Hz, 1 H) 7,31 (dd, J = 8,34, 1,52 Hz, 1 H) | 615,2, 617,2 |

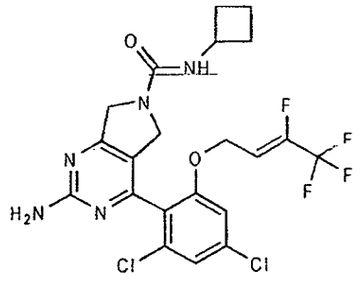
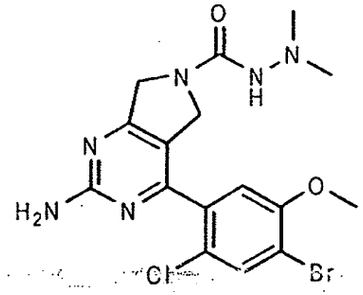
| | | | | | |
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| 273 |  | 2-amino-4-(2-cloro-6-metoxifenil)-N-ciclopropil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 0,33-0,43 (m. 2 H) 0,47-0,60 (m, 2 H) 2,49-2,58 (m. 1 H) 3,73 (s, 3 H) 4,08 (s, 2 H) 4,40 (s, 2 H) 6,46 (d, J = 2,78 Hz, 1 H) 6,78 (s, 2 H) 7,14 (dd, J = 8,08, 5,56 Hz, 2 H) 7,44 (t, J = 8,21 Hz, 1 H) | 360,2, 362,2 |
| 274 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-N-(1-metilciclopropil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 0,44-0,48 (m, 2 H) 0,55-0,68 (m, 2 H) 1,29 (s, 3 H) 3,50 (d, J = 13,39 Hz, 1 H) 3,86 (dd, J = 13,01, 1,89 Hz, 1 H) 4,26-4,34 (m; 4 H) 4,34-4,44 (m, 2 H) 5,99 (t, J = 2,02 Hz, 1 H) 6,46-6,55 (m, 1 H) 6,77 (s, 2 H) 7,18 (d, J = 2,02 Hz, 1 H) | 488,2, 490,2 |

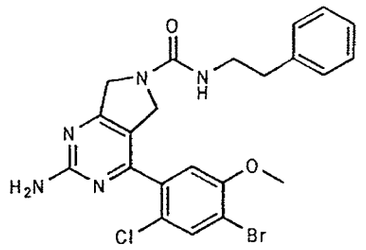
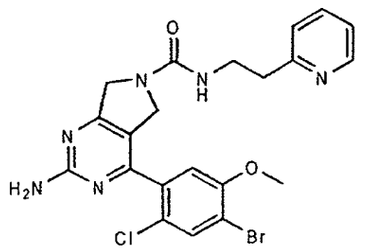
| | | | | | |
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| | | | | 7,25 (d, J = 1,77 Hz, 1 H) 7,28 (d. J = 1,26 Hz, 1 H) 7,32 (d, J = 1,77 Hz, 1 H) | |
| 275 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)propoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 0,35-0,45 (m, 2 H) 0,49-0,64 (m, 2 H) 1,34 (d, J = 2,02 Hz, 3 H) 2,52-2,58 (m, 1 H) 3,35-3,40 (m, 1 H) 3,75-3,88 (m, 1 H) 4,14-4,44 (m, 4 H) 4,51-4,65 (m, 1 H) 6,01 (t, J = 2,02 Hz, 1 H) 6,27-6,44 (m, 1 H) 6,74-6,79 (m, 2 H) 7,21-7,27 (m, 2 H) 7,29-7,36 (m, 2 H) | 488,1, 490,1 |

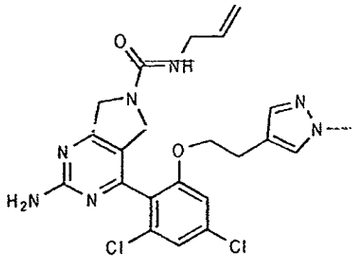
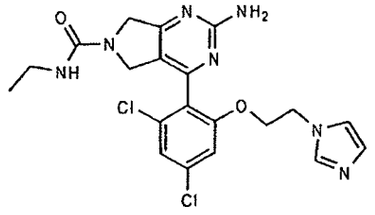
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| 276 |  | 4-(2,4-dibromo-5-metoxifenil}-6-[2-(1H-pirazol-1-il)etil]-6,7-dihidro-5H-pirrolo[3,4-d]pirimidin-2-amina | Ej. 105 | 1H RMN (400 MHz, DMSO-d6) δ ppm 3,80-3,91 (m, J = 3,79 Hz, 3 H) 4,25 (s, 1 H) 4,27-4,41 (m, 6 H) 4,45 (s, 1 H) 6,24 (d, J = 2,02 Hz, 1 H) 6,94 (s, 2 H) 7,13 (d, J = 2,78 Hz, 1 H) 7,45 (s, 1 H) 7,79 (d, J = 1,77 Hz, 1 H) 7,86 (d, J = 8,84 Hz, 1 H) | 494,0, 496,1 |
| 277 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-pirazol-1-il)etoxi]fenil}-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,02 (t, J = 7,20 Hz, 3 H) 2,98-3,14 (m, 2 H) 3,59 (d, J = !2,88 Hz, 1 H) 3,87-3,97 (m, 1 H) 4,33 (s, 4 H) 4,36-4,47 (m, 2 H) 6,00 (t, J = 2,02 Hz, 1 H) 6,23 (t, J = 4,80 Hz, 1 H) 6,78 (s, 2 H) 7,19 (d, J = 1,77 Hz, 1 H) 7,25 (d, J = 1,77 Hz, 1 | 462,1, 464,1 |

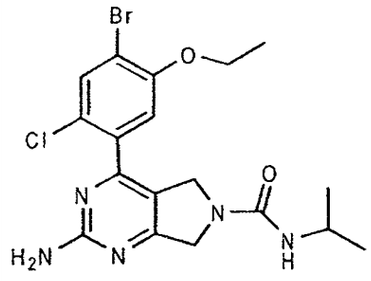
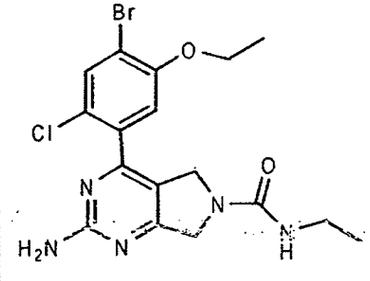
| | | | | | |
|---|---|---|---|---|---|
| | | | | H) 7,29 (d, J = 1,26 Hz, 1 H) 7,32 (d, J = 1,77 Hz, 1 H) | |
| 278 |  | 2-amino-N-ciclopropil-4-(2,4-dicloro-6-{[(2E)-4,4,4-trifluorobut-2-en-1-il]oxi}fenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 0,33-0,43 (m, 2 H) 0,47-0,59 (m, 2 H) 4,02-4,18 (m, 2 H) 4,39 (d, J = 7,33 Hz, 2 H) 4,74-4,91 (m, 2 H) 5,61-5,74 (m, 1 H) 6,43 (d, J = 2,53 Hz, 1 H) 6,57-6,67 (m, 1 H) 7,32 (d, J = 1,77 *Hz*, 1 H) 7,40 (d, J = 1,77 Hz, 1 H) | 488,0, 490,1 |
| 279 |  | 2-amino-N-ciclopropil-4-{2,4-dicloro-6-[2-(1-metil-1H-pirazol-4-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 0,34-0,44 (m, 2 H) 0,53 (dd, J = 6,82, 2,27 Hz, 2 H) 2,53-2,56 (m, 1 H) 2,61-2,70 (m, 2 H) 3,70 (s, 3 H) 3,85 (d, J = 13,14 Hz, 1 H) | 488,1, 490,1 |

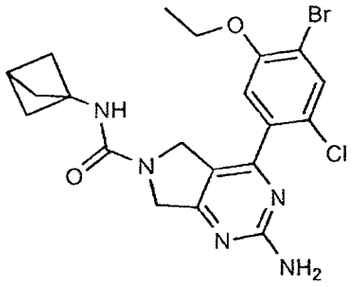
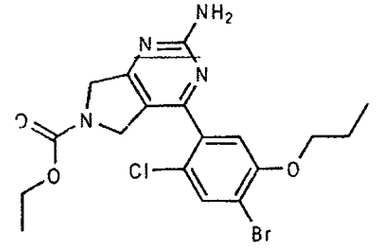
| | | | | | |
|---|---|---|---|---|---|
| | | | | 3,96-4,05 (m, 1 H) 4,06-4,16 (m, 2 H) 4,35-4,50 (m, 2 H) 6,41 (d, J = 2,02 Hz, 1 H) 6,85 (s, 2 H) 7,00 (s, 1 H) 7,17 (s, 1 H) 7,27 (d, J = 1,77 Hz, 1 H) 7,31 (d, J = 1,77 Hz, 1 H) | |
| 280 |  | 2-amino-4-(2,4-dicloro-6-hidroxifenil)-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,00 (t, J = 7,20 Hz, 3 H) 2,97-3,13 (m, 2 H) 4,14 (s, 2 H) 4,38-4,48 (m, 2 H) 6,35 (t, J = 5,43 Hz, 1 H) 6,76-6,83 (m, 2 H) 6,95 (d, J = 1,77 Hz, 1 H) 7,14 (d, J = 1,77 Hz, 1 H) 10,68 (s, 1 H) | 368,1, 370,0 |

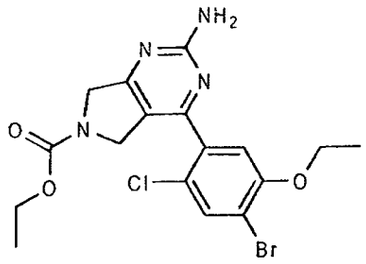
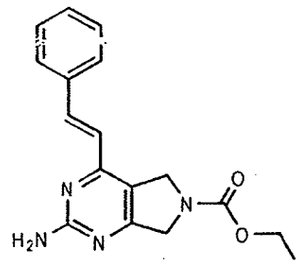
| | | | | | |
|---|---|---|---|---|---|
| 281 |  | 2-amino-N-ciclobutil-4-(2,4-dicloro-6-{[(2Z)-3,4,4,4-tetrafluorobut-2-en-1-il]oxi}fenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,46-1,65 (m, 2H) 1,85-2,00 (m, 2H) 2,02-2,14 (m, 2 H) 4,01-4,24 (m, 3 H) 4,35-4,44 (m, 2 H) 5,63-5,84 (m, 1 H) 6,49 (d, J = 7,83 Hz, 1 H) 6,86 (d, J = 2,53 Hz, 2 H) 7,42-7,49 (m, 1 H) 7,53-7,69 (m, 1 H) | 520,0, 522,0 |
| 282 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil}-N',N'-dimetil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carbohidrazida | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 2,46-2,57 (m, 6 H) 3,86 (s, 3 H) 4,20-4,34 (m, 2 H) 4,37-4,57 (m, 1 H) 6,91 (s, 2H) 7,16 (s, 1 H) 7,56 (s, 1 H) 7,87 (s, 1 H) | 441,9, 442,9 |

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|---|---|---|---|---|---|
| 283 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-N-(2-feniletil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 ... .. | 1H RMN (400 MHz, DMSO-d6) δ ppm 2,65-2,82 (m, 2 H) 3,16-3,30 (m, 2 H) 3,87 (s, 3 H) 4,27 (s, 2 H) 4,43 (s, 2 H) 6,53 (t, J = 5,43 Hz, 1 H) 6,92 (s, 2 H) 7,10-7,22 (m, 4 H) 7,24-7,37 (m, 2 H) 7,88 (s, 2 H) | 502,9, 503,9 |
| 284 |  | 2-amino-4-(4-bromo-2-cloro-5-metoxifenil)-N-(2-piridin-2-iletil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 102 | 1H RMN (400 MHz, DMSO-d6) δ ppm 2,81-2,93 (m, 2 H) 3,35-3,45 (m, 2 H) 4,19-4,29 (m, 2 H) 4,36-4,50 (m, 2 H) 6,54 (t, J = 5,68 Hz, 1 H) 6,91 (s, 2 H) 7,12-7,27 (m, 3H) 7,61 -7,74 (m, 1 H) 7,87 (s, 1 H) 8,47 (d, J = 1,01 Hz, 1 H) | 503,8, 504,9 |

| | | | | | |
|---|---|---|---|---|---|
| 285 |  | N-alil-2-amino-4-{2,4-dicloro-6-[2-(1-metil-1H-pirazol-4-il)etoxi]fenil}-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 18 | 1H RMN (400 MHz, MeOD) δ ppm 2,77 (t, 3 H) 3,79 (d, J = 5,31 Hz, 2 H) 3,96-4,12 (m, 2 H) 4,14-4,25 (m, 2 H) 4,49-4,69 (m, 2 H) 5,06 (dd, J = 10,11, 1,26 Hz, 1 H) 5,16 (dd, J = 17,18, 1,52 Hz, 1 H) 5,81-5,96 (m, 1 H) 7,04 (s, 1 H) 7,12-7,17 (m, 2 H) 7,19 (d, J = 1,77 Hz, 1 H) | 488,1, 489,1 |
| 286 |  | 2-amino-4-{2,4-dicloro-6-[2-(1H-imidazol-1-il)etoxi]fenil}-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,04 (t, J = 7,1 Hz, 3H), 3,04-3,13 (m, 2 H), 3,75 (d, J = 13,2 Hz, 1H), 4,01 (d, J = 13,2 Hz, 1H), 4,19-4,56 (m, 6H), 6,27 (s a, 1H), 6,71 (s, 1H), 6,75-6,86 (m, 3H), 7,28 (s, 2 H), 7,37 (s, 1H). | 462,2, 464,2 |

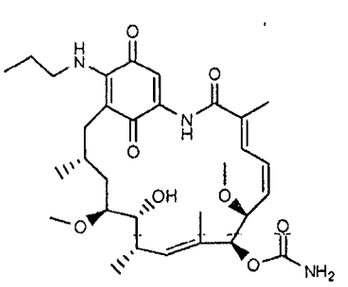
| | | | | | |
|---|---|---|---|---|---|
| 287 |  | 2-amino-4-(4-bromo-2-cloro-5-etoxifenil)-N-isopropil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | 1H RMN (400 MHz, DMSO-d6) δ ppm 1,06 (d, J = 6,5 Hz, 6H), 1,35 (t, J = 6,9 Hz, 3H), 3,75 (m, 1H), 4,09-4,17 (m, 2 H), 4,25 (s, 2 H), 4,42 (s, 2 H), 6,07 (d, J = 8,6 Hz, 1H), 6,88 (s, 2H), 7,15 (s, 1H), 7,86 (s, 1H). | 454,2, 456,2 |
| 288 |  | 2-amino-4-(4-bromo-2-cloro-5-etoxifenil)-N-etil-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | 1H RMN (300 MHz, DMSO-d6) δ ppm 0,98-1,07 (m, 3H), 1,30-1,41 (m, 3H), 3,01-3,14 (m, 2 H), 4,08-4,20 (m, 2 H), 4,26 (s, 2 H), 4,43 (s, 2 H), 6,39 (s a, 1H), 6,92 (s a, 2 H), 7,17 (s, 1H), 7,87 (s, 1H) | 440,2, 442,2 |

| | | | | | |
|---|---|---|---|---|---|
| 289 |  | 2-amino-N-biciclo[1.1.1]pent-1-il-4-(4-bromo-2-cloro-5-etoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxamida | Ej. 111 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,36 (t, J = 7,2 Hz, 3H), 1,95 (s, 6H), 2,36 (s, 1H), 4,10-4,18 (m, 2H, parcialmente oscurecido), 4,25 (s, 2 H), 4,40 (s, 2 H), 6,90 (s a, 2 H), 7,02 (s a, 1H), 7,16 (s, 1H), 7,87 (s, 1H) | 478,2, 480,2 |
| 290 |  | 2-amino-4-(4-bromo-2-cloro-5-propoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 108 | 1H RMN (300 MHz, DMSO-d6) δ ppm 0,96-1,04 (m, 3H), 1,14-1,29 (m, 3H) 1,69-1,82 (m, 2 H), 3,98-4,16 (m, 4H). 4,32-4,39 (m, 2 H), 4,46-4,56 (m, 2 H), 6,97 (s a, 2 H),7,15 (s, 1H), 7,86 (s, 1H) | 455,0, 457,0 |

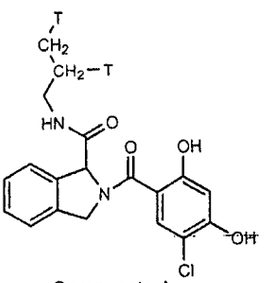
| | | | | | |
|---|---|---|---|---|---|
| 291 |  | 2-amino-4-(4-bromo-2-cloro-5-etoxifenil)-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 108 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,13-1,26 (m, 3H), 1,31-1,40 (m, 3H), 4,04-4,17 (m, 4H), 4,31-4,38 (m, 2 H), 4,47-4,54 (m, 2 H), 6,96 (s a, 2 H), 7,15 | 441,0, 443,0 |
| 292 |  | 2-amino-4-[(E)-2-fenilvinil]-5,7-dihidro-6H-pirrolo[3,4-d]pirimidina-6-carboxilato de etilo | Ej. 1 | 1H RMN (300 MHz, DMSO-d6) δ ppm 1,22-1,30 (m, 3H), 4,09-4,16 (m, 2 H), 4,42 (d, J = 7,6 Hz, 2 H), 4,67 (d, J = 7,5 Hz), 6,62 (s, 2 H), 7,11 (dd, J = 6,9, 15,8 Hz, 1H), 7,36-7,48 (m, 3H), 7,71-7,79 (m, 3H). | 311,4 |

**Ensayo Bioquímico de HSP-90**

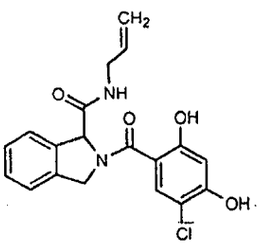
Se evaluó la potencia de los compuestos de la presente invención contra HSP-90 usando un ensayo de unión competitiva SPA (ensayo de centelleo por proximidad). En resumen, se une HSP-90 de longitud completa o N-terminal que contiene un marcador 6-His en su extremo C a cobre en perlas de centelleo de silicato de itrio a través del marcador de His. La propil-geldanamicina (pGA) tritiada, cuya estructura se muestra más adelante, es un análogo de un inhibidor natural de HSP-90 denominado geldanamicina. La pGA tritiada, que contiene un grupo propil-amina tritiado en la posición Nº 17, se une a HSP-90 y lleva el isótopo cerca de las perlas. La 17-n-propilamino-Geldanamicina puede prepararse como se describe en la Patente de Estados Unidos Nº 4.261.989, que se incorpora en este documento como referencia. A continuación se muestra un segundo compuesto tritiado que también puede usarse en este ensayo y se denomina Compuesto A.



pGA



Compuesto A



compuesto parental del compuesto A

La "T" en la estructura del Compuesto A anterior indica la posición de los átomos de hidrógeno tritiados marcados. Este compuesto tiene una $K_d$ de 40 nM y puede prepararse como se indica a continuación. El Compuesto A puede prepararse a partir del compuesto parental del Compuesto A (*N*-alil-2-(5-cloro-2,4-dihidroxibenzoil)isoindolina-1-carboxamida) como se describe a

continuación. Se añadió alilamina (2,5 ml, 5 mmol, 2 M en THF) a una solución de ácido Boc(R,S)-1,3-dihidro-2H-isoindolcarboxílico (263 mg, 1 mmol), diisopropiletil amina (0,9 ml, 5 mmol) y pentafluoruro de *O*-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio fósforo (HATU) (420 mg, 1,1 mmol) en 5 ml de DMF en una atmósfera de nitrógeno. La reacción se dejó en agitación a temperatura ambiente durante 12 horas. A la mezcla de reacción se le añadió $NaHCO_3$ saturado (30 ml) para interrumpir la reacción. Después, se añadió EtOAc (2 x 50 ml) para extraer la solución acuosa. La fase de EtOAc se secó sobre $Na_2SO_4$. El $Na_2SO_4$ se retiró por filtración y el filtrado se evaporó para dar un residuo oleoso de color pardo. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de elución EtOAc al 40→50% en hexanos), dando el producto intermedio deseado (321 mg, rendimiento cuantitativo) 1-[(alilamino)carbonil]-1,3-dihidro-2*H*-isoindolo-2-carboxilato de *terc*-butilo.

Se añadió cloruro de hidrógeno (3 ml, 12 mmol; 4 M en dioxano) a una solución de 1-[(alilamino)carbonil]-1,3-dihidro-2*H*-isoindolo-2-carboxilato de *terc*-butilo (1 mmol) en DCM (5 ml) a temperatura ambiente. La reacción se calentó y se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se evaporó para dar un residuo oleoso. El residuo (*N*-alilisoindolina-1-carboxamida) se usó para la siguiente etapa de reacción sin purificación adicional.

Después, se añadió *N*-alilisoindolina-1-carboxamida (1 mmol) a una solución de ácido 5-cloro-2,4-bis(metoximetoxi)benzoico (que puede prepararse como se muestra en el documento WO 2006/117669) (340 mg, 1,2 mmol), 4-metilmorfolina (2,2 ml, 20 mmol), clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (460 mg, 2,4 mmol) y 1-hidroxi benzotriazol (330 mg, 2,4 mmol)

en 12 ml de DMF en una atmósfera de nitrógeno. La reacción se dejó en agitación a temperatura ambiente durante 12 horas. A la mezcla de reacción se le añadió $H_2O$ (50 ml) para interrumpir la reacción. Después, se añadió EtOAc (2 x 100 ml) para extraer la solución acuosa. La fase de EtOAc se secó sobre $Na_2SO_4$. El $Na_2SO_4$ se retiró por filtración y el filtrado se evaporó, dando un residuo oleoso de color pardo. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de elución EtOAc al 50→60% en hexanos) para dar el producto intermedio deseado (423 mg, rendimiento del 91,8%) N-alil-2-[5-cloro-2,4-bis(metoximetoxi)benzoil]isoindolina-1-carboxamida.

Se añadió cloruro de hidrógeno (4 ml, 16 mmol; 4 M en dioxano) a una solución de N-alil-2-[5-cloro-2,4-bis(metoximetoxi)benzoil]isoindolina-1-carboxamida (392 mg, 0,85 mmol) en DCM (5 ml). La reacción se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se neutralizó con $NaHCO_3$ saturado (ac.) y después se extrajo con EtOAc (2 x 50 ml). Las capas orgánicas combinadas se secaron, se filtraron y se evaporaron para dar el producto final deseado en forma del compuesto parental (N-alil-2-(5-cloro-2,4-dihidroxibenzoil)isoindolina-1-carboxamida) en forma de un sólido de color blanco (221 mg, rendimiento del 69,7%). $^1$H RMN (400 MHz, DMSO-D6) δ ppm 3,57 (d, J = 79,33 Hz, 2 H) 4,65-4,93 (m, 1 H) 4,97-5,19 (m, 1 H) 5,42-5,70 (m, 1 H) 5,68-5,95 (m, 1 H) 6,40-6,71 (m, 1 H) 6,92 (s, 1 H) 7,15-7,67 (m, 4 H) 8,28 (s, 1 H) 10,06 (s, 1 H) 10,40 (s, 1 H). Anál. Calc. para $C_{19}H_{17}ClN_2O_4$: C, 61,21; H, 4,60; N, 7,51, Encontrado: C, 61,02; H, 4,63; N, 7,36.

Una vez que se había preparado el compuesto precursor, se preparó el Compuesto A usando procedimientos de hidrogenación convencionales usando gas tritio.

La señal beta emitida a partir del isótopo excita el centelleo, que crea una señal medible. A medida que los compuestos competitivos se añaden a la mezcla de ensayo, éstos compiten con pGA o Compuesto A tratado con tritio unido en el sitio de unión a ATP del extremo N de HSP-90. Cuando un compuesto desplaza el pGA o Compuesto A marcado, la señal se reduce (las partículas beta ya no están cerca de la perla). Esta reducción de señal se usa para cuantificar el alcance al cual el inhibidor/compuesto es competitivo con pGA o Compuesto A.

El ensayo de SPA para unión de $^{3}$H-pGA (denominado G1) y Compuesto A (denominado G2) a HSP-90 se realizó en placas blancas de fondo plano de 96 pocillos (Corning Nº 3604). Para G1, las soluciones de reacción típicas contenían HSP-90 30 nM y $^{3}$H-pGA 200 nM en tampón de unión (Hepes 100 mM, pH 7,5 y KCl 150 mM). Para G2, las soluciones de reacción típicas contenían HSP-90 5 nM y Compuesto A 50 nM. Para G1, en primer lugar el $^{3}$H-pGA se diluyó hasta el 33% de etiqueta con pGA no marcado que se sintetizó y purificó para dar una concentración final de 200 nM. Para G2, el Compuesto A marcado se diluyó con Compuesto A no marcado para proporcionar una proporción de marcado:no marcado de 1:2 para una concentración final de 50 nM. Se añadieron inhibidores a las soluciones de HSP-90/$^{3}$H-pGA (o HSP-90/Compuesto A) en once concentraciones diferentes para determinaciones de $K_i$. El intervalo de concentraciones de inhibidor fue 100 μM o un intervalo apropiado, para muestras sólidas y 10 μM para compuestos de biblioteca dirigidos y reservas de líquido 4 mM. Para determinar el porcentaje de inhibición, el compuesto se ensayó a 1 y 10 μM. El DMSO final en las muestras fue del 4%. Se añadieron perlas de Cobre-Ysi (Amersham, Nº RPNQ0096) que

se habían diluido en tampón de unión a cada pocillo para dar una concentración final de 100 μg/pocillo. Las placas se sellaron, se cubrieron con una tapa cubierta con papel de aluminio y se agitaron durante 30 minutos a temperatura ambiente. Se dejó que las perlas se asentaran durante 30 minutos después de lo cual las placas se recontaron usando un instrumento Packard TopCount NXT. Este procedimiento también se ha adaptado para rendimiento medio usando un Beckman Biomek FX. Las muestras se procesaron por duplicado y en dos días separados para asegurar un valor preciso de $K_i$.

Para las determinaciones de $K_i$, las cpm corregidas (cpm real menos el fondo) se representaron frente a la concentración de inhibidor usando software GraphPad Prism. Los datos se ajustaron a una ecuación de $CI_{50}$ genérica, Y = Yl / (1 + [X]/$CI_{50}$), donde Yl = intersección Y y [X] es el ligando/inhibidor competidor. Después, la $CI_{50}$ se usó para calcular la $K_i$ usando la ecuación de Cheng-Prusoff:

$$Ki\{cl\} = \frac{CI_{50}\{cl\}}{1 + ([hl]/kd\{hl\})}$$

donde cl = concentración de ligando frío (varía), [hl] = concentración de ligando caliente (200 nM o 50 nM) y Kd {hl} = 240 nM (para $^3$H-pGA) o 40 nM (para Compuesto A). El error se calculó de la manera siguiente: error de $CI_{50}$ / valor de $CI_{50}$ = error fraccionario y error fraccionario * valor de $K_i$ = error de $K_i$.

En los casos en los que el inhibidor se une a HSP-90 tan firmemente que la población de moléculas de inhibidor libres se agota significativamente por la formación del complejo enzima-inhibidor, la ecuación anterior no es válida. Esto normalmente es cierto cuando la $CI_{50}$ observada es aproximadamente la misma

que la concentración de HSP-90. Para un inhibidor de unión firme, se puede aplicar la siguiente ecuación:

$$\frac{EL}{EL_o} = \frac{-(K_I^{ap} + I_o - E_o) + \sqrt{(K_I^{ap} + I_o - E_o)^2 + 4xE_o xK_I^{ap}}}{2xE_o}$$

donde $K_I^{ap} = K_I x(1 + \frac{L_o}{K_L})$

EL y $EL_o$ son los complejos de radioligando-HSP-90 en presencia y ausencia de inhibidor, respectivamente. $EL/EL_o$ representa la señal fraccionaria en presencia de inhibidor. $I_o$, $E_o$ y $L_o$ son las concentraciones de inhibidor, HSP-90 y radioligando, respectivamente. $K_i$ es la constante de inhibición para el ligando, mientras que $K_L$ es la constante de afinidad de unión entre la enzima (HSP-90) y el ligando.

Los datos del ensayo de $K_I$ del compuesto de los Ejemplos 1-292 se enumeran en la siguiente Tabla 3.

**Tabla 3**

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 1 | 0,54 | 0,112 |
| 2 | 2,77 | |
| 3 | 0,052 | |
| 4 | 1,7 | 0,475 |
| 5 | 0,244 | |
| 6 | 4,6 | |
| 7 | 0,952 | 0,12 |
| 8 | 0,369 | |
| 9 | 4 | |
| 10 | | 19,2 |
| 11 | | 2,4 |
| 12 | | 16 |
| 13 | 0,388 | |
| 14 | 1,74 | |
| 15 | 0,57 | |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 17 | | 17,5 |
| 18 | 0,008 | |
| 20 | | 27 |
| 22 | | 21,5 |
| 23 | | 0% de inhibición a 10 μM |
| 24 | | 38 |
| 25 | | 0% de inhibición a 10 μM |
| 26 | 44 | |
| 27 | | 0% de inhibición a 10 μM |
| 29 | | 0,304 |
| 30 | | 0,56 |
| 31 | | 0,36 |
| 32 | 1,9 | 0,499 |
| 33 | 1,3 | 0,268 |
| 34 | 2,6 | 0,74 |
| 35 | 1,5 | 0,437 |
| 36 | 7,3 | 2,86 |
| 37 | 4 | 1,54 |
| 38 | 2,5 | 0,822 |
| 39 | 1,66 | 0,300 |
| 40 | 4 | 0,831 |
| 41 | 2,5 | 0,56 |
| 42 | 0,56 | 0,082 |
| 43 | 0,47 | 0,105 |
| 44 | 0,72 | 0,17 |
| 45 | 0,78 | 0,167 |
| 46 | | 0% de inhibición a 10 μM |
| 47 | | 32 |
| 48 | | 20 |
| 49 | | 3,4 |
| 50 | | 11,4 |
| 51 | 2,71 | |
| 52 | 0,626 | |
| 53 | 0,289 | |
| 54 | 0,4 | |
| 55 | 0,143 | |
| 56 | 0,104 | |
| 57 | 0,304 | |
| 58 | 0,648 | |
| 59 | 9,78 | |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 60 | 0,343 | |
| 61 | 0,154 | |
| 62 | 0,058 | |
| 63 | 3,32 | |
| 64 | 0,134 | |
| 65 | 0,409 | |
| 66 | 0,3 | |
| 67 | 0,169 | |
| 68 | 0,249 | |
| 69 | 0,089 | |
| 70 | 0,209 | |
| 71 | 0,209 | |
| 72 | 0,535 | |
| 73 | 0,314 | |
| 74 | 0,631 | |
| 75 | 1,59 | |
| 76 | 0,431 | |
| 77 | 0,155 | |
| 78 | 0,157 | |
| 79 | 0,111 | |
| 80 | 0,081 | |
| 81 | 36 | |
| 82 | 2,4 | |
| 83 | 2,95 | |
| 84 | 4,34 | |
| 85 | 24 | |
| 86 | 1,65 | |
| 87 | 1,95 | |
| 88 | 3,78 | |
| 89 | 2,38 | |
| 90 | | 1,93 |
| 91 | | 0,745 |
| 92 | | 0,619 |
| 93 | | 0,349 |
| 94 | 0,82 | 0,216 |
| 95 | 12 | 3,71 |
| 96 | 1,66 | 0,3 |
| 97 | | 1,5 |
| 98 | 1,5 | 0,245 |
| 100 | | 0,014 |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 101 | | 0,115 |
| 101a | | 0,149 |
| 102 | | 0,00918 |
| 102b | | 12 |
| 103 | | 0,0265 |
| 104 | | 0,765 |
| 105 | | 1,22 |
| 106 | | 0,319 |
| 107 | | 0,99 |
| 108 | | 0,0202 |
| 108a | | 1,9 |
| 109 | | 0,00825 |
| 110 | | 0,0101 |
| 111 | | 0,064 |
| 112 | | 0,17 |
| 113 | | 0,0245 |
| 114 | | 0,0165 |
| 115 | | 0,0665 |
| 116 | | 0,0274 |
| 117 | | 0,547 |
| 118 | | 0,19 |
| 119 | | 8,77 |
| 120 | | 0,324 |
| 121 | | 0.354 |
| 122 | | 1,05 |
| 123 | | 36 |
| 124 | | 0,844 |
| 125 | | 9,38 |
| 126 | | 2,35 |
| 127 | | 0,0688 |
| 127a | | 0,0628 |
| 127b | | 0,0839 |
| 128 | | 0,648 |
| 129 | | 0,449 |
| 130 | | 0,154 |
| 131 | | 0,775 |
| 132 | | 0,268 |
| 133 | | 0,273 |
| 134 | | 1,63 |
| 135 | | 1,14 |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 136 | | 0,267 |
| 137 | | 0,332 |
| 138 | | 0,132 |
| 139 | | 0,0128 |
| 140 | | 0,132 |
| 141 | | 0,154 |
| 142 | | 0,303 |
| 143 | | 1,3 |
| 144 | | 0,473 |
| 145 | | 0,434 |
| 146 | | 0,00792 |
| 147 | | 0,0517 |
| 148 | | 2,26 |
| 149 | | 0,329 |
| 150 | | 0,0528 |
| 151 | | 0,463 |
| 152 | | 0,332 |
| 153 | | 0,811 |
| 154 | | 0,029 |
| 155 | | 0,546 |
| 156 | | 0,0267 |
| 157 | | 1,2 |
| 158 | | 4,72 |
| 159 | | 0,062 |
| 160 | | 0,685 |
| 161 | | 0,592 |
| 162 | | 0,03 |
| 163 | | 0,104 |
| 164 | | 0,00838 |
| 165 | | 0,392 |
| 166 | | 2,99 |
| 167 | | 2,81 |
| 168 | | 0,067 |
| 169 | | 0,14 |
| 170 | | 1,3 |
| 171 | | 0,247 |
| 172 | | 0,0162 |
| 173 | | 1,02 |
| 174 | | 17,1 |
| 175 | | 0,378 |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 176 | | 0,319 |
| 177 | | 0,235 |
| 178 | | 2,14 |
| 179 | | 1,15 |
| 180 | | 2,28 |
| 181 | | 0,735 |
| 182 | | 0,24 |
| 183 | | 0,504 |
| 184 | | 0,658 |
| 185 | | 2,88 |
| 186 | | 0,802 |
| 187 | | 0,577 |
| 188 | | 1,77 |
| 189 | | 0,0116 |
| 190 | | 0,0201 |
| 191 | | 0,396 |
| 192 | | 0,014 |
| 193 | | 0,0296 |
| 194 | | 0,0466 |
| 195 | | 0,0467 |
| 196 | | 0,0355 |
| 197 | | 0,0139 |
| 198 | | 0,0091 |
| 199 | | 0,0427 |
| 200 | | 0,0144 |
| 201 | | 0,0117 |
| 202 | | 0,0631 |
| 203 | | 0,02 |
| 204 | | 0,00862 |
| 205 | | 0,0487 |
| 206 | | 0,0353 |
| 207 | | 0,07 |
| 208 | | 0,0379 |
| 209 | | 0,0214 |
| 210 | | 0,306 |
| 211 | | 0,00665 |
| 212 | | 0,224 |
| 213 | | 0,03 |
| 214 | | 0,255 |
| 215 | | 1,05 |

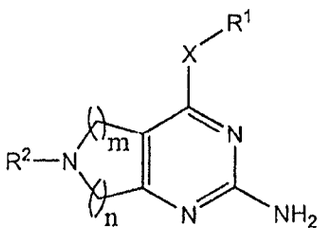
| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 216 | | 0,185 |
| 217 | | 0,0135 |
| 218 | | 0,00593 |
| 219 | | 0,0676 |
| 220 | | 0,121 |
| 221 | | 0,243 |
| 222 | | 0,0568 |
| 223 | | 0,0073 |
| 224 | | 0,0549 |
| 225 | | 0,0794 |
| 226 | | 0,105 |
| 227 | | 0,48 |
| 228 | | 0,179 |
| 229 | | 1,25 |
| 230 | | 0,225 |
| 231 | | 0,069 |
| 232 | | 3,18 |
| 233 | | 2,26 |
| 234 | | 0,184 |
| 235 | | 0,0318 |
| 236 | | 0,21 |
| 237 | | 0,205 |
| 238 | | 0,0455 |
| 239 | | 0,699 |
| 240 | | 0,13 |
| 241 | | 0,472 |
| 242 | | 1,08 |
| 243 | | 3,82 |
| 244 | | 39 |
| 245 | | 14,9 |
| 246 | | 0,00853 |
| 247 | | 0,00661 |
| 248 | | 0,016 |
| 249 | | 0,039 |
| 250 | | 0,0092 |
| 251 | | 0,144 |
| 252 | | 0,104 |
| 253 | | 0,0255 |
| 254 | | 0,145 |
| 255 | | 0,275 |

| Nº de Ejemplo | (G1):Ki (μM) | (G2): Ki (μM) |
|---|---|---|
| 256 | | 0,164 |
| 257 | | 6,29 |
| 258 | | 0,114 |
| 259 | | 5,85 |
| 260 | | 0,213 |
| 261 | | 0,0831 |
| 262 | | 0,267 |
| 263 | | 0,0355 |
| 264 | | 0,195 |
| 265 | | 0,098 |
| 266 | | 0,504 |
| 267 | | 0,0642 |
| 268 | | 0,46 |
| 269 | | 0,0911 |
| 270 | | 0,00352 |
| 271 | | 0,0148 |
| 272 | | 0,0649 |
| 273 | | 1,32 |
| 274 | | 0,0149 |
| 275 | | 0,0141 |
| 276 | | 0,775 |
| 277 | | 0,0125 |
| 278 | | 0,0352 |
| 279 | | 0,0108 |
| 280 | | 0,565 |
| 281 | | 0,098 |
| 282 | | 0,22 |
| 283 | | 0,53 |
| 284 | | 0,635 |
| 285 | | 0,023 |
| 286 | | 0,00693 |
| 287 | | 0,155 |
| 288 | | 0,0814 |
| 289 | | 0,0557 |
| 290 | | 0,807 |
| 291 | | 0,224 |
| 292 | | 2,51 |

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

## REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I)

en la que:

m es 1 ó 2, n es 1 ó 2, cuando m es 2, n es 1;

X es un enlace o un dirradical seleccionado del grupo constituido por -O-, -S-, -(alquileno $C_1$-$C_3$)-, -O-(alquileno $C_1$-$C_3$)-, -NH-(alquileno $C_1$-$C_3$)-, -S-(alquileno $C_1$-$C_3$)-, -C(O)-, -C(O)-O-, -C(O)-NH-, -OC(O)-NH-, -NH-C(O)-NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$-O- y -$S(O)_2$-NH-, donde cada extremo del dirradical puede estar conectado a $R^1$ o al anillo de aminopirimidina de fórmula I;

cuando se permita, cada átomo de nitrógeno o carbono de X está opcionalmente sustituido adicionalmente con un grupo seleccionado de -(alquileno $C_1$-$C_3$)$_t$-CN, -(alquileno $C_1$-$C_3$)$_t$-F, -(alquileno $C_1$-$C_3$)$_t$-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_3$)$_t$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_3$)$_t$-OH, -(alquileno $C_1$-$C_3$)$_t$-$NH_2$, -(alquileno $C_1$-$C_3$)$_t$-NH(alquilo $C_1$-$C_3$) y -(alquileno $C_1$-$C_3$)$_t$-N(alquil $C_1$-$C_3$)(alquilo $C_1$-$C_3$) y t es 0 ó 1;

$R^1$ se selecciona del grupo constituido por arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros, cicloalquilo $C_3$-$C_{12}$, heterociclilo de 3-12 miembros y carbociclilo $C_5$-$C_{12}$ insaturado no aromático, y cada $R^1$ está sustituido opcionalmente

además con 1-5 R, con la condición de que cuando $R^1$ sea fenilo, entonces $R^1$ esté sustituido adicionalmente con al menos dos R y al menos uno de los R no sea un halógeno;

R se selecciona del grupo constituido por $R^x$, -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_7$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 7-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 7-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), (alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)-(cicloalquilo ($C_3$-$C_{10}$), -(alquileno ($C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros);

$R^2$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)$_p$-C(O)-$R^b$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-O-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-C(O)-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-S(O)-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-$R^a$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-N($R^a$)$_2$, -(alquileno $C_1$-$C_6$)$_p$-S(O)$_2$-O$R^a$ y $R^3$, donde $R^3$ se selecciona de -(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros) y -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

cada $R^a$ se selecciona independientemente del grupo constituido por H, alquilo $C_1$-$C_8$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5 a 12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

dos $R^a$ unidos al mismo átomo de nitrógeno, junto con el átomo de nitrógeno, pueden formar opcionalmente un heterociclilo de 3-12 miembros o un heteroarilo de 5-12 miembros; donde dicho heterociclilo de 3-12 miembros y dicho heteroarilo de 5-12 miembros están opcionalmente sustituidos adicionalmente con 1-5 $R^x$;

$R^b$ se selecciona del grupo constituido por -$NR^aN(R^a)_2$, -$NR^aOR^a$, alquenilo $C_2$-$C_8$, alquinilo $C_2$-$C_8$, perfluoroalquilo $C_1$-$C_8$, -(alquileno $C_3$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{12}$), -(alquileno $C_1$-$C_6$)p-(cicloalquilo $C_3$-$C_{12}$), -(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-12 miembros), -(alquileno $C_1$-$C_6$)$_p$-(carbociclilo $C_5$-$C_{12}$ insaturado no aromático);

p es 0 ó 1;

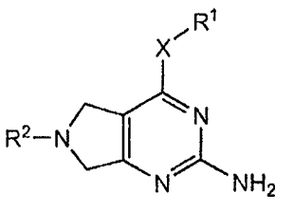
cada R, $R^a$, $R^b$ y $R^3$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$;

cada $R^x$ se selecciona independientemente del grupo constituido por -oxo-, -(alquileno $C_1$-$C_4$)-, halógeno, -CN, -OH, alquilo $C_1$-$C_6$, alquenilo $C_2$-$C_6$, alquinilo $C_2$-$C_6$, perfluoroalquilo $C_1$-$C_6$, -(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)-OH, -(alquileno $C_1$-$C_6$)-CN, -(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-

(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-(alquileno $C_1$-$C_6$)-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-C(O)-N(alquilo $C_1$-$C_6$)(alquilo $C_1$-$C_6$), (alquileno $C_1$-$C_6$)$_q$-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-halógeno, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-(perfluoroalquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heterociclilo de 3-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)$_q$-(heteroarilo de 5-6 miembros), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-O-(alquileno $C_1$-$C_6$)-N(alquilo $C_1$-$C_6$)$_2$, -(alquileno $C_1$-$C_6$)$_q$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-NH-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-N(alquil $C_1$-$C_6$)(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$- NHC(O)-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-NH-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-$NH_2$, -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH(alquilo $C_1$-$C_3$), -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-NH-(alquileno $C_1$-$C_3$)$_q$-(cicloalquilo $C_3$-$C_6$) y -(alquileno $C_1$-$C_6$)$_q$-$SO_2$-N(alquilo $C_1$-$C_3$)$_2$; cada q es independientemente 0 ó 1; cuando se permita, cada átomo de carbono de $R^x$ está opcionalmente sustituido adicionalmente con 1-3 flúor;

o una sal farmacéuticamente aceptable del mismo.

2. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el que m es 1 y n es 1, y el compuesto es de fórmula II,



II

o una sal farmacéuticamente aceptable del mismo.

3. El compuesto de cualquiera de las reivindicaciones 1-2, o una sal farmacéuticamente aceptable del mismo, en el que X es un enlace o -O-, $R^1$ es arilo $C_6$-$C_{12}$, heteroarilo de 5 a 12 miembros, o heterociclilo de 3-12 miembros, y $R^1$ está sustituido adicionalmente con 2-5 R.

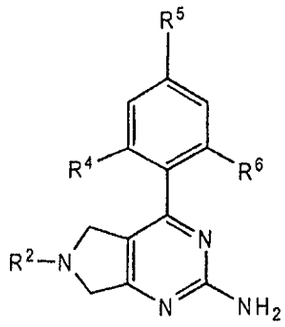
4. El compuesto de cualquiera de las reivindicaciones 1-3, o una sal farmacéuticamente aceptable del mismo, en el que X es un enlace y $R^1$ es un arilo $C_6$-$C_{12}$ sustituido adicionalmente con 2-5 R.

5. El compuesto de la reivindicación 4, o una sal farmacéuticamente aceptable del mismo, en el que $R^1$ es fenilo sustituido adicionalmente con 2-5 R y al menos uno de los R no es un halógeno.

6. El compuesto de cualquiera de las reivindicaciones 1-5, o una sal farmacéuticamente aceptable del mismo, en el que R se selecciona del grupo

constituido por F, Cl, Br, -OH, -CN, alquilo $C_{1-3}$, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); donde cada R está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

7. El compuesto de la reivindicación 2, de fórmula V,




V

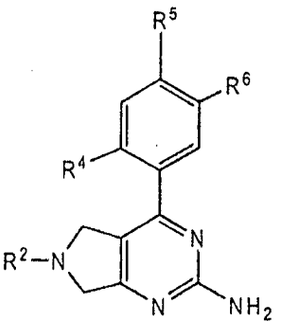
en la que

$R^4$ y $R^5$ son independientemente F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$ sin sustituir, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH sin sustituir o -O-(alquilo $C_1$-$C_6$) sin sustituir;

$R^6$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

o una sal farmacéuticamente aceptable del mismo.

8. El compuesto de la reivindicación 2, de fórmula VI



VI

en la que

$R^4$ y $R^5$ son independientemente F, Cl, Br, -OH, -CN, alquilo $C_1$-$C_3$ sin sustituir, perfluoroalquilo $C_1$-$C_3$, -(alquileno $C_1$-$C_6$)-OH sin sustituir o -O-(alquilo $C_1$-$C_6$) sin sustituir;

$R^6$ se selecciona del grupo constituido por -(alquileno $C_1$-$C_6$)-OH, -O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)-O-(alquilo $C_1$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquileno $C_1$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquenileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinilo $C_2$-$C_6$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(arilo $C_6$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(cicloalquilo $C_3$-$C_{10}$), -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heteroarilo de 5-10 miembros) y -(alquileno $C_1$-$C_6$)$_p$-O-(alquinileno $C_2$-$C_6$)$_p$-(heterociclilo de 3-10 miembros); y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

9. El compuesto de la reivindicación 7 o la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heteroarilo de 5-10 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

10. El compuesto de la reivindicación 7 o la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heteroarilo de 5 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

11. El compuesto de la reivindicación 7 o la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que $R^6$ es -O-(alquileno $C_1$-$C_6$)-(heterociclilo de 3-10 miembros), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

12. El compuesto de la reivindicación 7 o la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que $R^6$ es -O-(alquilo $C_1$-$C_6$) o -O-(alquenilo $C_2$-$C_6$), y $R^6$ está opcionalmente sustituido adicionalmente con 1-5 $R^x$.

13. El compuesto de cualquiera de las reivindicaciones 1-12, o una sal farmacéuticamente aceptable del mismo, en el que $R^2$ es -C(O)-N$(R^a)_2$.

14. El compuesto de cualquiera de las reivindicaciones 1-12, o una sal farmacéuticamente aceptable del mismo, en el que $R^2$ es -C(O)-$OR^a$.

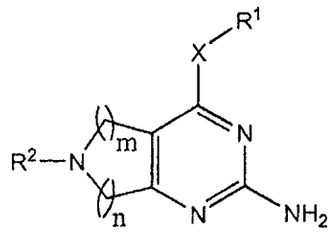
15. Una composición farmacéutica que comprende un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

16. El uso del compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para el tratamiento del cáncer.

17. Un procedimiento para modular la actividad de HSP-90, que comprende poner en contacto una célula con un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

## Resumen

La presente invención se refiere a compuestos de fórmula (I),



(I)

y sales farmacéuticamente aceptables de los mismos, a su síntesis y a su uso como inhibidores de HSP-90.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/000200

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2006/118598 A (RENOVIS INC [US]) 9 November 2006 (2006-11-09) the whole document | 1-17 |
| A | WO 2006/105372 A (CONFORMA THERAPEUTICS CORP [US]) 5 October 2006 (2006-10-05) the whole document | 1-17 |
| A | WO 03/062225 A (BAYER AG [US]) 31 July 2003 (2003-07-31) the whole document | 1-17 |

-/--

[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 |
|---|---|
| 19 May 2008 | 06/06/2008 |

| 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, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Cortés, José |

Form PCT/ISA/210 (second sheet) (April 2005)

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/000200

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | BENDERITTER, PASCAL ET AL: "2-Amino-6-iodo-4-tosyloxypyrimidine: A versatile key intermediate for regioselective functionalization of 2-aminopyrimidines in 4- and 6-positions" TETRAHEDRON, vol. 63, no. 50, 2 August 2007 (2007-08-02), pages 12465-12470, XP002480722 page 12469; compound 3.4.8. 2-amino-4-(3,4-dimethoxyphenyl)-7,8-dihydro-Pyrido[4,3-d]pyrimidine-6(5H)-carboxylic acid 1,1-dimethylethyl ester | 1,3-6, 13,14 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2008/000200

**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.:
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/IB2008/000200

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2006118598 A | 09-11-2006 | NONE | |
| WO 2006105372 A | 05-10-2006 | AU 2006230447 A1 | 05-10-2006 |
| | | CA 2602257 A1 | 05-10-2006 |
| | | EP 1869027 A2 | 26-12-2007 |
| | | KR 20080004550 A | 09-01-2008 |
| | | NO 20075099 B | 29-10-2007 |
| WO 03062225 A | 31-07-2003 | CA 2473510 A1 | 31-07-2003 |
| | | EP 1470121 A1 | 27-10-2004 |
| | | JP 2005521659 T | 21-07-2005 |
| | | MX PA04007191 A | 31-03-2005 |

Industria y Comercio
SUPERINTENDENCIA

# REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCIÓN [1] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [1]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [1]
- ◇ Descripción de la invención [1]
- ◇ Dibujos de ser estos pertinentes [ ]
- ◇ Comprobante de pago de las tasas establecidas [1]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica 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 [ ]

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-081255- -00000-0000
Fecha: 2009-08-04 15:43:11 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 519

Carrera 13 No. 27-00 Piso 5,7y10
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www.sic.gov.co
Bogotá D.C. - Colombia

REPÚBLICA DE COLOMBIA

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
PFIZER INC.

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 9 81255 |
| | Solicitud internacional | PCT/IB2008/000200 |
| | Fecha inicio fase nacional | 06/09/2009 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio No. | 10792 |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se 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
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 25 SET. 2009
adpall

# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
PFIZER INC.

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 9 81255 |
| | Solicitud internacional | PCT/IB2008/000200 |
| | Fecha inicio fase nacional | 06/09/2009 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio No. | 10793 |

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince 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 Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 25 SET. 2009
adpa11