

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-165091- -00000-0000

Fecha: 2011-11-30 18:53:04

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYI

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 96



# Industria y Comercio

## SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL  
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE  
INVENCION

TITULO: DERIVADOS DE PIRIMIDINA NOVEDOSOS Y SU USO EN EL  
TRATAMIENTO DEL CANCER Y ENFERMEDADES ADICIONALES

SOLICITANTES: ASTRAZENECA AB; DAINIPPON SUMITOMO  
PHARMA CO., LTD

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia ; 6-8 Doscho-machi 2 chome,  
Chuo-ku, Osaka 541-8524 Japón.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 30 de Noviembre de 2011

# OLARTEMOURE

OLARTE MOURE & ASOCIAD

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

  
**Industria y Comercio**  
SUPERINTENDENCIA



No. 11-165091- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 411 PRESENTACION Folios: 96

## PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

### PATENTE PCT

ENTRADA EN FASE NACIONAL

P2011/000190

#### SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE**  
(71)

**Nombre:** ASTRAZENECA AB;  
DAINIPPON SUMITOMO PHARMA CO., LTD  
**Dirección:** S-151- 85 Sodertalje Suecia;  
6-8 Doscho-machi 2 chome, Chuo-ku, Osaka  
541-8524 Japón.  
**Nacionalidad o Domicilio:** Suecia; Japón  
**Lugar de Constitución:** Suecia; Japon  
**Teléfono:** \_\_\_\_\_ **Fax:** \_\_\_\_\_  
**E-mail:** \_\_\_\_\_

#### IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual \_\_\_\_\_

Número \_\_\_\_\_

**REPRESENTANTE**  
**O APODERADO**

**Nombre:** CARLOS R. OLARTE  
**Dirección:** Carrera 5 No. 34-03 Bogotá  
**Teléfono:** 601-7700 **Fax:** 601-7799  
**E-mail:** office@olartemoure.com

#### IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual \_\_\_\_\_

Número 79.782.747  
TP 74.295

**INVENTOR (ES)**  
(72)

**Nombre:** (1) Nicholas James BENNETT; (2) Thomas MCINALLY;  
(3) Stephen THOM.  
**Dirección:** (1), (2) y (3) AstraZeneca R&D Alderley, Alderley, Park,  
Macclesfield Cheshire SK10 4TK, Reino Unido.  
**Nacionalidad o Domicilio:** (1), (2) y (3) Británica

5

#### PCT (86)

Solicitud Internacional No. PCT/GB2010/050825 Fecha Mayo 20, 2010

Publicación Internacional No. WO 2010/133885 Fecha Noviembre 25, 2010

6

**Título (54)** DERIVADOS DE PIRIMIDINA NOVEDOSOS Y SU USO EN EL  
TRATAMIENTO DEL CANCER Y ENFERMEDADES ADICIONALES

**Clasificación Internacional (51)** C07D 239/49; C07D 401/12; C07D 403/12; C07D  
413/12; A61K 31/505; A61K 31/5377; A61P 35/00.

**Prioridad**  
SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

Mayo 21, 2009

(31) Número de Solicitud

61/180.238

9

**Comprobante de pago No.** 11- **Fecha** Noviembre de 2011

10

**ANEXOS**

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso. *Adjunto copia Simple ver. Exp. N. 08-129.814*

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar 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.

☒

Otros. Búsqueda Internacional

11

**FIGURA CARACTERÍSTICA:**

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

*Carlos R. Olarte*  
C.C. 79.782.747 Btá T.P. 74.295

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

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

|                                                                                                                               |                |                                              |
|-------------------------------------------------------------------------------------------------------------------------------|----------------|----------------------------------------------|
| <br>Industria y Comercio<br>SUPERINTENDENCIA | RECIBO DE CAJA | No. 11 - 115951                              |
|                                                                                                                               |                | Bogotá D.C., Noviembre 29 de 2011 - 14:40:25 |

|                                        |                |
|----------------------------------------|----------------|
| RECIBIDO DE : OLARTE MOURE & ASOCIADOS | NI 830.122.870 |
|----------------------------------------|----------------|

|                          |                 |           |           |            |              |
|--------------------------|-----------------|-----------|-----------|------------|--------------|
| *** Soporte del Pago *** |                 |           |           |            |              |
| TIPO PAGO                | BANCO           | CUENTA    | No. PAGO  | FECHA PAGO | VR. PAGO     |
| CONSIGNACION             | BANCO DE BOGOTA | 062754387 | 408396074 | 29/11/2011 | 4.599.000.00 |

|                           |                                            |               |              |
|---------------------------|--------------------------------------------|---------------|--------------|
| *** Conceptos Pagados *** |                                            |               |              |
| CANT. RENTISTICO          | CONCEPTO                                   | Vr. UNDITARIO | Vr. CONCEPTO |
| 1 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN | 571.000.00    | 571.000.00   |
|                           |                                            |               | \$571.000.00 |
| =====                     |                                            |               |              |

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

Responsable: \_\_\_\_\_

Recibo de Caja Aplicado al Expediente No. \_\_\_\_\_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-165091- -00000-0000

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Act. 411 PRESENTACION    Folios: 96

Traducción oficial de un documento cuyo original está en inglés

No. 11426

El Ministerio de Relaciones Exteriores en Estocolmo certifica por el presente documento que Mrs. Anna-Karin Östin, de la Oficina de Registro de Compañías de Suecia, Sundsvall, ha expedido y firmado la anterior certificación en su calidad oficial.

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo.

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

Sello: "Anne-Marie Bonde - Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anders Burén, debidamente autorizado para firmar en nombre de Astrazeneca AB ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde - Notario Público de Estocolmo".



Traductor Oficial  
JORGE E. SIERRA REYES  
Licencia 376-1993 Ministerio

*Apostilla adjunta:*

|                                                        |                                             |
|--------------------------------------------------------|---------------------------------------------|
| APOSTILLE<br>(Convention du La Haye du 5 octobre 1961) |                                             |
| 1. País:                                               | Suecia                                      |
| <u>El presente documento público</u>                   |                                             |
| 2. Ha sido firmado por:                                | Anne-Marie Bonde                            |
| 3. Actuando en calidad de:                             | Notario Público                             |
| 4. Lleva el sello / estampilla de:                     | Notario Público de Estocolmo.               |
| <u>Certificado</u>                                     |                                             |
| 5. En:                                                 | Estocolmo                                   |
| 6. El:                                                 | Día 26 de Octubre de 2007                   |
| 7. Por:                                                | Björn Sandin, Notario Público               |
| 8. Bajo el No.                                         | 4071                                        |
| 9. Sello / estampilla:                                 | Björn Sandin, Notario Público de Estocolmo. |
| 10. Firma:                                             | (Firmado)                                   |

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Min. Rel."*

*Fecha: 13 de Noviembre de 2007.*

*Traductor: Jorge Enrique Sierra Reyes.*

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

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

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

*E-mail: [treseser1@yahoo.com](mailto:treseser1@yahoo.com) No. 10-054*

  
Traductor Oficial  
**JORGE E. SIERRA REYES**  
Licencia 376 - 1993 Minjusticia

**APOSTILLE**

**(Convention de La Haye du 5 octobre 1961)**

**1. Country : Sweden**

**This public document**

**2. has been signed by Anne-Marie Bonde**

**3. acting in the capacity of Notary Public**

**4. bears the seal/stamp of**

**Notary Public in Stockholm**

**Certified**

**5. at Stockholm**

**6. the 26.10.2007**

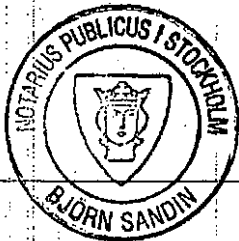
**7. by Björn Sandin**

**Notary Public**

**8. No 4071**

**9. Seal/stamp:**

**10. Signature:**



A handwritten signature in dark ink, appearing to read "Björn Sandin".

# OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte  
J. Ian Raisbeck  
Ana María Frieri  
Juan Guillermo Moure  
Natalia Castro

Zayde Chahí  
Simón Salas  
Alexander Agudé  
Camilo A. Rodríguez  
Lina Mosquera  
Catalina Barbastefan

Of Counsel  
Guillermo Chahí  
Graciela Mel  
Jacqueline Chaparr  
Cruz E. de Montcalan

## Power of Attorney

## Poder

The undersigned,

El suscrito,

domiciled in

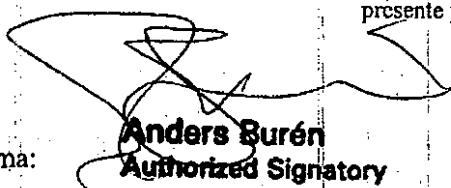
domiciliado en

  
Vasna Malarehamnen 9 S-151 85 Södertälje, Sweden

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

por medio del presente otorga a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, 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:

  
Anders Burén  
Authorized Signatory

Date/Fecha:

24 OCTOBER 2007

City/Country/Ciudad,País:

SÖDERTÄLJE



6

OL

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm  
hereby certify that  
ANDERS BURÉN  
duly authorized to sign for  
ASTRAZENECA AB  
has issued and signed the foregoing document.

Fee 340:- Stockholm 2007-10-26  
Crowns Ex officio:



Anders Burén  
Authorized Signatory



**MODEL OF NOTARIAL CERTIFICATION**

**Notarial Certification**

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

2. That the grantor has executed the foregoing document as **DULY AUTHORISED SIGNATORY** of **ASTRAZENECA AB**

3. That **ASTRAZENECA AB** having its principal place of business located in **SODERTALJE, SWEDEN**

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):

1. **CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB**
2. **AUTHORISATION IN FAVOUR OF SIGNATORY**

**NOTARY PUBLIC (Signature):**

**Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)**

**SEAL (optional)**

**Certificación Notarial**

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

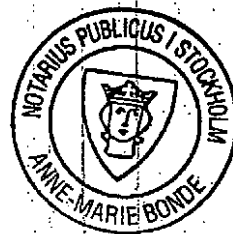
2. Que el otorgante ha suscrito el referido documento en su carácter de

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 legítima.

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):



Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

851 81 Sundsvall Tel. 060-18 40 00 Fax: 060 129840.  
bolagsverket@bolagsverket (illegible)

Certificado de Existencia

Yo, Anna-Karin Östin, de Bolagsverket, la Oficina de Registro de Compañías de Suecia, certifico por medio del presente documento que AstraZeneca AB

Registro No. 556011-7482

es una compañía debidamente constituida según las leyes de Suecia, vigente y con existencia corporativa legal hasta donde muestran los registros de esta oficina en la fecha que se indica más adelante.

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

Bolagsverket, la Oficina de registro de Compañías de Suecia, es el Registrador Oficial de las Compañías Limitadas y otras formas de empresas comerciales en Suecia. Antes de que se expida un Certificado de existencia, los registros radicados en esta oficina se examinan para tener la seguridad de que la compañía en cuestión llena los siguientes requerimientos:

- La compañía tiene una Junta Directiva competente
- La compañía tiene un Auditor titulado calificado.



Traductor Oficial  
JORGE E. SIERRA REYES  
Licencia 376 - 1993 Minjusticia

- La compañía ha llenado sus obligaciones con respecto a la radicación correcta de su informe anual.
- La compañía no es el sujeto de acciones legales de división de compañías, terminación o bancarrota.
- La compañía no ha sido disuelta como resultado de una fusión y no ha salido del registro por ninguna otra razón.

El Certificado está firmado por un funcionario autorizado para expedir estos y similares documentos en nombre de Bolagsverket, la Oficina de Registro de Compañías de Suecia.

Sello: "Anne-Marie Bonde - Notario Público de Estocolmo".

#### Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex officio:

(Firmado) Sello: "Anne-Marie Bonde - Notario Público de Estocolmo".

*Apostilla adjunta:*

  
Traductor Oficial  
JORGE E. SIERRA REYES  
Licencia 376 - 1993 Minjusticia

7

|                                           |                                             |
|-------------------------------------------|---------------------------------------------|
| APOSTILLE                                 |                                             |
| (Convention du La Haye du 5 octobre 1961) |                                             |
| 1. País:                                  | Suecia                                      |
| <u>El presente documento público</u>      |                                             |
| 2. Ha sido firmado por:                   | Anne-Marie Bonde                            |
| 3. Actuando en calidad de:                | Notario Público                             |
| 4. Lleva el sello / estampilla de:        | Notario Público de Estocolmo.               |
| <u>Certificado</u>                        |                                             |
| 5. En:                                    | Estocolmo                                   |
| 6. El:                                    | Día 26 de Octubre de 2007                   |
| 7. Por:                                   | Björn Sandin, Notario Público               |
| 8. Bajo el No.                            | 4070                                        |
| 9. Sello / estampilla:                    | Björn Sandin, Notario Público de Estocolmo. |
| 10. Firma:                                | (Firmado)                                   |

*Certificación:*

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

*Fecha: 13 de Noviembre de 2007.*

*Traductor: Jorge Enrique Sierra Reyes.*

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

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

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

*E-mail: [treseser1@yahoo.com](mailto:treseser1@yahoo.com) No. 10-053*

  
Traductor Oficial  
JORGE E. SIERRA REYES  
Licencia 376 - 1993 Minjusticia

**APOSTILLE**

**(Convention de La Haye du 5 octobre 1961)**

**1. Country : Sweden**

**This public document**

**2. has been signed by Anne-Marie Bonde**

**3. acting in the capacity of Notary Public**

**4. bears the seal/stamp of**

**Notary Public in Stockholm**

**Certified**

**5. at Stockholm**

**6. the 26.10.2007**

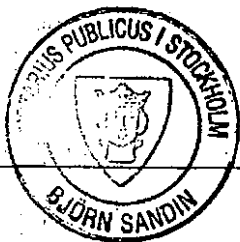
**7. by Björn Sandin**

**Notary Public**

**8. No 4070**

**9. Seal/stamp:**

**10. Signature:**



# Bolagsverket

851 81 Sundsvall  
Besökare: Badhusparken  
Tel: 060-18 40 00 • Fax: 060-12 98 40  
bolagsverket@bolagsverket.se • bolagsverket.se



## Certificate of Good Standing

I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

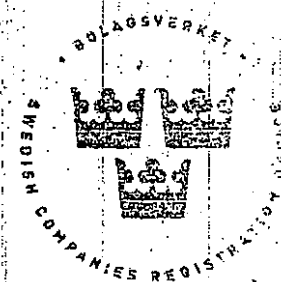


**AstraZeneca AB**  
registration number: 556011-7482

is a duly incorporated company under the laws of Sweden and is in good standing and has a legal corporate existence as far as the records of this office show as of the date stated below.

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 8<sup>th</sup> day of August in the year of two thousand and seven.

  
Anna-Karin Östin



Bolagsverket, the Swedish Companies Registration Office, is the official registrar of limited companies and other forms of business enterprise in Sweden. Before a Certificate of Good Standing is issued, the records kept by this office are examined to ensure that the following requirements are fulfilled for the company in question:

- the company has a registered competent board of directors
- the company has a registered qualified auditor
- the company has fulfilled its obligations regarding the correct filing of its annual report
- the company is not the subject of company division, winding up or bankruptcy proceedings
- the company has not been dissolved as the result of a merger and has not been struck off the register for any other reason

The Certificate is signed by an official authorized to issue these and similar documents on behalf of Bolagsverket, the Swedish Companies Registration Office.



I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm

hereby certify that

ANNA-KARIN ÖSTIN

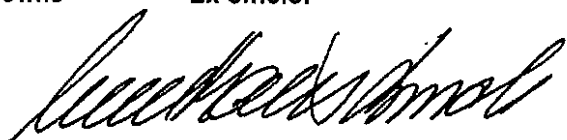
duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

has issued and signed the foregoing document in original of which this is a true copy.

Fee 340:- Stockholm 2007-10-26

Crowns Ex officio:



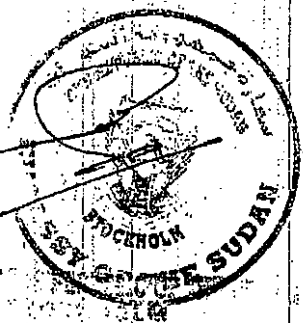
1142p  
The Ministry for Foreign  
Affairs in Stockholm, hereby  
certifies that  
Mr. S. Anna - Karin *Björk*

Swedish Companies Registration  
Office, Sundsvall

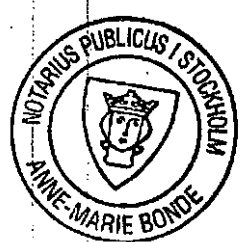
has issued and signed the  
foregoing attestation in his  
official capacity

Fee Stockholm this *14th* day of *August*  
19*07* - PAID

*Agnete Ederlund*



SIGNATURE OF *Agnete Ederlund*  
AND STAMP OF *Sec MFA*  
SIGNATURE *per Hanne Huseini*  
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ough, Leicestershire LE11 5RH (GB). THOM, Stephen [GB/GB]; AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

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(74) Agent: ASTRAZENECA INTELLECTUAL PROPERTY; AstraZeneca AB, S-151 85 Södertälje (SE).

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(71) Applicants (for all designated States except MG, US):  
ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE). DAINIPPON SUMITOMO PHARMA CO., LTD [JP/JP]; 2-6-8 Dosco-machi 2 chome, Chuo-ku, Osaka 5418524 (JP).

(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, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

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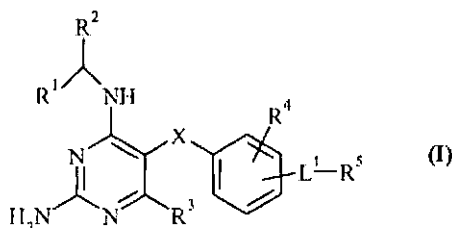
(72) Inventors; and

(75) Inventors/Applicants (for US only): BENNETT, Nicholas, James [GB/GB]; AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). MCINALLY, Thomas [GB/GB]; AstraZeneca R&D Charnwood, Bakewell Road, Loughbor-

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(54) Title: NOVEL PYRIMIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF CANCER AND FURTHER DISEASES"



(57) Abstract: The invention concerns compounds of Formula (I); wherein  $L^1$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $X$  are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the treatment of disease, for example cancer.

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## NOVEL PYRIMIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF CANCER AND FURTHER DISEASES

### Field of the Invention

The present invention relates to novel pyrimidine derivatives and, more particularly, to novel pyrimidine derivatives that act as TLR7 agonists. This invention also relates to methods for the preparation of such pyrimidine derivatives and novel intermediates in the preparation thereof, to pharmaceutical compositions containing such pyrimidine derivatives, to the use of such pyrimidine derivatives in the preparation of medicaments, and to the use of such pyrimidine derivatives in the treatment of conditions mediated by TLR7, such as allergic diseases, autoimmune diseases, viral diseases and, in particular, cancer.

### Background of the Invention

Toll-like receptors (TLRs) are expressed on a variety of immune cells, including macrophages and dendritic cells (DCs). TLRs recognise molecular motifs on pathogens called pathogen-associated molecular patterns (PAMPs) (1). To date, 13 TLRs have been identified in man, these include TLRs 1, 2, 4, 5 and 6, which are confined to the cell surface and TLRs 3, 7, 8 and 9 which are expressed in endosomes. Different TLRs recognise different pathogen-derived ligands, for example TLRs 2 (bacterial lipoproteins), 3 (double-stranded RNA/poly (I:C)), 4 (lipopolysaccharides), 5 (flagellin), 7 (single-stranded RNA) and 9 (CpG-containing DNA) (2). Ligation of TLRs on antigen-presenting cells, such as DCs, leads to production of proinflammatory cytokines, DC maturation and priming of the adaptive immune system (3). TLR7 and TLR9 are expressed by plasmacytoid dendritic cells (pDCs) and ligand recognition leads to the secretion of interferon- $\alpha$  (INF- $\alpha$ ) (4). Preclinical studies investigating the effects of activation of TLRs, using bacterial or viral components, dosed as monotherapy and/or combined with anti-tumor agents, have shown tumour growth inhibition in a variety of murine tumour models (5).

Several small molecule TLR7 agonists have been described, including the imidazoquinoline, imiquimod, which has been used to treat a number of dermatological conditions e.g. genital warts, molluscum contagiosum and melanoma. In the case of melanoma, topically applied imiquimod (Aldara, Graceway Pharmaceuticals, Bristol, TN) demonstrated therapeutic responses in cutaneous metastatic melanoma and lentigo maligna

(6) and has been approved for the treatment of superficial basal cell carcinoma (BCC) (7). Preclinical and clinical studies indicate that imiquimod is likely to function through the induction of type 1 IFN and IFN-inducible genes, which in turn can have direct effects on tumour cell growth and/or harness components of the adaptive immune system (6, 7).

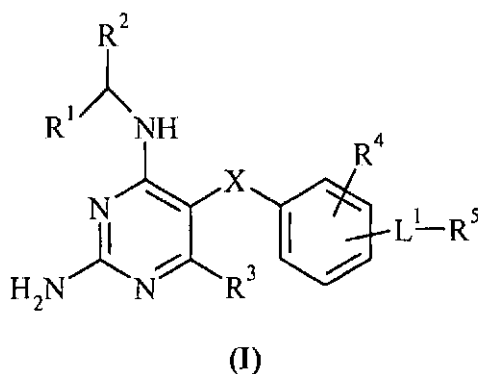
5 852A is another imidazoquinoline, which unlike imiquimod, is suitable for systemic administration. Currently 852A is in phase II clinical trials in a number of cancer indications, including melanoma (8).

Nevertheless, there remains a need for further TLR7 agonists which are more effective in the treatment of disease, for example cancer, by reason of their superior  
10 potency and/or advantageous physical properties (for example, higher permeability, and/or lower plasma protein binding) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other known TLR7 agonists, for example 852A.

As now demonstrated herein, the pyrimidine derivatives of the present invention are capable of activating TLR7 *in vitro*. As a consequence of this activity, the pyrimidine  
15 derivatives of the present invention are expected to have value in the prevention or treatment of human disease, for example cancer, either as a monotherapy or in combination with other chemotherapeutic agents or radiotherapy regimens.

#### Summary of the Invention

According to a first aspect of the present invention, there is therefore provided a  
20 compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

**X** represents -CH<sub>2</sub>-, -NR<sup>8</sup>-, -O- or -S(O)<sub>n</sub>-;

25 **R<sup>1</sup>** represents C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkoxy, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkoxy or hydroxyC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl;

$R^2$  represents hydrogen,  $C_{1-6}$ alkyl or phenyl wherein said phenyl is optionally substituted with 1, 2 or 3 substituents selected from  $R^6$ ;

$R^3$  represents  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy or  $-S-C_{1-6}$ alkyl;

$R^4$  represents hydrogen, halogen,  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy;

5  $L^1$  represents a direct bond,  $-(CR^9R^{10})_m-$ ,  $-CH=CH-(CR^9R^{10})_q-$ ,  $-C\equiv C-(CR^9R^{10})_q-$ ,  $-O-(CR^9R^{10})_q-$ ,  $-C(O)-O-(CR^9R^{10})_q-$  or  $-O-(CH_2)_q-NR^8-(CH_2)_q-$ ;

$R^5$  represents methyl, hydroxy,  $-NR^{11}R^{12}$ ,  $C_{3-6}$ cycloalkyl, phenyl or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

$R^6$  represents  $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, hydroxy, halogen, cyano,  $-S(O)_n-C_{1-6}$ alkyl or  $-CH_2-C(O)-O-C_{1-6}$ alkyl;

$R^7$  represents  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl or  $-(CH_2)_q-NR^{11}R^{12}$ ;

15  $R^8$  represents hydrogen or  $C_{1-6}$ alkyl;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represents hydrogen or methyl;

$R^{11}$  and  $R^{12}$  independently represent hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy $C_{2-4}$ alkyl;

$m$  represents 1, 2, 3, 4, 5 or 6;

$n$  represents 0, 1 or 2; and

20  $q$ , independently, represents 0, 1, 2, 3, 4, 5 or 6;

with the proviso that the compound of Formula (I) is other than:

[3-(2-amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)]-benzoic acid ethyl ester;

[3-(2-amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)-phenyl]-methanol;

methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate;

25 (4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxyphenyl)methanol;

methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate;

(4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorophenyl)methanol;

or (4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenyl)methanol.

30 In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

**X** represents  $-\text{CH}_2-$ ,  $-\text{NR}^8-$ ,  $-\text{O}-$  or  $-\text{S}(\text{O})_n-$ ;

**R<sup>1</sup>** represents  $\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkoxy,  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl, hydroxy $\text{C}_{1-6}$ alkyl, hydroxy $\text{C}_{1-6}$ alkoxy or hydroxy $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl;

**R<sup>2</sup>** represents hydrogen,  $\text{C}_{1-6}$ alkyl or phenyl wherein said phenyl is optionally substituted with 1, 2 or 3 substituents selected from **R<sup>6</sup>**;

**R<sup>3</sup>** represents  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy or  $-\text{S}-\text{C}_{1-6}$ alkyl;

**R<sup>4</sup>** represents hydrogen, halogen,  $\text{C}_{1-6}$ alkyl or  $\text{C}_{1-6}$ alkoxy;

**L<sup>1</sup>** represents a direct bond,  $-(\text{CR}^9\text{R}^{10})_m-$ ,  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}(\text{O})-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  or  $-\text{O}-(\text{CH}_2)_q-\text{NR}^8-(\text{CH}_2)_q-$ ;

**R<sup>5</sup>** represents methyl, hydroxy,  $-\text{NR}^{11}\text{R}^{12}$ ,  $\text{C}_{3-6}$ cycloalkyl, phenyl or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from **R<sup>7</sup>**;

**R<sup>6</sup>** represents  $\text{C}_{1-6}$ alkyl, fluoro $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy, hydroxy, halogen, cyano,  $-\text{S}(\text{O})_n-\text{C}_{1-6}$ alkyl or  $-\text{CH}_2-\text{C}(\text{O})-\text{O}-\text{C}_{1-6}$ alkyl;

**R<sup>7</sup>** represents  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl, hydroxy, hydroxy $\text{C}_{1-6}$ alkyl or  $-(\text{CH}_2)_q-\text{NR}^{11}\text{R}^{12}$ ;

**R<sup>8</sup>** represents hydrogen or  $\text{C}_{1-6}$ alkyl;

**R<sup>9</sup>** and **R<sup>10</sup>**, identically or differently on each occurrence, represents hydrogen or methyl;

**R<sup>11</sup>** and **R<sup>12</sup>** independently represent hydrogen,  $\text{C}_{1-4}$ alkyl or  $\text{C}_{1-4}$ alkoxy $\text{C}_{2-4}$ alkyl;

**m** represents 1, 2, 3, 4, 5 or 6;

**n** represents 0, 1 or 2; and

**q** represents 0, 1, 2, 3, 4, 5 or 6;

with the proviso that the compound of Formula (I) is other than:

[3-(2-amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)]-benzoic acid ethyl ester;  
methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate;  
or  
methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate.

It is to be understood that any suitable **R<sup>4</sup>** and **L<sup>1</sup>-R<sup>5</sup>** group of Formula (I) may be bonded to any available carbon atom of the phenyl ring, but not to the same carbon atom, and that **R<sup>5</sup>** may be linked to the phenyl ring *via* any suitable linker selected from **L<sup>1</sup>**.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that certain compounds of Formula (I) above may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is to be understood that the present invention encompasses all such solvated forms that activate TLR7.

It is also to be understood that certain compounds of the Formula (I) may exist in crystalline form and exhibit polymorphism. The present invention encompasses all such forms that activate TLR7.

The term "halogen" or "halo" is used herein to denote fluoro, chloro, bromo and iodo.

The term "C<sub>1-6</sub>alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length which may be straight-chained or branched. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. For example, "C<sub>1-6</sub>alkyl" includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, *tert*-pentyl, hexyl and isohexyl. The term "C<sub>1-4</sub>alkyl" and "C<sub>1-7</sub>alkyl" are to be construed accordingly.

The term "C<sub>3-6</sub>cycloalkyl" is intended to mean a saturated 3 to 6 membered monocyclic carbon ring. For example "C<sub>3-6</sub>cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C<sub>1-6</sub>alkoxy" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to oxygen. For example, "C<sub>1-6</sub>alkoxy" includes, but is not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term "C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked *via* oxygen to another saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl" includes, but is not limited to, methoxyethyl, methoxypropyl, ethoxypropyl, propoxyethyl and butoxypropyl. The term "C<sub>1-4</sub>alkoxyC<sub>2-4</sub>alkyl" is to be construed accordingly.

The term "hydroxyC<sub>1-6</sub>alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, wherein one of the hydrogen atoms has been replaced by a hydroxy group. For example "hydroxyC<sub>1-6</sub>alkyl" includes, but is not limited to, hydroxymethyl, hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl, 4-hydroxybutyl, hydroxypentyl, hydroxyhexyl and hydroxyisohexyl.

The term "hydroxyC<sub>1-6</sub>alkoxy" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to oxygen and wherein one of the hydrogen atoms has been replaced by a hydroxy group. For example "hydroxyC<sub>1-6</sub>alkoxy" includes, but is not limited to, hydroxymethoxy, hydroxyethoxy, 2-hydroxypropoxy, 3-hydroxypropoxy, 1-hydroxyisopropoxy, 4-hydroxybutoxy, hydroxypentoxo and hydroxyhexoxy.

The term "hydroxyC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked *via* oxygen to another saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, and wherein one of the hydrogen atoms of one, but not both, of the carbon chains has been replaced by a hydroxy group. For example "hydroxyC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl" includes, but is not limited to, hydroxymethoxymethyl, hydroxyethoxymethyl, 2-hydroxypropoxyethyl, 3-hydroxypropoxyethyl, 1-hydroxyisopropoxyethyl, 4-hydroxybutoxypentyl, hydroxypentoxethyl and hydroxyhexoxyethyl.

The term "aryl" is intended to mean phenyl or naphthyl.

Unless stated otherwise, the term "heterocyclic ring" is intended to mean a 4, 5, 6 or 7 membered fully saturated or partially saturated monocyclic ring which comprises 1, 2 or 3 heteroatoms selected from nitrogen, oxygen or sulphur linked *via* ring carbon atoms or ring nitrogen atoms. Examples of 4, 5, 6 or 7 membered heterocyclic rings include, but are

not limited to, azetidiny, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, pyrrolinyl, pyrrolidinyl, thiazolidinyl, morpholinyl, oxetanyl, piperidinyl, piperazinyl, dihydropyridinyl, dihydropyrimidinyl, azepanyl and diazepanyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O<sub>2</sub>) group.

In further embodiments of the first aspect of the present invention, each of the following definitions of L<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, X, and q in paragraphs (1) to (61) hereinafter may be used individually or in combination with one or more of the other following definitions to limit the broadest definition of Formula (I). For example, the skilled person would understand that paragraphs (24), (26), (34), (42) and (58) could be combined to provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R<sup>4</sup> represents C<sub>1-6</sub>alkoxy, L<sup>1</sup> represents -O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- and is bonded at the para position of the phenyl ring relative to linkage -X-, q represents 1, 2 or 3 and R<sup>5</sup> represents NR<sup>11</sup>R<sup>12</sup> wherein R<sup>11</sup> and R<sup>12</sup> both represent methyl. Or, for example, the skilled person would understand that paragraphs (36), (51) and (61) could be combined to provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein L<sup>1</sup> represents -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, q represents 0 and R<sup>5</sup> represents methyl.

(1) X represents -CH<sub>2</sub>-;

(2) X represents -NR<sup>8</sup>-;

(3) X represents -O-;

(4) X represents -S(O)<sub>n</sub>-;

(5) R<sup>1</sup> represents C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkoxy, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkoxy;

(6) R<sup>1</sup> represents C<sub>1-6</sub>alkyl or hydroxyC<sub>1-6</sub>alkyl

(7) R<sup>1</sup> represents C<sub>1-6</sub>alkyl;

(8) R<sup>1</sup> represents butyl;

(9) R<sup>2</sup> represents hydrogen or C<sub>1-6</sub>alkyl;

(10) R<sup>2</sup> represents hydrogen;

(11) R<sup>2</sup> represents C<sub>1-6</sub>alkyl;

(12) R<sup>2</sup> represents phenyl wherein said phenyl is optionally substituted with 1, 2 or 3 substituents selected from R<sup>6</sup>;

- (13)  $R^2$  represents phenyl wherein said phenyl is optionally substituted with 1, 2 or 3 substituents selected from halogen or fluoro $C_{1-6}$ alkyl;
- (14)  $R^2$  represents phenyl wherein said phenyl is optionally substituted with a single substituent selected from  $-CH_2-C(O)-O-C_{1-6}$ alkyl;
- 5 (15)  $R^2$  represents phenyl wherein said phenyl is optionally substituted with a single substituent selected from  $-CH_2-C(O)-O-CH_3$  or  $-CH_2-C(O)-O-CH_2-CH_3$ ;
- (16)  $R^3$  represents  $C_{1-6}$ alkyl;
- (17)  $R^3$  represents methyl;
- (18)  $R^3$  represents  $C_{1-6}$ alkoxy;
- 10 (19)  $R^3$  represents  $-S-C_{1-6}$ alkyl;
- (20)  $R^4$  is bonded at the ortho position of the phenyl ring relative to linkage  $-X-$ ;
- (21)  $R^4$  represents hydrogen, fluorine, methyl or  $C_{1-6}$ alkoxy
- (22)  $R^4$  represents hydrogen or  $C_{1-6}$ alkoxy;
- (23)  $R^4$  represents hydrogen;
- 15 (24)  $R^4$  represents  $C_{1-6}$ alkoxy;
- (25)  $R^4$  represents methoxy;
- (26)  $L^1$  is bonded at the para position of the phenyl ring relative to linkage  $-X-$ ;
- (27)  $L^1$  is bonded at the meta position of the phenyl ring relative to linkage  $-X-$ ;
- (28)  $L^1$  is bonded at the ortho position of the phenyl ring relative to linkage  $-X-$ ;
- 20 (29)  $L^1$  represents  $-(CR^9R^{10})_m-$ ,  $-CH=CH-(CR^9R^{10})_q-$  or  $-C\equiv C-(CR^9R^{10})_q-$ ;
- (30)  $L^1$  represents  $-O-(CR^9R^{10})_q-$  or  $-C(O)-O-(CR^9R^{10})_q-$ ;
- (31)  $L^1$  represents  $-O-(CH_2)_q-NR^8-(CH_2)_q-$ ;
- (32)  $L^1$  represents  $-O-(CR^9R^{10})_q-$  or  $-C(O)-O-(CR^9R^{10})_q-$  wherein q represents 1, 2, 3, 4 or 5 and  $R^5$  represents  $-NR^{11}R^{12}$  or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;
- 25 (33)  $L^1$  represents  $-O-(CR^9R^{10})_q-$  or  $-C(O)-O-(CR^9R^{10})_q-$  wherein  $R^9$  and  $R^{10}$  both represent hydrogen, q represents 1, 2, 3, 4 or 5 and  $R^5$  represents  $-NR^{11}R^{12}$  or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and
- 30

heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

(34)  $L^1$  represents  $-O-(CR^9R^{10})_q-$ ;

(35)  $L^1$  represents  $-O-(CR^9R^{10})_q-$  wherein  $R^9$  and  $R^{10}$  both represent hydrogen;

5 (36)  $L^1$  represents  $-C(O)-O-(CR^9R^{10})_q-$ ;

(37)  $L^1$  represents a direct bond;

(38)  $R^5$  represents hydroxy,  $-NR^{11}R^{12}$ ,  $C_{3-6}$ cycloalkyl, phenyl or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

10 (39)  $R^5$  represents  $-NR^{11}R^{12}$ ,  $C_{3-6}$ cycloalkyl, phenyl or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

15 (40)  $R^5$  represents  $NR^{11}R^{12}$  or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

(41)  $R^5$  represents  $NR^{11}R^{12}$ ;

20 (42)  $R^5$  represents  $NR^{11}R^{12}$  wherein  $R^{11}$  and  $R^{12}$  both represent methyl;

(43)  $R^5$  represents a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

25 (44)  $R^5$  represents a nitrogen-linked monocyclic 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom *via* which the heterocyclic ring is linked to  $L^1$ , 1 or 2 further heteroatoms independently selected from O, N or S wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

30 (45)  $R^5$  represents piperazinyl, piperidinyl or pyrrolidinyl wherein said piperazinyl, piperidinyl or pyrrolidinyl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;

- (46)  $R^5$  represents piperazin-1-yl, piperidin-1-yl or pyrrolidin-1-yl wherein said piperazin-1-yl, piperidin-1-yl or pyrrolidin-1-yl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^7$ ;
- (47)  $R^5$  represents piperazinyl, piperidinyl or pyrrolidinyl wherein said piperazinyl, piperidinyl or pyrrolidinyl ring is optionally substituted with a single methyl substituent;
- (48)  $R^5$  represents piperazin-1-yl, piperidin-1-yl or pyrrolidin-1-yl wherein said piperazin-1-yl, piperidin-1-yl or pyrrolidin-1-yl ring is optionally substituted with a single methyl substituent;
- (49)  $R^5$  represents an unsubstituted piperazinyl, piperidinyl or pyrrolidinyl ring;
- (50)  $R^5$  represents phenyl;
- (51)  $R^5$  represents methyl;
- (52)  $R^5$  represents hydroxy;
- (53)  $R^8$  represents hydrogen or methyl;
- (54)  $R^8$  represents hydrogen;
- (55)  $R^8$  represents methyl;
- (56)  $q$  represents 1, 2, 3, 4, 5 or 6;
- (57)  $q$  represents 1, 2, 3 or 4;
- (58)  $q$  represents 1, 2 or 3;
- (59)  $q$  represents 2 or 3;
- (60)  $q$  represents 3;
- (61)  $q$  represents 0.

Particular novel compounds of Formula (I) include, but are not limited to, the following compounds:

- 5-(4-methoxybenzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine;
- 4-(2-amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)-phenol;
- 5-(4-(2-(dimethylamino)ethoxy)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine;
- 5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine;
- 6-methyl- $N^4$ -pentyl-5-(4-(2-(piperidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine;
- 6-methyl- $N^4$ -pentyl-5-(4-(2-(pyrrolidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine;
- 5-(4-(2-(benzyl(methyl)amino)ethoxy)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine;
- 3-(4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenoxy)propan-1-ol;

6-methyl-*N*<sup>4</sup>-pentyl-5-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)pyrimidine-2,4-diamine;  
6-methyl-5-(4-(3-(4-methylpiperazin-1-yl)propoxy)benzyl)-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5 methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate;  
(*S*)-methyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate;  
(*S*)-methyl 4-((2-amino-4-(1-hydroxyheptan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate;  
10 (*S*)-4-(dimethylamino)butyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate benzene sulphonate;  
methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-methoxybenzoate;  
methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-fluorobenzoate;  
15 methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate;  
5-(2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
2-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenol;  
5-(2-ethoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5-(2-(3-(dimethylamino)propoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
20 5-(3-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenol;  
5-(3-(3-(dimethylamino)propoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
6-methyl-*N*<sup>4</sup>-pentyl-5-(3-(2-(piperidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine;  
5-(3-(2-(dimethylamino)ethoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
25 6-methyl-*N*<sup>4</sup>-pentyl-5-(3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine;  
5-(3-((dimethylamino)methyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5-(4-(3-(dimethylamino)prop-1-ynyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5-(4-(3-(dimethylamino)propyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
5-(3-(3-(dimethylamino)propyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;  
30 5-(4-(3-(dimethylamino)propoxy)-2-methylbenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;

(*R*)-methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate;

(*R*)-methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate;

5 and pharmaceutically acceptable salts thereof.

In one embodiment there is provided (*S*)-4-(dimethylamino)butyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate.

In a further embodiment there are provided compounds of Formula (I) selected from:

10 3-(4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxyphenoxy)propan-1-ol;

5-(2-methoxy-4-(3-morpholinopropoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;

15 5-(2-methoxy-4-(3-(4-methylpiperazin-1-yl)propoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine;

5-(4-(4-(dimethylamino)butyl)-2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine; and

(*S*)-2-(2-amino-5-(4-(hydroxymethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)pentan-1-ol;

20 and pharmaceutically acceptable salts thereof.

In one embodiment of the invention there is provided any Example described herein, or a pharmaceutically acceptable salt thereof.

A suitable pharmaceutically-acceptable salt of a compound of the Formula (I) is, for example, an acid-addition salt of a compound of the Formula (I), for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, 25 sulphuric, trifluoroacetic, citric or maleic acid.

The compounds of the invention may be administered in the form of a pro-drug, that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed 30 when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in-vivo*

cleavable amide derivatives that may be formed at an amino group in a compound of the Formula (I).

Accordingly, the present invention includes those compounds of the Formula (I) as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula (I) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula (I) may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents :-

- a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);
- f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);
- g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and
- h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses an amino group is, for example, an *in-vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with C<sub>1-10</sub>alkanoyl groups such as an acetyl, benzoyl,

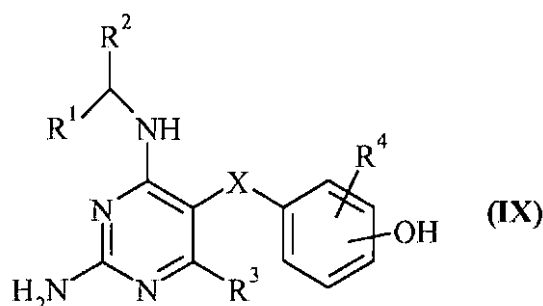
phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C<sub>1-4</sub>alkyl)piperazin-1-ylmethyl.

The *in-vivo* effects of a compound of the Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula (I). As stated hereinbefore, the *in-vivo* effects of a compound of the Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

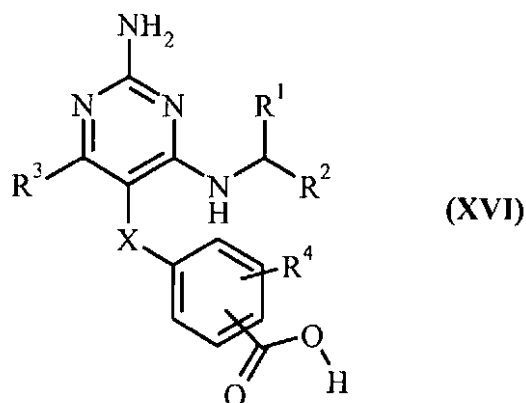
#### Preparation of Compounds of Formula (I)

Certain processes for the synthesis of compounds of Formula (I) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, which comprises a process (a), (b), (c) or (d) wherein, unless otherwise defined, the variables are as defined hereinbefore for compounds of Formula (I):

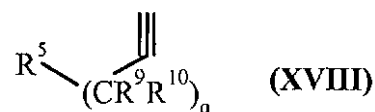
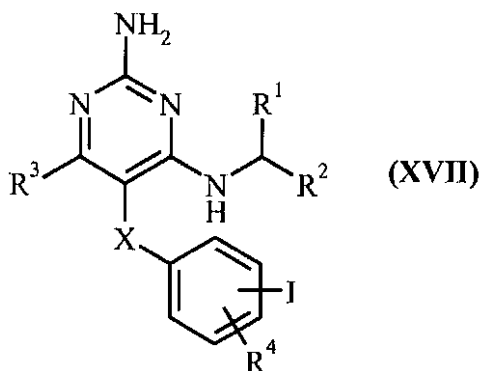
(a) when R<sup>3</sup> represents C<sub>1-6</sub>alkyl and L<sup>1</sup> represents -O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, reaction of a compound of Formula (IX) with a group halo-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-R<sup>5</sup>;



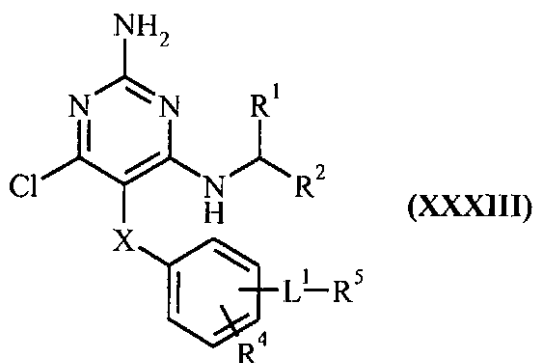
(b) when L<sup>1</sup> represents -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- and R<sup>5</sup> represents NR<sup>11</sup>R<sup>12</sup>, reaction of an acid of Formula (XVI) with an alcohol of formula OH-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-NR<sup>11</sup>R<sup>12</sup> in the presence of oxalyl chloride or thionyl chloride, a suitable coupling agent and optionally a suitable base;



(c) when  $\text{L}^1$  represents  $-(\text{CR}^9\text{R}^{10})_m-$  (and  $m$  represents 2, 3, 4, 5 or 6),  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$  or  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ , reaction of a compound of Formula (XVII) with a compound of Formula (XVIII) in the presence of copper iodide, a suitable catalyst and a suitable base;



(d) when  $\text{R}^3$  represents  $\text{C}_{1-6}$ alkoxy or  $-\text{S}-\text{C}_{1-6}$ alkyl, reaction of a compound of Formula (XXXIII) with the appropriate alcohol or alkylthiol in the presence of a suitable base;

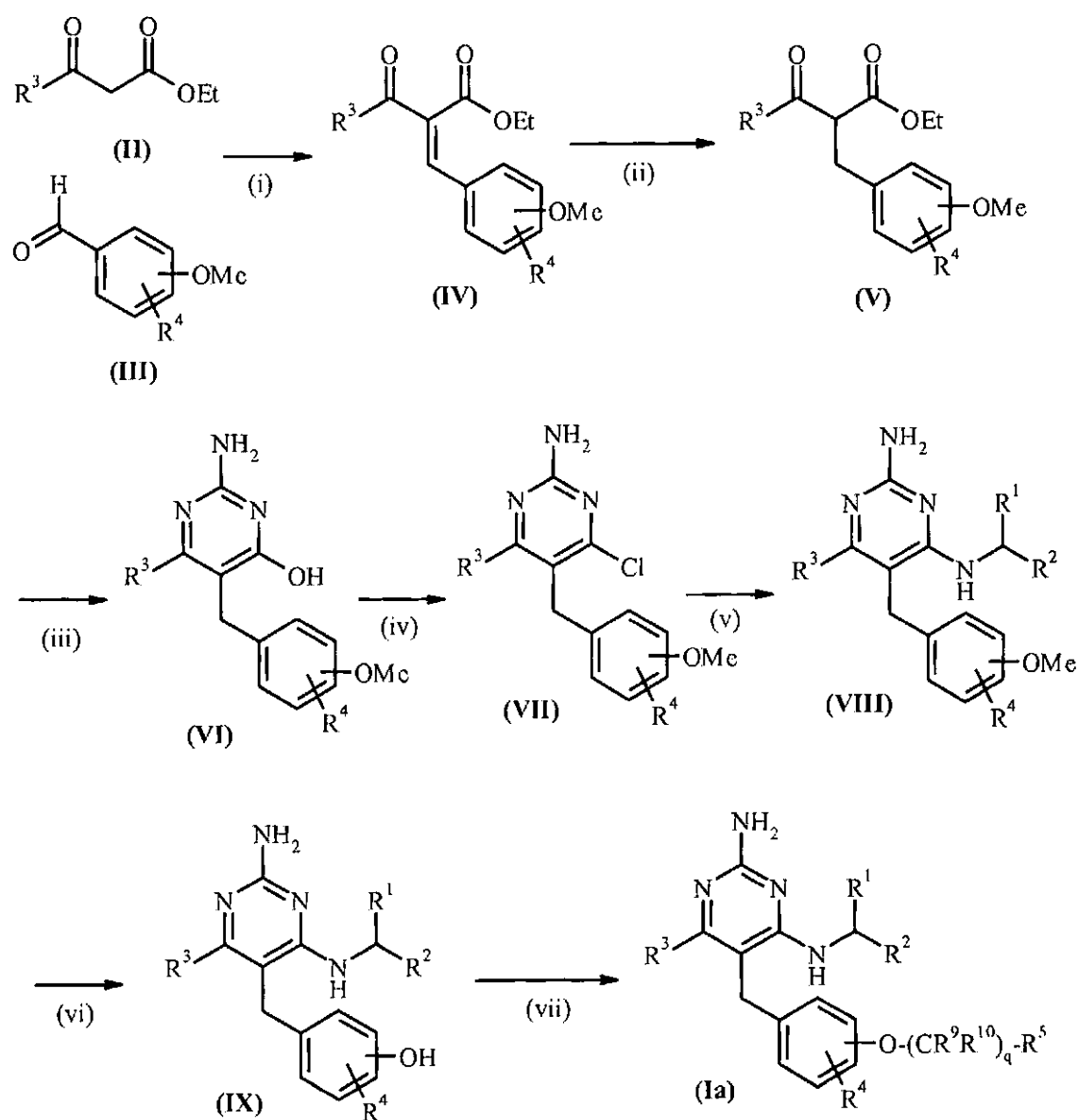


and thereafter, if necessary:

- (i) converting a compound of Formula (I) into another compound of Formula (I);
- (ii) removing any protecting groups;
- (iii) separating a racemic mixture into separate enantiomers;
- (iv) preparing a pharmaceutically acceptable salt thereof; and/or

(v) preparing a crystalline form thereof.

Compounds of Formula (Ia) in which X represents CH<sub>2</sub>, R<sup>3</sup> represents C<sub>1-6</sub>alkyl, L<sup>1</sup> represents -O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, Et represents an ethyl group, R<sup>4</sup> is other than C<sub>1-6</sub>alkoxy and all other variables are as defined hereinbefore for compounds of Formula (I), may be prepared as described in the following reaction Scheme 1.



Scheme 1

Step (i) - A compound of Formula (IV) can be prepared by reaction of a compound of Formula (III) with a compound of Formula (II). The reaction may be carried out in the

presence of acetic acid and piperidine in a suitable solvent, such as toluene, and at a suitable temperature, for example 50°C to 150°C.

Step (ii) - Compounds of Formula (V) can be prepared by reduction of a compound of Formula (IV). The reaction may be carried out with a catalyst such as Pd/C under a H<sub>2</sub> atmosphere (1-20 bar) in a suitable solvent, such as EtOH, and at a suitable temperature, for example 20°C to 100°C.

Step (iii) - Compounds of Formula (VI) may be prepared by reacting a compound of Formula (V) with guanidine or guanidine carbonate in a suitable solvent, such as MeOH or EtOH, and at a suitable temperature, for example 50°C to 150°C.

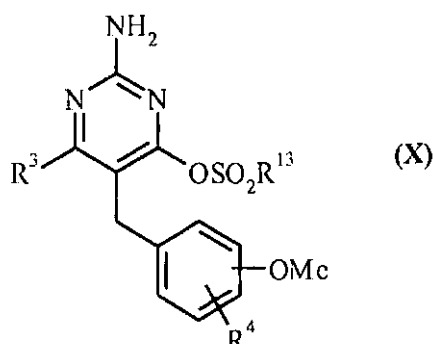
Step (iv) - Compounds of Formula (VII) may be prepared by reacting a compound of Formula (VI) with phosphorous oxychloride, at a suitable temperature, for example 50°C to 110°C.

Step (v) - Compounds of Formula (VIII) may be prepared by reacting a compound of Formula (VII) with an excess of amine of formula NH<sub>2</sub>CHR<sup>1</sup>R<sup>2</sup> in a suitable solvent, such as butanol or 1,4-dioxane, at a suitable temperature, for example 50°C to 150°C. Alternatively, the reaction may be performed in a microwave at a suitable temperature, for example 50°C to 200°C.

Step (vi) - Compounds of Formula (IX) may be prepared by reacting a compound of Formula (VIII) with a solution of BBr<sub>3</sub> in a suitable solvent, such as DCM, and at a suitable temperature, for example 0°C to 15°C.

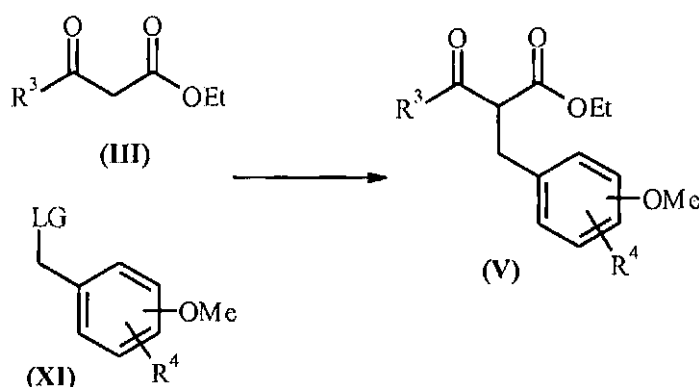
Step (vii) - compounds of Formula (IX) may be reacted with a group halo-R<sup>5</sup> or halo-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-R<sup>5</sup> in the presence of a suitable base, for example Cs<sub>2</sub>CO<sub>3</sub>, in a suitable solvent, for example NMP or DMF, optionally in the presence of NaI and at a suitable temperature, for example 50°C to 150°C, to provide a compound of Formula (Ia).

Alternatively, compounds of Formula (VIII) may be prepared by reacting a compound of Formula (X), in which R<sup>13</sup> represents an aryl group, with excess of amine of formula NH<sub>2</sub>CHR<sup>1</sup>R<sup>2</sup>. The reaction may be carried out in a suitable solvent, such as butanol or 1,4-dioxane, and at a suitable temperature, for example 50°C to 150°C. Alternatively, the reaction may be performed in a microwave at a suitable temperature, for example 50°C to 200°C.



A compound of Formula (X) may be prepared by reacting a compound of Formula (VI) with an aryl sulphonylchloride of formula  $R^{13}SO_2Cl$ . The reaction may be carried out in a suitable solvent, such as DCM, in the presence of a suitable base, such as triethylamine or DIPEA, and with the addition of a catalyst, such as DMAP, at a suitable temperature, for example  $0^\circ C$  to  $50^\circ C$ .

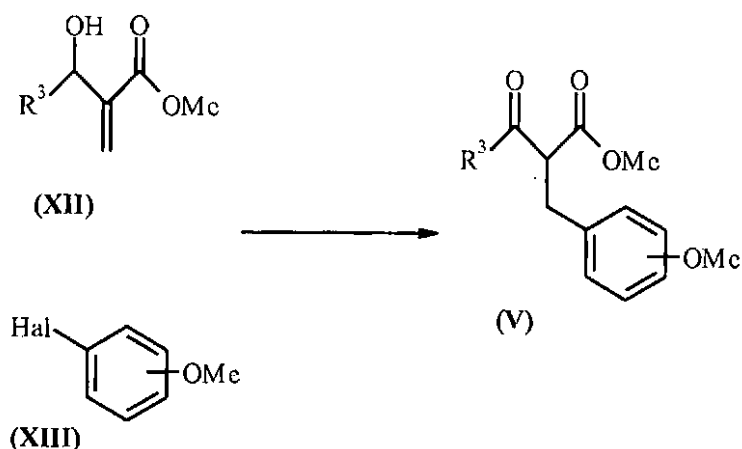
Alternatively compounds of Formula (V) may be prepared as shown in Scheme 2 by reacting a compound of Formula (III) with a base, such as NaH, in a suitable solvent, such as THF or DMF, at a suitable temperature, for example  $0^\circ C$  to r.t. ( $20^\circ C$ ), followed by addition of a compound of Formula (XI) wherein LG represents a suitable leaving group, for example bromine or chlorine. The reaction is then preferably heated, for example at  $50^\circ C$  to  $100^\circ C$ , optionally in the presence of an additive such as KI.



Scheme 2

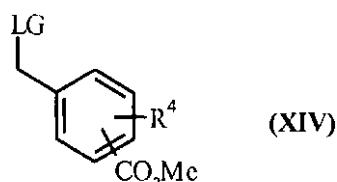
Alternatively compounds of Formula (V) may be prepared by a Heck reaction between a compound of Formula (XII) and a compound of Formula (XIII) as shown in Scheme 3 wherein Hal represents bromine or iodine. The reaction may be carried out using a palladium catalyst, such as  $Pd(OAc)_2$  or 1,1'-bis(di-*tert*-butylphosphino)ferrocene-palladium(II) chloride (Pd-118), a base such as  $NaHCO_3$  or dicyclohexylmethylamine, and

tetrabutylammonium chloride or bromide. The reaction is performed in a suitable solvent, such as THF or DMA, and at a suitable temperature, for example 50°C to 150°C.

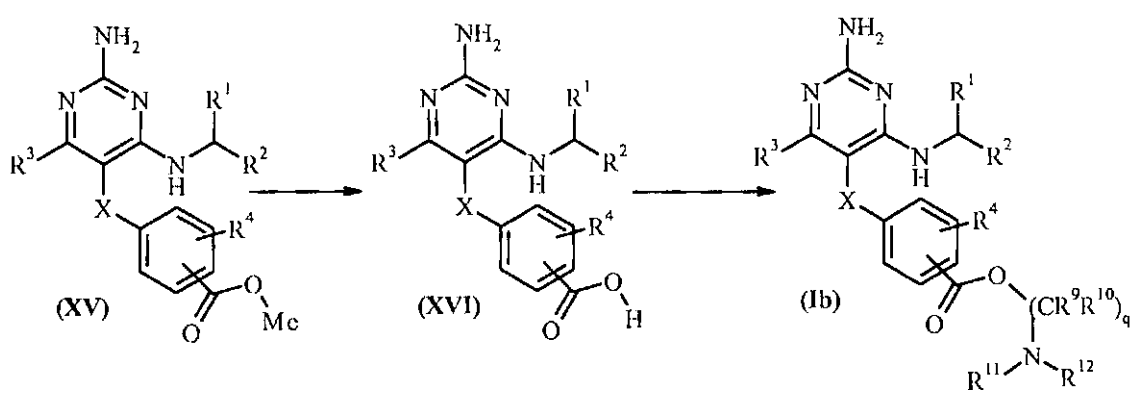


Scheme 3

Alternatively compounds of Formula (I) wherein X represents CH<sub>2</sub>, and L<sup>1</sup> represents -C(O)-O- and R<sup>5</sup> represents methyl can be prepared according to Scheme 2 from compounds of Formula (XIV) where LG represents bromo and which are either commercially available or prepared by bromination of the appropriate precursor using *N*-bromosuccinimide in the presence of light and a radical initiator such as di-benzoyl peroxide or 2,2'-azobisisobutyronitrile in a suitable solvent, such as DCM, CHCl<sub>3</sub> or CCl<sub>4</sub>.

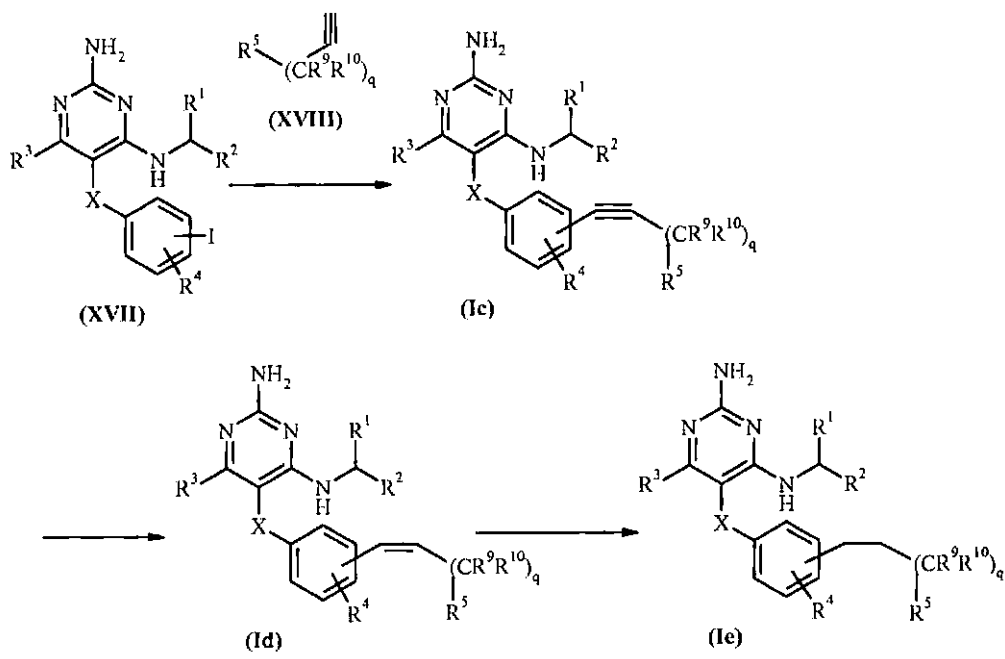


Compounds of Formula (Ib) wherein L<sup>1</sup> represents -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- and R<sup>5</sup> represents NR<sup>11</sup>R<sup>12</sup> may be prepared according to Scheme 4 from compounds of type (XV) by hydrolysis of the ester in the presence of a base, such as aqueous LiOH containing an alcohol such as EtOH, and at a suitable temperature, for example 20°C to 50°C, followed by activation of the acid of Formula (XVI), for example with COCl<sub>2</sub> or SOCl<sub>2</sub> or with a coupling agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate or benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, and reaction with a suitable alcohol group containing NR<sup>11</sup>R<sup>12</sup> in an organic solvent such as NMP, DMF, MeCN or THF and usually in the presence of a suitable base, for example triethylamine or DIPEA, and at a suitable temperature, for example 0°C to 50°C.



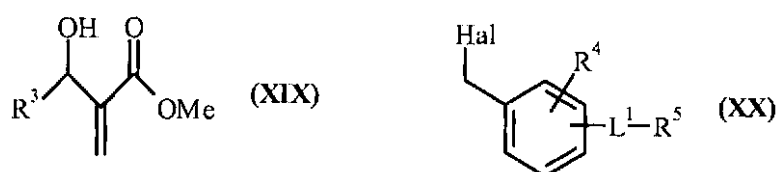
Scheme 4

Compounds of Formula (Ic), (Id) or (Ie) wherein L<sup>1</sup> represents -(CR<sup>9</sup>R<sup>10</sup>)<sub>m</sub>- (and m represents 2, 3, 4, 5 or 6), -CH=CH-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- or -C≡C-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- may be prepared according to Scheme 5 from compounds of Formula (XVII) by reaction with alkynes of Formula (XVIII) in the presence of CuI followed by addition of compounds of Formula (XVII) and a Pd(0) catalyst, such as Pd(PPh<sub>3</sub>)<sub>4</sub>, in a suitable solvent, such as THF, in the presence of a suitable base, such as triethylamine or DIPEA, and at a suitable temperature, e.g. 50°C-100°C for 6-24 hours, to give compounds of Formula (Ic). Reduction of compounds of Formula (Ic) with a catalyst, such as Pd/C, in a suitable solvent, such as EtOH under a pressure of H<sub>2</sub>, e.g. 1-3 bar, provides compounds of Formula (Id). Further reduction under the same conditions provides compounds of Formula (Ie).

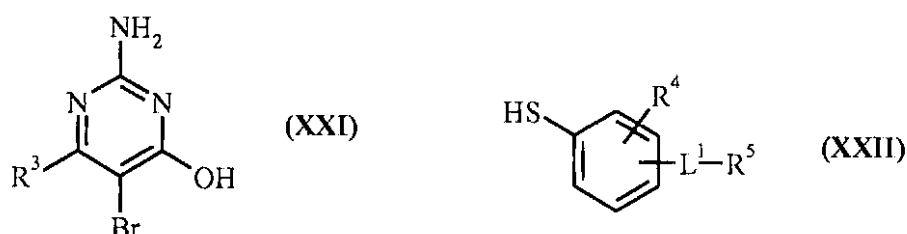


Scheme 5

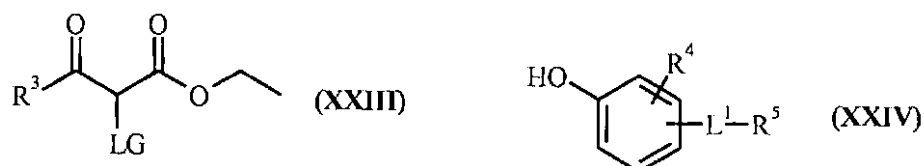
Compounds of Formula (I) where  $L^1$  represents a direct bond and  $R^5$  represents a monocyclic 4, 5, 6 or 7 membered heterocyclic ring may be prepared according to Scheme 3 from compounds of Formula (XIX) and compounds of Formula (XX) and following the steps in reaction Scheme 1 from compounds of Formula (V). The reaction may be carried out using a palladium catalyst, such as palladium acetate or Pd-118, a base such as  $\text{NaHCO}_3$  or dicyclohexylmethylamine, and tetrabutylammonium chloride or bromide. The reaction is performed in a suitable solvent such as THF or DMA and at a suitable temperature, for example  $50^\circ\text{C}$  to  $150^\circ\text{C}$



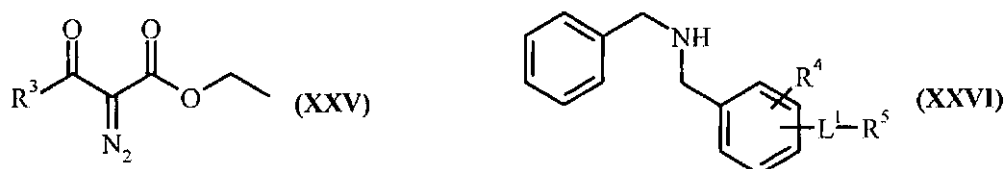
A compound of Formula (I) in which X represents a sulphur atom may be prepared by reacting a compound of Formula (XXI) with a compound of Formula (XXII) and then by following the steps in reaction Scheme 1 from Formula (VI). The reaction may be carried out in a suitable solvent, such as ethylene glycol, and a base such as  $\text{K}_2\text{CO}_3$ , and at a suitable temperature, for example  $80^\circ\text{C}$  to  $200^\circ\text{C}$ .



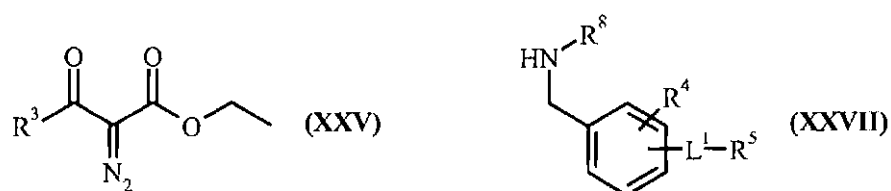
A compound of Formula (I) in which X represents an oxygen atom may be prepared by reacting a compound of Formula (XXIII), where LG represents a suitable leaving group, for example bromine, with a compound of Formula (XXIV) and then by following the steps in reaction Scheme 1 from Formula (V). The reaction may be carried out in a suitable solvent, such as THF, and in the presence of a base, such as  $\text{K}_2\text{CO}_3$ , and at a suitable temperature, for example  $20^\circ\text{C}$  to  $100^\circ\text{C}$ .



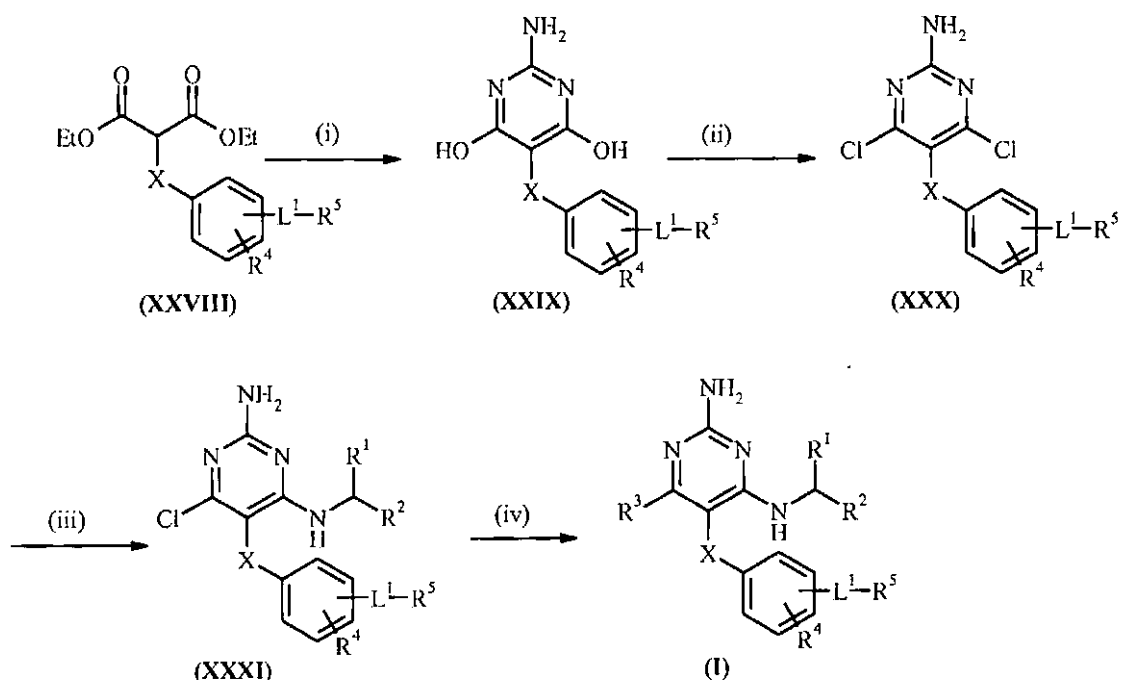
A compound of Formula (I) in which X represents a group NH may be prepared by reacting a compound of Formula (XXV) with a compound of Formula (XXVI) then by following the steps in reaction Scheme 1 from Formula (V). The benzyl protecting group may be removed by catalytic hydrogenation at a convenient step in the route. The reaction  
 5 may be carried out in a suitable solvent, such as toluene, and with a suitable catalyst, such as rhodium acetate, and at a suitable temperature, for example 50°C to 150°C.



A compound of Formula (I) in which X represents a group NR<sup>8</sup>, wherein R<sup>8</sup> is C<sub>1-6</sub>alkyl, may be prepared by reacting a compound of Formula (XXV) with a compound  
 10 of Formula (XXVII) then by following the steps in reaction Scheme 1 from Formula (V).



A compound of Formula (I) in which R<sup>3</sup> represents a group C<sub>1-6</sub>alkoxy or -S-C<sub>1-6</sub>alkyl may be prepared according to Scheme 6.



Scheme 6

Step (i) - Compounds of Formula (XXIX) may be prepared by reacting a compound of Formula (XXVIII) with guanidine or guanidine carbonate in a suitable solvent, such as MeOH or EtOH, and at a suitable temperature, for example 50°C-150°C.

Step (ii) - Compounds of Formula (XXX) may be prepared by reacting a compound of Formula (XXIX) with POCl<sub>3</sub>, at a suitable temperature, for example 50°C to 110°C.

Step (iii) - Compounds of Formula (XXXI) may be prepared by reacting a compound of Formula (XXX) with excess of an amine of Formula NH<sub>2</sub>CHR<sup>1</sup>R<sup>2</sup>, in a suitable solvent, such as butanol or 1,4-dioxane, and at a suitable temperature, for example 50°C to 150°C. Alternatively, the reaction can be performed in a microwave at a suitable temperature, for example 0°C to 200°C.

Step (iv) - A compound of Formula (I) may be prepared by reacting a compound of Formula (XXXI) with the appropriate alcohol or alkylthiol in the presence of a suitable base, such as NaH.

#### **Biological Assays**

The ability of compounds to activate TLR7 *in vitro* was assessed using the human TLR7 assay described below.

##### **Human TLR7 assay**

Recombinant human TLR7 was stably expressed in a HEK293 cell line already stably expressing the pNiFty2-SEAP reporter plasmid; integration of the reporter gene was maintained by selection with the antibiotic zeocin. The most common variant sequence of human TLR7 (represented by the EMBL sequence AF240467) was cloned into the mammalian cell expression vector pUNO and transfected into this reporter cell-line. Transfectants with stable expression were selected using the antibiotic blasticidin. In this reporter cell-line, expression of secreted alkaline phosphatase (SEAP) is controlled by an NFkB/ELAM-1 composite promoter comprising five NFkB sites combined with the proximal ELAM-1 promoter. TLR signaling leads to the translocation of NFkB and activation of the promoter results in expression of the SEAP gene. TLR7-specific activation was assessed by determining the level of SEAP produced following overnight incubation of the cells at 37°C with the standard compound in the presence of 0.1% (v/v) dimethylsulfoxide (DMSO). Concentration dependent induction of SEAP production by compounds was expressed as the concentration of compound which produced half of the maximal level of SEAP induction for that compound (EC<sub>50</sub>). TLR7 activity for compounds

of the present invention was assessed using the human TLR7 assay and the results are shown in Table 1 below wherein the degree of TLR7 activation for each compound is expressed as a pEC<sub>50</sub> value.

Table 1

| Ex. No. | pEC50 | Ex. No. | pEC50 | Ex. No. | pEC50 |
|---------|-------|---------|-------|---------|-------|
| 1       | 5.7   | 15      | 6.9   | 29      | 6.5   |
| 2       | 5.9   | 16      | 7.3   | 30      | 7     |
| 3       | 7.2   | 17      | 5.5   | 31      | 7     |
| 4       | 7.2   | 18      | 5.7   | 32      | 6.6   |
| 5       | 6.9   | 19      | 7.2   | 33      | 6.6   |
| 6       | 7     | 20      | 6.9   | 34      | 5.7   |
| 7       | 6.2   | 21      | 6.5   | 35      | 6.5   |
| 8       | 6.3   | 22      | 5.9   | 36      | 7.3   |
| 9       | 7.2   | 23      | 5.6   | 37      | 8.1   |
| 10      | 7.1   | 24      | 5.3   | 38      | 8.2   |
| 11      | 8.6   | 25      | 6.1   | 39      | 8.4   |
| 12      | 7.2   | 26      | 6.2   | 40      | 7.7   |
| 13      | 7     | 27      | 6.4   |         |       |
| 14      | 8     | 28      | 5.9   |         |       |

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier. The pharmaceutical composition may be used in the treatment of cancer. The composition may be in a form suitable for oral administration, for example as a tablet or capsule; for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository.

The compound of Formula (I), or a pharmaceutically acceptable salt thereof, could also be administered as an air spray for inhalation. The air spray (e.g., spray, aerosol, dry powder preparation, etc.) could be optionally formulated as an aqueous solution or suspension, or as an aerosol delivered from a pressurized pack such as a pressurised metered dose inhaler by using, for example, a liquefied propellant. A dry powder preparation may also be used. An aerosol appropriate for inhalation may be either a suspension or solution, and would typically contain the compound of Formula (I), or a

pharmaceutically acceptable salt thereof, and any appropriate propellants such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or a mixture thereof. Specifically, it may contain hydrofluoroalkane, particularly 1,1,1,2-tetrafluoroethane, heptafluoroalkane (HFA) such as 1,1,1,2,3,3,3-heptafluoro-n-propane, or a mixture thereof. An aerosol may optionally contain an additional preparation excipient well-known to those skilled in the art such as surfactant (e.g., oleic acid or lecithin) and cosolvent (e.g., ethanol), etc. Specifically, an aerosol preparation could be delivered using the inhaler known as "Turbuhaler™".

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compound of Formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m<sup>2</sup> body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of

active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

As used herein, the term "treatment" is intended to have its normal everyday meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology.

As used herein, the term "prophylaxis" is intended to have its normal everyday meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

The compounds defined in the present invention are effective activators of TLR7 *in vitro*. Accordingly, the compounds of the present invention are expected to be potentially useful agents in the treatment of diseases or medical conditions mediated alone or in part by TLR7. For example, the following diseases and conditions listed in paragraphs 1 to 8 below may be treatable with compounds of the present invention.

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and

- chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and
- 5 iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
2. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous
- 10 dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-
- 15 Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;
3. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune, degenerative
- 20 or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;
4. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-
- 25 vaginitis; Peyronie's disease; erectile dysfunction (both male and female);
5. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;
6. other auto-immune and allergic disorders including rheumatoid arthritis, irritable
- 30 bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic

thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome;

7. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

8. infectious diseases: virus diseases such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus, molluscum contagiosum, variola, human immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus (CMV), varicella zoster virus (VZV), rhinovirus, adenovirus, coronavirus, influenza, para-influenza; bacterial diseases such as tuberculosis and mycobacterium avium, leprosy; other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection and leishmaniasis.

It is envisaged that for the methods of treatment mentioned herein, the compound of Formula (I) will be administered to a mammal, more particularly a human being. Similarly, for the uses of a compound of Formula (I) for the treatment of diseases or medical conditions mentioned herein, it is envisaged that the compound of Formula (I) will be administered to a mammal, more particularly a human being.

According to a another aspect of the invention, there is therefore provided a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a further aspect of the invention, there is provided a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof for use in the treatment of a disease mediated through TLR7. In one embodiment of the invention, said disease mediated through TLR7 is cancer. In a further embodiment of the invention, said cancer is selected from prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors. In one embodiment of the invention, said disease mediated through TLR7 is asthma, COPD,

allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

According to a further aspect of the invention, there is provided the use of a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a disease mediated through TLR7. In one embodiment of the invention, said disease mediated through TLR7 is cancer. In a further embodiment of the invention, said cancer is selected from prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors. In one embodiment of the invention, said disease mediated through TLR7 is asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

According to a further aspect of the invention, there is provided the use of a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cancer. In one embodiment of the invention, said cancer is selected from prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors.

According to a further aspect of the invention, there is provided the use of a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

In one aspect of the invention there is provided the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.

According to a further aspect of the invention, there is provided a method of using a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for the treatment of cancer. In one embodiment of the invention, said cancer is selected from prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors.

According to a further aspect of the invention, there is provided a method of using a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for the treatment of asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

5 According to a further aspect of the invention, there is provided a method of treating a human suffering from a disease in which activation of TLR7 is beneficial, comprising the steps of administering to a person in need thereof of a therapeutically effective amount of a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof. In one embodiment of the invention, the disease  
10 in which activation of TLR7 is beneficial is cancer. In a further embodiment of the invention, said cancer is selected from prostate cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, ovarian cancer, colon cancer, stomach cancer, skin cancer, cerebral tumor, malignant myeloma and lymphoproliferative tumors. In one embodiment of the invention, the disease in which activation of TLR7 is beneficial  
15 is asthma, COPD, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, hepatitis B, hepatitis C, HIV, HPV, bacterial infections or dermatosis.

In any aspect or embodiment described herein the cancer may be prostate cancer.

In any aspect or embodiment described herein the cancer may be breast cancer.

In any aspect or embodiment described herein the cancer may be lung cancer.

20 In any aspect or embodiment described herein the cancer may be uterus cancer.

In any aspect or embodiment described herein the cancer may be pancreatic cancer.

In any aspect or embodiment described herein the cancer may be liver cancer.

In any aspect or embodiment described herein the cancer may be renal cancer.

In any aspect or embodiment described herein the cancer may be ovarian cancer.

25 In any aspect or embodiment described herein the cancer may be colon cancer.

In any aspect or embodiment described herein the cancer may be stomach cancer.

In any aspect or embodiment described herein the cancer may be skin cancer.

In any aspect or embodiment described herein the cancer may be cerebral tumor.

30 In any aspect or embodiment described herein the cancer may be malignant myeloma cancer.

In any aspect or embodiment described herein the cancer may be lymphoproliferative tumors.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

- 5 (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, 10 cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimetotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like 15 etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH 20 agonists (for example goserelin, leuporelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 $\alpha$ -reductase such as finasteride;
- (iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2- 25 chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, **47**, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];
- (iv) inhibitors of growth factor function: for example such inhibitors include growth 30 factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin<sup>TM</sup>], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor

antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as

- 5 *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), crbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin
- 10 growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3
- 15 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial
- 20 growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212),
- 25 compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin)];
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669,
- 30 WO 01/92224, WO 02/04434 and WO 02/08213;
- (vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme  
5 pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines  
10 such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies, approaches to decrease the function of immune suppressive cells such as regulatory T cells, myeloid-derived suppressor cells or  
15 IDO (indoleamine 2,3,-deoxygenase)-expressing dendritic cells, and approaches using cancer vaccines consisting of proteins or peptides derived from tumour-associated antigens such as NY-ESO-1, MAGE-3, WT1 or Her2/neu.

According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional  
20 anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

According to this aspect of the invention there is provided a combination suitable for use in the treatment of cancer comprising a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, and any one of the anti tumour agents listed under (i) – (ix) above.

25 Therefore in a further aspect of the invention there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above.

Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention  
30 “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential

28

or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

According to another feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above, in the manufacture of a medicament for use in cancer in a warm-blooded animal, such as man.

According to another feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above for use in the treatment of cancer in a warm-blooded animal, such as man.

Therefore in an additional feature of the invention, there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above.

According to a further aspect of the present invention there is provided a kit comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with an anti-tumour agent selected from one listed under (i) – (ix) herein above.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
- b) an anti-tumour agent selected from one listed under (i) – (ix) herein above; in a second unit dosage form; and
- 5 c) container means for containing said first and second dosage forms.

In one aspect of the invention the compounds of Formula (I) may be useful as vaccine adjuvants.

As a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein, for use as a vaccine adjuvant.

10 As a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein, as a vaccine adjuvant, in the manufacture of a vaccine for the treatment of a disease or condition.

The invention still further provides a method of treating, or reducing the risk of, a disease or condition, which method comprises administering to a patient in need thereof a therapeutically effective amount of a vaccine and a compound of formula (I), or a

15 pharmaceutically acceptable salt thereof, as defined herein.

The invention still further provides a method of increasing the response to a vaccine in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a vaccine and a compound of formula (I), or a

20 pharmaceutically acceptable salt thereof, as defined herein.

### Examples

The invention will now be illustrated with the following Examples in which generally, unless stated otherwise, all starting materials are commercially available. All

25 solvents and commercial reagents used in the Examples were of laboratory grade and were used as received. All operations were carried out at ambient temperature, *i.e.* in the range 17 to 28°C, typically 20°C, and where appropriate, under an atmosphere of an inert gas such as nitrogen. 'Microwave' heating refers to heating to constant temperature, using variable power microwave irradiation in a CEM Discover<sup>TM</sup> microwave reactor.

30 Hydrogenation reactions were carried out using a Büchi Peterlic<sup>TM</sup> system or a ThalesNano H-Cube<sup>TM</sup> system, as detailed. Concentration of all solutions was carried out by

evaporation under reduced pressure (*in vacuo*), *e.g.* using a Büchi Rotavapor<sup>TM</sup> rotary evaporator.

Thin Layer Chromatography (TLC) was carried out using aluminium- or glass-backed plates coated with silica (particle size <63 µm; porosity 60 Å; surface area ~500 m<sup>2</sup>/g), with a fluorescent (UV<sub>254</sub>) indicator. Following elution, the plates were visualized by either UV<sub>254</sub> irradiation, or developed with a suitable indicator, such as iodine (pre-absorbed onto silica), an aqueous solution of potassium permanganate, or an aqueous solution of cerium (IV) ammonium nitrate. Examples of indicator preparations can be found in 'Experimental Organic Chemistry: Preparative and Microscale' 2<sup>nd</sup> Ed. (Harwood, L., Moody, C. and Percy, J.), WileyBlackwell, 1998.

Analytical HPLC was carried out using either a Waters XBridge<sup>TM</sup> C8 3.5 µm column eluting with a gradient of MeCN in either 0.1% aqueous trifluoroacetic acid, 0.1% aqueous formic acid, 0.1% aqueous ammonium acetate or 0.1% aqueous NH<sub>3</sub>; a Waters XBridge<sup>TM</sup> C18 3.5 µm column with a gradient of MeCN in 0.1% aqueous NH<sub>3</sub>; a Waters Symmetry<sup>TM</sup> C18 3.5 µm column with a gradient of MeCN in 0.1% aqueous trifluoroacetic acid; a Waters Sunfire<sup>TM</sup> C8 3.5 µm column with a gradient of MeCN in 0.1% aqueous trifluoroacetic acid; or a Phenomenex Gemini<sup>TM</sup> C18 3 µm column with a gradient of MeCN in 0.1% aqueous trifluoroacetic acid. UV spectra of the eluted peaks were measured using a diode array on an Agilent 1100<sup>TM</sup> system, or equivalent.

Medium pressure liquid chromatography (MPLC) on silica (particle size <63 µm; porosity 60 Å; surface area ~500 m<sup>2</sup>/g) was carried out using pre-packed Biotage FLASH<sup>TM</sup> columns or equivalent, *e.g.* Thomson SINGLE StEP<sup>TM</sup>, Biotage Isolute<sup>TM</sup>, Teledyne Isco RediSep<sup>TM</sup>, or Silicycle UltraPure silica columns at recommended solvent flow rates and sample loadings. Fraction purity was determined by either TLC or analytical HPLC.

Preparative HPLC was carried out using either a Phenomenex Gemini<sup>TM</sup> C18 5 µm column, a Waters Sunfire<sup>TM</sup> C18 5 µm column, a Waters XBridge<sup>TM</sup> C8 5 µm column or a Waters XTerra<sup>TM</sup> 5 µm, unless otherwise detailed, using either MeCN in aqueous 0.1-0.2% trifluoroacetic acid, MeCN in aqueous 0.1-0.2% ammonium acetate, or MeCN in an aqueous 0.1-0.2% NH<sub>3</sub> solution as eluent, as detailed. Fractions were collected following detection by UV spectroscopy at a wavelength such as 220 or 254 nm. Fraction purity was determined by either TLC or analytical HPLC.

Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on Bruker Avance 600 (600 MHz), a Bruker DRX 500 (500 MHz) or a Varian UnityInova 500 MHz, 400 MHz or 300 MHz instrument. Either the central peaks of chloroform-*d* ( $\text{CDCl}_3$ ;  $\delta_{\text{H}}$  7.27 ppm), dimethylsulfoxide-*d*<sub>6</sub> ( $\text{d}_6$ -DMSO;  $\delta_{\text{H}}$  2.50 ppm) or an internal standard of tetramethylsilane (TMS;  $\delta_{\text{H}}$  0.00 ppm) were used as references. Unless otherwise specified,  $^1\text{H}$  NMR spectra were determined using deuterated DMSO. The following abbreviations are used for NMR data: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, tt = triplet of triplets, br = broad, quintet = qn. Mass spectra were recorded on an Agilent MSD or similar equipment (+ve and -ve APCI and/or electrospray (unless otherwise stated: in "multimode +")) following analytical HPLC.

All other processes were carried out using standard laboratory techniques, *e.g.* as detailed in 'Experimental Organic Chemistry: Preparative and Microscale' 2<sup>nd</sup> Ed. (Harwood, L., Moody, C. and Percy, J.), WileyBlackwell, 1998.

The following abbreviations may be used in the scientific parts of this specification:

EtOAc = ethyl acetate; DCM = dichloromethane; NMP = *N*-methylpyrrolidinone; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; THF = tetrahydrofuran; MeOH = methanol; EtOH = ethanol; MeCN = acetonitrile; Pd/C = palladium on carbon; DMAP = 4-dimethylaminopyridine; sat. = saturated; aq. = aqueous; DMA = *N,N*-dimethylacetamide; conc. = concentrated; r.t. = room temperature; h = hours; min(s) = mins.; M = molar; MS = mass spectrometry; APCI = atmospheric chemical ionisation method; ESI = electron spray ionisation method; SCX = Solid phase extraction with a sulfonic acid sorbent; HPLC = High performance liquid chromatography; RPHPLC = Reverse-phase high performance liquid chromatography; FCC = flash column chromatography using silica; DIPEA = diisopropylethylamine.

**Example 1: 5-(4-Methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

**(i) 2-(4-Methoxy-benzyl)-3-oxo-butyric acid ethyl ester**

Ethyl acetoacetate (11.7 mL) was added to a solution of 4-methoxy-benzaldehyde (10.0 g) in toluene (150 mL). Piperidine (0.80 mL) and acetic acid (2.30 mL) were then added and the mixture was heated at reflux for 20 h. The solvent was then removed and the resulting orange oil was dissolved in EtOH (0.30 L) and 10% Pd/C (0.50 g) was added and stirred under  $\text{H}_2$  (2 bar) for 3 h. The reaction mixture was filtered through diatomaceous earth (Celite<sup>TM</sup>) and the solvent removed by evaporation. The crude product was purified by

FCC to give the subtitle compound as an oil (12.7 g); <sup>1</sup>H NMR: 7.19 (1H, t), 6.75 (3H, m), 4.15 (2H, q), 3.78 (4H, m), 3.13 (2H, d), 2.20 (3H, s), 1.26 (3H, t); LC-MS *m/z* 249 ESI.

(ii) 2-Amino-5-(4-methoxy-benzyl)-6-methyl-pyrimidin-4-ol

Guanidium carbonate (3.90 g) was added to a solution of the product from step (i) (5.30 g) in ethanol (50.0 mL) and heated at 80°C for 15 h. After cooling the product was filtered off as a solid, this was suspended in water and collected by filtration, washed with EtOAc and dried to give the subtitle compound (3.40 g); <sup>1</sup>H NMR: 10.83 (1H, s), 7.08 (2H, d), 6.79 (2H, d), 6.34 (2H, s), 3.69 (3H, s), 3.56 (2H, s), 2.00 (3H, s); LC-MS *m/z* 246 ESI.

(iii) 4-Chloro-5-(4-methoxy-benzyl)-6-methyl-pyrimidin-2-ylamine

The product of step (ii) (1.00 g) was added to POCl<sub>3</sub> (10.0 mL) and the mixture was heated at 100°C for 15 h. The solvent was removed and the residue diluted with water and adjusted to pH 7 with sat NaHCO<sub>3</sub>. This mixture was heated at 50°C for 2 h, then extracted with EtOAc, dried and solvent removed to give the subtitle compound as a white solid (0.71 g); <sup>1</sup>H NMR: 7.02 (2H, d), 6.85 (2H, d), 6.84 (2H, s), 3.88 (2H, s), 3.71 (3H, s), 2.21 (3H, s); LC-MS *m/z* 263 ESI.

(iv) 5-(4-Methoxy-benzyl)-6-methyl-N<sup>4</sup>-pentyl-pyrimidine-2,4-diamine

To the product of step (iii) (3.00 g) in dioxane (30.0 mL), pentylamine (5.30 mL) was added and the mixture was heated at 100°C for 48 h. The solvent was removed and the residue was dissolved in EtOAc and washed with sat. NaHCO<sub>3</sub>, dried and solvent removed.

The crude compound was purified by FCC to give the title compound as a white solid (2.30 g); <sup>1</sup>H NMR: 7.02 (2H, d), 6.81 (2H, d), 6.31-6.22 (1H, m), 5.83 (2H, s), 3.69 (3H, s), 3.66 (2H, s), 3.25 (2H, q), 2.03 (3H, s), 1.43 (2H, q), 1.28-1.06 (4H, m), 0.81 (3H, t); LC-MS *m/z* 315.

Example 2: 4-(2-Amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)-phenol

A solution of BBr<sub>3</sub> (1M in DCM, 14.6 mL) was added to a solution of the product of Example 1 (2.30 g) in DCM at 0°C and stirred for 1 h. Ice and water were added and the mixture was stirred for 30 min, then the organic phase was separated, the aqueous layer was extracted with EtOAc, and the combined organics were dried and the solvent was removed by evaporation. The crude product was purified by FCC to give the title compound as a cream solid (1.11 g); <sup>1</sup>H NMR: 11.96 (1H, s), 7.57 (1H, s), 7.07 (2H, s), 6.93 (2H, d), 6.67 (2H, d), 3.69 (2H, s), 3.38-3.32 (2H, m), 2.16 (3H, s), 1.46 (2H, q), 1.27-1.18 (2H, m), 1.15-1.07 (2H, m), 0.82 (3H, t); LC-MS *m/z* 301.

**Example 3: 5-(4-(2-(Dimethylamino)ethoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

To a suspension of the product of Example 2 (0.10 g) in DMF (2.00 mL), Cs<sub>2</sub>CO<sub>3</sub> (0.24 g) was added and stirred at r.t. for 30 min. A mixture of 2-dimethylaminoethylchloride hydrochloride (0.096 g), Cs<sub>2</sub>CO<sub>3</sub> (0.24 g) and NaI (0.05 g) was also stirred for 30 min and the two mixtures combined and heated at 110°C for 2 h. The reaction was filtered, diluted with water, extracted with EtOAc, dried and the solvent removed. The crude product was purified by RPHPLC to afford the title compound as a colourless oil (0.035 g); <sup>1</sup>H NMR: 7.00 (2H, d), 6.81 (2H, d), 6.04 (1H, t), 5.62 (2H, s), 3.97 (2H, t), 3.65 (2H, s), 3.24 (2H, q), 2.57 (2H, t), 2.19 (6H, s), 2.01 (3H, s), 1.43 (2H, qn), 1.27-1.08 (4H, m), 0.81 (3H, t); LC-MS *m/z* 372.

**Example 4: 5-(4-(3-(Dimethylamino)propoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using dimethylamino-propylchloride hydrochloride (0.105g) to give the product as a colourless oil (0.039 g); <sup>1</sup>H NMR: 7.02 (2H, d), 6.81 (2H, d), 6.53 (1H, s), 6.10 (2H, s), 3.93 (2H, t), 3.68 (2H, s), 3.30-3.24 (2H, m), 2.53-2.48 (2H, m), 2.27 (6H, s), 2.06 (3H, s), 1.86 (2H, qn), 1.43 (2H, qn), 1.26-1.06 (4H, m), 0.81 (3H, t); LC-MS *m/z* 386.

**Example 5: 6-Methyl-*N*<sup>4</sup>-pentyl-5-(4-(2-(piperidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using *N*-(2-chloroethyl)-piperidine hydrochloride (0.12 g) to give the product as a white solid (0.058 g); <sup>1</sup>H NMR: 7.00 (2H, d), 6.81 (2H, d), 6.03 (1H, t), 5.61 (2H, s), 3.98 (2H, t), 3.65 (2H, s), 3.23 (2H, q), 2.60 (2H, t), 2.42-2.37 (4H, m), 2.01 (3H, s), 1.50-1.33 (8H, m), 1.26-1.18 (2H, m), 1.16-1.07 (2H, m), 0.81 (3H, t); LC-MS *m/z* 412.

**Example 6: 6-Methyl-*N*<sup>4</sup>-pentyl-5-(4-(2-(pyrrolidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using *N*-(2-chloroethyl)-pyrrolidine hydrochloride (0.115g) to give the product as a colourless oil (0.035 g). <sup>1</sup>H NMR: 7.00 (2H, d), 6.81 (2H, d), 6.04 (1H, t), 5.61 (2H, s), 3.99 (2H, t), 3.65 (2H, s), 3.24 (2H, q), 2.74 (2H, t), 2.37-2.20 (4H, m), 2.02 (3H, s), 1.69-1.63 (4H, m), 1.48-1.37 (2H, m), 1.27-1.08 (4H, m), 0.81 (3H, t); LC-MS *m/z* 398.

**Example 7: 5-(4-(2-(Benzyl(methyl)amino)ethoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentyl-pyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using *N*-(2-chloroethyl)-*N*-methylbenzylamine hydrochloride (0.147 g) to give the product as a colourless oil (0.032 g); <sup>1</sup>H NMR: 7.35-7.18 (5H, m), 7.00 (2H, d), 6.81 (2H, d), 6.05 (1H, t), 5.62 (2H, s), 4.10-4.01 (2H, m), 3.65 (2H, s), 3.55 (2H, s), 3.24 (2H, q), 2.70 (2H, t), 2.21 (3H, s), 2.01 (3H, s), 1.43 (2H, qn), 1.27-1.09 (4H, m), 0.81 (3H, t); LC-MS *m/z* 448.

**Example 8: 3-(4-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-phenoxy)propan-1-ol**

To a suspension of the product of Example 2 (0.35 g) in DMF (10.0 mL), Cs<sub>2</sub>CO<sub>3</sub> (0.25 g) was added and the mixture was stirred at r.t. for 30 min. 3-Bromo-1-propanol (0.158 mL) and NaI (0.05 g) were added and the mixture was heated at 100°C for 9 h. The reaction was diluted with water, extracted with EtOAc, dried and the solvent removed. The crude product was purified by FCC eluting with 10:1 DCM-MeOH to afford the title compound as a colourless oil (0.24 g) which solidified upon standing; <sup>1</sup>H NMR: 7.00 (2H, d), 6.80 (2H, d), 6.05 (1H, t), 5.62 (2H, s), 4.50 (1H, t), 3.96 (2H, t), 3.64 (2H, s), 3.53 (2H, q), 3.24 (2H, q), 2.01 (3H, s), 1.82 (2H, qn), 1.43 (2H, qn), 1.28-1.17 (2H, m), 1.17-1.07 (2H, m), 0.82 (3H, t); LC-MS *m/z* 359.

**Example 9: 6-Methyl-*N*<sup>4</sup>-pentyl-5-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)pyrimidine-2,4-diamine**

**(i) 5-(4-(3-Chloropropoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

To a solution the product of Example 8 (0.32 g) in DCM (5 mL), SOCl<sub>2</sub> (0.5 mL) was added and the solution was stirred at r.t. for 36 h. The solvent was removed and the crude material was purified by FCC eluting with DCM and then 20:1 DCM-MeOH to give the subtitle compound as an orange oil (0.124 g); <sup>1</sup>H NMR: 7.88 (1H, t), 7.07 (2H, d), 6.87 (2H, d), 4.04 (2H, t), 3.79-3.74 (4H, m), 3.36-3.25 (2H, m), 2.20 (3H, s), 2.17-2.10 (2H, m), 1.51-1.43 (2H, m), 1.27-1.15 (2H, m), 1.12-1.02 (2H, m), 0.80 (3H, t).

**(ii) 6-Methyl-*N*<sup>4</sup>-pentyl-5-(4-(3-(pyrrolidin-1-yl)propoxy)benzyl)pyrimidine-2,4-diamine**

To a suspension of triethylamine (0.09 mL), NaI (0.01 g) and the product of step (i) (0.04 g) in DMF (2 mL) was added pyrrolidine (0.027 mL). The mixture was heated at 80°C for 15 h, then cooled to r.t., diluted with water, extracted with EtOAc, dried and the solvent removed. The crude product was purified by RPHPLC to afford the title compound as an

orange oil (7 mg); <sup>1</sup>H NMR: 7.86 (s, 1H), 7.41 (s, 2H), 7.07 (d, 2H), 6.86 (d, 2H), 4.00 (t, 2H), 3.76 (s, 2H), 3.22 (t, 2H), 3.17 (s, 2H), 2.19 (s, 3H), 2.15-2.06 (m, 2H), 2.02-1.83 (m, 4H), 1.30-1.15 (m, 4H), 1.15-1.03 (m, 6H), 0.81 (t, 3H); LC-MS *m/z* 412.

**Example 10: 6-Methyl-5-(4-(3-(4-methylpiperazin-1-yl)propoxy)benzyl)-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 9 step (ii) using the product of Example 9 step (i) (0.04 g) and 1-methylpiperazine (0.0354 mL) to give the product as a yellow oil (9 mg); <sup>1</sup>H NMR 7.00 (2H, d), 6.79 (2H, d), 6.02 (1H, t), 5.61 (2H, s), 3.92 (2H, t), 3.64 (2H, s), 3.23 (2H, q), 2.42-2.24 (10H, m), 2.13 (3H, s), 2.01 (3H, s), 1.81 (2H, qn), 1.42 (2H, qn), 1.28-1.16 (2H, m), 1.16-1.06 (2H, m), 0.81 (3H, t); LC-MS *m/z* 441.

**Example 11: 5-(4-(3-(Dimethylamino)propoxy)-2-methoxybenzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

**(i) 4-(3-(Dimethylamino)propoxy)-2-methoxybenzaldehyde**

3-Dimethylaminopropylchloride hydrochloride (2.493 g) and NaI (0.394 g) were added to 4-hydroxy-2-methoxybenzaldehyde (2 g) and Cs<sub>2</sub>CO<sub>3</sub> (12.85 g) in DMF (50 mL). The resulting suspension was stirred at 100°C for 1 h. The reaction mixture was filtered and diluted with EtOAc (100 mL). The organic phase was washed with water and brine, dried, filtered and concentrated by evaporation to afford the subtitle compound as a yellow oil (2.23 g); <sup>1</sup>H NMR: 10.17 (1H, s), 7.65 (1H, d), 6.67 (1H, d), 6.64 (1H, dd), 4.12 (2H, t), 3.90 (3H, s), 2.35 (2H, t), 2.14 (6H, s), 1.87 (2H, qn).

**(ii) Ethyl 2-(4-(3-(dimethylamino)propoxy)-2-methoxybenzylidene)-3-oxobutanoate**

Ethyl acetoacetate (1.489 mL), piperidine (0.047 mL) and acetic acid (0.145 mL) were added to a solution of the product from step (i) (2.23 g) in toluene (50 mL), and the mixture was stirred at 110°C for 5 days. The solvent was removed under reduced pressure to afford the subtitle compound (3.57 g) that was used in the next step without purification.

**(iii) Ethyl 2-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-3-oxobutanoate**

A suspension of the product from step (ii) (3.57 g) and 10% Pd/C (0.2 g) in EtOH (50 mL) was hydrogenated under 3 bar at r.t. for 16 h. The reaction mixture was filtered through diatomaceous earth (Celite<sup>TM</sup>) and the filtrate was concentrated by evaporation. The crude product was purified by FCC eluting with 0-10% MeOH in EtOAc to afford the subtitle compound (1.25 g) as a yellow oil; <sup>1</sup>H NMR: 6.95 (1H, d), 6.51 (1H, d), 6.40 (1H, dd),

4.10-4.00 (2H, m), 3.96 (2H, t), 3.83 (1H, t), 3.77 (3H, s), 3.01-2.81 (2H, m), 2.34 (2H, t), 2.14 (9H, s), 1.82 (2H, qn), 1.12 (3H, t).

(iv) 2-Amino-5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ol

5 Guanidine carbonate (0.716 g) was added in one portion to a solution of the product from step (iii) (1.25 g) in EtOH (20 mL) and the mixture was stirred at 80°C for 15 h. The solvent was evaporated, the residue diluted with EtOAc (20 mL), washed with water, dried and evaporated. The residue was suspended in hexane-EtOAc (5:1; 20 mL) and the solid was collected by filtration to afford the subtitle compound as a pale yellow solid (0.87 g);  
10 <sup>1</sup>H NMR: 6.72 (d, 1H), 6.60 (s, 2H), 6.48 (d, 1H), 6.35 (dd, 1H), 3.93 (t, 2H), 3.78 (s, 3H), 3.46 (s, 2H), 2.33 (t, 2H), 2.13 (s, 6H), 1.90 (s, 3H), 1.84-1.78 (m, 2H).

(v) 4-Chloro-5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-2-amine

The subtitle compound was prepared using the method of Example 1 step (iii) and the  
15 product of step (iv) to give a tan solid (0.71 g); <sup>1</sup>H NMR: 6.83 (s, 2H), 6.57 (d, 1H), 6.54 (d, 1H), 6.41 (dd, 1H), 4.00 (t, 2H), 3.81 (s, 3H), 3.75 (s, 2H), 3.05-2.95 (m, 2H), 2.63 (s, 6H), 2.15 (s, 3H), 2.11-2.01 (m, 2H).

(vi) 5-(4-(3-(Dimethylamino)propoxy)-2-methoxybenzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine

20 Amylamine (0.127 mL) was added to a solution of the product from step (v) (100 mg) in NMP (2 mL) and stirred at 150°C for 15 h. The mixture was diluted with EtOAc (10 mL) washed with sat. NaHCO<sub>3</sub> (10 mL), water (10 mL), and sat. brine (10 mL) dried, and the solvent removed by evaporation. The crude product was purified by RPHPLC and then trituration with diethyl ether gave the title compound as a white solid (8 mg); <sup>1</sup>H NMR:  
25 6.60 (d, 1H), 6.53 (d, 1H), 6.37 (dd, 1H), 5.86 (t, 1H), 5.61 (s, 2H), 3.93 (t, 2H), 3.82 (s, 3H), 3.52 (s, 2H), 3.21 (q, 2H), 2.35-2.30 (m, 2H), 2.12 (s, 6H), 1.98 (s, 3H), 1.80 (q, 2H), 1.46-1.36 (m, 2H), 1.28-1.18 (m, 2H), 1.17-1.08 (m, 2H), 0.82 (t, 3H); LC-MS *m/z* 416.

The title compound can also be made by the following method:

Methanesulfonyl chloride (0.040 mL) was added to the mixture of the product from  
30 Example 36 (0.17 g) and triethylamine (0.072 mL) in THF (5 mL) at 0°C and the mixture was stirred for 30 min. Sat. NaHCO<sub>3</sub> was added and the mixture was extracted twice with CHCl<sub>3</sub>, then the combined organic layers were dried and concentrated. The residue was

dissolved in DMF (5 mL), then dimethylamine (40% aq. solution, 2 mL) was added and the mixture was stirred at r.t. for 18 h. The mixture was then treated with 4% NH<sub>3</sub> solution and brine and extracted twice with EtOAc. The combined organic layers were washed twice with brine, dried and concentrated. The residue was purified by FCC to give the title compound as a white solid (0.10 g); <sup>1</sup>H NMR: 6.61 (d, 1H), 6.53 (d, 1H), 6.37 (dd, 1H), 6.18 (br t, 1H), 5.91 (brs, 2H), 3.94 (t, 2H), 3.82 (s, 3H), 3.53 (s, 2H), 3.22 (q, 2H), 2.42 (t, 2H), 2.20 (s, 6H), 2.00 (s, 3H), 1.85 (tt, 2H), 1.42 (tt, 2H), 1.24 (m, 2H), 1.13 (m, 2H), 0.82 (t, 3H); LC-MS *m/z* 415 ESI.

**Example 12: Methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate**

**(i) Methyl 4-(2-(ethoxycarbonyl)-3-oxobutyl)-3-methoxybenzoate**

NaH (60% in mineral oil, 1.45 g) was added portionwise over 10 min to a solution of ethyl acetoacetate (4.4 mL) in THF (60 mL) at 0°C and the mixture was stirred for 10 min. A solution of methyl 4-(bromomethyl)-3-methoxybenzoate (7.5 g) in THF (40 mL) was added and the mixture was warmed to 70°C and stirred for 15 h. The reaction was poured into ice/water (300 mL) and stirred for 30 min. The aqueous mixture was extracted with EtOAc, dried and concentrated by evaporation to afford the subtitle compound. The reaction was repeated on an identical scale. The two batches of crude product were combined and purified by FCC eluting with 8:2 to 7:3 isohexane-EtOAc to afford the subtitle compound as a colourless oil (14.7 g); <sup>1</sup>H NMR: 7.48 (dd, 1H), 7.45 (d, 1H), 7.24 (d, 1H), 4.05 (q, 2H), 3.95 (dd, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.10 (dd, 1H), 3.00 (dd, 1H), 2.17 (s, 3H), 1.09 (t, 3H).

**(ii) Methyl 4-((2-amino-4-hydroxy-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate**

The subtitle compound was formed using the method of Example 1 step (ii) and the product from step (i) (14.7 g) to give the subtitle compound as a colourless solid (8.6 g), which was used without further purification; <sup>1</sup>H NMR: 10.78 (s, 1H), 7.46 (d, 1H), 7.45 (s, 1H), 6.98 (d, 1H), 6.34 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.61 (s, 2H), 1.93 (s, 3H); LC-MS *m/z* 304.

**(iii) Methyl 4-((2-amino-4-chloro-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate**

The subtitle compound was formed using the method of Example 1 step (iii) and the product from step (ii) (8.6 g) to give the subtitle compound as a colourless solid (9.05 g),

which was used without further purification; <sup>1</sup>H NMR: 7.50 (s, 2H), 7.49 (d, 1H), 6.90 (s, 1H), 6.81 (d, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.84 (s, 2H), 2.16 (s, 3H).

(iv) Methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate

5 Pentylamine (7.22 mL) was added to a solution of the product of step (iii) (5 g) in NMP (80 mL) and the mixture was stirred at 150°C for 15 h. The reaction mixture was cooled, diluted with EtOAc (200 mL), washed with water (3 × 200 mL), brine (100 mL), dried and concentrated by evaporation. The residue was suspended in diethyl ether (20 mL) and the solid produced was collected by filtration to give the title compound as a colourless solid  
10 (1.21 g); <sup>1</sup>H NMR 7.48 (d, 1H), 7.45 (dd, 1H), 6.81 (d, 1H), 6.07 (t, 1H), 5.68 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H), 3.68 (s, 2H), 3.25-3.20 (m, 2H), 1.93 (s, 3H), 1.47-1.38 (m, 2H), 1.27-1.08 (m, 4H), 0.81 (t, 3H); LC-MS *m/z* 373.

Example 13: (S)-Methyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate

15 (S)-Methyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate  
(S)-2-Aminopentan-1-ol (0.769 g) was added to a solution of the product from Example 12 step (iii) (1.2 g) in NMP (20 mL) and the mixture was stirred at 120°C for 60 h. The reaction mixture was then cooled, diluted with EtOAc (50 mL), washed with saturated  
20 NaHCO<sub>3</sub> (2 × 50 mL), brine (50 mL), dried and concentrated by evaporation. The crude product was purified by FCC eluting with 20:1 to 10:1 DCM-MeOH to produce an orange oil (0.475 g). A 100 mg sample was further purified by RPHPLC to give the title compound as an orange gum (15 mg); <sup>1</sup>H NMR: 7.48 (d, 1H), 7.46 (dd, 1H), 6.89 (d, 1H), 5.68 (s, 2H), 5.50 (d, 1H), 4.58-4.48 (m, 1H), 4.17-4.05 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H),  
25 3.70 (s, 2H), 3.39-3.20 (m, 2H), 1.99 (s, 3H), 1.54-1.39 (m, 1H), 1.33-1.20 (m, 1H), 1.16-1.02 (m, 2H), 0.76 (t, 3H); LC-MS *m/z* 389.

Example 14: (S)-Methyl 4-((2-amino-4-(1-hydroxyheptan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate

30 (i) (E)-tert-Butyl hept-2-enoate

To a solution of valeraldehyde (5.81 g) in THF (100 mL) was added *tert*-butoxycarbonylmethylenetriphenylphosphorane (25.4 g) and the mixture was stirred for 16 h at r.t. The

solvents were removed by evaporation and the resulting residue was slurried in diethyl ether and then the mixture was filtered. The filtrate was concentrated by evaporation and the residue was purified by FCC eluting with 97:3 isohexane-EtOAc to give the subtitle compound (8.5 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.86 (dt, 1H), 5.73 (dt, 1H), 2.25-2.09 (m, 2H), 1.47 (s, 9H), 1.47-1.27 (m, 4H), 0.90 (t, 3H).

(ii) (S)-tert-Butyl 3-(benzyl((S)-1-phenylethyl)amino)heptanoate

*n*-Butyllithium (2.5 M in hexanes, 27.66 mL) was added to a stirred solution of (S)-*N*-benzyl-1-phenylethanamine (15.59 g) in THF (150 mL) at -78°C. The reaction mixture was stirred for 30 min then the product from step (i) (8.5 g) in THF (50 mL) was added and the reaction mixture was stirred for 2h at -78°C. The mixture was quenched with sat. NH<sub>4</sub>Cl solution and warmed to r.t. The mixture was partitioned between EtOAc and water, the organic phase was washed with water, dried, and concentrated by evaporation. The residue was purified by FCC eluting with 95:5 isohexane-EtOAc to give the subtitle compound (12.7g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.49-7.15 (m, 10H), 3.87-3.70 (m, 2H), 3.48 (d, 1H), 3.35-3.21 (m, 1H), 1.99-1.78 (m, 2H), 1.53 (s, 3H), 1.39 (s, 9H), 1.36-1.14 (m, 6H), 0.88 (t, 3H); LC-MS *m/z* 396 ESI.

(iii) (S)-3-(Benzyl((S)-1-phenylethyl)amino)heptanoic acid

The product from step (ii) (12 g) was dissolved in DCM (40 mL) and trifluoroacetic acid (2 mL) and the resulting mixture was stirred for 24 h. The solvents were removed by evaporation to give the subtitle compound (17 g); LC-MS *m/z* 340 ESI.

(iv) (S)-3-(Benzyl((S)-1-phenylethyl)amino)heptan-1-ol

The product from step (iii) (12 g) was dissolved in THF (120 mL) and borane-THF complex (1 M in THF, 132.3 mL) was added dropwise. The mixture was then stirred at r.t. overnight then MeOH was added followed by 2 M HCl (20 mL). The mixture was concentrated by evaporation and the resulting residue was dissolved in MeOH and purified *via* SCX resin. The resulting residue was further purified *via* FCC eluting with 9:1 to 4:1 isohexane-EtOAc to give the subtitle compound (6 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.45-7.13 (m, 10H), 4.00-3.91 (m, 1H), 3.85 (d, 1H), 3.69 (d, 1H), 3.56-3.43 (m, 1H), 3.27-3.15 (m, 1H), 2.84-2.71 (m, 1H), 2.61 (s, 1H), 1.77-1.63 (m, 1H), 1.55 (s, 2H), 1.47-1.20 (m, 8H), 0.93 (t, 3H); LC-MS *m/z* 326 ESI.

(v) (S)-3-Aminoheptan-1-ol

A solution of the product from step (iv) (5 g) and 5% Pd/C (0.5 g) in EtOH (25 mL) was hydrogenated using a pressure of 5 bar at r.t. for 5 days. A further portion of 5% Pd/C (1.50 g) was then added, and the mixture was hydrogenated using a pressure of 5 bar at r.t. for a further 1 day. The reaction mixture was then filtered and the solvent removed by evaporation to give the subtitle compound (1.8 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.89-3.74 (m, 2H), 2.94-2.84 (m, 1H), 2.79-2.41 (m, 3H), 1.70-1.60 (m, 1H), 1.55-1.38 (m, 2H), 1.39-1.19 (m, 5H), 0.96-0.83 (m, 3H).

(vi) (S)-Methyl 4-((2-amino-4-(1-hydroxyheptan-3-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate

The title compound was prepared by the method of Example 13 using the product from Example 12 step (iii) (0.1 g) and the product of step (v) (0.08 g). The crude product was purified by RPHPLC to give the title compound as a colourless gum (9 mg); <sup>1</sup>H NMR: 7.49 (d, 1H), 7.46 (dd, 1H), 6.90 (d, 1H), 6.44-6.25 (m, 2H), 4.39-4.33 (m, 1H), 4.29-4.20 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.74 (s, 2H), 3.30-3.28 (m, 2H), 2.03 (s, 3H), 1.66-1.47 (m, 2H), 1.47-1.32 (m, 2H), 1.29-0.97 (m, 4H), 0.76 (t, 3H); LC-MS *m/z* 417.

**Example 15: (S)-4-(Dimethylamino)butyl 4-((2-amino-4-(1-hydroxypentan-2-yl-amino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate benzenesulfonate salt**

(i) (S)-4-((2-Amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoic acid

(S)-2-Amino-1-pentanol (192 mg) was added to a stirred suspension of the product of Example 12 step (iii) (0.30 g) in butan-1-ol (2 mL) and the mixture was heated in a microwave at 180°C for 2 h. 5M KOH (0.5 mL) was added and the mixture was then heated to 120°C over a period of 1 h in a microwave. The mixture was then concentrated by evaporation and the residue was diluted with MeOH (2 mL). Glacial acetic acid was added dropwise until the pH ~ 7 and the mixture was then purified by RPHPLC to give the subtitle compound as a colourless solid (53 mg); <sup>1</sup>H NMR: 7.47 (d, 1H), 7.41 (dd, 1H), 6.85 (d, 1H), 5.74 (s, 2H), 5.52 (d, 1H), 4.15-4.06 (m, 1H), 3.90 (s, 3H), 3.68 (s, 2H), 3.38-3.33 (m, 1H), 3.28-3.22 (m, 1H), 2.02 (s, 3H), 1.52-1.41 (m, 1H), 1.32-1.21 (m, 3H), 1.15-1.03 (m, 2H), 0.76 (t, 3H); LC-MS *m/z* 375.

(ii) (S)-4-(Dimethylamino)butyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoate benzene sulfonate

A solution of 1-propanephosphonic acid cyclic anhydride (0.35 mL) (1.57 M in THF) was added to a suspension of the product of step (i) (69 mg), triethylamine (0.077 mL), 4-(dimethylamino)-1-butanol (0.12 mL) and 4-dimethylaminopyridine (4.50 mg) in DMF (2 mL). The mixture was stirred at r.t. for 60 h and was then diluted with EtOAc (10 mL).

5 The solution was washed with water (2 × 10 mL) dried and concentrated by evaporation. The crude product was purified by RPHPLC to produce a colourless gum which was dissolved in MeCN (0.5 mL). Benzenesulphonic acid (7.9 mg) was added and the solvent was evaporated to give a residue which was triturated with diethyl ether to give the title compound as a colourless solid (27.0 mg); <sup>1</sup>H NMR: 7.61-7.58 (m, 1H), 7.48-7.45 (m, 3H),  
10 7.34-7.27 (m, 5H), 6.93 (d, 1H), 6.21-6.06 (m, 1H), 4.63-4.57 (m, 1H), 4.27 (t, 2H), 4.20-4.12 (m, 1H), 3.92 (s, 3H), 3.73 (s, 2H), 3.41-3.33 (m, 4H), 2.42 (s, 6H), 2.03 (s, 3H), 1.77-1.67 (m, 2H), 1.66-1.57 (m, 1H), 1.53-1.43 (m, 1H), 1.34-1.21 (m, 2H), 1.15-1.03 (m, 2H), 0.77 (t, 3H); LC-MS *m/z* 474.

**Example 16: Methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-methoxybenzoate**

**(i) Methyl 3-(bromomethyl)-4-methoxybenzoate**

Methyl 4-methoxy-3-methylbenzoate (16 g) was dissolved in EtOAc (100 mL) and then *N*-bromosuccinimide (18.96 g) and 2,2'-azobisisobutyronitrile (1 g) were added. The mixture was then heated to 80°C for 4 h. After cooling to r.t. sat. sodium thiosulfate solution was  
20 added, the organic phase was separated, washed with brine, dried and the solvents removed by evaporation. The crude product was dissolved in mixture of isohexane-EtOAc (9:1) and a solid was produced which was collected to give the subtitle compound (11.82 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.05-7.98 (m, 2H), 6.91 (d, 1H), 4.55 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H).  
LC-MS *m/z* 260.

**(ii) Methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-methoxybenzoate**

The title compound was prepared using the product from step (i) (11.82 g) and the method of Example 12 steps (i)-(iv) to give a solid product (2.0 g); <sup>1</sup>H NMR: 7.83 (d, 1H), 7.32 (s, 1H), 7.11 (d, 1H), 6.08 (s, 1H), 5.69 (s, 2H), 3.94 (s, 3H), 3.73 (s, 3H), 3.63 (s, 2H), 3.25-  
30 3.07 (m, 2H), 1.93 (s, 3H), 1.50-1.33 (m, 2H), 1.25-1.01 (m, 4H), 0.79 (t, 3H); LC-MS *m/z* 373.

**Example 17: Methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-fluorobenzoate**

**(i) Methyl 4-fluoro-3-methylbenzoate**

SOCl<sub>2</sub> (5.68 mL) was added dropwise to a solution of 4-fluoro-3-methylbenzoic acid (10 g) in MeOH (150 mL) at 0°C over a period of 10 mins. under N<sub>2</sub>. The resulting mixture was stirred at r.t. for 24 h and then the solvent was removed by evaporation. The residue was dissolved in EtOAc, washed with sat. NaHCO<sub>3</sub>, sat. brine, dried and then concentrated by evaporation to afford the subtitle compound (9.85 g); <sup>1</sup>H NMR: 7.93-7.83 (m, 2H), 7.04 (dd, 1H), 3.90 (s, 3H), 2.31 (s, 3H).

**(ii) Methyl 3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-4-fluorobenzoate**

The title compound was prepared using the product from step (i) (12.8 g) and the method of Example 12 steps (i)-(iv) to give a colourless solid (0.27 g); <sup>1</sup>H NMR: 7.89-7.81 (m, 1H), 7.46 (dd, 1H), 7.32 (dd, 1H), 6.31 (t, 1H), 5.74 (s, 2H), 3.78 (s, 3H), 3.77 (s, 2H), 3.27-3.22 (m, 2H), 1.95 (s, 3H), 1.44 (qn, 2H), 1.27-1.07 (m, 4H), 0.79 (t, 3H); LC-MS *m/z* 361.

**Example 18: Methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate**

**(i) Methyl 4-(bromomethyl)-3-fluorobenzoate**

The subtitle compound was prepared from 3-fluoro-4-methylbenzoic acid (15 g) by the method of Example 17 step (i) to give the product (14.5 g) as an orange oil; <sup>1</sup>H NMR: 7.70 (dd, 1H), 7.62 (dd, 1H), 7.45 (dd, 1H), 3.85 (s, 3H), 2.31 (d, 3H).

**(ii) Methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate**

The title compound was prepared using the product from step (i) (12.8 g) and the method of Example 12 steps (i)-(iv) to give a colourless solid (40 mg); <sup>1</sup>H NMR: 7.70-7.63 (m, 2H), 6.97 (dd, 1H), 6.53-6.41 (m, 1H), 6.00 (s, 2H), 3.84 (s, 3H), 3.81 (s, 2H), 3.28-3.21 (m, 2H), 1.97 (s, 3H), 1.44 (qn, 2H), 1.29-1.07 (m, 4H), 0.81 (t, 3H); LC-MS *m/z* 361.

**Example 19: 5-(2-Methoxybenzyl)-6-methyl-N4-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 1 from 2-methoxybenzaldehyde (10 g) to give the product as a light brown solid (0.74 g); <sup>1</sup>H NMR: 7.19

(1H, td), 7.00 (1H, d), 6.86-6.73 (2H, m), 6.03-5.90 (1H, m), 5.76 (2H, s), 3.86 (3H, s), 3.65 (2H, s), 3.29-3.16 (2H, m), 2.02 (3H, s), 1.51-1.39 (2H, m), 1.31-1.12 (4H, m), 0.84 (3H, t); LC-MS *m/z* 315.

**Example 20: 2-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenol**

5 Prepared by the method of Example 2 using the product of Example 19 (0.6 g) to give the product as a colourless solid (0.52 g); <sup>1</sup>H NMR: 11.87 (1H, s), 7.89 (1H, t), 7.34 (2H, s), 7.05 (1H, t), 6.88-6.78 (2H, m), 6.74-6.68 (1H, m), 3.67 (2H, s), 3.37 (2H, q), 2.20 (3H, s), 1.49 (2H, qn), 1.29-1.11 (4H, m), 0.82 (3H, t); LC-MS *m/z* 301.

**Example 21: 5-(2-Ethoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

10 A suspension of the product of Example 20 (0.1 g) and Cs<sub>2</sub>CO<sub>3</sub> (0.5 g) in DMF (2 mL) was stirred for 30 mins. Bromoethane (0.03 mL) was then added and the resulting suspension was heated at 80°C for 1 h. The mixture was then cooled, filtered and EtOAc (10 mL) and water (5 mL) were added. The organic phase was separated, dried and concentrated to give a crude product which was purified by RPHPLC to give the title compound as a colourless  
15 solid (27 mg); <sup>1</sup>H NMR: 7.13 (1H, td), 6.96 (1H, d), 6.82-6.74 (2H, m), 5.93 (1H, t), 5.62 (2H, s), 4.09 (2H, q), 3.62 (2H, s), 3.23 (2H, q), 1.99 (3H, s), 1.41 (2H, qn), 1.39 (3H, t), 1.28-1.08 (4H, m), 0.82 (3H, t); LC-MS *m/z* 329.

**Example 22: 5-(2-(3-(Dimethylamino)propoxy)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

20 The title compound was prepared by the method of Example 3 using the product of Example 20 (0.1 g) and *N,N*-dimethylaminopropylchloride hydrochloride (0.105 g) to give a colourless solid (27 mg); <sup>1</sup>H NMR: 7.14 (1H, td), 6.96 (1H, d), 6.81-6.74 (2H, m), 5.92 (1H, t), 5.63 (2H, s), 4.05 (2H, t), 3.63 (2H, s), 3.23 (2H, q), 2.41 (2H, t), 2.15 (6H, s), 1.99 (3H, s), 1.90 (2H, qn), 1.42 (2H, qn), 1.28-1.17 (2H, m), 1.17-1.07 (2H, m), 0.81 (3H, t);  
25 LC-MS *m/z* 386.

**Example 23: 5-(3-Methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 1 from 3-methoxybenzaldehyde (10 g) to give a light brown solid (3.7 g); <sup>1</sup>H NMR: 7.16 (1H, dd), 6.75-6.66  
30 (3H, m), 6.30 (1H, s), 5.82 (2H, s), 3.72 (2H, s), 3.70 (3H, s), 3.30-3.23 (2H, m), 2.03 (3H, s), 1.49-1.39 (2H, m), 1.29-1.08 (4H, m), 0.82 (3H, t); LC-MS *m/z* 315.

**Example 24: 3-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenol**

The title compound was prepared by the method of Example 2 using the product of Example 23 (0.9 g) to give a light brown solid (0.72 g); <sup>1</sup>H NMR: 9.25 (1H, s), 7.20-6.93 (2H, m), 6.65 (2H, s), 6.60-6.53 (2H, m), 6.50 (1H, s), 3.71 (2H, s), 3.43-3.20 (2H, m), 2.10 (3H, s), 1.46 (2H, qn), 1.31-1.06 (4H, m), 0.82 (3H, t); LC-MS *m/z* 301.

**Example 25: 5-(3-(3-(Dimethylamino)propoxy)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using the product of Example 24 (0.1 g) and *N,N*-dimethylaminopropylchloride hydrochloride (0.105 g) to give a colourless solid (0.054 g); <sup>1</sup>H NMR: 7.14 (1H, dd), 6.72-6.64 (3H, m), 6.10 (1H, t), 5.63 (2H, s), 3.92 (2H, t), 3.69 (2H, s), 3.25 (2H, q), 2.31 (2H, t), 2.12 (6H, s), 2.01 (3H, s), 1.80 (2H, qn), 1.43 (2H, qn), 1.28-1.19 (2H, m), 1.18-1.09 (2H, m), 0.82 (3H, t); LC-MS *m/z* 386.

**Example 26: 6-Methyl-N<sup>4</sup>-pentyl-5-(3-(2-(piperidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using the product of Example 24 (0.1 g) and *N*-2-chloroethylpiperidinehydrochloride (0.122 g) to give a colourless oil (0.045 g); <sup>1</sup>H NMR: 7.14 (1H, dd), 6.74-6.65 (3H, m), 6.09 (1H, t), 5.63 (2H, s), 3.98 (2H, t), 3.69 (2H, s), 3.24 (2H, q), 2.60 (2H, t), 2.42-2.37 (4H, m), 2.01 (3H, s), 1.51-1.33 (8H, m), 1.27-1.19 (2H, m), 1.17-1.10 (2H, m), 0.81 (3H, t); LC-MS *m/z* 412.

**Example 27: 5-(3-(2-(Dimethylamino)ethoxy)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using the product of Example 24 (0.1 g) and *N*-2-dimethylaminochloride hydrochloride (0.096 g) to give a light brown solid (0.022 g); <sup>1</sup>H NMR: 7.15 (1H, dd), 6.72 (1H, d), 6.69-6.65 (2H, m), 6.10 (1H, t), 5.63 (2H, s), 3.97 (2H, t), 3.69 (2H, s), 3.25 (2H, q), 2.58 (2H, t), 2.19 (6H, s), 2.01 (3H, s), 1.43 (2H, qn), 1.29-1.09 (4H, m), 0.82 (3H, t); LC-MS *m/z* 372.

**Example 28: 6-Methyl-N<sup>4</sup>-pentyl-5-(3-(2-(pyrrolidin-1-yl)ethoxy)benzyl)pyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 3 using the product of Example 24 (0.1 g) and *N*-2-chloroethylpyrrolidine hydrochloride (0.115 g) to give a

colourless oil (0.036 g); <sup>1</sup>H NMR: 7.15 (1H, dd), 6.74-6.65 (3H, m), 6.11 (1H, s), 5.65 (2H, s), 3.99 (2H, t), 3.70 (2H, s), 3.27-3.22 (2H, m), 2.74 (2H, t), 2.44-2.36 (4H, m), 2.02 (3H, s), 1.71-1.63 (4H, m), 1.44 (2H, qn), 1.30-1.19 (2H, m), 1.18-1.10 (2H, m), 0.82 (3H, t); LC-MS *m/z* 398.

5 **Example 29: 5-(3-((Dimethylamino)methyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

**(i) Ethyl 2-(3-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenyl)acetate**

The method of Example 12 using methyl 3-bromomethylbenzoate (6 g) was used to provide the subtitle compound as an orange oil which solidified on standing (0.7 g); <sup>1</sup>H  
10 NMR: 7.79-7.71 (2H, m), 7.45-7.32 (2H, m), 6.36 (1H, s), 5.78 (2H, s), 4.29 (2H, q), 3.82 (2H, s), 3.29-3.22 (2H, m), 2.01 (3H, s), 1.49-1.38 (2H, m), 1.28-1.07 (7H, m), 0.79 (3H, t).

**(ii) 3-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)phenyl)methanol**

A solution of the product of step (i) (0.21 g) in THF (2 mL) was added to a solution of  
15 LiAlH<sub>4</sub> (1M in THF, 0.88 mL) in THF (2 mL) at 0°C. The mixture was stirred at r.t. for 2 h. A further portion of LiAlH<sub>4</sub> (0.88 mL) was then added and the mixture was stirred at r.t. for 15 h. The mixture was then poured cautiously into 2M NaOH (20 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried and concentrated by evaporation to give the subtitle compound as a colourless solid which was  
20 used without further purification (0.176 g); <sup>1</sup>H NMR: 7.19 (1H, dd), 7.09 (2H, d), 7.07 (2H, s), 6.97 (1H, d), 6.12 (1H, t), 5.10 (1H, t), 4.43 (2H, d), 3.72 (2H, s), 3.24 (2H, q), 2.01 (3H, s), 1.44 (2H, qn), 1.28-1.10 (4H, m), 0.82 (3H, t).

**(iii) 5-(3-(Chloromethyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**

SOCl<sub>2</sub> (0.049 mL) was added to a stirred solution of the product from step (ii) (0.176 g) in  
25 DCM (5 mL) at r.t. The mixture was stirred for 1 h, then the solvent was removed to give the subtitle compound as a yellow oil that was used without further purification (0.182 g); <sup>1</sup>H NMR: 7.97 (1H, t), 7.34-7.25 (3H, m), 7.21 (2H, s), 7.15-7.09 (1H, m), 4.72 (2H, s), 3.86 (2H, s), 3.37 (2H, q), 2.19 (3H, s), 1.47 (2H, qn), 1.27-1.17 (2H, m), 1.15-1.06 (2H, m), 0.80 (3H, t).

30 **(iv) 5-(3-((Dimethylamino)methyl)benzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine**  
2M Dimethylamine solution in EtOH (0.4 mL) was added to a solution of the product of step (iii) (0.09 g) in DMF (2 mL) and the mixture was stirred at r.t. for 15 h. Sat NaHCO<sub>3</sub>

was then added and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with water (3 × 5 mL), dried and concentrated to a residue which was purified by RPHPLC to give the title compound as an off white solid (44 mg); <sup>1</sup>H NMR: 7.19 (1H, dd), 7.07-7.03 (2H, m), 6.98 (1H, d), 6.13 (1H, s), 5.63 (2H, s), 3.72 (2H, s), 3.29 (2H, s), 3.24 (2H, q), 2.10 (6H, s), 2.00 (3H, s), 1.43 (2H, qn), 1.27-1.20 (2H, m), 1.18-1.10 (2H, m), 0.82 (3H, t); LC-MS *m/z* 342.

**Example 30: 5-(4-(3-(Dimethylamino)prop-1-ynyl)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

**(i) 5-(4-Iodobenzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The method of Example 12 using 4-iodobenzylbromide and ethylacetoacetate was used to provide the subtitle compound as a solid (60mg); <sup>1</sup>H NMR: 7.59 (2H, d), 6.91 (2H, d), 6.16-6.09 (1H, m), 5.69-5.63 (2H, m), 3.69 (2H, s), 3.27-3.18 (2H, m), 1.99 (3H, s), 1.46-1.37 (2H, m), 1.28-1.06 (4H, m), 0.82 (3H, t); LC-MS *m/z* 411.

**(ii) 5-(4-(3-(Dimethylamino)prop-1-ynyl)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

1-Dimethylamino-2-propyne (24 mg) was dissolved in THF (2 mL) purged with nitrogen and CuI (4.64 mg) was added. The mixture was stirred for 30 mins. and added to a suspension of the product of step (i) (0.1 g) and Pd(PPh<sub>3</sub>)<sub>4</sub> (14.08 mg) in a 1:1 mixture of THF and triethylamine (2 mL). The reaction mixture was then heated to 100°C for 16 h, cooled and concentrated by evaporation. The residue was purified by RPHPLC to give the title compound as a solid (9 mg); <sup>1</sup>H NMR: 7.31 (2H, d), 7.09 (2H, d), 6.16-6.11 (1H, m), 5.65 (2H, s), 3.74 (2H, s), 3.41 (2H, s), 2.22 (6H, s), 2.00 (3H, s), 1.46-1.40 (2H, m), 1.27-1.16 (4H, m), 1.14-1.06 (2H, m), 0.81 (3H, t); LC-MS *m/z* 366.

**Example 31: 5-(4-(3-(Dimethylamino)propyl)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The product of Example 30 (8 mg) was dissolved in EtOH and hydrogenated in a H-cube<sup>TM</sup> hydrogenator using a 10% Pt/C reaction cartridge (available from ThalesNano Nanotechnology, Hungary) using the "full H<sub>2</sub> mode". The solvent was removed by evaporation and the resulting residue was purified *via* RPHPLC to give the title compound as a solid (1 mg); <sup>1</sup>H NMR: 7.06 (2H, d), 7.00 (2H, d), 6.09-6.03 (1H, m), 5.62 (2H, s), 3.68 (2H, s), 3.25-3.19 (2H, m), 2.19-2.13 (2H, m), 2.09 (6H, s), 2.00 (3H, s), 1.66-1.59

(2H, m), 1.46-1.38 (2H, m), 1.25-1.17 (4H, m), 1.16-1.08 (2H, m), 0.81 (3H, t); LC-MS  $m/z$  370.

**Example 32: 5-(3-(3-(Dimethylamino)propyl)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

5 **(i) 5-(3-(3-(Dimethylamino)prop-1-ynyl)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

The method of Example 30 using 3-iodobenzyl bromide was used to provide the subtitle compound (60 mg); LC-MS  $m/z$  366.

**(ii) 5-(3-(3-(Dimethylamino)propyl)benzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

10 The method of Example 31 using the product from step (i) (0.06 g) was used to provide the subtitle compound as a solid (8 mg);  $^1\text{H}$  NMR: 7.15 (1H, t), 7.00-6.89 (3H, m), 6.12-6.06 (1H, m), 5.62 (2H, s), 3.70 (2H, s), 3.29 (2H, s), 3.28-3.21 (2H, m), 2.18-2.13 (2H, m), 2.08 (6H, s), 2.01 (3H, s), 1.69-1.57 (2H, m), 1.49-1.38 (2H, m), 1.27-1.18 (2H, m), 1.18-1.07 (2H, m), 0.82 (3H, t); LC-MS  $m/z$  370.

15 **Example 33: 5-(4-(3-(Dimethylamino)propoxy)-2-methylbenzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

**(i) 5-(4-Methoxy-2-methylbenzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

The method of Example 1 using 4-methoxy-2-methylbenzaldehyde (10 g) was used to provide the subtitle compound as a cream solid (0.67 g);  $^1\text{H}$  NMR: 6.77 (d, 1H), 6.59 (dd, 1H), 6.49 (d, 1H), 5.97 (t, 1H), 5.63 (s, 2H), 3.68 (s, 3H), 3.52 (s, 2H), 3.22 (q, 2H), 2.32 (s, 3H), 1.90 (s, 3H), 1.42 (qn, 2H), 1.29-1.09 (m, 4H), 0.82 (t, 3H).

**(ii) 4-((2-Amino-4-(pentylamino)pyrimidin-5-yl)methyl)-3-methylphenol**

The method of Example 2 using the product of step (i) (0.5 g) was used to provide the subtitle compound as a colourless solid that was used without purification (0.350 g);  $^1\text{H}$  NMR: 8.96 (s, 1H), 6.58 (s, 1H), 6.48-6.30 (m, 2H), 5.95 (s, 1H), 5.62 (s, 2H), 3.48 (s, 2H), 3.22 (q, 2H), 2.25 (s, 3H), 1.90 (s, 3H), 1.41 (qn, 2H), 1.28-1.09 (m, 4H), 0.82 (t, 3H); LC-MS  $m/z$  313 (multimode -).

**(iii) 5-(4-(3-(Dimethylamino)propoxy)-2-methylbenzyl)-6-methyl- $N^4$ -pentylpyrimidine-2,4-diamine**

30 The method of Example 3 using the product of step (ii) (0.1 g) and dimethylaminopropylchloride hydrochloride (0.075 g) was used to provide the title compound as a colourless solid (13 mg);  $^1\text{H}$  NMR: 6.76 (d, 1H), 6.57 (dd, 1H), 6.47 (d, 1H), 5.97 (t, 1H), 5.63 (s,

2H), 3.91 (t, 2H), 3.52 (s, 2H), 3.22 (q, 2H), 2.34-2.27 (m, 5H), 2.12 (s, 6H), 1.90 (s, 3H), 1.79 (qn, 2H), 1.46-1.36 (m, 2H), 1.27-1.06 (m, 4H), 0.81 (t, 3H); LC-MS  $m/z$  400.

**Example 34: (R)-Methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate**

5 **(i) 4-((2-Amino-4-bromo-6-methylpyrimidin-5-yl)methyl)phenol and 4-((2-amino-4-chloro-6-methylpyrimidin-5-yl)methyl)phenol**

A solution of  $\text{BBr}_3$  (1 M in DCM, 15.2 mL) was added portion-wise to a stirred suspension to the product of Example 1 step (iii) (1 g) in DCM (20 mL) at 0 °C, over a period of 10 mins. under  $\text{N}_2$ . The resulting mixture was stirred at 0°C for 1 h. The mixture  
10 was then diluted with 2M HCl (30 mL) and MeOH (10 mL) then stirred at r.t. for 30 mins. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried and concentrated by evaporation to afford a 1:1 mixture of the subtitle compounds (0.230 g) which were used in the subsequent step without purification;  $^1\text{H}$  NMR: 6.90 (4H, d), 6.67 (4H, d), 3.89-3.79 (4H, m), 2.22 (3H, s),  
15 2.20 (3H, s).

**(ii) 4-Bromo-5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methylpyrimidin-2-amine and 4-Chloro-5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methylpyrimidin-2-amine**

3-(Dimethylamino)propyl chloride hydrochloride (0.437 g) was added to a stirred suspension of the product of step (i) (0.23 g),  $\text{Cs}_2\text{CO}_3$  (2.401 g) and NaI (0.069 g) in DMF  
20 (10 mL). The resulting suspension was stirred at 80°C for 3 h., cooled, and diluted with EtOAc (20 mL). The organic phase was washed with water (3 × 30 mL), brine (30 mL) dried and concentrated by evaporation. The crude product was purified by FCC eluting with DCM then 10:2 DCM-MeOH to afford a 1:1 mixture of the subtitle compounds (0.043 g) which were used in the subsequent step without purification;  $^1\text{H}$  NMR: 7.00 (d,  
25 4H), 6.88-6.79 (m, 4H), 3.94 (t, 4H), 3.89 (s, 2H), 3.87 (s, 2H), 2.41 (t, 4H), 2.19 (s, 18H), 1.84 (qn, 4H).

**(iii) (E)-tert-Butyl 3-(3-(hydroxymethyl)phenyl)acrylate**

A mixture of (3-bromophenyl)methanol (7.3 g), *tert*-butyl acrylate (15 g), palladium acetate (0.235g) and tri(*o*-tolyl)phosphine (1.25 g) in MeCN (80 mL) was heated at 90°C  
30 for 2 h. The solution was then cooled, concentrated by evaporation. The resulting residue was dissolved in EtOAc, washed with water, dried and concentrated by evaporation. The crude product was purified by FCC eluting with using 8:2 to 7:3 isohexane-EtOAc to give

the subtitle compound (7.8 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.58 (1H, d), 7.52 (1H, s), 7.45-7.33 (3H, m), 6.38 (1H, d), 4.72 (2H, s), 1.53 (9H, s).

(iv) (R)-tert-Butyl 3-(benzyl((S)-1-phenylethyl)amino)-3-(3-((tert-butyldimethylsilyloxy)methyl)phenyl)propanoate

- 5 A solution of butyl lithium (2.5 M in hexane, 34 mL) was added to a solution of (S)-(-)-N-benzyl-α-methylbenzylamine in THF (200 mL) at -78°C and the mixture was stirred for 45 mins. A solution of the product of step (iii) (7.8 g) in THF (20 mL) was added and stirring was continued for 3 h. Then the cooling bath was removed, NH<sub>4</sub>Cl solution was added and the solution was allowed to warm to r.t. EtOAc and water were added, the
- 10 organic phase was separated, dried and concentrated to give a residue which was passed through silica gel eluting with 4:1 isohexane-EtOAc. Removal of solvent by evaporation gave a residue which was dissolved in DMF (120 mL). Imidazole (5 g) and tert-butyl-dimethylsilylchloride were added and the solution was stirred at r.t. for 2 h. EtOAc and water were then added, the organic phase was separated, dried and concentrated to give the
- 15 crude product which was purified by FCC eluting with 95:5 isohexane-EtOAc to give the subtitle compound (18 g); LC-MS *m/z* 560 (APCI +).

(v) (R)-3-(Benzyl((S)-1-phenylethyl)amino)-3-(3-((tert-butyldimethylsilyloxy)methyl)phenyl)propan-1-ol

- The product of step (iv) (18 g) was dissolved in THF (120 mL) and a solution of LiAlH<sub>4</sub> (1M in THF, 45 mL) was added. The mixture was then stirred at r.t. for 4 h. and then water
- 20 was added. 45% NaOH solution and water were added and the mixture stirred for 1 h. The solvent was then removed by decantation to give a residue which was dissolved in diethyl ether. The organic solution was washed with brine, dried and concentrated by evaporation to give the subtitle compound (15.5 g); LC-MS *m/z* 490 (APCI +).

- 25 (vi) (3-((R)-1-(Benzyl((S)-1-phenylethyl)amino)-3 (methoxymethoxy)propyl)-phenyl)methanol

- To a solution of the product from step (v) and DIPEA (17 mL) in DCM (160 mL) at 0°C was added chloromethyl methylether. The mixture was warmed to r.t. and stirred for 18 h. A further aliquot of chloromethyl methylether (0.4 mL) was added and the mixture further
- 30 stirred for 18 h. The mixture was washed with water, dried and concentrated by evaporation. The resulting residue was dissolved in THF (250 mL). Tetrabutylammonium fluoride solution (75 wt% in water, 10 mL) was added and the mixture stirred for 4 h.

Brine and EtOAc were added, the organic phase was separated, washed with brine, dried and concentrated by evaporation to give the crude product which was purified by FCC eluting with 7:3 isohexane-EtOAc to give the subtitle compound (10.9 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.45-7.18 (10H, m), 4.71 (2H, d), 4.42 (2H, s), 4.15-4.08 (1H, m), 3.98-3.94 (1H, m), 3.84-3.64 (2H, m), 3.28-3.22 (5H, m), 2.20-2.10 (1H, m), 1.90-1.78 (1H, m), 1.69 (1H bs), 1.16 (3H, d).

(vii) 3-((R)-1-(Benzyl((S)-1-phenylethyl)amino)-3-(methoxymethoxy)propyl)benzyl methanesulfonate

Methane sulphonyl chloride (1.912 mL) was added dropwise to a solution of the product from step (vi) (9.5 g) and triethylamine (4.8 mL) in DCM (100 mL) at 0-5°C under N<sub>2</sub>. The resulting mixture was stirred for 1 h, then the solvent was removed to give the crude subtitle compound which was used in the next step without further purification (11.27 g); LC-MS *m/z* 498 (APCI +)

(viii) 2-(3-((R)-1-(Benzyl((S)-1-phenylethyl)amino)-3-(methoxymethoxy)propyl)-phenyl)acetonitrile

KCN (6 g) was added in one portion to the product of step (vii) (11.27 g) in DMSO (30 mL) and DMF (30 mL) and the mixture was warmed to 50°C under N<sub>2</sub>. The resulting mixture was stirred at 50°C for 18 h then partitioned between EtOAc and water. The organic phase was separated, washed with water, dried and concentrated by evaporation to give the crude subtitle compound which was used in the next step without further purification (7.69 g); LC-MS *m/z* 429 (APCI +).

(ix) Methyl 2-(3-((R)-1-(benzyl((S)-1-phenylethyl)amino)-3-hydroxypropyl)phenyl)acetate

A solution of KOH (2.81 g) dissolved in water (10 mL) was added to a stirred solution of the product of step (viii) (7.69 g, 17.94 mmol) in EtOH (50 mL) at r.t. The mixture was stirred at reflux for 24 h. The mixture was then concentrated by evaporation and the resulting residue azeotroped with toluene. MeOH (100 mL) followed by conc. HCl (3 mL) were added to the residue and the mixture was stirred at r.t. for 3 days. The mixture was then concentrated by evaporation and the resulting residue was partitioned between EtOAc and water. The organic phase was separated, washed with water, dried and concentrated by evaporation. The crude product was purified by FCC eluting with 7:3 isohexane-EtOAc to afford the subtitle compound as an oil (2.32 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.43-7.19 (m, 14H); 4.14-4.08 (m, 1H); 3.96-3.92 (m, 2H); 3.70 (s, 3H); 3.66 (s, 2H); 3.62-3.53 (m, 2H); 3.41-

3.35 (m, 1H); 2.24-2.15 (m, 1H); 1.84 (br s, 1H); 1.74-1.65 (m, 1H); 1.04 (d, 3H); LC-MS  $m/z$  418 (APCI +).

(x) (R)-methyl 2-(3-(1-amino-3-hydroxypropyl)phenyl)acetate

A suspension of the product of step (ix) (2.3 g) and Pd/C (0.9 g) in MeOH (60 mL) was stirred under a H<sub>2</sub> pressure of 45psi at r.t. for 24 h. The mixture was then filtered through diatomaceous earth (Celite<sup>TM</sup>) and the solvent was evaporated to give a residue which was purified by FCC eluting with 84:16 DCM-MeOH to give the subtitle compound as an oil (480 mg); <sup>1</sup>H NMR: 7.26-7.07 (m, 4H); 3.89 (t, 1H); 3.64 (s, 2H); 3.61 (s, 3H); 3.47-3.37 (m, 2H); 1.71-1.60 (m, 2H).

(xi) (R)-methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)benzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate

A solution of the products of step (ii) (0.045 g) and the product of step (x) (0.107 g) in butan-1-ol (3 mL) were sealed into a microwave tube and heated to 170°C in a microwave reactor for 2.5 h. The solvent was then removed by evaporation and the resulting residue was partitioned between EtOAc (5 mL) and water (5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (5 mL). The combined organic phases were dried and concentrated by evaporation to give a residue which was purified by RPHPLC to give the title compound as a colourless gum (11 mg); <sup>1</sup>H NMR: 7.20-7.13 (m, 1H), 7.10-7.00 (m, 5H), 6.82 (d, 2H), 6.41 (d, 1H), 5.60 (s, 2H), 5.36-5.26 (m, 1H), 4.52 (t, 1H), 3.94 (t, 2H), 3.78 (d, 1H), 3.69 (d, 1H), 3.60 (s, 3H), 3.57 (s, 4H), 2.37-2.31 (m, 2H), 2.14 (s, 6H), 2.02 (s, 3H), 1.91-1.77 (m, 4H); LC-MS  $m/z$  522.

Example 35: (R)-Methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate

(R)-Methyl 2-(3-(1-(2-amino-5-(4-(3-(dimethylamino)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)-3-hydroxypropyl)phenyl)acetate

A solution of the product of Example 11 step (v) (0.15 g) and the product of Example 34 step (x) (0.184 g) in butan-1-ol (3 mL) were sealed into a microwave tube and heated to 170°C in a microwave reactor for 2 h. The solvent was then removed by evaporation and the resulting residue was diluted with MeOH (2 mL) and conc. H<sub>2</sub>SO<sub>4</sub> (0.5 mL). The mixture was then stirred at 65°C for 2 h, allowed to cool, adjusted to pH 7 with sat. NaHCO<sub>3</sub> and then extracted EtOAc (3 × 10 mL). The combined organic phases were dried

and concentrated by evaporation to give a crude product which was purified by RPHPLC to give the title compound as a colourless solid (43.0 mg); <sup>1</sup>H NMR: 7.16 (1H, dd), 7.09-7.00 (2H, m), 6.67 (1H, d), 6.55 (1H, d), 6.40 (1H, dd), 6.21 (1H, d), 5.58 (2H, s), 5.32-5.24 (1H, m), 4.47 (1H, s), 3.96 (2H, t), 3.82 (3H, s), 3.65-3.55 (9H, m), 2.34 (2H, t), 2.14 (6H, s), 2.01 (3H, s), 1.87-1.77 (4H, m); LC-MS *m/z* 552.

**Example 36: 3-(4-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxyphenoxy)propan-1-ol**

**(i) 4-(3-(*tert*-Butyldimethylsilyloxy)propoxy)-2-methoxybenzaldehyde**

(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (6.85 mL) and K<sub>2</sub>CO<sub>3</sub> (4.09 g, 29.6 mmol) were added to a solution of 4-hydroxy-2-methoxybenzaldehyde (3.00 g) in DMF (30 mL) and the mixture was stirred for 14 h at r.t. Brine was added, and the mixture was then extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the subtitle compound as colourless oil (5.97 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 10.29 (1H, s), 7.80 (1H, d), 6.55 (1H, dd), 6.45 (1H, d), 4.15 (2H, t), 3.90 (3H, s), 3.81 (2H, t), 2.00 (2H, tt), 0.89 (9H, s), 0.05 (6H, s).

**(ii) 4-(3-(*tert*-Butyldimethylsilyloxy)propoxy)-2-methoxyphenyl)methanol**

NaBH<sub>4</sub> (0.35 g) was added to a solution of the product of step (i) (5.97 g) in THF/McOH (30 mL / 3 mL) at 0°C, and then the mixture was stirred for 1 h. The reaction was quenched with brine, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by FCC to give subtitle compound as colourless oil (5.76 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.14 (1H, d), 6.46 (2H, m), 4.61 (2H, s), 4.06 (2H, t), 3.85 (3H, s), 3.81 (2H, t), 2.15 (1H, br s), 1.99 (2H, tt), 0.89 (9H, s), 0.05 (6H, s).

**(iii) Methyl 2-(4-(3-(*tert*-butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-3-oxobutanoate**

Methanesulfonyl chloride (0.93 mL) was added to the mixture of the product from step (ii) (2.50 g) and DIPEA (2.09 mL) in THF (30 mL) at r.t. and the mixture was stirred for 2 h. The resulting solid was removed by filtration. The filtrate was concentrated *in vacuo*, and then dissolved in DMF (20 mL). Methyl acetoacetate (0.99 mL) was added to a suspension of NaH (55% oil dispersion, 0.37 g) in DMF (15 mL) at 0°C and the mixture was stirred for 15 min. The DMF solution described above and KI (1.27 g) were added to the mixture

and it was all stirred at 80°C for 4 h. The mixture was cooled to r.t. and diluted with EtOAc. The mixture was then washed with sat. NaHCO<sub>3</sub> and brine. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the subtitle compound as colourless oil (1.80 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.99 (1H, d), 6.42 (1H, d), 6.38 (1H, dd), 4.03 (2H, t), 3.89 (1H, t), 3.81 (3H, s), 3.80 (2H, t), 3.67 (3H, s), 3.09 (2H, m), 2.17 (3H, s), 1.97 (2H, tt), 0.88 (9H, s), 0.04 (6H, s).

(iv) 2-Amino-5-(4-(3-(*tert*-butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-ol

Guanidium carbonate (0.98 g) was added to a solution of the product from step (iii) (1.78 g) in MeOH (50 mL) and the mixture was heated at 65°C for 7 h. The mixture was then cooled to r.t. and water (50 mL) was added. The resulting solid was collected by filtration and washed with EtOH/water (50 mL /50 mL), water (50 mL), EtOH (50 mL) to afford subtitle compound as a white solid (1.53 g); <sup>1</sup>H NMR: 6.71 (1H, d), 6.41 (1H, d), 6.37 (1H, dd), 6.32 (2H, br s), 3.97 (2H, t), 3.79 (3H, s), 3.75 (2H, t), 3.45 (2H, s), 1.92 (3H, s), 1.85 (2H, tt), 0.85 (9H, s), 0.02 (6H, s); LC-MS *m/z* 433 ESI.

(v) 2-Amino-5-(4-(3-(*tert*-butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-6-methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate

*N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>3</sup>,*N*<sup>3</sup>-tetramethylpropane-1,3-diamine (0.88 mL) and 2,4,6-trimethylbenzene-1-sulfonyl chloride (1.15 g) were added to the solution of the product from step (iv) (1.52 g) in THF (15 mL) and the mixture was stirred at r.t. After 22 h, 0.1N HCl aq. (45 mL) was added and the mixture was then extracted twice with CHCl<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the subtitle compound as pale yellow oil (1.92 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.94 (2H, s), 6.71 (1H, d), 6.41 (1H, d), 6.33 (1H, dd), 4.72 (2H, br s), 4.02 (2H, t), 3.81 (2H, t), 3.79 (3H, s), 3.76 (2H, s), 2.61 (6H, s), 2.31 (3H, s), 2.26 (3H, s), 1.98 (2H, tt), 0.89 (9H, s), 0.05 (6H, s); LC-MS *m/z* 616 ESI.

(vi) 5-(4-(3-(*tert*-Butyldimethylsilyloxy)propoxy)-2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine

Trifluoroacetic acid (0.48 mL) and amylamine (1.78 mL) were added to the solution of the product from step (v) (1.90 g) in propionitrile (19 mL) and the mixture was stirred at 100°C for 3 h. The solvent was then removed by evaporation and the resulting residue was diluted with EtOAc (50 mL) and washed with 4% NH<sub>3</sub> solution (20 mL × 4) and brine (20

mL), then dried (MgSO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the subtitle compound as pale yellow oil (1.03 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.82 (1H, d), 6.47 (1H, d), 6.40 (1H, dd), 5.10 (2H, br s), 4.03 (2H, t), 3.88 (3H, s), 3.79 (2H, t), 3.72 (1H, q), 3.60 (2H, s), 3.28 (2H, q), 2.36 (3H, s), 1.97 (2H, tt), 1.44 (2H, tt), 1.25 (2H, m), 1.15 (2H, m), 0.89 (9H, s), 0.86 (3H, t), 0.05 (6H, s); LC-MS *m/z* 502 ESI.

(vii) 3-(4-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxyphenoxy)propan-1-ol

Tetrabutylammonium fluoride (1.0 M THF solution, 4.1 mL) was added to the solution of the product from step (vi) (1.03 g) in THF (6 mL) and the mixture was stirred at r.t. for 4 h.

The mixture was then diluted with EtOAc (30 mL), and washed with 4% NH<sub>3</sub> solution (20 mL), brine (20 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the title compound as a white solid (0.51 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.82 (1H, d), 6.48 (1H, d), 6.38 (1H, dd), 4.87 (1H, br t), 4.69 (2H, br s), 4.10 (2H, t), 3.88 (3H, s), 3.86 (2H, t), 3.61 (2H, s), 3.28 (2H, dq), 2.32 (3H, s), 2.04 (2H, tt), 1.90 (1H, br s), 1.44 (2H, tt), 1.25 (2H, m), 1.15 (2H, m), 0.84 (3H, t); LC-MS *m/z* 388 ESI.

**Example 37: 5-(2-Methoxy-4-(3-morpholinopropoxy)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

Methanesulfonyl chloride (0.030 mL) was added to the mixture of the product from Example 36 (0.14 g) and triethylamine (0.053 mL) in THF (5 mL) at 0°C. The resulting mixture was stirred for 30 min. Sat. NaHCO<sub>3</sub> was then added and then the solution was extracted twice with CHCl<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The resulting residue was dissolved in DMF (5 mL). Morpholine (0.33 mL) was added and the mixture was stirred at 60°C for 5 h. 4% NH<sub>3</sub> solution was then added and brine and the mixture was extracted twice with EtOAc. The combined organic layers were washed twice with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The resulting residue was purified by FCC to give the title compound as a white solid (0.13 g); <sup>1</sup>H NMR: 6.59 (1H, d), 6.52 (1H, d), 6.37 (1H, dd), 5.89 (1H, br t), 5.65 (2H, br s), 3.94 (2H, t), 3.82 (3H, s), 3.55 (4H, t), 3.51 (2H, s), 3.20 (2H, q), 2.39 (2H, t), 2.34 (4H, m), 1.98 (3H, s), 1.83 (2H, tt), 1.41 (2H, tt), 1.24 (2H, m), 1.14 (2H, m), 0.84 (3H, t); LC-MS *m/z* 457 ESI.

**Example 38: 5-(2-Methoxy-4-(3-(4-methylpiperazin-1-yl)propoxy)benzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

The title compound was prepared by the method of Example 37 using the product from Example 36 (0.14 g) as a white solid (0.13 g); <sup>1</sup>H NMR: 6.59 (1H, d), 6.52 (1H, d), 6.37 (1H, dd), 5.88 (1H, br t), 5.64 (2H, br s), 3.93 (2H, t), 3.82 (3H, s), 3.51 (2H, s), 3.21 (2H, q), 2.36 (2H, t), 2.29 (8H, m), 2.12 (3H, s), 1.98 (3H, s), 1.82 (2H, tt), 1.41 (2H, tt), 1.24 (2H, m), 1.14 (2H, m), 0.82 (3H, t); LC-MS *m/z* 470 ESI.

**Example 39: 5-(4-(4-(Dimethylamino)butyl)-2-methoxybenzyl)-6-methyl-N<sup>4</sup>-pentylpyrimidine-2,4-diamine**

**(i) Methyl 4-(4-(*tert*-butyldimethylsilyloxy)but-1-ynyl)-2-methoxybenzoate**

4-(*tert*-Butyldimethylsilyloxy)butyne (3.7 g) and methyl 4-bromo-2-methoxybenzoate (4.0 g) were dissolved in THF (30 mL purged with N<sub>2</sub>) and CuI (0.61 g), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.8 g) and triethylamine (4.1 mL) were added. The mixture was then heated to 100°C for 6 h, cooled and diluted with EtOAc (10 mL). The solution was washed with 0.2N HCl (2 × 10 mL), sat. NaHCO<sub>3</sub> (2 × 10 mL) and brine. The organic phase was dried and concentrated by evaporation. The resulting residue was purified by FCC to give the subtitle compound as colourless oil (5.6 g); <sup>1</sup>H NMR: 7.61 (1H, d), 7.08 (1H, d), 6.99 (1H, dd), 3.80-3.75 (8H, m), 2.63 (2H, t), 0.87 (9H, s), 0.06 (6H, s); ESI *m/z* 349 (M+1).

**(ii) Methyl 4-(4-(*tert*-butyldimethylsilyloxy)butyl)-2-methoxybenzoate**

The product from step (i) (5.6 g) was dissolved in MeOH. 10% Pd/C (50% wet) (1.0 g) was added and the mixture was stirred under H<sub>2</sub> for 7 h at r.t. The Pd/C was filtered off and the filtrate was concentrated to give the subtitle compound as colourless oil (5.6 g); <sup>1</sup>H NMR: 7.56 (1H, d), 6.95 (1H, d), 6.82 (1H, dd), 3.79 (3H, s), 3.74 (3H, s), 3.58 (2H, t), 3.58 (2H, t), 1.64-1.57 (2H, m), 1.50-1.44 (2H, m), 0.83 (9H, s), 0.01 (6H, s); MS:ESI 353 (M+1).

**(iii) 4-(4-(*tert*-Butyldimethylsilyloxy)butyl)-2-methoxyphenyl)methanol**

The product from step (ii) (5.6 g) in THF (30 mL) was added to the suspension of LiAlH<sub>4</sub> (0.61 g) in THF (50 mL) and the mixture was stirred for 0.5 h at r.t. The mixture was then cooled with an ice-bath and sat. Na<sub>2</sub>SO<sub>4</sub> (2 mL) was added slowly and the mixture was stirred for 2 h at r.t. The mixture was then dried (Na<sub>2</sub>SO<sub>4</sub>), precipitate was filtered off using diatomaceous earth (Celite<sup>TM</sup>) and the filtrate was concentrated to give the subtitle compound as colourless oil (4.4 g); <sup>1</sup>H NMR: 7.22 (1H, d), 6.73-6.71 (2H, m), 4.87 (1H, t),

4.42 (2H, d), 3.73 (3H, s), 3.60-3.56 (2H, m), 2.55 (2H, t), 1.61-1.57 (2H, m), 1.50-1.43 (2H, m), 0.84 (9H, s), 0.01 (6H, s).

(iv) *tert*-Butyl(4-(4-(chloromethyl)-3-methoxyphenyl)butoxy)dimethylsilane

Methanesulfonyl chloride (54  $\mu$ L) was added to the mixture of the product from step (iii) (195 mg) and DIPEA (155  $\mu$ L) in THF (3 mL) at 0°C. After stirring for 10 mins, LiCl (42 mg) was added and the mixture was stirred for 2 h and then diluted with EtOAc (10 mL). The solution was washed with 0.2N HCl (2  $\times$  10 mL), sat. NaHCO<sub>3</sub> (2  $\times$  10 mL) and brine. The organic phase was dried and concentrated to give the subtitle compound as colourless oil (200 mg); <sup>1</sup>H NMR: 7.26 (1H, d), 6.84 (1H, d), 6.74 (1H, dd), 4.65 (2H, s), 3.80 (3H, s), 3.58 (2H, t), 2.57 (2H, t), 1.63-1.58 (2H, m), 1.48-1.34 (2H, m), 0.84 (9H, s), 0.00 (6H, s).

(v) methyl 2-(4-(4-(*tert*-butyldimethylsilyloxy)butyl)-2-methoxybenzyl)-3-oxobutanoate

Methyl acetoacetate (161  $\mu$ L) was added to the suspension of NaH (55% oil dispersion, 43 mg) in THF (5 mL) at 0°C and the mixture was stirred for 0.5 h. The product from step (iv) (200 mg) in THF (5 mL) and KI (83 mg) were added and the mixture was stirred at 80°C for 2h. The mixture was then cooled to r.t. and diluted with EtOAc (30 mL). The mixture was then washed with 0.1N HCl (2  $\times$  10 mL), sat. NaHCO<sub>3</sub> (2  $\times$  10 mL) and brine. The organic phase was dried and concentrated and the residue was purified by FCC to give the subtitle compound as colourless oil (200 mg); <sup>1</sup>H NMR: 6.93 (1H, d), 6.76 (1H, d), 6.64 (1H, dd), 3.89-3.85 (1H, m), 3.85 (3H, s), 3.62-3.55 (5H, m), 2.98-2.89 (2H, m), 2.54-2.50 (2H, m), 2.12 (3H, s), 1.59-1.56 (2H, m), 1.46-1.42 (2H, m), 0.84 (9H, s), 0.00 (6H, s); MS:ESI 423 (M+1).

(vi) 2-Amino-5-(4-(4-(*tert*-butyldimethylsilyloxy)butyl)-2-methoxybenzyl)-6-methylpyrimidin-4-ol

Guanidium carbonate (109 mg) was added to a solution of the product from step (v) (200 mg) in MeOH (5 mL) and the mixture was heated at 65°C for 12 h. The mixture was then cooled to r.t. and diluted with EtOAc (30 mL). The mixture was then washed with sat. NaHCO<sub>3</sub> (2  $\times$  10 mL) and brine. The organic phase was dried and concentrated and the residue was purified by FCC to give the subtitle compound as colourless oil (147 mg); <sup>1</sup>H NMR: 6.73-6.69 (2H, m), 6.59 (1H, dd), 6.30 (2H, brs), 3.77 (3H, s), 3.57(2H, t), 3.37 (2H, s), 2.52-2.50 (2H, m), 2.94 (3H, s), 1.59-1.56 (2H, m), 1.46-1.42 (2H, m), 0.84 (9H, s), 0.00 (6H, s).

(vii) 2-Amino-5-(4-(4-(*tert*-butyldimethylsilyloxy)butyl)-2-methoxybenzyl)-6-

methylpyrimidin-4-yl 2,4,6-trimethylbenzenesulfonate

The subtitle compound was prepared by the method of Example 35 step (v) using the product from step (vi) (142 mg) to give a colourless oil (260 mg); <sup>1</sup>H NMR: 7.07 (2H, s), 6.75-6.72 (3H, m), 6.61-6.98 (2H, m), 3.72 (3H, s), 3.61-3.57 (4H, m), 2.55-2.51 (2H, m), 2.42 (6H, s), 2.28 (3H, s), 2.24 (3H, s), 1.61-1.54 (2H, m), 1.53-1.42 (2H, m), 0.84 (9H, s), 0.00 (6H, s).

(viii) 5-(4-(4-(*tert*-Butyldimethylsilyloxy)butyl)-2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>pentylpyrimidine-2,4-diamine

The subtitle compound was prepared by the method of Example 36 step (vi) using the product from step (vii) (260 mg) to give a colourless oil (101 mg); <sup>1</sup>H NMR: 6.78 (1H, s), 6.60 (2H, s), 6.01 (1H, br s), 5.72 (2H, br s), 3.81 (3H, s), 3.58-3.54 (4H, m), 3.25-3.17 (2H, m), 2.53-2.49 (2H, m), 1.96 (3H, s), 1.63-1.51 (2H, m), 1.50-1.37 (4H, m), 1.30-1.08 (4H, m), 0.84-0.78 (12H, m), 0.00 (6H, s); MS:ESI 501 (M+1).

(ix) 4-(4-((2-Amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxyphenyl)butan-1-ol

The subtitle compound was prepared by the method of Example 36 step (vii) using the product from step (x) (100 mg) to give a colourless oil (71 mg); <sup>1</sup>H NMR: 6.79 (1H, s), 6.61-6.50 (2H, m), 5.95 (1H, t), 5.64 (2H, br s), 4.36 (1H, t), 3.82 (3H, s), 3.55 (2H, s), 3.39-3.33 (2H, m), 3.22-3.17 (2H, m), 2.52-2.49 (2H, m), 1.96 (3H, s), 1.57-1.53 (2H, m), 1.42-1.37 (4H, m), 1.22-1.10 (4H, m), 0.80 (3H, t); MS:ESI 387 (M+1).

(x) 5-(4-(4-(Dimethylamino)butyl)-2-methoxybenzyl)-6-methyl-*N*<sup>4</sup>-pentylpyrimidine-2,4-diamine

The title compound was prepared by the method of Example 37 using the product from step (ix) to give a white solid (58 mg); <sup>1</sup>H NMR: 6.79 (1H, s), 6.61-6.50 (2H, m), 5.94-5.92 (1H, m), 5.63 (2H, s), 3.82 (3H, s), 3.54 (2H, s), 3.22-3.17 (2H, m), 2.52-2.49 (2H, m), 2.18-2.14 (2H, m), 2.05 (6H, s), 1.95 (3H, s), 1.55-1.49 (2H, m), 1.44-1.32 (4H, m), 1.24-1.09 (4H, m), 0.81 (3H, t); MS:ESI 414 (M+1).

**Example 40: (S)-2-(2-Amino-5-(4-(hydroxymethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)pentan-1-ol**

(i) (S)-Methyl 4-((2-amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)-methyl)-3-methoxybenzoate

(*S*)-2-Aminopentan-1-ol (0.481 g) was added to a suspension of the product from Example 12 step (iii) (0.5 g) in dioxane (5 mL) and the mixture was heated in a CEM microwave at 170°C for 9 h. The mixture was then cooled, the solvent was removed by evaporation. The residue was purified by FCC using 5% MeOH in DCM to give the subtitle compound  
 5 (0.250 g) as a orange gum; <sup>1</sup>H NMR: 7.53–7.42 (2H, m), 6.89 (1H, d), 5.75 (2H, d), 5.58 (1H, d), 4.61–4.54 (1H, m), 4.17–4.08 (1H, m), 3.92 (3H, s), 3.83 (3H, s), 3.69 (2H, d), 3.28–3.23 (m, 1H), 2.00 (3H, d), 1.53–1.40 (m, 1H), 1.35–1.19 (m, 2H), 1.16–1.02 (m, 2H), 0.77 (3H, t); LC-MS *m/z* 389.

(ii) (*S*)-4-((2-Amino-4-(1-hydroxypentan-2-ylamino)-6-methylpyrimidin-5-yl)methyl)-3-methoxybenzoic acid  
 10

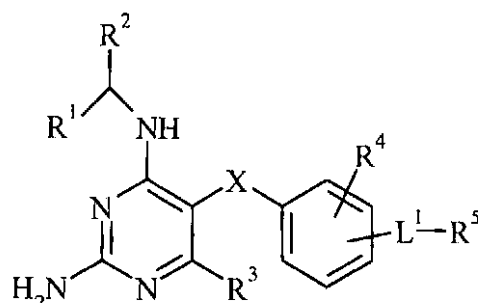
The product from step (i) (220 mg) was dissolved in THF (3 mL) and water (3 mL) and LiOH solution (3 M, 0.944 mL) was then added. The mixture was then heated in a CEM microwave for 6 h at 120°C. The solvent was then removed by evaporation and the resulting residue was dissolved in water and acidified with 2 M HCl to pH7. The resulting  
 15 solid precipitate was filtered off and dried under high vacuum overnight to give subtitle compound (90 mg); <sup>1</sup>H NMR: 7.53–7.42 (2H, m), 6.92 (1H, d), 6.61 (2H, d), 4.21 (1H, d), 3.91 (3H, d), 3.75 (2H, s), 2.09 (3H, s), 1.53–1.42 (1H, m), 1.40–1.20 (2H, m), 1.09 (2H, q), 0.78 (3H, t); LC-MS *m/z* 375.

(iii) (*S*)-2-(2-Amino-5-(4-(hydroxymethyl)-2-methoxybenzyl)-6-methylpyrimidin-4-ylamino)pentan-1-ol  
 20

Borane-THF complex (1 M, 3 mL, 3.00 mmol) was added to the product of step (ii) (85 mg) and the mixture was heated to 80°C for 2 h. MeOH was then carefully added and the mixture was heated to 80°C for 1 h. The solvent was then removed by evaporation and the resulting residue was dissolved in MeOH and loaded onto a SCX cartridge. The cartridge  
 25 was washed with MeOH and eluted with a solution of 0.7 M NH<sub>3</sub> in MeOH. The solvents were evaporated to give title compound as a colourless gum (40 mg); <sup>1</sup>H NMR: 6.94 (1H, s), 6.74 (2H, q), 5.66 (2H, s), 5.48 (1H, t), 5.14 (1H, s), 4.59 (1H, s), 4.45 (2H, s), 4.15–4.04 (1H, m), 3.84 (3H, d), 3.59 (2H, d), 3.25 (1H, dd), 2.03 (3H, s), 1.54–1.44 (1H, m), 1.32–1.23 (2H, m), 1.11 (2H, m), 0.81–0.76 (3H, t); LC-MS *m/z* 361.

**CLAIMS**

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

Wherein:

**X** represents -CH<sub>2</sub>-, -NR<sup>8</sup>-, -O- or -S(O)<sub>n</sub>-;

**R<sup>1</sup>** represents C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkoxy, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkoxy or hydroxyC<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl;

10 **R<sup>2</sup>** represents hydrogen, C<sub>1-6</sub>alkyl or phenyl wherein said phenyl is optionally substituted with 1, 2 or 3 substituents selected from R<sup>6</sup>;

**R<sup>3</sup>** represents C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or -S-C<sub>1-6</sub>alkyl;

**R<sup>4</sup>** represents hydrogen, halogen, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy;

15 **L<sup>1</sup>** represents a direct bond, -(CR<sup>9</sup>R<sup>10</sup>)<sub>m</sub>-, -CH=CH-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, -C≡C-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, -O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- or -O-(CH<sub>2</sub>)<sub>q</sub>-NR<sup>8</sup>-(CH<sub>2</sub>)<sub>q</sub>-;

**R<sup>5</sup>** represents methyl, hydroxy, -NR<sup>11</sup>R<sup>12</sup>, C<sub>3-6</sub>cycloalkyl, phenyl or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected from O, N or S wherein said phenyl and heterocyclic rings are optionally substituted with 1, 2 or 3 substituents selected from R<sup>7</sup>;

20 **R<sup>6</sup>** represents C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, hydroxy, halogen, cyano, -S(O)<sub>n</sub>-C<sub>1-6</sub>alkyl or -CH<sub>2</sub>-C(O)-O-C<sub>1-6</sub>alkyl;

**R<sup>7</sup>** represents C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl or -(CH<sub>2</sub>)<sub>q</sub>-NR<sup>11</sup>R<sup>12</sup>;

**R<sup>8</sup>** represents hydrogen or C<sub>1-6</sub>alkyl;

25 **R<sup>9</sup>** and **R<sup>10</sup>**, identically or differently on each occurrence, represents hydrogen or methyl;

**R<sup>11</sup>** and **R<sup>12</sup>** independently represent hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxyC<sub>2-4</sub>alkyl;

**m** represents 1, 2, 3, 4, 5 or 6;

**n** represents 0, 1 or 2; and

**q** represents 0, 1, 2, 3, 4, 5 or 6;

with the proviso that the compound of Formula (I) is other than:

[3-(2-amino-4-methyl-6-pentylamino-pyrimidin-5-ylmethyl)]-benzoic acid ethyl ester;

5 methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-methoxybenzoate;

or

methyl 4-((2-amino-4-methyl-6-(pentylamino)pyrimidin-5-yl)methyl)-3-fluorobenzoate.

2. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof,  
10 wherein **X** represents -CH<sub>2</sub>-.

3. A compound according to Claim 1 or Claim 2, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>1</sup> represents C<sub>1-6</sub>alkyl.

15 4. A compound according to any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>2</sup> represents hydrogen.

5. A compound according to any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>2</sup> represents phenyl wherein said phenyl is optionally  
20 substituted with 1, 2 or 3 substituents selected from **R**<sup>6</sup>.

6. A compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>3</sup> represents methyl.

25 7. A compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>4</sup> represents C<sub>1-6</sub>alkoxy.

8. A compound according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein **R**<sup>4</sup> represents hydrogen.

9. A compound according to any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein  $R^4$  is bonded at the ortho position of the phenyl ring relative to linkage  $-X-$ .
10. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein  $q$  represents 1, 2 or 3.
11. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein  $q$  represents 2 or 3.
12. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  represents  $-(CR^9R^{10})_m-$ ,  $-CH=CH-(CR^9R^{10})_q-$  or  $-C\equiv C-(CR^9R^{10})_q-$ .
13. A compound according to any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  represents  $-O-(CR^9R^{10})_q-$ .
14. A compound according to any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is bonded at the para position of the phenyl ring relative to linkage  $-X-$ .
15. A compound according to any one of Claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is bonded at the meta position of the phenyl ring relative to linkage  $-X-$ .
16. A compound according to any one of Claims 1 to 8 or 10 to 13, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  is bonded at the ortho position of the phenyl ring relative to linkage  $-X-$ .
17. A compound according to any one of Claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein  $R^5$  represents  $NR^{11}R^{12}$  or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2 or 3 heteroatoms independently selected

from O, N or S wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>7</sup>.

18. A compound according to any one of Claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> represents NR<sup>11</sup>R<sup>12</sup> and R<sup>11</sup> and R<sup>12</sup> both represent methyl.

19. A pharmaceutical composition which comprises a compound according to any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

20. A compound according to any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use as a medicament.

21. A compound according to any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

22. Use of a compound according to any one of Claims 1 to 18, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer.

23. A method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 18.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2010/050825

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/49 C07D401/12 C07D403/12 C07D413/12 A61K31/505  
A61K31/5377 A61P35/00

ADD.

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN 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 99/50249 A2 (DU PONT PHARM CO [US])<br>7 October 1999 (1999-10-07)<br>page 1, line 5 - line 16; examples A-1091<br>- A-1104<br>-----                                                                                                          | 1-23                  |
| A         | US 2005/054590 A1 (AVERETT DEVRON R [US])<br>10 March 2005 (2005-03-10)<br>paragraphs [0001], [0048]; examples 3-5<br>-----                                                                                                                      | 1-23                  |
| X,P       | WO 2009/067081 A1 (ASTRAZENECA AB [SE];<br>DAINIPPON SUMITOMO PHARMA CO [JP]; BENNETT<br>NICHOL) 28 May 2009 (2009-05-28)<br>page 1, line 28 - line 30; claim 1;<br>examples<br>20(iv), 21(v), 22(v), 34(v), 40(v), 89(ii), 89(i<br>ii)<br>----- | 1-23                  |

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*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.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

30 July 2010

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3015

Authorized officer

Mooren, Nicolai

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/050825

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|----|---------------------|----------------------------|---------------------|
| WO 9950249                                | A2 | 07-10-1999          | AU 3213799 A               | 18-10-1999          |
|                                           |    |                     | CA 2333927 A1              | 07-10-1999          |
|                                           |    |                     | EP 1054871 A2              | 29-11-2000          |
|                                           |    |                     | JP 2003504301 T            | 04-02-2003          |
| US 2005054590                             | A1 | 10-03-2005          | US 2009298863 A1           | 03-12-2009          |
| WO 2009067081                             | A1 | 28-05-2009          | AR 069412 A1               | 20-01-2010          |
|                                           |    |                     | AU 2008326863 A1           | 28-05-2009          |
|                                           |    |                     | CA 2704214 A1              | 28-05-2009          |
|                                           |    |                     | PE 12362009 A1             | 16-09-2009          |
|                                           |    |                     | US 2009209524 A1           | 20-08-2009          |
|                                           |    |                     | UY 31481 A1                | 17-07-2009          |

**DERIVADOS DE PIRIMIDINA NOVEDOSOS Y SU USO EN EL TRATAMIENTO  
DEL CANCER Y ENFERMEDADES ADICIONALES.**

**Campo de la invención**

5           La presente invención se refiere a nuevos derivados de pirimidina y, más particularmente, a nuevos derivados de pirimidina que actúan como agonistas de TLR7. Esta invención también se refiere a métodos para la preparación de dichos derivados de pirimidina y nuevos intermedios en la preparación de los mismos, a composiciones farmacéuticas que contienen dichos derivados de pirimidina, al uso de dichos derivados de  
10       pirimidina en la preparación de medicamentos, y al uso de dichos derivados de pirimidina en el tratamiento de afecciones provocadas por TLR7, como enfermedades alérgicas, enfermedades autoinmunes, enfermedades virales y, en particular, cáncer.

**Antecedentes de la invención**

          Los receptores tipo Toll (TLR) se expresan en una variedad de células inmunes,  
15       incluidos macrófagos y células dendríticas (DC). Los TLR reconocen motivos moleculares en patógenos llamados patrones moleculares asociados a patógenos (PAMP) (1). Hasta el momento, se han identificado 13 TLR en el hombre, incluidos los TLR 1, 2, 4, 5 y 6, que se encuentran confinados en la superficie celular y los TLR 3, 7, 8 y 9 los cuales se expresan en endosomas. Los diferentes TLR reconocen diferentes ligandos derivados de  
20       patógenos, por ejemplo los TLR 2 (lipoproteínas bacterianas), 3 (ARN de doble hebra/poli (I:C)), 4 (lipopolisacáridos), 5 (flagelina), 7 (ARN de hebra única) y 9 (ADN que contiene CpG) (2). La ligazón de los TLR a células que presentan antígenos, como los DC, conduce a la producción de citocinas proinflamatorias, la maduración de DC y el cebado del sistema inmune adaptativo (3). TLR7 y TLR9 se expresan mediante células dendríticas  
25       plasmocitoides (pDC) y el reconocimiento de ligandos conduce a la secreción de interferón- $\alpha$  (INF- $\alpha$ ) (4). Los estudios preclínicos que investigan los efectos de la activación de TLR, que utilizan componentes bacterianos o virales, dosificados como monoterapia y/o combinados con un agente antitumoral, han mostrado inhibición del crecimiento tumoral en varios modelos tumorales murinos (5).

30       Se han descrito varios agonistas de TLR7 de molécula pequeñas incluidos la imidazoquinolina, el imiquimod, que se ha utilizado para tratar varias afecciones dermatológicas, por ejemplo, verrugas genitales, molluscum contagiosum y melanoma. En

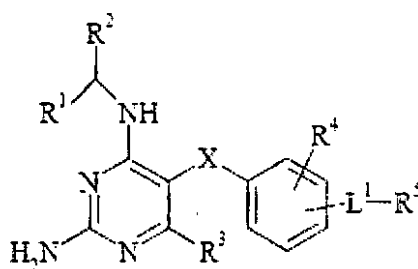
el caso del melanoma, el imiquimod aplicado tópicamente (Aldara, Graceway Pharmaceuticals, Bristol, TN) demostró respuestas terapéuticas en la metástasis del melanoma cutáneo y el lentigo maligno (6) y ha sido aprobado para el tratamiento de carcinoma de células basales superficiales (BCC) (7). Los estudios preclínicos y clínicos indican que es posible que el imiquimod funcione a través de la inducción de genes tipo IFN 1 y genes IFN inducibles, los cuales a su vez pueden tener efectos directos en el crecimiento de células tumorales y/o componentes de enganche del sistema inmune adaptativo (6,7). El 852A es otra imidazoquinolina la cual, a diferencia del imiquimod, es apropiada para la administración sistémica. Actualmente el 852A se encuentra en la fase II de las pruebas clínicas para varias indicaciones para el cáncer, incluido el melanoma (8).

Sin embargo, todavía existe la necesidad de más agonistas de TLR7 que sean más efectivos en el tratamiento de enfermedades, por ejemplo del cáncer, debido a su potencia superior y/o a las propiedades físicas ventajosas (por ejemplo, mayor permeabilidad, y/o unión de proteína al plasma más baja) y/o perfiles de toxicidad favorables y/o perfiles metabólicos favorables, en comparación con otros agonistas de TLR7 conocidos, por ejemplo el 852A.

Como se demuestra en la presente, los derivados de pirimidina de la presente invención son capaces de activar el TLR7 *in vitro*. Como consecuencia de esta actividad, se espera que los derivados de pirimidina de la presente invención tengan un valor en la prevención o el tratamiento de enfermedades humanas, por ejemplo cáncer, ya sea como monoterapia o en combinación con agentes quimioterapéuticos o regímenes de radioterapia.

### Sumario de la invención

De conformidad con un primer aspecto de la presente invención, se proporciona por lo tanto un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo:



(I)

donde:

X representa  $-\text{CH}_2-$ ,  $-\text{NR}^8-$ ,  $-\text{O}-$  o  $-\text{S}(\text{O})_n-$ ;

$\text{R}^1$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{2-6}$ , alcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxialquilo $\text{C}_{1-6}$ , hidroxialcoxi $\text{C}_{1-6}$  o hidroxialcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ ;

5  $\text{R}^2$  representa hidrógeno, alquilo $\text{C}_{1-6}$  o fenilo donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^6$ ;

$\text{R}^3$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$  o  $-\text{S}$ -alquilo $\text{C}_{1-6}$ ;

$\text{R}^4$  representa hidrógeno, halógeno, alquilo $\text{C}_{1-6}$  o alcoxi $\text{C}_{1-6}$ ;

10  $\text{L}^1$  representa un enlace directo,  $-(\text{CR}^9\text{R}^{10})_m-$ ,  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}(\text{O})-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{O}-(\text{CH}_2)_q-\text{NR}^8-(\text{CH}_2)_q-$ ;

$\text{R}^5$  representa metilo, hidroxilo,  $-\text{NR}^{11}\text{R}^{12}$ , cicloalquilo $\text{C}_{3-6}$ , un anillo fenilo o un anillo monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dichos anillos fenilo y heterocíclicos se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^7$ ;

15  $\text{R}^6$  representa alquilo $\text{C}_{1-6}$ , fluoroalquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , hidroxilo, halógeno, ciano,  $-\text{S}(\text{O})_n$ -alquilo $\text{C}_{1-6}$  o  $-\text{CH}_2-\text{C}(\text{O})-\text{O}$ -alquilo $\text{C}_{1-6}$ ;

$\text{R}^7$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxilo, hidroxialquilo $\text{C}_{1-6}$ , o  $-(\text{CH}_2)_q-\text{NR}^{11}\text{R}^{12}$ ;

$\text{R}^8$  representa hidrógeno o alquilo $\text{C}_{1-6}$ ;

20  $\text{R}^9$  y  $\text{R}^{10}$ , idéntica o diferentemente en cada caso, representa hidrógeno o metilo;

$\text{R}^{11}$  y  $\text{R}^{12}$  independientemente representan hidrógeno, alquilo $\text{C}_{1-4}$  o alcoxi $\text{C}_{1-4}$ alquilo $\text{C}_{2-4}$ ;

m representa 1, 2, 3, 4, 5 ó 6;

n representa 0, 1 ó 2; y

q, independientemente, representa 0, 1, 2, 3, 4, 5 ó 6;

25 con la condición de que el compuesto de la Fórmula (I) no sea:

etil éster del ácido [3-(2-amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)]-benzoico; [3-(2-amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)-fenil]-metanol;

4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo; (4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxifenil)metanol;

30 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo; (4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorofenil)metanol; o (4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-ilmetil)fenil)metanol.

En una realización se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable de este, donde:

- X representa  $-\text{CH}_2-$ ,  $-\text{NR}^8-$ ,  $-\text{O}-$  o  $-\text{S}(\text{O})_n-$ ;
- 5  $\text{R}^1$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{2-6}$ , alcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxialquilo $\text{C}_{1-6}$ , hidroxialcoxi $\text{C}_{1-6}$  o hidroxialcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ ;
- $\text{R}^2$  representa hidrógeno, alquilo $\text{C}_{1-6}$  o fenilo donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^6$ ;
- $\text{R}^3$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$  o  $-\text{S}-$ alquilo $\text{C}_{1-6}$ ;
- 10  $\text{R}^4$  representa hidrógeno, halógeno, alquilo $\text{C}_{1-6}$  o alcoxi $\text{C}_{1-6}$ ;
- $\text{L}^1$  representa un enlace directo,  $-(\text{CR}^9\text{R}^{10})_m-$ ,  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}(\text{O})-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{O}-(\text{CH}_2)_q-\text{NR}^8-(\text{CH}_2)_q-$ ;
- $\text{R}^5$  representa metilo, hidroxilo,  $-\text{NR}^{11}\text{R}^{12}$ , cicloalquilo $\text{C}_{3-6}$ , un anillo fenilo o un anillo monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos
- 15 seleccionados independientemente de O, N o S donde dichos anillos fenilo y heterocíclicos se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^7$ ;
- $\text{R}^6$  representa alquilo $\text{C}_{1-6}$ , fluoroalquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , hidroxilo, halógeno, ciano,  $-\text{S}(\text{O})_n$ -alquilo $\text{C}_{1-6}$  o  $-\text{CH}_2-\text{C}(\text{O})-\text{O}-$ alquilo $\text{C}_{1-6}$ ;
- $\text{R}^7$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxilo, hidroxialquilo $\text{C}_{1-6}$ , o
- 20  $-(\text{CH}_2)_q-\text{NR}^{11}\text{R}^{12}$ ;
- $\text{R}^8$  representa hidrógeno o alquilo $\text{C}_{1-6}$ ;
- $\text{R}^9$  y  $\text{R}^{10}$ , idéntica o diferentemente en cada caso, representa hidrógeno o metilo;
- $\text{R}^{11}$  y  $\text{R}^{12}$  independientemente representan hidrógeno, alquilo $\text{C}_{1-4}$  o alcoxi $\text{C}_{1-4}$ alquilo $\text{C}_{2-4}$ ;
- m representa 1, 2, 3, 4, 5 ó 6;
- 25 n representa 0, 1 ó 2; y
- q representa 0, 1, 2, 3, 4, 5 ó 6;

con la condición de que el compuesto de la Fórmula (I) no sea:

- etil éster del ácido [3-(2-amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)]-benzoico;
- 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo; o
- 30 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo.

Se debe entender que cualquier grupo  $\text{R}^4$  y  $\text{L}^1-\text{R}^5$  apropiado de la fórmula (I) se puede unir a cualquier átomo de carbono disponible del anillo fenilo, pero no al mismo

átomo de carbono, y que R<sup>5</sup> se puede unir al anillo fenilo mediante cualquier enlazador apropiado seleccionado de L<sup>1</sup>.

Se debe entender que, en la medida en que ciertos compuestos de la fórmula (I) que se definieron anteriormente pueden existir en formas ópticamente activas o racémicas, en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquiera de dichas formas ópticamente activas o racémicas que poseen la actividad mencionada anteriormente. La síntesis de formas ópticamente activas se puede realizar mediante técnicas estándar de química orgánica conocidas en el arte, por ejemplo, mediante la síntesis a partir de materiales de partida ópticamente activos o mediante la resolución de una forma racémica. De modo similar, la actividad mencionada anteriormente se puede evaluar utilizando técnicas de laboratorio estándar a las que se hace referencia más adelante.

Se debe entender que ciertos compuestos de la fórmula (I) anterior, pueden existir tanto en formas no solvatadas como solvatadas, como ser, por ejemplo, formas hidratadas. Se debe entender que la presente invención abarca todas estas formas solvatadas que activan a los TLR7.

También se debe entender que ciertos compuestos de la fórmula (I) pueden existir en forma cristalina y exhibir polimorfismo. La presente invención abarca todas estas formas que activan a los TLR7.

El término “halógeno” o “halo” se utiliza en la presente para denominar al flúor, cloro, bromo y yodo.

El término “alquiloC<sub>1-6</sub>” significa una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada. Sin embargo las referencias a los grupos alquilo individuales como “propilo” son específicas únicamente para la versión de cadena lineal y las referencias a los grupos alquilo de cadena ramificada individuales como “*terc*-butilo” son específicas únicamente para la versión de cadena ramificada. Por ejemplo, “alquiloC<sub>1-6</sub>” incluye, aunque no taxativamente, metilo, etilo, propilo, isopropilo, butilo, *terc*-butilo, pentilo, *terc*-pentilo, hexilo e isohexilo. Los términos “alquiloC<sub>1-4</sub>” y “alquiloC<sub>1-7</sub>” deben interpretarse de igual modo.

El término “cicloalquiloC<sub>3-6</sub>” significa un anillo de carbono monocíclico de 3 a 6 miembros. Por ejemplo “cicloalquiloC<sub>3-6</sub>” incluye ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

El término “alcoxiC<sub>1-6</sub>” significa una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, unida a oxígeno. Por ejemplo, “alcoxiC<sub>1-6</sub>” incluye, aunque no taxativamente, metoxi, etoxi, propoxi, butoxi, pentoxi y hexoxi.

5 El término “alcoxiC<sub>1-6</sub>alquiloC<sub>1-6</sub>” significa una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, unida mediante oxígeno a otra cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada. Por ejemplo, “alcoxiC<sub>1-6</sub>alquiloC<sub>1-6</sub>” incluye, aunque no taxativamente, metoxietilo, metoxipropilo, etoxipropilo, 10 propoxietilo y butoxipropilo. El término “alcoxiC<sub>1-4</sub>alquiloC<sub>2-4</sub>” se debe interpretar de igual modo.

El término “hidroxialquiloC<sub>1-6</sub>” significa una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, donde uno de los átomos de hidrógeno ha sido remplazado por un grupo hidroxil. Por ejemplo 15 “hidroxialquiloC<sub>1-6</sub>” incluye, aunque no taxativamente, hidroximetilo, hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 1-hidroxiisopropilo, 4-hidroxibutilo, hidroxipentilo, hidroxihexilo e hidroxiohexilo.

El término “hidroxialcoxiC<sub>1-6</sub>” significa una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, unida a 20 oxígeno y donde uno de los átomos de hidrógeno ha sido remplazado por un grupo hidroxil. Por ejemplo “hidroxialcoxiC<sub>1-6</sub>” incluye, aunque no taxativamente, hidroximetoxi, hidroxietoxi, 2-hidroxipropoxi, 3-hidroxipropoxi, 1-hidroxiisopropoxi, 4-hidroxibutoxi, hidroxipentoxi e hidroxiohexoxi.

El término “hidroxialcoxiC<sub>1-6</sub>alquiloC<sub>1-6</sub>” significa una cadena de carbono saturada 25 de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, unida mediante oxígeno a otra cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser una cadena lineal o ramificada, y donde uno de los átomos de hidrógeno de una, pero no ambas, de las cadenas de carbono ha sido remplazado por un grupo hidroxil. Por ejemplo “hidroxialcoxiC<sub>1-6</sub>alquiloC<sub>1-6</sub>” incluye, aunque no 30 taxativamente, hidroximetoximetilo, hidroxietoximetilo, 2-hidroxipropoxietilo, 3-hidroxipropoxietilo, 1-hidroxiisopropoxietilo, 4-hidroxibutoxipentilo, hidroxipentoxietilo e hidroxiohexoxietilo.

El término "arilo" significa fenilo o naftilo.

A menos que se indique lo contrario, el término "anillo heterocíclico" significa un anillo monocíclico parcialmente saturado o totalmente saturado de 4,5,6 ó 7 miembros, que comprende 1,2 ó 3 heteroátomos seleccionados de nitrógeno, oxígeno o azufre unidos  
5 mediante anillos de átomos de carbono o anillos de átomos de nitrógeno. Los ejemplos de anillos heterocíclicos de 4, 5, 6 ó 7 miembros incluyen, aunque no taxativamente, azetidínilo, tetrahidrofuranilo, dihidropiranilo, tetrahidropiranilo, pirrolínilo, pirrolidinilo, tiazolidínilo, morfolínilo, oxetanilo, piperidínilo, piperazinilo, dihidropiridinilo, dihidropirimidinilo, azepanilo y diazepanilo. Esta definición comprende además anillos  
10 que contienen azufre donde el átomo de azufre se ha oxidado en un grupo S(O) o S(O<sub>2</sub>).

En otras realizaciones del primer aspecto de la presente invención, cada una de las siguientes definiciones de L<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, X, y q en los párrafos (1) a (61) a continuación, se pueden utilizar individualmente o en combinación con una o más de las otras definiciones para limitar la definición más amplia de la fórmula  
15 (I). Por ejemplo, el entendido en la técnica entenderá que los párrafos (24), (26), (34), (42) y (58) se podrían combinar para proporcionar un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable de los mismos, donde R<sup>4</sup> representa alcoxiC<sub>1-6</sub>, L<sup>1</sup> representa -O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- y está unido en la posición para del anillo fenilo, en relación al enlace -X-, q representa 1, 2 ó 3 y R<sup>5</sup> representa NR<sup>11</sup>R<sup>12</sup> donde R<sup>11</sup> y R<sup>12</sup> representan ambos metilo.  
20 O, por ejemplo, el entendido en la técnica entenderá que los párrafos (36), (51) y (61) se podrían combinar para proporcionar un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, donde L<sup>1</sup> representa -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-, q representa 0 y R<sup>5</sup> representa metilo.

- (1) X representa -CH<sub>2</sub>-;
- 25 (2) X representa -NR<sup>8</sup>-;
- (3) X representa -O-;
- (4) X representa -S(O)<sub>n</sub>-;
- (5) R<sup>1</sup> representa alquiloC<sub>1-6</sub>, alcoxiC<sub>2-6</sub>, alcoxiC<sub>1-6</sub>alquiloC<sub>1-6</sub>, hidroxialquiloC<sub>1-6</sub>, hidroxialcoxiC<sub>1-6</sub>;
- 30 (6) R<sup>1</sup> representa alquiloC<sub>1-6</sub> o hidroxialquiloC<sub>1-6</sub>;
- (7) R<sup>1</sup> representa alquiloC<sub>1-6</sub>;
- (8) R<sup>1</sup> representa butilo;

- (9)  $R^2$  representa hidrógeno o alquiloC<sub>1-6</sub>;
- (10)  $R^2$  representa hidrógeno;
- (11)  $R^2$  representa alquiloC<sub>1-6</sub>;
- (12)  $R^2$  representa fenilo donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3  
5 sustituyentes seleccionados de  $R^6$ ;
- (13)  $R^2$  representa fenilo donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3  
sustituyentes seleccionados de halógeno o fluoroalquiloC<sub>1-6</sub>;
- (14)  $R^2$  representa fenilo donde dicho fenilo se sustituye opcionalmente por un único  
sustituyente seleccionado de  $-\text{CH}_2\text{-C(O)-O-alquiloC}_{1-6}$ ;
- 10 (15)  $R^2$  representa fenilo donde dicho fenilo se sustituye opcionalmente por un único  
sustituyente seleccionado de  $-\text{CH}_2\text{-C(O)-O-CH}_3$  o  $-\text{CH}_2\text{-C(O)-O-CH}_2\text{-CH}_3$ ;
- (16)  $R^3$  representa alquiloC<sub>1-6</sub>;
- (17)  $R^3$  representa metilo;
- (18)  $R^3$  representa alcoxiC<sub>1-6</sub>;
- 15 (19)  $R^3$  representa -S-alquiloC<sub>1-6</sub>;
- (20)  $R^4$  está unido en la posición orto del anillo fenilo, en relación al enlace -X-;
- (21)  $R^4$  representa hidrógeno, flúor, metilo o alcoxiC<sub>1-6</sub>;
- (22)  $R^4$  representa hidrógeno o alcoxiC<sub>1-6</sub>;
- (23)  $R^4$  representa hidrógeno;
- 20 (24)  $R^4$  representa alcoxiC<sub>1-6</sub>;
- (25)  $R^4$  representa metoxi;
- (26)  $L^1$  está unido en la posición para del anillo fenilo, en relación al enlace -X-;
- (27)  $L^1$  está unido en la posición meta del anillo fenilo, en relación al enlace -X-;
- (28)  $L^1$  está unido en la posición orto del anillo fenilo, en relación al enlace -X-;
- 25 (29)  $L^1$  representa  $-(\text{CR}^9\text{R}^{10})_m-$ ,  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$ , o  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ ,
- (30)  $L^1$  representa  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{C(O)-O}-(\text{CR}^9\text{R}^{10})_q-$ ;
- (31)  $L^1$  representa  $-\text{O}-(\text{CH}_2)_q\text{-NR}^8\text{-(CH}_2)_q-$ ;
- (32)  $L^1$  representa  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{C(O)-O}-(\text{CR}^9\text{R}^{10})_q-$  donde q representa 1, 2, 3, 4  
ó 5 y  $R^5$  representa  $-\text{NR}^{11}\text{R}^{12}$  o un anillo monocíclico de 4, 5, 6 ó 7 miembros  
30 heterocíclico que comprende 1, 2 ó 3 heteroátomos seleccionados  
independientemente de O, N o S, donde dichos anillos fenilo y heterocíclico se  
sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;

- (33)  $L^1$  representa  $-O-(CR^9R^{10})_q-$  o  $-C(O)-O-(CR^9R^{10})_q-$  donde  $R^9$  y  $R^{10}$  representan ambos hidrógeno,  $q$  representa 1, 2, 3, 4 ó 5 y  $R^5$  representa  $-NR^{11}R^{12}$  o un anillo monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dichos anillos fenilo y heterocíclico se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (34)  $L^1$  representa  $-O-(CR^9R^{10})_q-$ ;
- (35)  $L^1$  representa  $-O-(CR^9R^{10})_q-$  donde  $R^9$  y  $R^{10}$  representan ambos hidrógeno;
- (36)  $L^1$  representa  $-C(O)-O-(CR^9R^{10})_q-$ ;
- (37)  $L^1$  representa un enlace directo;
- (38)  $R^5$  representa hidroxilo,  $-NR^{11}R^{12}$ , cicloalquilo $C_{3-6}$ , fenilo o un anillo monocíclico, o heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dichos anillos fenilo y heterocíclico se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (39)  $R^5$  representa,  $-NR^{11}R^{12}$ , cicloalquilo $C_{3-6}$ , un anillo fenilo o monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dichos anillos fenilo y heterocíclico se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (40)  $R^5$  representa,  $-NR^{11}R^{12}$  o un anillo monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dicho anillo heterocíclico se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (41)  $R^5$  representa  $NR^{11}R^{12}$ ;
- (42)  $R^5$  representa  $NR^{11}R^{12}$  donde  $R^{11}$  y  $R^{12}$  representan ambos metilo;
- (43)  $R^5$  representa un anillo monocíclico, o heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dicho anillo heterocíclico se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (44)  $R^5$  representa un anillo monocíclico unido a nitrógeno, de 4,5,6 ó 7 miembros que comprenden opcionalmente, además del átomo de nitrógeno mediante el

cual el anillo heterocíclico está unido a  $L^1$ , 1 o 2 heteroátomos más, seleccionados independientemente de O, N o S donde dicho anillo heterocíclico se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;

- (45)  $R^5$  representa piperazinilo, piperidinilo o pirrolidinilo donde dicho anillo piperazinilo, piperidinilo o pirrolidinilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (46)  $R^5$  representa piperazin-1-ilo, piperidin-1-ilo o pirrolidin-1-ilo donde dicho anillo piperazin-1-ilo, piperidin-1-ilo o pirrolidin-1-ilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ ;
- (47)  $R^5$  representa piperazinilo, piperidinilo o pirrolidinilo donde dicho anillo piperazinilo, piperidinilo o pirrolidinilo se sustituye opcionalmente por un único sustituyente metilo;
- (48)  $R^5$  representa piperazin-1-ilo, piperidin-1-ilo o pirrolidin-1-ilo donde dicho anillo piperazin-1-ilo, piperidin-1-ilo o pirrolidin-1-ilo se sustituye opcionalmente por un único sustituyente metilo;
- (49)  $R^5$  representa un anillo piperazinilo, piperidinilo o pirrolidinilo no sustituido;
- (50)  $R^5$  representa fenilo;
- (51)  $R^5$  representa metilo;
- (52)  $R^5$  representa hidroxilo;
- (53)  $R^8$  representa hidrógeno o metilo;
- (54)  $R^8$  representa hidrógeno;
- (55)  $R^8$  representa metilo;
- (56) q representa 1, 2, 3, 4, 5 ó 6;
- (57) q representa 1, 2, 3 ó 4;
- (58) q representa 1, 2 ó 3;
- (59) q representa 2 ó 3;
- (60) q representa 3;
- (61) q representa 0.

Los nuevos compuestos particulares de la fórmula (I) incluyen, aunque no taxativamente, los siguientes compuestos:

5-(4-metoxibencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina;  
[4-(2-amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)]-fenol;

- 5-(4-(2-(dimetilamino)etoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(4-(3-(dimetilamino)propoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 6-metil-N<sup>4</sup>-pentil-5-(4-(2-(piperidin-1-il)etoxi)bencil)pirimidina-2,4-diamina;  
 6-metil-N<sup>4</sup>-pentil-5-(4-(2-(pirrolidin-1-il)etoxi)bencil)pirimidina-2,4-diamina;  
 5-(4-(2-(bencil(metil)amino)etoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 3-(4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenoxi)propan-1-ol;  
 6-metil-N<sup>4</sup>-pentil-5-(4-(3-(pirrolidin-1-il)propoxi)bencil)pirimidina-2,4-diamina;  
 6-metil-5-(4-(3-(4-metilpiperazin-1-il)propoxi)bencil)-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo;  
 4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato  
 de (S)-metilo;  
 4-((2-amino-4-(1-hidroxiheptan-3-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato  
 de (S)-metilo;  
 4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato  
 de (S)-4-(dimetilamino)butilo; Benceno sulfonato;  
 3-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-metoxibenzoato de metilo;  
 3-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-fluorobenzoato de metilo;  
 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo;  
 5-(2-metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 2-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenol;  
 5-(2-etoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(2-(3-(dimetilamino)propoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(3-metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 3-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenol;  
 5-(3-(3-(dimetilamino)propoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 6-metil-N<sup>4</sup>-pentil-5-(3-(2-(piperidin-1-il)etoxi)bencil)pirimidina-2,4-diamina;  
 5-(3-(2-(dimetilamino)etoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 6-metil-N<sup>4</sup>-pentil-5-(3-(2-(pirrolidin-1-il)etoxi)bencil)pirimidina-2,4-diamina;  
 5-(3-(3-(dimetilamino)metil)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(4-(3-(dimetilamino)prop-1-inil)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;  
 5-(4-(3-(dimetilamino)propil)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina;

5-(3-(3-(dimetilamino)propil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina;  
5-(4-(3-(dimetilamino)propoxi)-2-metilbencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina;  
2-(3-(1-(2-amino-5-(4-(3-(dimetilamino)propoxi)bencil)-6-metilpirimidin-4-ilamino)-3-hidroxi-  
propil)fenil)acetato de (R)-metilo;  
5 2-(3-(1-(2-amino-5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metilpirimidin-4-ilamino)-3-hidroxi-  
propil)fenil)acetat de (R)-metilo;  
y sales farmacéuticamente aceptables de este.

En una realización, se proporciona 4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de (*S*)-4-(dimetilamino)butilo.

10 En una realización adicional, se proporcionan compuestos de Fórmula (I) seleccionados de:

3-(4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxifenoxi)propan-1-ol;

5-(2-metoxi-4-(3-morpholinopropoxi)benzil)-6-metil- $N^4$ -pentilpirimidina-2,4-  
15 diamina;

5-(2-metoxi-4-(3-(4-metilpiperazin-1-il)propoxi)benzil)-6-metil- $N^4$ -  
pentilpirimidina-2,4-diamina;

5-(4-(4-(dimetilamino)butil)-2-metoxibenzil)-6-metil- $N^4$ -pentilpirimidina-2,4-  
diamina; y

20 (*S*)-2-(2-amino-5-(4-(hidroximetil)-2-metoxibenzil)-6-metilpirimidin-4-ilamino)pentan-1-ol;

y sales farmacéuticamente aceptables de estos.

En una realización de la invención, se proporciona cualquier Ejemplo descrito en la presente, o una sal farmacéuticamente aceptable de este.

25 Una sal apropiada farmacéuticamente aceptable de un compuesto de fórmula (I) es, por ejemplo una sal de adición de ácido de un compuesto de la fórmula (I), por ejemplo, una sal de adición de ácido con un ácido orgánico o inorgánico, por ejemplo, ácido clorhídrico, bromhídrico, sulfúrico, trifluoroacético, cítrico o maleico.

Los compuestos de la invención se pueden administrar en la forma de un  
30 profármaco, que es un compuesto que se desintegra en el cuerpo humano o animal para liberar un compuesto de la invención. Un profármaco se puede utilizar para alterar las propiedades físicas y/o las propiedades farmacocinéticas de un compuesto de la invención.

Un profármaco se puede formar cuando el compuesto de la invención contiene un grupo apropiado o sustituyente al cual se le puede unir un grupo modificador de propiedades. Los ejemplos de profármacos incluyen derivados de amida escindibles *in vivo*, que se pueden formar en un grupo amino en un compuesto de la fórmula (I).

5 Por consiguiente, la presente invención incluye aquellos compuestos de la fórmula I, según se definieron anteriormente, que se vuelven disponibles mediante síntesis orgánica y que se vuelven disponibles dentro del cuerpo humano o animal mediante la escisión de un profármaco de estos. Por consiguiente, la presente invención incluye aquellos compuestos de la fórmula (I) que se producen mediante medios de síntesis orgánica y  
10 también aquellos compuestos que se producen en el cuerpo humano o animal mediante el metabolismo de un compuesto precursor, es decir, un compuesto de la fórmula (I) puede ser un compuesto producido sintéticamente o un compuesto producido metabólicamente.

Un profármaco apropiado, farmacéuticamente aceptable de un compuesto de la fórmula (I) es aquel en el que el juicio médico razonable considera que es apropiado para  
15 ser administrado al cuerpo humano o animal sin actividades farmacológicas no deseadas ni toxicidad indebida.

Se han descrito varias formas de profármaco, por ejemplo, en los siguientes documentos:-

- a) Methods in Enzymology, Vol. 42, p. 309-396, editado por K. Widder, *et al.*  
20 Academic Press, 1985);
- b) Design of Pro-drugs, editado por H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, editado por Krogsgaard-Larsen y H. Bundgaard, Capítulo 5 "Design and Application of Prodrugs", por H. Bundgaard p. 113-191 (1991);
- 25 d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988);
- f) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984);
- g) T. Higuchi y V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volumen 14; y
- 30 h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

Un profármaco apropiado, farmacéuticamente aceptable de un compuesto de la fórmula (I) que posee un grupo amino es, por ejemplo, un derivado amida del mismo,

escindible *in vivo*. Las amidas apropiadas, farmacéuticamente aceptables de un grupo amino incluyen, por ejemplo, una amida formada por grupos alcanoilo $C_{1-10}$  como un acetilo, benzoilo, fenilacetilo y grupos benzoilo y fenilacetilo sustituidos. Los ejemplos de

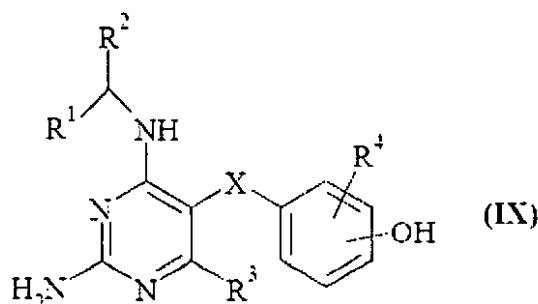
sustituyentes de anillo en los grupos fenilacetilo y benzoilos incluyen aminometil, *N*-alquilaminometilo, *N,N*-dialquilaminometilo, morfolinometilo, piperazin-1-ilmetilo y 4-(alquil $C_{1-4}$ )piperazin-1-ilmetilo.

Los efectos *in vivo* de un compuesto de la fórmula (I) los puede ejercer en parte uno o más metabolitos que se forman dentro del cuerpo humano o animal después de la administración de un compuesto de la fórmula (I). Como se estableció anteriormente, los efectos *in vivo* de un compuesto de la fórmula (I) también se pueden ejercer mediante el metabolismo de un compuesto precursor (un profármaco).

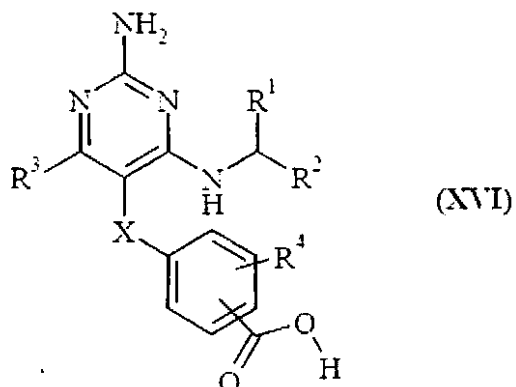
#### **Preparación de los compuestos de fórmula (I)**

Ciertos procesos para la síntesis de compuestos de la fórmula (I) se proporcionan como otra característica de la invención. Por lo tanto, de conformidad con otro aspecto de la invención, se proporciona un proceso para la preparación de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo, que comprende un proceso (a), (b), (c) o (d) donde, a menos que se defina lo contrario, las variables son según se las definió anteriormente para los compuestos de la fórmula (I):

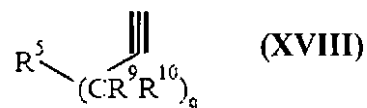
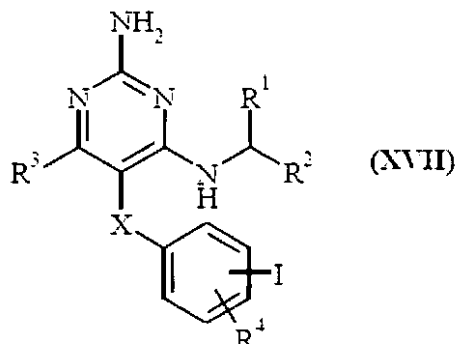
(a) cuando  $R^3$  representa alquilo $C_{1-6}$  y  $L^1$  representa  $-O-(CR^9R^{10})_q-$ , la reacción de un compuesto de la fórmula (IX) con un grupo halo- $(CR^9R^{10})_q-R^5$ ;



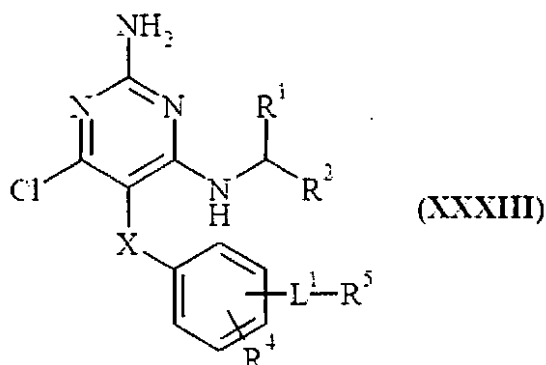
(b) cuando  $L^1$  representa  $-C(O)-O-(CR^9R^{10})_q-$  y  $R^5$  representa  $NR^{11}R^{12}$ , reacción de un ácido de la fórmula (XVI) con un alcohol de fórmula  $OH-(CR^9R^{10})_q-NR^{11}R^{12}$  en presencia de cloruro de oxalilo o cloruro de tionilo, un agente de acoplamiento apropiado y opcionalmente una base apropiada;



(c) cuando  $L^1$  representa  $-(CR^9R^{10})_m-$  (y m representa 2, 3, 4, 5 ó 6),  $-\text{CH}=\text{CH}-(CR^9R^{10})_q-$  o  $-\text{C}\equiv\text{C}-(CR^9R^{10})_q-$ , reacción de un compuesto de fórmula (XVII) con un compuesto de fórmula (XVIII) en presencia de un yoduro de cobre, un catalizador apropiado y una base apropiada;



(d) cuando  $R^3$  representa alcoxi $C_{1-6}$  o -S-alquilo $C_{1-6}$ , reacción de un compuesto de la fórmula (XXXIII) con el alcohol apropiado o alquiltiol en presencia de una base apropiada;

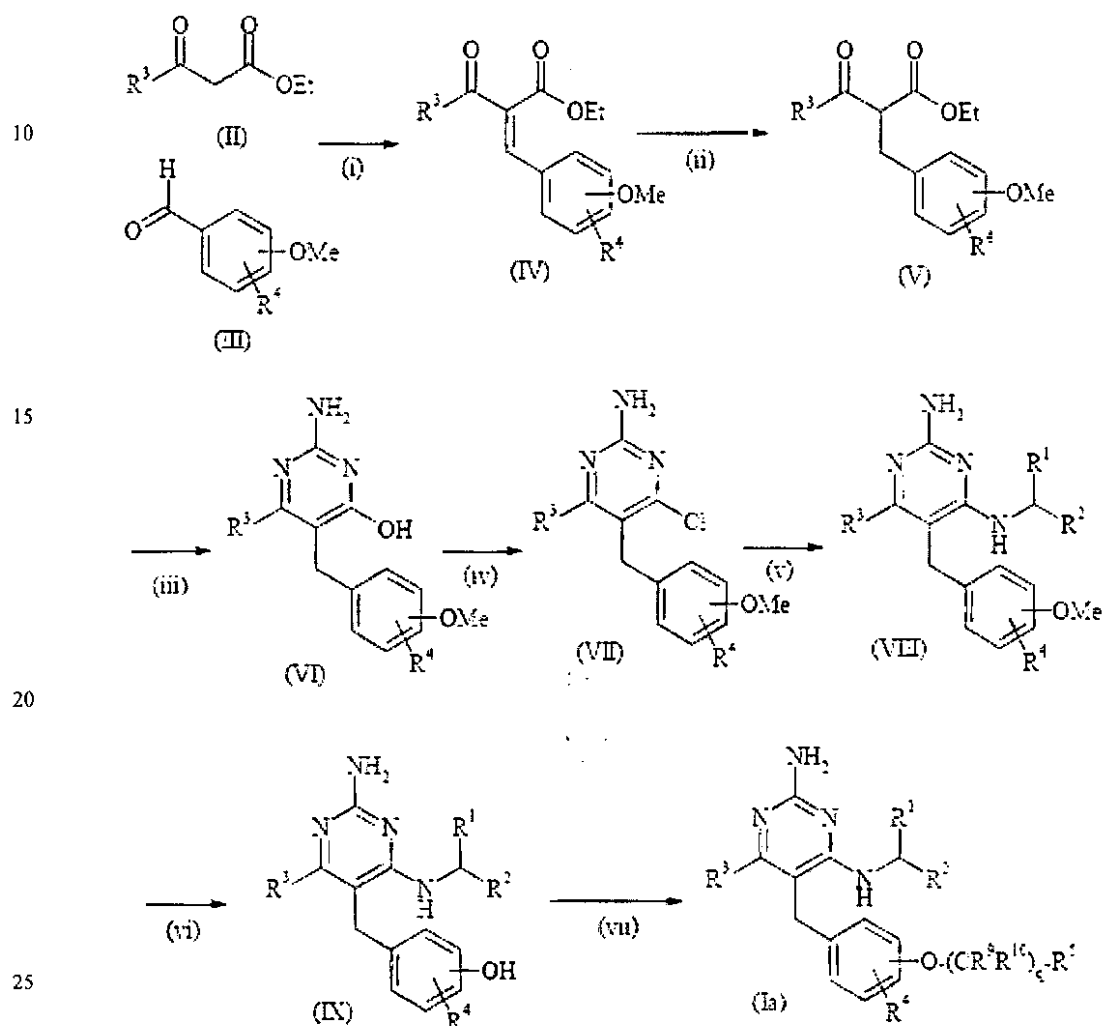


y los siguientes de ser necesarios:

- (i) convertir un compuesto de la Fórmula (I) en otro compuesto de la Fórmula (I);
- (ii) retirar todo grupo protector;
- (iii) separar una mezcla racémica en enantiómeros separados;
- (iv) preparar una sal farmacéuticamente aceptable del mismo; y/o

(v) preparar una forma cristalina de este.

Los compuestos de la fórmula (Ia) en los cuales X representa  $\text{CH}_2$ ,  $\text{R}^3$  representa alquilo $\text{C}_{1-6}$ ,  $\text{L}^1$  representa  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$ , Et representa un grupo etilo,  $\text{R}^4$  es otro que no sea alcoxi $\text{C}_{1-6}$  y todas las demás variables son como se definió anteriormente para los compuestos de la fórmula (I), se pueden preparar según se describe en el siguiente esquema de reacción 1.



Esquema 1

Etapa (i) – Se puede preparar un compuesto de fórmula (IV) mediante la reacción de un compuesto de la fórmula (III) con un compuesto de la fórmula (II). La reacción se puede realizar en presencia de ácido acético y piperidina en un solvente apropiado, como tolueno, y en una temperatura apropiada, por ejemplo de 50°C a 150°C.

Etapa (ii) - Se pueden preparar compuestos de la fórmula (V) mediante la reducción de un compuesto de la fórmula (IV). La reacción se puede realizar con un catalizador como Pd/C o bajo una atmósfera de H<sub>2</sub> (1-20 bar) en un solvente apropiado, como EtOH, y una temperatura apropiada, por ejemplo de 20°C a 100°C.

5 Etapa (iii)- Se pueden preparar los compuestos de la fórmula (VI) haciendo reaccionar un compuesto de la fórmula (V) con guanidina o carbonato de guanidina en un solvente apropiado, como MeOH o EtOH, y una temperatura apropiada, por ejemplo de 50°C a 150°C.

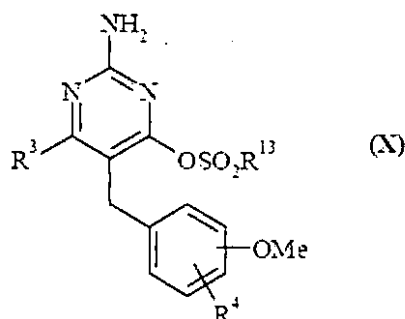
10 Etapa (iv)- Se pueden preparar compuestos de la fórmula (VII) haciendo reaccionar un compuesto de la fórmula (VI) con oxiclورو de fósforo, a una temperatura apropiada, por ejemplo de 50°C a 110°C.

Etapa (v)- Se pueden preparar compuestos de la fórmula (VIII) haciendo reaccionar un compuesto de la fórmula (VII) con un exceso de amina de la fórmula NH<sub>2</sub>CHR<sup>1</sup>R<sup>2</sup> en un solvente apropiado, como butanol o 1,4-dioxano, en una temperatura apropiada, por  
15 ejemplo de 50°C a 150°C. Alternativamente, la reacción se puede realizar en un microondas a una temperatura apropiada, por ejemplo de 50°C a 200°C.

Etapa (vi)- Se pueden preparar los compuestos de la fórmula (IX) haciendo reaccionar un compuesto de la fórmula (VIII) con una solución de BBr<sub>3</sub> en un solvente apropiado, como DCM, y en una temperatura apropiada, por ejemplo de 0°C a 15°C.

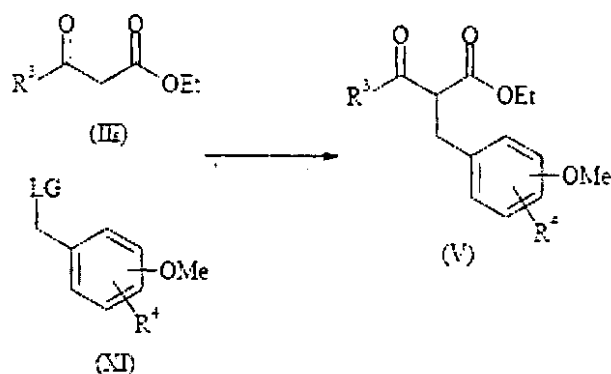
20 Etapa (vii) – los compuestos de la fórmula (IX) se pueden hacer reaccionar con un grupo halo R<sup>5</sup> o halo-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>-R<sup>5</sup> en presencia de una base apropiada, por ejemplo Cs<sub>2</sub>CO<sub>3</sub>, en un solvente apropiado, por ejemplo NMP o DMF, opcionalmente en presencia de NaI y a una temperatura apropiada, por ejemplo, de 50°C a 150°C, para proporcionar un compuesto de la fórmula (Ia).

25 En forma alternativa, los compuestos de la fórmula (VIII) se pueden preparar haciendo reaccionar un compuesto de la fórmula (X), en el cual R<sup>13</sup> representa un grupo arilo, con exceso de amina de la fórmula NH<sub>2</sub>CHR<sup>1</sup>R<sup>2</sup>. La reacción se puede realizar en un solvente apropiado, como butanol o 1,4-dioxano, y a una temperatura apropiada, por ejemplo de 50°C a 150°C. Alternativamente, la reacción se puede realizar en un  
30 microondas a una temperatura apropiada, por ejemplo, de 50°C a 200°C.



Se puede preparar un compuesto de la fórmula (X) haciendo reaccionar un compuesto de la fórmula (VI) con un sulfonylchloruro de arilo de fórmula  $R^{13}SO_2Cl$ . La reacción se puede realizar en un solvente apropiado, como DCM, en presencia de una base apropiada, como trietilamina o una DIPEA, y con la adición de un catalizador, como DMAP, a una temperatura apropiada, por ejemplo de  $0^\circ C$  a  $50^\circ C$ .

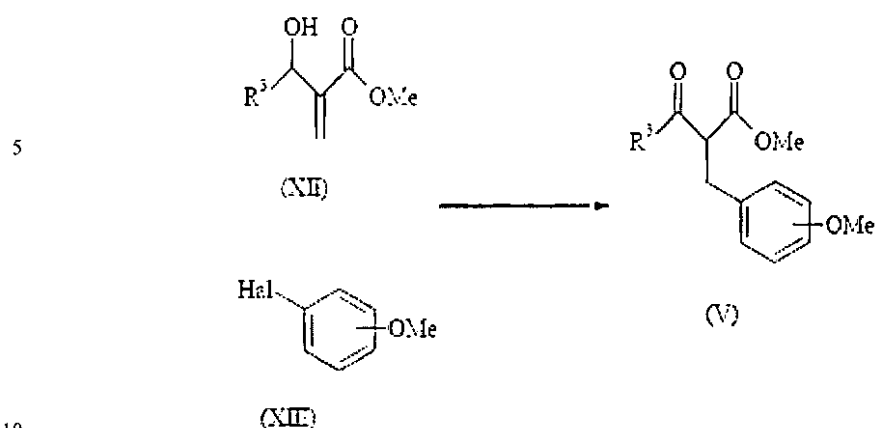
En forma alternativa, se pueden preparar compuestos de la fórmula (V) como se muestra en el Esquema 2, haciendo reaccionar un compuesto de la fórmula (III) con una base, como NaH, en un solvente apropiado, como THF o DMF, a una temperatura apropiada, por ejemplo de  $0^\circ C$  a  $20^\circ C$ , seguido de la adición de un compuesto de la fórmula (XI) donde LG representa un grupo saliente, por ejemplo, bromo o cloro. Después preferentemente se calienta la reacción, por ejemplo de  $50^\circ C$  a  $100^\circ C$ , opcionalmente en presencia de un aditivo como KI.



Esquema 2

En forma alternativa, se pueden preparar compuestos de la fórmula (V) mediante una reacción Heck entre un compuesto de la fórmula (XII) y un compuesto de la fórmula (XIII), según se muestra en el Esquema 3 donde Hal representa bromo o yodo. La reacción se puede realizar utilizando un catalizador de paladio, como  $Pd(OAc)_2$  o cloruro de 1,1'-bis(di-terc-butilfosfino)ferrocenopaladio(II) ( $Pd-118$ ), una base como  $NaHCO_3$  o dicitohexilmetilamina y cloruro o bromuro de tetrabutilamonio. La reacción se realiza en

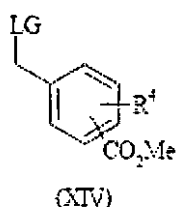
un solvente adecuado, como THF o DMA, y a una temperatura apropiada, por ejemplo de 50°C a 150°C.



Esquema 3

En forma alternativa los compuestos de fórmula (I) donde X representa CH<sub>2</sub>, y L<sup>1</sup> representa -C(O)-O- y R<sup>5</sup> representa metilo, se puede preparar según el Esquema 2, a partir de compuestos de la fórmula (XIV) donde LG representa bromo y que se encuentran disponibles comercialmente o se preparan mediante la brominación del precursor apropiado, utilizando N-bromosuccinimida en presencia de luz y un iniciador radical como di-benzoilo peróxido o 2,2'-azobisisobutironitrilo en un solvente apropiado, como DCM, CHCl<sub>3</sub> o CCl<sub>4</sub>.

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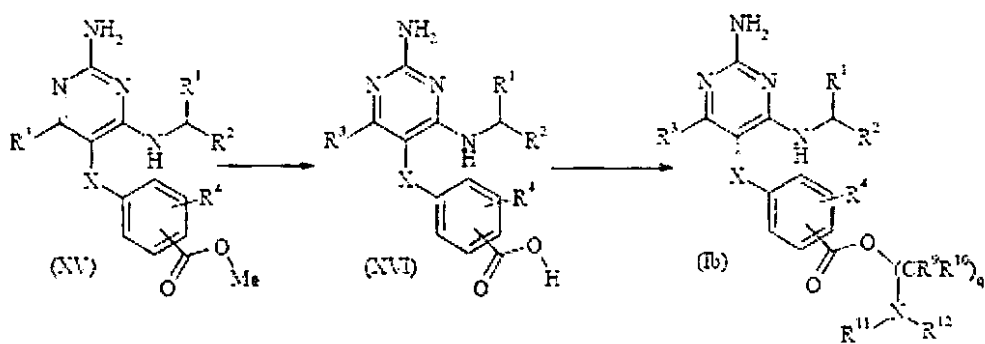
Los compuestos de la fórmula (Ib) donde L<sup>1</sup> representa -C(O)-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>q</sub>- y R<sup>5</sup> representa NR<sup>11</sup>R<sup>12</sup> se pueden preparar según el Esquema 4 a partir de compuestos de tipo (XV) mediante hidrólisis del éster en presencia de una base, como LiOH acuoso que contiene un alcohol como EtOH, y a una temperatura apropiada, por ejemplo, de 20°C a 50°C, seguido de la activación del ácido de la fórmula (XVI), por ejemplo, con COCl<sub>2</sub> o SOCl<sub>2</sub> o con un agente de acoplamiento como hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio o hexafluorofosfato de benzotriazol-1-

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iloxitripirrolidinofosfonio, y haciéndolo reaccionar con un grupo alcohol apropiado que contiene  $\text{NR}^{11}\text{R}^{12}$  en un solvente orgánico como NMP, DMF, MeCN o THF y generalmente en presencia de una base apropiada, por ejemplo trietilamina o DIPEA, y a una temperatura apropiada, por ejemplo de 0°C a 50°C.

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Esquema 4

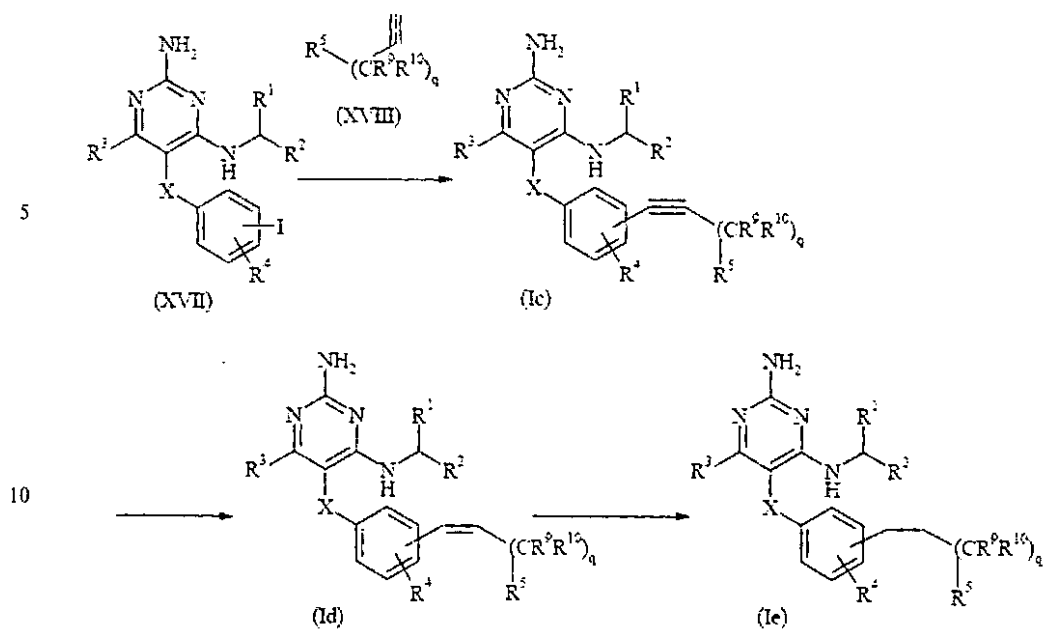
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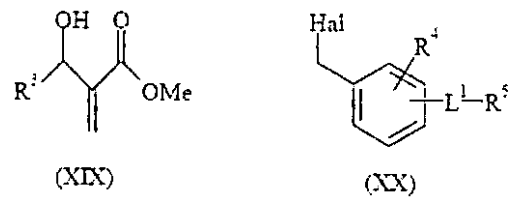
Los compuestos de la fórmula (Ic), (Id) o (Ie) donde  $\text{L}^1$  representa  $-(\text{CR}^9\text{R}^{10})_m-$  (y  $m$  representa 2, 3, 4, 5 ó 6),  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$  se pueden preparar según el Esquema 5 a partir de compuestos de la fórmula (XVII) haciéndolos reaccionar con alquinos de la fórmula (XVIII) en presencia de  $\text{CuI}$ , seguido de la adición de compuestos de la fórmula (XVII) y un catalizador  $\text{Pd}(0)$ , como  $\text{Pd}(\text{PPh}_3)_4$ , en un solvente apropiado, como THF, en presencia de una base apropiada, como trietilamina o DIPEA, y a una temperatura apropiada, por ejemplo de 50°C a 100°C durante 6-24 horas, para obtener los compuestos de la fórmula (Ic). La reducción de los compuestos de la fórmula (Ic) con un catalizador, como  $\text{Pd/C}$ , en un solvente apropiado, como EtOH, bajo una presión de  $\text{H}_2$ , como 1-3 bar, proporciona compuestos de fórmula (Id). Más reducción bajo las mismas condiciones proporciona los compuestos de la fórmula (Ie).

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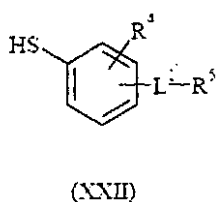
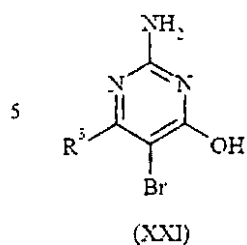
Esquema 5

Los compuestos de la fórmula (I) donde L<sup>1</sup> representa un enlace directo y R<sup>5</sup> representa un anillo monocíclico, heterocíclico de 4, 5, 6 ó 7 miembros se pueden preparar según el Esquema 3 a partir de compuestos de fórmula (XIX) y compuestos de fórmula (XX) y siguiendo las etapas del esquema de reacción 1 a partir de compuestos de fórmula (V). La reacción se puede realizar utilizando un catalizador de paladio, como acetato de paladio o Pd-118, una base como NaHCO<sub>3</sub> o diciclohexilmetilamina, y cloruro o bromuro de tetrabutilamonio. La reacción se realiza en un solvente adecuado, como THF o DMA, y a una temperatura apropiada, por ejemplo de 50°C a 150°C.

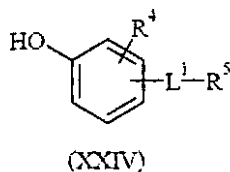
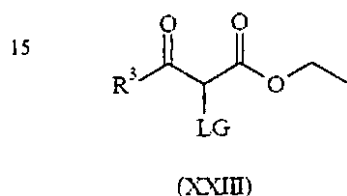


Un compuesto de fórmula (I) en el cual X representa un átomo de azufre se puede preparar haciendo reaccionar un compuesto de fórmula (XXI) con un compuesto de fórmula (XXII) y después, siguiendo las etapas del esquema de reacción 1 de la fórmula

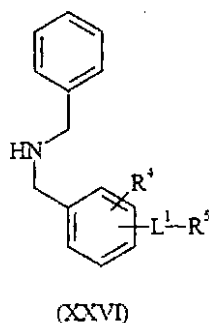
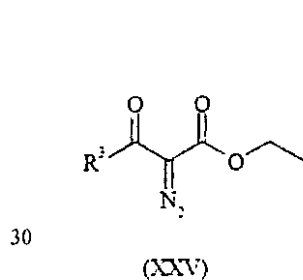
(VI). La reacción se puede realizar en un solvente apropiado, como etilenglicol, y una base como  $K_2CO_3$ , y a una temperatura apropiada, por ejemplo de  $80^\circ C$  a  $200^\circ C$ .



Un compuesto de fórmula (I) en el cual X representa un átomo de oxígeno se puede preparar haciendo reaccionar un compuesto de fórmula (XXIII), donde LG representa un grupo saliente apropiado, por ejemplo bromo, con un compuesto de fórmula (XXIV) y después, siguiendo las etapas del esquema de reacción 1 de la fórmula (V). La reacción se puede realizar en un solvente apropiado, como THF, y en presencia de una base, como  $K_2CO_3$ , y a una temperatura apropiada, por ejemplo de  $20^\circ C$  a  $100^\circ C$ .

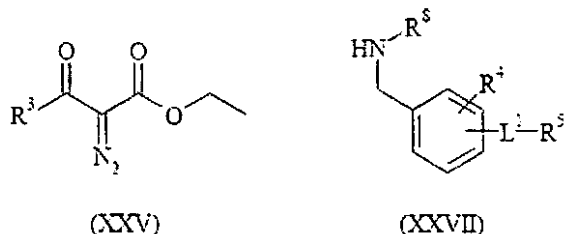


Un compuesto de fórmula (I) en el cual X representa un grupo NH se puede preparar haciendo reaccionar un compuesto de fórmula (XXV) con un compuesto de fórmula (XXVI) y después, siguiendo las etapas del esquema de reacción 1 de la fórmula (V). El grupo protector de bencilo se puede retirar mediante hidrogenación catalítica en una etapa conveniente en el camino. La reacción se puede realizar en un solvente apropiado, como tolueno, y con un catalizador apropiado, como acetato de rodio, y a una temperatura apropiada, por ejemplo de  $50^\circ C$  a  $150^\circ C$ .



Un compuesto de fórmula (I) en el cual X representa un grupo  $\text{NR}^8$ , donde  $\text{R}^8$  es alquilo $\text{C}_{1-6}$  se puede preparar haciendo reaccionar un compuesto de fórmula (XXV) con un compuesto de fórmula (XXVII) y siguiendo las etapas del esquema de reacción 1 de la fórmula (V).

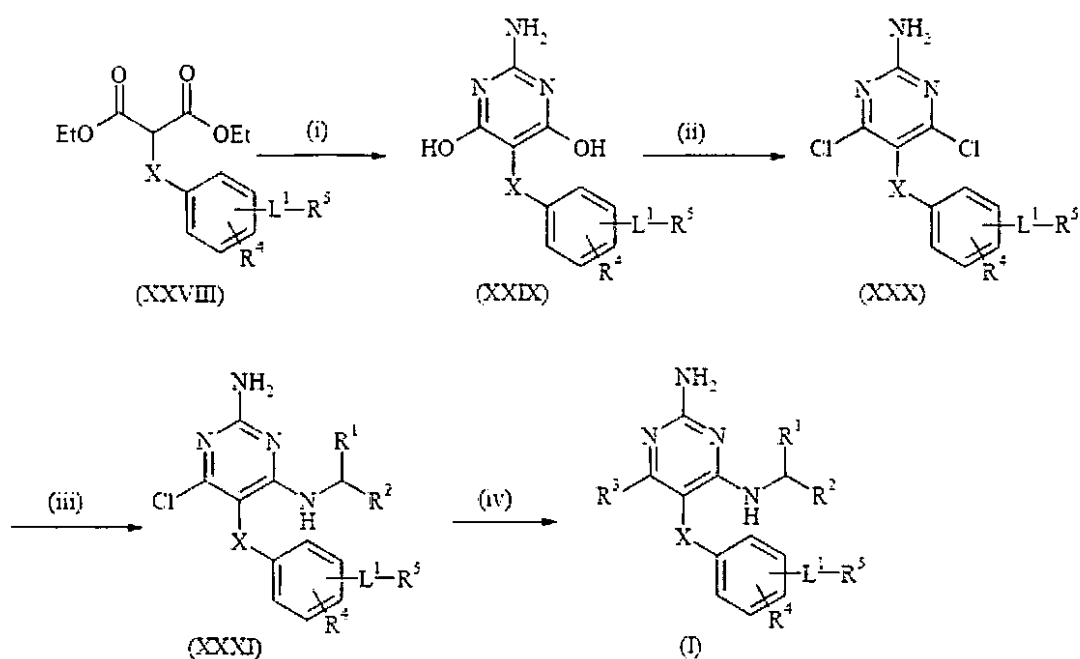
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Un compuesto de la fórmula (I) en el cual  $\text{R}^3$  representa un grupo alcoxi $\text{C}_{1-6}$  o  $-\text{S}$ -alquilo $\text{C}_{1-6}$  se puede preparar de conformidad con el Esquema 6.

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Esquema 6

Etapa (i)- Los compuestos de la fórmula (XXIX) se pueden preparar haciendo reaccionar un compuesto de la fórmula (XXVIII) con guanidina o carbonato de guanidina en un solvente apropiado, como MeOH o EtOH, y a una temperatura apropiada, por ejemplo de 50°C - 150°C.

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Etapa (ii)- Se pueden preparar compuestos de la fórmula (XXX) haciendo reaccionar un compuesto de la fórmula (XXIX) con  $\text{POCl}_3$ , a una temperatura apropiada, por ejemplo de 50°C a 110°C.

Etapa (iii)- Se pueden preparar compuestos de la fórmula (XXXI) haciendo reaccionar un compuesto de la fórmula (XXX) con un exceso de amina de la fórmula  $\text{NH}_2\text{CHR}^1\text{R}^2$  en un solvente apropiado, como butanol o 1,4-dioxano, y a una temperatura apropiada, por ejemplo de 50°C a 150°C. Alternativamente, la reacción se puede realizar en un microondas a una temperatura apropiada, por ejemplo de 0°C a 200°C.

Etapa (iv) – Se puede preparar un compuesto de fórmula (I) haciendo reaccionar un compuesto de la fórmula (XXXI) con el alcohol o alquiltiol apropiado, en presencia de una base apropiada, como NaH.

#### Ensayos biológicos

Se evaluó la capacidad de los compuestos para activar al TLR7 *in vitro*, utilizando el ensayo de TLR7 humano que se describe a continuación.

#### Ensayo de TLR7 humano

Se expresó de forma estable el TLR7 humano recombinante en una línea celular HEK293 que ya expresaba establemente el plásmido indicador pNiFty—SEAP; la integración del gen indicador se mantuvo mediante selección con el antibiótico zeocina. La secuencia variante más común de TLR7 humano (representada por la secuencia de EMBL AF240467) se clonó en el vector de expresión de célula de mamífero pUNO y se transfectó a esta línea celular indicadora. Se seleccionaron los transfectantes con expresión estable utilizando el antibiótico blasticidina. En esta línea celular indicadora, la expresión de la fosfatasa alcalina secretada (SEAP) es controlada por un promotor compuesto de NFkB/ELAM-1 que comprende cinco sitios NFkB combinados con el promotor ELAM-1 proximal. La señal TLR conduce a la translocación de NFkB y la activación del promotor resulta en la expresión del gen SEAP. Se evaluó la activación específica del TLR7 mediante la determinación del nivel de SEAP producido después de la incubación de las células, durante toda la noche, a 37°C, con el compuesto estándar, en presencia de 0,1% (v/v) de dimetilsulfóxido (DMSO). La inducción dependiente de la concentración de la producción de SEAP por los compuestos se expresó como la concentración de compuesto que produjo la mitad del nivel máximo de inducción de SEAP para ese compuesto ( $\text{EC}_{50}$ ). La actividad de TLR7 para los compuestos de la presente invención se evaluó utilizando el ensayo de TLR7 humano y los resultados se muestran en la Tabla 1 a continuación, donde el grado de activación de TLR7 para cada compuesto se expresa como un valor  $\text{pEC}_{50}$ .

Tabla 1

| Número de ejemplo | pEC50 |
|-------------------|-------|
| 1                 | 5,7   |
| 2                 | 5,9   |
| 3                 | 7,2   |
| 4                 | 7,2   |
| 5                 | 6,9   |
| 6                 | 7     |
| 7                 | 6,2   |
| 8                 | 6,3   |
| 9                 | 7,2   |
| 10                | 7,1   |
| 11                | 8,6   |
| 12                | 7,2   |
| 13                | 7     |
| 14                | 8     |
| 15                | 6,9   |
| 16                | 7,3   |
| 17                | 5,5   |
| 18                | 5,7   |
| 19                | 7,2   |
| 20                | 6,9   |
| 21                | 6,5   |
| 22                | 5,9   |
| 23                | 5,6   |
| 24                | 5,3   |
| 25                | 6,1   |
| 26                | 6,2   |
| 27                | 6,4   |
| 28                | 5,9   |

|    |     |
|----|-----|
| 29 | 6,5 |
| 30 | 7   |
| 31 | 7   |
| 32 | 6,6 |
| 33 | 6,6 |
| 34 | 5,7 |
| 35 | 6,5 |
| 36 | 7,3 |
| 37 | 8,1 |
| 38 | 8,2 |
| 39 | 8,4 |
| 40 | 7,7 |

De conformidad con otro aspecto de la invención también se proporciona una composición farmacéutica que incluye un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, como se los definió anteriormente, asociados con un vehículo, diluyente o excipiente farmacéuticamente aceptable. Las composiciones farmacéuticas pueden usarse en el tratamiento del cáncer. La composición puede ser en una forma apropiada para la administración oral, por ejemplo como tableta o cápsula; para inyección parenteral (inclusive intravenosa, subcutánea, intramuscular, intravascular o infusión), como solución estéril, suspensión o emulsión; para administración tópica como ungüento o crema; o para administración rectal como supositorio.

El compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, también se podrían administrar como un aerosol para inhalación. El aerosol (por ejemplo, atomizador, aerosol, preparación de polvo seco, etc.) se podría formular opcionalmente como una solución acuosa o suspensión, o como un aerosol suministrado desde un envase presurizado como un inhalador de dosis con medidor, presurizado, utilizando, por ejemplo, un propelente licuado. También se puede utilizar una preparación de polvo seco. Un aerosol apropiado para la inhalación puede ser ya sea una suspensión o solución, y generalmente contendría el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, y cualquier otro propelente adecuado como fluorocarbono o clorofluorocarbono que contenga hidrógeno, o una mezcla de estos. Específicamente,

puede contener hidrofluoroalcano, particularmente 1, 1, 1, 2- tetrafluoroetano, heptafluoroalcano (HFA) como 1, 1, 1, 2, 3, 3, 3-heptafluoro-n-propano, o una mezcla de estos. Un aerosol puede contener opcionalmente un excipiente de preparación adicional, conocido por los entendidos en la técnica, como un surfactante (por ejemplo, ácido oleico o lecitina) y cosolvente (por ejemplo; etanol ), etc. Específicamente, se podría suministrar una preparación en aerosol utilizando el inhalador conocido como "Turbuhaler<sup>TM</sup>".

Para la administración oral, el compuesto de la invención se puede mezclar con un vehículo o un adyuvante, por ejemplo, lactosa, sacarosa, sorbitol, manitol; un almidón, por ejemplo, almidón de papa, almidón de maíz o amilopectina, un derivado de celulosa, un aglutinante, por ejemplo, gelatina o polivinilpirrolidona; y/o un lubricante, por ejemplo, estearato de magnesio, estearato de calcio, glicoles de polietileno, un cera, parafina, y similares, y luego comprimirlo en pastillas. Si se requieren pastillas recubiertas, se pueden recubrir los centros, preparados como se describió antes, con una solución concentrada de azúcar que puede contener, por ejemplo, goma arábica, gelatina, talco y dióxido de titanio. Alternativamente, se puede recubrir la tableta con un polímero apropiado disuelto en un solvente orgánico que se vuelve volátil fácilmente.

Para la preparación de cápsulas de gelatina blanda, se puede mezclar el compuesto de la invención, por ejemplo, con un aceite vegetal o un glicol de polietileno. Las cápsulas de gelatina dura pueden contener gránulos del compuesto utilizando ya sea los excipientes para pastillas mencionados anteriormente. También se pueden llenar cápsulas de gelatina dura con formulaciones del compuesto líquidas o semisólidas.

Las preparaciones líquidas para aplicación oral pueden ser en forma de jarabes o suspensiones, por ejemplo, soluciones que contengan el compuesto de la invención, haciendo un equilibrio entre azúcar y una mezcla de etanol, agua, glicerol y propilenglicol. Opcionalmente dichas preparaciones líquidas pueden contener agentes colorantes, agentes saborizantes, sacarina y/o carboximetilcelulosa como un agente espesante u otros excipientes conocidos para aquellos entendidos en el área.

El compuesto de la formula (I) normalmente se administrará a un animal de sangre caliente en una unidad de dosis en el rango de 5 a 5000 mg/m<sup>2</sup> del área corporal del animal, es decir, aproximadamente 0,1 a 100 mg/kg y esto normalmente proporciona una dosis terapéuticamente efectiva. Una forma de unidad de dosis como un comprimido o cápsula generalmente contendrá, por ejemplo 1-250 mg de ingrediente activo.

Preferiblemente se utiliza una dosis diaria en el rango de 1-50mg/kg. Sin embargo, la dosis diaria necesariamente variará en función del huésped que se está tratando, la vía particular de administración, y la gravedad de la enfermedad que se está tratando. Por consiguiente, el médico que trate cualquier paciente particular podrá determinar la dosificación óptima.

5 Para más información sobre las vías de administración y el régimen de dosificación, véase el Capítulo 25.3 del Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

En el contexto de la presente memoria descriptiva, el término "terapia" también incluye "profilaxis" a menos que se especifique lo contrario. Los términos "terapéutico" y  
10 "terapéuticamente" se interpretarán de conformidad a esto.

Según se utiliza en la presente, el término "tratamiento" tiene el significado que se le atribuye normalmente de tratar una enfermedad a los efectos de aliviar por completo o parcialmente uno, alguno todos sus síntomas, o de corregir o compensar la patología subyacente.

15 Según se utiliza en la presente, el término "profilaxis" tiene el significado que se le atribuye normalmente e incluye profilaxis primaria para impedir el desarrollo de la enfermedad y profilaxis secundaria, en la cual la enfermedad ya se ha desarrollado y el paciente es protegido temporal o permanentemente de la exacerbación o empeoramiento de la enfermedad, o del desarrollo de nuevos síntomas asociados a la enfermedad.

20 Los compuestos definidos en la presente invención son activadores efectivos de TLR7 *in vitro*. Por consiguiente, se espera que los compuestos de la presente invención sean agentes potencialmente útiles en el tratamiento de enfermedades o afecciones médicas provocadas solo o en parte por el TLR7. Por ejemplo, las siguientes enfermedades y afecciones enumeradas en los párrafos 1 a 8 a continuación, pueden tratarse con  
25 compuestos de la presente invención.

1. tracto respiratorio: enfermedades obstructivas de las vías respiratorias que incluyen: asma, incluido el bronquial, alérgico, intrínseco, extrínseco, inducido por ejercicio, inducido por fármacos (incluido el inducido por la aspirina y medicamentos antiinflamatorios no esteroideos NSAID), e inducido por inhalación de polvo, tanto  
30 intermitente como persistente de todas las intensidades, y otras causas de hiperreactividad de las vías respiratorias; enfermedad pulmonar obstructiva crónica (COPD); bronquitis, incluida la bronquitis infecciosa y eosinofílica; enfisema, bronquiectasia, fibrosis quística;

- sarcoidosis; pulmón del granjero y otras enfermedades relacionadas; pneumonitis por hipersensibilidad, fibrosis pulmonar, incluida la alveolitis fibrosa criptogénica, pneumonía intersticial idiopática, terapia anti-neoplásica complicada por fibrosis e infección crónica, inclusive tuberculosis y aspergilosis y otras infecciones micóticas; complicaciones de los trasplantes de pulmón, trastornos trombóticos y vasculíticos, e hipertensión pulmonar; actividad antitusígena inclusive el tratamiento de tos crónica asociada a afecciones inflamatorias y secretorias de las vías respiratorias, y tos iatrogénica; rinitis aguda y crónica incluida la rinitis medicamentosa y rinitis vasomotora; rinitis alérgica estacional y perenne inclusive rinitis nerviosa (fiebre del heno); poliposis nasal, infección viral aguda incluida resfriado común, e infección debida a virus sincitial respiratorio, influenza, coronavirus (incluido SRAS) y adenovirus;
2. piel: psoriasis, dermatitis atópica, dermatitis por contacto u otras dermatitis eczematosas, reacciones de hipersensibilidad retardada; fito-y fotodermatitis; dermatitis seborreica, dermatitis herpetiforme, lichen planus, liquen escleroso y atrófico, hipoderma gangrenoso, sarcoidosis cutánea, lupus eritematoso discoide, pénfigo, penfigoide, epidermolisis bullosa, urticaria, angioedema, vasculitis, eritema tóxico, eosinofilias cutáneas, alopecia areata, patrón masculino de calvicie, síndrome de Sweet, síndrome de Weber-Christian, eritema multiforme; celulitis, tanto infecciosa como no infecciosa; paniculitis, linfomas cutáneos, cáncer de piel no-melanoma y otras lesiones displásicas; trastornos inducidos por fármacos inclusive erupciones fijas medicamentosas;
3. ojos: blefaritis, conjuntivitis, inclusive conjuntivitis alérgica vernal y perenne; iritis, uveítis anterior y posterior; coroiditis; trastornos autoinmunes, degenerativos o inflamatorios que afectan la retina; oftalmitis inclusive oftalmitis simpática; sarcoidosis; infecciones inclusive virales, micóticas y bacteriales;
4. genitourinaria: nefritis inclusive intersticial y glomerulonefritis; síndrome nefrótico; cistitis inclusive cistitis aguda y crónica (intersticial) y úlcera de Hunner, uretritis aguda y crónica, prostatitis, epididimitis, ooforitis y salpingitis; vulvovaginitis; enfermedad de Peyronie; disfunción eréctil (tanto masculina como femenina);
5. rechazo al alotransplante: agudo y crónico luego de, por ejemplo, transplante de riñón, corazón, hígado, pulmón, médula ósea, piel o córnea o luego de transfusiones de sangre; o enfermedad de injerto contra huésped crónica;

6. otros trastornos alérgicos y autoinmunes inclusive artritis reumatoide, síndrome de intestino irritable, lupus eritematoso sistémico, esclerosis múltiple, tiroiditis de Hashimoto, enfermedad de Graves, enfermedad de Addison, diabetes mellitus, púrpura trombocitopénica idiopática, fasciitis eosinofílica, síndrome de hiper IgE, síndrome antifosfolípido y síndrome de Sazary;

7. oncología: tratamiento de cánceres comunes inclusive tumores de próstata, mama, pulmón, ovario, páncreas, intestino y colon, estomago, piel y cerebro y malignidades que afectan la médula espinal (inclusive las leucemias) y sistemas linfoproliferativos, como linfoma de Hodgkin y no de Hodgkin; inclusive la prevención y tratamiento de

enfermedades metastáticas y recurrencia tumoral, y síndromes paraneoplásicos; y,

8. enfermedades infecciosas: enfermedades virales como verrugas genitales, verrugas comunes, verrugas plantares, hepatitis B, hepatitis C, virus del herpes simple, molluscum contagiosum, viruela, síndrome de inmunodeficiencia humano (VIH), virus del papiloma humano (VPH), citomegalovirus (CMV), virus varicela zoster (VVZ), rinovirus, adenovirus, coronavirus, gripe, virus paragripal; enfermedades bacterianas como tuberculosis y mycobacterium avium, lepra; otras enfermedades infecciosas, como enfermedades fungosas, clamidia, candida, aspergillus, meningitis criptocócica, pneumocistitis Carinii, criptosporidosis, histoplasmosis, toxoplasmosis, infección por tripanosoma y leishmaniosis.

Se prevé que para los métodos de tratamiento mencionados anteriormente, el compuesto de fórmula (I) se administrará a un mamífero, más particularmente a un ser humano. De modo similar, para los usos de un compuesto de fórmula (I) para el tratamiento de enfermedades o afecciones médicas aquí mencionados, se prevé que el compuesto de fórmula (I) se administre a un mamífero, más particularmente a un ser humano.

De conformidad con otro aspecto de la invención se proporciona por lo tanto, un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para ser utilizado como medicamento.

De conformidad con otro aspecto más de la invención se proporciona por lo tanto, un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para ser utilizado en el tratamiento de una enfermedad provocada a través del TLR7. En una realización de la invención, dicha

enfermedad provocada a través del TLR7 es cáncer. En otra realización de la invención, dicho cáncer se selecciona de cáncer de próstata, cáncer de mama, cáncer de pulmón, cáncer de útero, cáncer de páncreas, cáncer de hígado, cáncer renal, cáncer de ovario, cáncer de colon, cáncer de estómago, cáncer de piel, tumor cerebral, mieloma maligno y tumores linfoproliferativos. En una realización de la invención, dicha enfermedad provocada a través del TLR7 es asma, COPD, rinitis alérgica, conjuntivitis alérgica, dermatitis atópica, hepatitis B, hepatitis C, VIH, VPH, infecciones bacterianas o dermatosis.

De conformidad con otro aspecto más de la invención se proporciona el uso de un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para la preparación de un medicamento para el tratamiento de una enfermedad provocada a través del TLR7. En una realización de la invención, dicha enfermedad provocada a través del TLR7 es cáncer. En otra realización de la invención, dicho cáncer se selecciona de cáncer de próstata, cáncer de mama, cáncer de pulmón, cáncer de útero, cáncer de páncreas, cáncer de hígado, cáncer renal, cáncer de ovario, cáncer de colon, cáncer de estómago, cáncer de piel, tumor cerebral, mieloma maligno y tumores linfoproliferativos. En una realización de la invención, dicha enfermedad provocada a través del TLR7 es asma, COPD, rinitis alérgica, conjuntivitis alérgica, dermatitis atópica, hepatitis B, hepatitis C, VIH, VPH, infecciones bacterianas o dermatosis.

De conformidad con otro aspecto más de la invención se proporciona el uso de un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para la preparación de un medicamento para el tratamiento del cáncer. En una realización de la invención, dicho cáncer se selecciona de cáncer de próstata, cáncer de mama, cáncer de pulmón, cáncer de útero, cáncer de páncreas, cáncer de hígado, cáncer renal, cáncer de ovario, cáncer de colon, cáncer de estómago, cáncer de piel, tumor cerebral, mieloma maligno y tumores linfoproliferativos.

De conformidad con otro aspecto más de la invención se proporciona el uso de un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para la preparación de un medicamento para el tratamiento del asma, COPD, rinitis alérgica, conjuntivitis alérgica, dermatitis atópica, hepatitis B, hepatitis C, VIH, VPH, infecciones bacterianas o dermatosis.

En un aspecto de la invención, se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable de este para uso en el tratamiento del cáncer.

De conformidad con otro aspecto más de la invención se proporciona un método para utilizar un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para el tratamiento del cáncer. En una realización de la invención, dicho cáncer se selecciona de cáncer de próstata, cáncer de mama, cáncer de pulmón, cáncer de útero, cáncer de páncreas, cáncer de hígado, cáncer renal, cáncer de ovario, cáncer de colon, cáncer de estómago, cáncer de piel, tumor cerebral, mieloma maligno y tumores linfoproliferativos.

De conformidad con otro aspecto más de la invención se proporciona un método de uso de un compuesto de la fórmula (I), según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, para el tratamiento del asma, COPD, rinitis alérgica, conjuntivitis alérgica, dermatitis atópica, hepatitis B, hepatitis C, VIH, VPH, infecciones bacterianas o dermatosis.

De conformidad con otro aspecto de la invención, se proporciona un método para tratar a un ser humano que sufra de una enfermedad en la cual la activación de TLR7 es beneficiosa, comprende las etapas de administrar a una persona que lo necesite una cantidad terapéuticamente efectiva de un compuesto de fórmula (I) según se definió anteriormente, o una sal farmacéuticamente aceptable de este. En una realización de la invención, la enfermedad en la cual la activación de TLR7 es beneficiosa es cáncer. En otra realización de la invención, dicho cáncer se selecciona de cáncer de próstata, cáncer de mama, cáncer de pulmón, cáncer de útero, cáncer de páncreas, cáncer de hígado, cáncer renal, cáncer de ovario, cáncer de colon, cáncer de estómago, cáncer de piel, tumor cerebral, mieloma maligno y tumores linfoproliferativos. En una realización de la invención, la enfermedad en la cual la activación de TLR7 es beneficiosa es asma, COPD, rinitis alérgica, conjuntivitis alérgica, dermatitis atópica, hepatitis B, hepatitis C, VIH, VPH, infecciones bacterianas o dermatosis.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de próstata.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de mama.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de pulmón.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de útero.

5 En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de páncreas.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de hígado.

10 En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de riñón.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de ovario.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de colon.

15 En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de estómago.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de piel.

20 En cualquier aspecto o realización descritos en la presente, el cáncer puede ser tumor cerebral.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser cáncer de melanoma maligno.

En cualquier aspecto o realización descritos en la presente, el cáncer puede ser tumores linfoproliferativos.

25 El tratamiento anticancerígeno que aquí se define puede ser aplicado como tratamiento único o puede incluir, además del compuesto de la invención, cirugía convencional, radioterapia o quimioterapia. Dicha quimioterapia puede incluir una o más de las siguientes categorías de agentes anti-tumorales:-

(i) otros fármacos antiproliferativos/antineoplásticos y combinaciones de estos,  
30 utilizados en oncología médica, como agentes alquilantes (por ejemplo, cisplatinos, oxaliplatinas, carboplatinos, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfán, temozolamida y nitrosoureas); antimetabolitos (por ejemplo, gemcitabina y

antifolatos como las fluoropirimidinas como 5- fluorouracil y tegafur, raltrexed, metotrexato, citocina arabinosida e hidroxiurea); antibióticos antitumorales (por ejemplo, antraciclinas como la adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo, alcaloides de la vinca como la vincristina, vinblastina, vindesina y vinorelbina y taxoides como el taxol y el taxotere, e inhibidores de la polocinasa); inhibidores de la topoisomerasa (por ejemplo, epipodofilotoxinas como etoposida y teniposida, amsacrina, topotecan y camptothecin);

(ii) agentes citoestáticos como los antiestrógenos (por ejemplo, tamoxifen, fulvestrant, toremifeno, raloxifeno, droloxifeno e idoxifeno), antiandrógenos (por ejemplo, bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas LHRH o agonistas de LHRH (por ejemplo, goserelina, leuprorelina y buserelina), progestágenos (por ejemplo, acetato de megestrol), inhibidores de aromatasa (por ejemplo, anastrozol, letrozol, vorazol y exemestan) e inhibidores de 5 $\alpha$ - reductasa como la finasterida;

(iii) agentes anti invasión [por ejemplo inhibidores de la familia c-Src quinasa como 4-(6-cloro-2,3-metilenodioxianilino)-7-[2-(4-metilpiperazin-1-il)etoxi]-5-tetrahidropiran- 4-iloxiquinazolina (AZD0530; Solicitud de Patente Internacional WO 01/94341), N-(2-cloro-6-metilfenil)-2-{6-[4-(2-hidroxietil)piperazin-1-il]-2-metilpirimidin-4-ilamino}tiazol-5-carboxamida (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, 47, 6658-6661) y bosutinib (SKI-606) e inhibidores de metaloproteinasas como marimastat, inhibidores de la función del receptor del activador del plasminógeno uroquinasa o anticuerpos de heparanasa];

(iv) inhibidores de la función del factor de crecimiento: por ejemplo dichos inhibidores incluyen anticuerpos del factor de crecimiento y anticuerpos del receptor del factor de crecimiento (por ejemplo, el anticuerpo anti-erbB2 trastuzumab [Herceptin<sup>TM</sup>], el anticuerpo anti-EGFR panitumumab, el anticuerpo anti-erbB1 cetuximab [Erbix, C225] y cualquier anticuerpo del factor de crecimiento o del receptor del factor de crecimiento divulgados por Stern et al. *Critical reviews in oncology/hematology*, 2005, Vol. 54, pp11-29); dichos inhibidores incluyen también inhibidores de tirosina quinasa, por ejemplo inhibidores de la familia del factor de crecimiento epidermal (por ejemplo, los inhibidores de tirosina quinasa de la familia EGFR como N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, ZD1839), N-(3-etilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI-774) y 6-acrilamido-N-(3-cloro-4-

- fluorofenil)-7-(3-morfolinopropoxi)-quinazolin-4-amina (CI 1033), inhibidores de la tirosina quinasa erbB2 como lapatinib); inhibidores de la familia del factor de crecimiento hepatocita; inhibidores de la familia del factor de crecimiento de insulina; inhibidores de la familia del factor de crecimiento derivado de plaquetas como imatinib y/o nilotinib
- 5 (AMN107); inhibidores quinasa serina/treonina (por ejemplo, inhibidores de la señal Ras/Raf como inhibidores de farnesil transferasa, por ejemplo sorafenib (BAY 43-9006), tipifarnib (R115777) y lonafarnib (SCH66336)), inhibidores de la señal celular a través de MEK y/o quinasa AKT, inhibidores c-kit, inhibidores de quinasa abl, inhibidores de quinasa PI3, inhibidores de quinasa Plt3, inhibidores de quinasa CSF-1R, inhibidores de
- 10 quinasa del receptor IGF (factor de crecimiento similar a la insulina); inhibidores de quinasa aurora (por ejemplo, AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 y AX39459) e inhibidores de quinasa dependientes de ciclina como los inhibidores de CDK2 y/o CDK4;
- (v) agentes antiangiogénicos como aquellos que inhiben los efectos del factor de
- 15 crecimiento endotelial vascular, [por ejemplo, el anticuerpo de factor de crecimiento celular entotelial anti vascular como el bevacizumab (Avastin™) y por ejemplo, un inhibidor del receptor de tirosina quinasa (VEGF) como el vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) y 4-(4-fluoro-2-metilindol-5-iloxi)-6-metoxi-7-(3-pirrolidin-1-ilpropoxi) quinazolina (AZD2171;
- 20 Ejemplo 240 dentro de WO 00/47212) , compuestos como los divulgados en las solicitudes de patente internacionales WO97/22596, WO 97/30035, WO 97/32856 y WO 98/13354 y compuestos que funcionan mediante otros mecanismos (por ejemplo, linomida, inhibidores de la función de las integrinas  $\alpha v \beta 3$  y angioestatina)];
- (vi) agentes de daño vascular como Combrestatin A4 y compuestos divulgado en las
- 25 Solicitudes de patente internacional WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;
- (vii) un antagonista del receptor de endotelina, por ejemplo zibotentan (ZD4054) o atrasentan;
- (viii) terapias anti sentido, por ejemplo aquellas dirigidas a los objetivos enumerados
- 30 anteriormente, como ISIS 2503, un antisentido anti-ras;
- (ix) abordajes terapéuticos de genes, incluidos por ejemplo, abordajes que sustituyen genes aberrantes como ser el p53 aberrante o BRCA1 aberrante o BRCA2, GDEPT

(terapia de profármacos de enzimas dirigidos a los genes) abordajes tales como los que utilizan citocina deaminasa, timidina quinasa o una enzima nitrorreductasa bacteriana y abordajes para aumentar la tolerancia del paciente a la quimioterapia o radioterapia como la terapia génica de resistencia a múltiples fármacos; y

- 5 (x) abordajes inmunoterapéuticos, incluyendo por ejemplo abordajes ex-vivo e in-vivo para aumentar la inmunogenicidad de las células tumorales de los pacientes, como la transfección con citoquinas como interleucina 2, interleucina 4 o factor estimulante de colonia macrófago granulocito, abordajes para disminuir la anergia de células-T, abordajes que utilizan células inmunes transfectadas como ser las células dendríticas citoquinas –
- 10 transfectadas, abordajes que utilizan líneas de células de tumor citoquinas-transfectadas, y abordajes que utilizan anticuerpos anti-idiotípicos, abordajes para reducir la función de células inmunosupresoras como las células T regulatorias, las células supresoras derivadas de origen mieloide o las células dendríticas que expresan la IDO (indolamina 2,3,-
- 15 desoxigenasa) y abordajes que utilizan vacunas para el cáncer que consisten en proteínas o péptidos derivados de antígenos asociados a tumores como NY-ESO-1, MAGE-3, WT1 o Her2/neu.

De conformidad con este aspecto de la invención se proporciona un producto farmacéutico que comprende un compuesto de fórmula (I) como se define anteriormente y una sustancia antitumoral adicional como se define anteriormente para el tratamiento

20 conjunto del cáncer.

De conformidad con este aspecto de la invención, se proporciona una combinación apropiada para el uso en el tratamiento del cáncer, que comprende un compuesto de fórmula I, según se definió anteriormente, o una sal farmacéuticamente aceptable del mismo, y cualquiera de los agentes antitumorales enumerados anteriormente del (i)-(ix).

25 Por lo tanto, en otro aspecto de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente.

En la presente, cuando se utiliza el término “combinación” se debe entender que se refiere a la administración simultánea, separada o secuencial. En un aspecto de la

30 invención “combinación” se refiere a la administración simultánea. En otro aspecto de la invención “combinación” se refiere a la administración separada. En otro aspecto de la invención “combinación” se refiere a la administración secuencial. Cuando la

administración es secuencial o separada, la demora en la administración del segundo componente no debe ser tanta como para que se pierda el efecto beneficioso de la combinación.

De conformidad con otro aspecto de la invención, se proporciona una composición  
5 farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente, en asociación con un diluyente o vehículo farmacéuticamente aceptable.

De conformidad con otro aspecto de la invención, se proporciona una composición  
10 farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente, en asociación con un diluyente o vehículo farmacéuticamente aceptable, para usar en el tratamiento del cáncer.

De conformidad con otra característica de la invención, se proporciona el uso de un  
15 compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente, en la elaboración de un medicamento para usar en un animal de sangre caliente como el hombre.

De conformidad con otra característica de la invención, se proporciona un  
20 compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente, para usar en el tratamiento del cáncer en un animal de sangre caliente como el hombre.

Por lo tanto, en una característica adicional de esta invención se proporciona un  
25 método para tratar el cáncer en un animal de sangre caliente como el ser humano, que necesite tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente.

30 De conformidad con otro aspecto de la presente invención, se proporciona un kit que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del

mismo, en combinación con un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente.

De conformidad con otro aspecto de la presente invención se proporciona un kit compuesto de:

- 5 a) un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, en forma de una primera dosis;
- b) un agente antitumoral seleccionado de uno de los enumerados del (i) al (ix) anteriormente; en una segunda forma de unidad de dosis; y
- c) métodos contenedores para contener la primera y segunda dosis mencionada.

10 En un aspecto de la invención, los compuestos de Fórmula (I) pueden ser útiles como adyuvantes de vacuna.

Como aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de este, como se define en la presente, para uso como un adyuvante de vacuna.

15 Como aspecto adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de este, como se define en la presente, como un adyuvante de vacuna, en la fabricación de una vacuna para el tratamiento de una enfermedad o un trastorno.

La invención proporciona además un procedimiento para tratar o reducir el riesgo  
20 de una enfermedad o un trastorno, método que comprende administrar a un paciente que lo necesite una cantidad terapéuticamente efectiva de una vacuna y un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de este, como se define en la presente.

La invención proporciona además un método para aumentar la respuesta a una vacuna en un paciente, método que comprende administrar a un paciente que lo necesite  
25 una cantidad terapéuticamente efectiva de una vacuna y un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de este, como se define en la presente.

### **Ejemplos**

La invención se ilustrará ahora con los siguientes ejemplos en los cuales generalmente, a menos que se indique lo contrario, todos los materiales de partida se  
30 encuentran disponibles comercialmente. Todos los solventes y reactivos comerciales utilizados en los ejemplo eran de categoría de laboratorio y se utilizaron todos tal como se recibieron. Todas las operaciones se realizaron a temperatura ambiente, es decir, en el

espectro de 17 a 28°C, típicamente 20°C, y, cuando correspondía, en una atmósfera de un gas inerte como el nitrógeno. Calentamiento en “microondas” se refiere al calentamiento a temperatura constante, utilizando irradiación de microondas variable en un reactor de microondas CEM Discover™. Las reacciones de hidrogenación se realizaron utilizando un sistema Büchi Peteric™ o un sistema ThalesNano H-Cube™, según se describe. La concentración de todas las soluciones se realizó mediante la evaporación bajo presión reducida (al vacío), por ejemplo, utilizando un evaporador rotativo Büchi Rotavapor™.

La cromatografía de capa fina (TLC) se realizó utilizando placas con respaldo de vidrio o aluminio recubierto con sílice (tamaño de partícula <63 µm; porosidad 60 Å; área de superficie ~500 m<sup>2</sup>/g), con un indicador fluorescente (UV<sub>254</sub>). Después de la elución, se visualizaron las placas ya sea mediante irradiación UV<sub>254</sub>, o desarrollado con un indicador apropiado, como yodo (preabsorbido en sílice), una solución acuosa de permanganato de potasio o una solución acuosa de nitrato de amonio y cerio(IV). Se pueden encontrar ejemplos de preparaciones indicadoras en "Experimental Organic Chemistry: Preparative and Microscale" 2<sup>nda</sup> Ed. (Harwood, L., Moody, C. y Percy, J.), WileyBlackwell, 1998.

La HPLC analítica se realizó utilizando ya sea una columna Waters XBridge™ C8 3,5 µm, eluyéndola con un gradiente de MeCN en un 0,1% de ácido trifluoroacético acuático, un 0,1% de ácido fórmico acuoso, un 0,1% de acetato de amonio acuoso o un 0,1% de NH<sub>3</sub> acuoso; una columna Waters XBridge™ C18 3,5 µm con un gradiente de MeCN en un 0,1% de NH<sub>3</sub> acuoso; una columna Waters Symmetry™ C18 3,5 µm con un gradiente de MeCN en un 0,1% de ácido trifluoroacético acuoso; una columna Waters Sunfire™ C8 3,5 µm con un gradiente de MeCN en un 0,1% de ácido trifluoroacético acuoso; o una columna Phenomenex Gemini™ C18 3 µm con un gradiente de MeCN en un 0,1% de ácido trifluoroacético acuoso. El espectro UV de los picos eluidos se midió utilizando un haz de diodos en un sistema Agilent 1100®, o equivalente.

La cromatografía líquida de presión media (MPLC) en sílice (tamaño de partícula <63 µm; porosidad 60 Å; área de superficie ~500 m<sup>2</sup>/g) se realizó utilizando columnas pre envasadas Biotage FLASH™ o equivalente, por ejemplo columnas de sílice Thomson SINGLE StEP™, Biotage Isolute™, Teledyne Isco RediSep™ o Silicycle UltraPure a una velocidad de flujo de solvente recomendada y cargado de muestras. La pureza de fracción se determinó ya sea mediante TLC o HPLC analítica.

La HPLC preparativa se realizó utilizando ya sea una columna Phenomenex Gemini<sup>TM</sup> C18 5 µm, una columna Waters Sunfire<sup>TM</sup> C18 5 µm, una columna Waters XBridge<sup>TM</sup> C8 5 µm o una Waters XTerra<sup>TM</sup> 5 µm, a menos que se indique lo contrario, utilizando ya sea MeCN en 0,1-0,2% de ácido trifluoroacético acuoso, MeCN en 0,1-0,2% de acetato de amonio acuoso, o MeCN en una 0,1-0,2% de una solución acuosa de NH<sub>3</sub> como eluyente, según se detalla. Las fracciones se recolectaron después de la detección mediante espectroscopía UV con una longitud de onda como 220 ó 254 nm. La pureza de fracción se determinó ya sea mediante TLC o HPLC analítica.

Los espectros de resonancia magnética nuclear de protón (<sup>1</sup>H NMR) se registraron en un instrumento Bruker Avance 600 (600 MHz), un Bruker DRX 500 (500 MHz) o un Varian UnityInova de 500 MHz, de 400 MHz ó 300 MHz. Como referencia se utilizaron ya sea los picos centrales de cloroformo-*d* (CDCl<sub>3</sub>; δ<sub>H</sub> 7,27 ppm), dimetilsulfóxido-*d*<sub>6</sub> (d<sub>6</sub>-DMSO; δ<sub>H</sub> 2,50 ppm) o un estándar interno de tetrametilsilano (TMS; δ<sub>H</sub> 0.00 ppm). A menos que se indique lo contrario, los espectros de <sup>1</sup>H NMR se determinaron utilizando DMSO deuterado. Las siguientes abreviaturas se utilizan para los datos de NMR: s = singulete, d = doblete, t = triplete, q = cuarteto, m = multiplete, dd = doblete de dobletes, tt = triplete of tripletes, br = ancho, quinteto= qn. El espectro de masa se registró en un Agilent MSD o equipamiento similar (+ve y -ve APCI y/o electrospray (a menos que se indique lo contrario, en "multimodo+")) seguido de la HPLC analítica.

Todos los demás procedimientos se realizaron utilizando técnicas estándar de laboratorio, por ejemplo, como se detalla en "Experimental Organic Chemistry: Preparative and Microscale" 2<sup>nda</sup> Ed. (Harwood, L., Moody, C. y Percy, J.), WileyBlackwell, 1998.

Las siguientes abreviaturas pueden usarse en las partes científicas de esta memoria:

|       |                                  |
|-------|----------------------------------|
| EtOAc | =acetato de etilo;               |
| DCM   | =diclorometano;                  |
| NMP   | = <i>N</i> -metilpirrolidinona;  |
| DMF   | = <i>N,N</i> - dimetilformamida; |
| DMSO  | =dimetilsulfóxido;               |
| THF   | =tetrahidrofurano;               |
| MeOH  | =metanol;                        |
| EtOH  | =etanol;                         |

|    |        |                                                                |
|----|--------|----------------------------------------------------------------|
|    | MeCN   | =acetonitrilo;                                                 |
|    | Pd/C   | =paladio sobre carbono;                                        |
|    | DMAP   | =4-dimetilaminopiridina;                                       |
|    | sat.   | =saturado;                                                     |
| 5  | aq.    | =acuoso;                                                       |
|    | DMA    | = <i>N,N</i> - dimetil-acetamida;                              |
|    | conc.  | =concentrado;                                                  |
|    | ta     | =temperatura ambiente;                                         |
|    | h      | =horas;                                                        |
| 10 | min(s) | =minuto(s);                                                    |
|    | M      | =molar;                                                        |
|    | MS     | =espectrometría de masa;                                       |
|    | APCI   | =método de ionización química atmosférica;                     |
|    | ESI    | =método de ionización por electrospray;                        |
| 15 | SCX:   | =extracción de fase sólida con un sorbente de ácido sulfónico; |
|    | HPLC   | =Cromatografía líquida de alto rendimiento;                    |
|    | RPHPLC | =Cromatografía líquida de alto rendimiento de fase inversa;    |
|    | FCC    | =Cromatografía de columna ultrarrápida de sílice;              |
|    | DIPEA  | =diisopropiletilamina.                                         |

20

### **Ejemplo 1: 5-(4-Metoxibencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina**

#### **(i) Etil éster del ácido 2-(4-metoxi-bencil)-3-oxo-butírico**

Se agregó acetoacetato de etilo (11,7 mL) a una solución de 4-metoxi-benzaldehído (10,0 g) en tolueno (150 mL). Se agregaron piperidina (0,80 mL) y ácido acético (2,30 mL) y la

25 mezcla se calentó a reflujo durante 20 h. El solvente se eliminó y el aceite anaranjado resultante se disolvió en EtOH (0,30 L), se agregó 10% de Pd/C (0,50 g) y se agitó bajo H<sub>2</sub> (2 bar) durante 3 h. La mezcla de reacción se filtró a través de tierra de diatomeas (Celite<sup>TM</sup>) y el solvente se eliminó mediante evaporación. El producto en bruto se purificó mediante FCC para proporcionar el compuesto del subtítulo como un aceite (12,7 g); <sup>1</sup>H

30 NMR: 7,19 (1H, t), 6,75 (3H, m), 4,15 (2H, q), 3,78 (4H, m), 3,13 (2H, d), 2,20 (3H, s), 1,26 (3H, t); LC-MS *m/z* 249 ESI.

#### **(ii) 2-Amino-5-(4-metoxi-bencil)-6-metil-pirimidin-4-ol**

Se agregó carbonato de guanidio (3,90 g) a una solución del producto de la etapa (I) (5,30 g) en etanol (50,0 mL) y se calentó a 80°C durante 15 h. Después de enfriar el producto se filtró como un sólido, se suspendió en agua y recogió por filtración, se lavó con EtOAc y se secó para proporcionar el compuesto del subtítulo (3,40 g); <sup>1</sup>H NMR: 10,83 (1H, s), 7,08 (2H, d), 6,79 (2H, d), 6,34 (2H, s), 3,69 (3H, s), 3,56 (2H, s), 2,00 (3H, s); LC-MS *m/z* 246 ESI.

(iii) 4-Cloro-5-(4-metoxi-bencil)-6-metil-pirimidin-2-ilamina

El producto de la etapa (ii) (1,00 g) se agregó a POCl<sub>3</sub> (10,0 mL) y la mezcla se calentó a 100°C durante 15 h. El solvente se eliminó y el residuo se diluyó con agua y el pH se ajustó a 7 con NaHCO<sub>3</sub> sat. Esta mezcla se calentó a 50°C durante 2 h, se extrajo con EtOAc, se secó y se eliminó el solvente para proporcionar el compuesto del subtítulo como un sólido blanco (0,71 g); <sup>1</sup>H NMR: 7,02 (2H, d), 6,85 (2H, d), 6,84 (2H, s), 3,88 (2H, s), 3,71 (3H, s), 2,21 (3H, s); LC-MS *m/z* 263 ESI.

(iv) 5-(4-Metoxi-bencil)-6-metil-*N*<sup>4</sup>-pentil-pirimidina-2,4-diamina

Al producto de la etapa (iii) (3,00 g) en dioxano (30,0 mL), se agregó pentilamina (5,30 mL) y la mezcla se calentó a 100°C durante 48 h. El solvente se eliminó y el residuo se disolvió en EtOAc y se lavó con NaHCO<sub>3</sub> sat., se secó y se eliminó el solvente. El compuesto bruto se purificó mediante FCC para proporcionar el compuesto del título como un sólido blanco (2,30 g); <sup>1</sup>H NMR: 7,02 (2H, d), 6,81 (2H, d), 6,31-6,22 (1H, m), 5,83 (2H, s), 3,69 (3H, s), 3,66 (2H, s), 3,25 (2H, q), 2,03 (3H, s), 1,43 (2H, q), 1,28-1,06 (4H, m), 0,81 (3H, t); LC-MS *m/z* 315.

**Ejemplo 2: 4-(2-Amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)-fenol**

Una solución de BBr<sub>3</sub> (1M en DCM, 14.6 mL) se agregó a una solución del producto del Ejemplo 1 (2,30 g) en DCM a 0°C y se agitó durante 1 h. Se agregaron hielo y agua y la mezcla se agitó durante 30 min, después la fase orgánica se separó, la capa acuosa se extrajo con EtOAc, y los orgánicos combinados se secaron y el solvente se eliminó mediante evaporación. El producto en bruto se purificó mediante FCC para proporcionar el compuesto del título como un sólido color crema (1,11 g); <sup>1</sup>H NMR: 11,96 (1H, s), 7,57 (1H, s), 7,07 (2H, s), 6,93 (2H, d), 6,67 (2H, d), 3,69 (2H, s), 3,38-3,32 (2H, m), 2,16 (3H, s), 1,46 (2H, q), 1,27-1,18 (2H, m), 1,15-1,07 (2H, m), 0,82 (3H, t); LC-MS *m/z* 301.

**Ejemplo 3: 5-(4-(2-(Dimetilamino)etoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

A una suspensión del producto del Ejemplo 2 (0,10 g) en DMF (2,00 mL), se agregó Cs<sub>2</sub>CO<sub>3</sub> (0,24 g) y se agitó a temperatura ambiente durante 30 min. Una mezcla de  
5 hidrocloreuro de 2-dimetilaminoetilcloruro (0,096 g), Cs<sub>2</sub>CO<sub>3</sub> (0,24 g) y NaI (0,05 g) también se agitó durante 30 min y las dos mezclas se combinaron y se calentaron a 110°C durante 2 h. La reacción se filtró, se diluyó con agua, se extrajo con EtOAc, se secó y se eliminó el solvente. El producto en bruto se purificó mediante RPHPLC para proporcionar el compuesto del título como un aceite incoloro (0,035 g); <sup>1</sup>H NMR: 7,00 (2H, d), 6,81  
10 (2H, d), 6,04 (1H, t), 5,62 (2H, s), 3,97 (2H, t), 3,65 (2H, s), 3,24 (2H, q), 2,57 (2H, t), 2,19 (6H, s), 2,01 (3H, s), 1,43 (2H, qn), 1,27-1,08 (4H, m), 0,81 (3H, t); LC-MS *m/z* 372.

**Ejemplo 4: 5-(4-(3-(Dimetilamino)propoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando  
15 hidrocloreuro de dimetilamino-propilcloruro (0,105g) para proporcionar el producto como un aceite incoloro (0,039 g); <sup>1</sup>H NMR: 7,02 (2H, d), 6,81 (2H, d), 6,53 (1H, s), 6,10 (2H, s), 3,93 (2H, t), 3,68 (2H, s), 3,30-3,24 (2H, m), 2,53-2,48 (2H, m), 2,27 (6H, s), 2,06 (3H, s), 1,86 (2H, qn), 1,43 (2H, qn), 1,26-1,06 (4H, m), 0,81 (3H, t); LC-MS *m/z* 386.

**Ejemplo 5: 6-Metil-N<sup>4</sup>-pentil-5-(4-(2-(piperidin-1-il)etoxi)bencil)pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando  
hidrocloreuro de N-(2-cloroetil)-piperidina (0,12 g) para proporcionar el producto como un  
sólido blanco (0,058 g); <sup>1</sup>H NMR: 7,00 (2H, d), 6,81 (2H, d), 6,03 (1H, t), 5,61 (2H, s),  
3,98 (2H, t), 3,65 (2H, s), 3,23 (2H, q), 2,60 (2H, t), 2,42-2,37 (4H, m), 2,01 (3H, s), 1,50-  
25 1,33 (8H, m), 1,26-1,18 (2H, m), 1,16-1,07 (2H, m), 0,81 (3H, t); LC-MS *m/z* 412.

**Ejemplo 6: 6-Metil-N<sup>4</sup>-pentil-5-(4-(2-(pirrolidin-1-il)etoxi)bencil)pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando  
hidrocloreuro de N-(2-cloroetil)-pirrolidina (0,115g) para proporcionar el producto como un  
30 aceite incoloro (0,035 g).

<sup>1</sup>H NMR: 7,00 (2H, d), 6,81 (2H, d), 6,04 (1H, t), 5,61 (2H, s), 3,99 (2H, t), 3,65 (2H, s), 3,24 (2H, q), 2,74 (2H, t), 2,37-2,20 (4H, m), 2,02 (3H, s), 1,69-1,63 (4H, m), 1,48-1,37 (2H, m), 1,27-1,08 (4H, m), 0,81 (3H, t); LC-MS *m/z* 398.

**Ejemplo 7: 5-(4-(2-(Bencil(metil)amino)etoxi)bencil)-6-metil-*N*<sup>4</sup>-pentil-pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando hidrocloreuro de N-(2-cloroetil)-N-metilbencilamina (0,147 g) para proporcionar el producto como un aceite incoloro (0,032 g); <sup>1</sup>H NMR: 7,35-7,18 (5H, m), 7,00 (2H, d), 6,81 (2H, d), 6,05 (1H, t), 5,62 (2H, s), 4,10-4,01 (2H, m), 3,65 (2H, s), 3,55 (2H, s), 3,24 (2H, q), 2,70 (2H, t), 2,21 (3H, s), 2,01 (3H, s), 1,43 (2H, qn), 1,27-1,09 (4H, m), 0,81 (3H, t); LC-MS *m/z* 448.

**Ejemplo 8: 3-(4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-fenoxi)propan-1-ol**

A una suspensión del producto del Ejemplo 2 (0,35 g) en DMF (10,0 mL), se agregó Cs<sub>2</sub>CO<sub>3</sub> (0,25 g) y la mezcla se agitó a temperatura ambiente durante 30 min. Se agregaron 3-bromo-1-propanol (0,158 mL) y NaI (0,05 g) y la mezcla se calentó a 100°C durante 9 h. La reacción se diluyó con agua, se extrajo con EtOAc, se secó y se eliminó el solvente. El producto en bruto se purificó mediante FCC eluyendo con 10:1 DCM-MeOH para proporcionar el compuesto del título como un aceite incoloro (0,24 g) que se solidificó al reposar; <sup>1</sup>H NMR: 7,00 (2H, d), 6,80 (2H, d), 6,05 (1H, t), 5,62 (2H, s), 4,50 (1H, t), 3,96 (2H, t), 3,64 (2H, s), 3,53 (2H, q), 3,24 (2H, q), 2,01 (3H, s), 1,82 (2H, qn), 1,43 (2H, qn), 1,28-1,17 (2H, m), 1,17-1,07 (2H, m), 0,82 (3H, t); LC-MS *m/z* 359.

**Ejemplo 9: 6-Metil-*N*<sup>4</sup>-pentil-5-(4-(3-(pirrolidin-1-il)propoxi)bencil)pirimidina-2,4-diamina**

**(i) 5-(4-(3-Cloropropoxi)bencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina**

A una solución del producto del Ejemplo 8 (0,32 g) en DCM (5 mL) se agregó SOCl<sub>2</sub> (0,5 mL) y la solución se agitó a temperatura ambiente durante 36 h. El solvente se eliminó y el material en bruto se purificó mediante FCC eluyendo con DCM y 20:1 DCM-MeOH para proporcionar el compuesto del subtítulo como un aceite anaranjado (0,124 g); <sup>1</sup>H NMR: 7,88 (1H, t), 7,07 (2H, d), 6,87 (2H, d), 4,04 (2H, t), 3,79-3,74 (4H, m), 3,36-3,25 (2H, m), 2,20 (3H, s), 2,17-2,10 (2H, m), 1,51-1,43 (2H, m), 1,27-1,15 (2H, m), 1,12-1,02 (2H, m), 0,80 (3H, t).

(ii) 6-Metil-*N*<sup>4</sup>-pentil-5-(4-(3-(pirrolidin-1-il)propoxi)bencil)pirimidina-2,4-diamina

A una suspensión de trietilamina (0,09 mL), NaI (0,01 g) y el producto de la etapa (i) (0,04 g) en DMF (2 mL) se agregó pirrolidina (0,027 mL). La mezcla se calentó a 80°C durante 15 h, después enfriado a temperatura ambiente, se diluyó con agua, se extrajo con EtOAc, se secó y se eliminó el solvente. El producto en bruto se purificó mediante RPHPLC para proporcionar el compuesto del título como un aceite anaranjado (7 mg); <sup>1</sup>H NMR: 7,86 (s, 1H), 7,41 (s, 2H), 7,07 (d, 2H), 6,86 (d, 2H), 4,00 (t, 2H), 3,76 (s, 2H), 3,22 (t, 2H), 3,17 (s, 2H), 2,19 (s, 3H), 2,15-2,06 (m, 2H), 2,02-1,83 (m, 4H), 1,30-1,15 (m, 4H), 1,15-1,03 (m, 6H), 0,81 (t, 3H); LC-MS *m/z* 412.

**Ejemplo 10: 6-Metil-5-(4-(3-(4-metilpiperazin-1-il)propoxi)bencil)-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 9 etapa (ii) utilizando el producto del Ejemplo 9 etapa (i) (0,04 g) y 1-metilpiperazina (0,0354 mL) para proporcionar el producto como un aceite amarillo (9 mg); <sup>1</sup>H NMR 7,00 (2H, d), 6,79 (2H, d), 6,02 (1H, t), 5,61 (2H, s), 3,92 (2H, t), 3,64 (2H, s), 3,23 (2H, q), 2,42-2,24 (10H, m), 2,13 (3H, s), 2,01 (3H, s), 1,81 (2H, qn), 1,42 (2H, qn), 1,28-1,16 (2H, m), 1,16-1,06 (2H, m), 0,81 (3H, t); LC-MS *m/z* 441.

**Ejemplo 11: 5-(4-(3-(Dimetilamino)propoxi)-2-metoxibencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina**

(i) 4-(3-(Dimetilamino)propoxi)-2-metoxibenzaldehído

Se agregaron hidrocloreuro de 3-dimetilaminopropilcloruro (2,493 g) y NaI (0,394 g) a 4-hidroxi-2-metoxibenzaldehído (2 g) y Cs<sub>2</sub>CO<sub>3</sub> (12,85 g) en DMF (50 mL). La suspensión resultante se agitó a 100°C durante 1 h. La mezcla de reacción se filtró y se diluyó con EtOAc (100 mL). La fase orgánica se lavó con agua y salmuera, se secó, se filtró y concentró mediante evaporación para proporcionar el compuesto del subtítulo como un aceite amarillo (2,23 g); <sup>1</sup>H NMR: 10,17 (1H, s), 7,65 (1H, d), 6,67 (1H, d), 6,64 (1H, dd), 4,12 (2H, t), 3,90 (3H, s), 2,35 (2H, t), 2,14 (6H, s), 1,87 (2H, qn).

(ii) 2-(4-(3-(Dimetilamino)propoxi)-2-metoxibencilidane)-3-oxobutanoato de etilo

Se agregaron acetoacetato de etilo (1,489 mL), piperidina (0,047 mL) y ácido acético (0,145 mL) a una solución del producto de la etapa (i) (2,23 g) en tolueno (50 mL) y la mezcla se agitó a 110°C durante 5 días. El solvente se eliminó bajo presión reducida para

proporcionar el compuesto del subtítulo (3,57 g) que se usó en la siguiente etapa sin purificación.

(iii) 2-(4-(3-(Dimetilamino)propoxi)-2-metoxibencil)-3-oxobutanoato de etilo

Una suspensión del producto de la etapa (ii) (3,57 g) y 10% de Pd/C (0,2 g) en EtOH (50 mL) se hidrogenó bajo 3 bar a temperatura ambiente durante 16 h. La mezcla de reacción se filtró a través tierra de diatomeas (Celite™) y el filtrado se concentró mediante evaporación. El producto en bruto se purificó mediante FCC eluyendo con 0-10% MeOH en EtOAc para proporcionar el compuesto del subtítulo (1,25 g) como un aceite amarillo; <sup>1</sup>H NMR: 6,95 (1H, d), 6,51 (1H, d), 6,40 (1H, dd), 4.10-4.00 (2H, m), 3,96 (2H, t), 3,83 (1H, t), 3,77 (3H, s), 3,01-2,81 (2H, m), 2,34 (2H, t), 2,14 (9H, s), 1,82 (2H, qn), 1,12 (3H, t).

(iv) 2-Amino-5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metilpirimidin-4-ol

Se agregó en una porción carbonato de guanidina (0,716 g) a una solución del producto de la etapa (iii) (1,25 g) en EtOH (20 mL) y la mezcla se agitó a 80°C durante 15 h. El solvente se evaporó. El residuo se diluyó con EtOAc (20 mL), se lavó con agua, se secó y se evaporó. El residuo se suspendió en hexano-EtOAc (5:1; 20 mL) y el sólido se recogió por filtración para proporcionar el compuesto del subtítulo como un sólido amarillo claro (0,87 g);

<sup>1</sup>H NMR: 6,72 (d, 1H), 6,60 (s, 2H), 6,48 (d, 1H), 6,35 (dd, 1H), 3,93 (t, 2H), 3,78 (s, 3H), 3,46 (s, 2H), 2,33 (t, 2H), 2,13 (s, 6H), 1,90 (s, 3H), 1,84-1,78 (m, 2H).

(v) 4-Cloro-5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metilpirimidin-2-amina

El compuesto del subtítulo se preparó utilizando el Método del Ejemplo 1 etapa (iii) y el producto de la etapa (iv) para proporcionar un sólido color tostado (0,71 g); <sup>1</sup>H NMR: 6,83 (s, 2H), 6,57 (d, 1H), 6,54 (d, 1H), 6,41 (dd, 1H), 4.00 (t, 2H), 3,81 (s, 3H), 3,75 (s, 2H), 3,05-2,95 (m, 2H), 2,63 (s, 6H), 2,15 (s, 3H), 2,11-2,01 (m, 2H).

(vi) 5-(4-(3-(Dimetilamino)propoxi)-2-metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina

Se agregó amilamina (0,127 mL) a una solución del producto de la etapa (v) (100 mg) en NMP (2 mL) y se agitó a 150°C durante 15 h. La mezcla se diluyó con EtOAc (10 mL) lavado con NaHCO<sub>3</sub> sat. (10 mL), agua (10 mL), y salmuera sat (10 mL) se secó y el solvente se eliminó mediante evaporación. El producto en bruto se purificó mediante RPHPLC y la tritución con dietil éter proporcionó el compuesto del título como un sólido

blanco (8 mg); <sup>1</sup>H NMR: 6,60 (d, 1H), 6,53 (d, 1H), 6,37 (dd, 1H), 5,86 (t, 1H), 5,61 (s, 2H), 3,93 (t, 2H), 3,82 (s, 3H), 3,52 (s, 2H), 3,21 (q, 2H), 2,35-2,30 (m, 2H), 2,12 (s, 6H), 1,98 (s, 3H), 1,80 (q, 2H), 1,46-1,36 (m, 2H), 1,28-1,18 (m, 2H), 1,17-1,08 (m, 2H), 0,82 (t, 3H); LC-MS *m/z* 416.

- 5 El compuesto del título puede también se puede producir mediante el siguiente Método:  
Se agregó cloruro de metanosulfonilo (0,040 mL) a la mezcla del producto del Ejemplo 36 (0,17 g) y trietilamina (0,072 mL) en THF (5 mL) a 0°C y la mezcla se agitó durante 30 min. Se agregó NaHCO<sub>3</sub> sat. y la mezcla se extrajo dos veces con CHCl<sub>3</sub>, después las capas orgánicas combinadas se secaron y concentraron. El residuo se disolvió en DMF (5 mL).
- 10 Se agregó (solución al 40% ac., 2 mL) y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se trató con 4% de NH<sub>3</sub> solución y salmuera y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con salmuera, se secaron y concentraron. El residuo se purificó mediante FCC para proporcionar el compuesto del título como un sólido blanco (0,10 g); <sup>1</sup>H NMR: 6,61 (d, 1H), 6,53 (d, 1H), 6,37 (dd, 1H),
- 15 6,18 (br t, 1H), 5,91 (brs, 2H), 3,94 (t, 2H), 3,82 (s, 3H), 3,53 (s, 2H), 3,22 (q, 2H), 2,42 (t, 2H), 2,20 (s, 6H), 2,00 (s, 3H), 1,85 (tt, 2H), 1,42 (tt, 2H), 1,24 (m, 2H), 1,13 (m, 2H), 0,82 (t, 3H); LC-MS *m/z* 415 ESI.

**Ejemplo 12: 4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo**

20 **(i) 4-(2-(Etoxicarbonil)-3-oxoButil)-3-metoxibenzoato de metilo**

- Se agregó NaH (60% en aceite mineral, 1,45 g) en porciones durante 10 min a una solución de acetoacetato de etilo (4.4 mL) en THF (60 mL) a 0°C y la mezcla se agitó durante 10 min. Se agregó una solución de 4-(bromometil)-3-metoxibenzoato de metilo (7,5 g) en THF (40 mL) y la mezcla se calentó hasta 70°C y se agitó durante 15 h. La reacción se
- 25 vertió en hielo/agua (300 mL) y se agitó durante 30 min. La mezcla acuosa se extrajo con EtOAc, se secó y concentró mediante evaporación para proporcionar el compuesto del subtítulo. La reacción se repitió a una escala idéntica. Las dos cargas de producto bruto se combinaron y se purificó mediante FCC eluyendo con 8:2 a 7:3 isohexano-EtOAc para proporcionar el compuesto del subtítulo como un aceite incoloro (14.7 g); <sup>1</sup>H NMR: 7,48
- 30 (dd, 1H), 7,45 (d, 1H), 7,24 (d, 1H), 4,05 (q, 2H), 3,95 (dd, 1H), 3,86 (s, 3H), 3,84 (s, 3H), 3,10 (dd, 1H), 3,00 (dd, 1H), 2,17 (s, 3H), 1,09 (t, 3H).

**(ii) 4-((2-Amino-4-hidroxi-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de metilo**

El compuesto del subtítulo se formó utilizando el Método del Ejemplo 1 etapa (ii) y el producto de la etapa (i) (14.7 g) para proporcionar el compuesto del subtítulo como un sólido incoloro (8,6 g), que se utilizó sin purificación adicional; <sup>1</sup>H NMR: 10,78 (s, 1H), 7,46 (d, 1H), 7,45 (s, 1H), 6,98 (d, 1H), 6,34 (s, 2H), 3,89 (s, 3H), 3,83 (s, 3H), 3,61 (s, 2H), 1,93 (s, 3H); LC-MS *m/z* 304.

(iii) 4-((2-Amino-4-cloro-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de metilo

El compuesto del subtítulo se formó utilizando el Método del Ejemplo 1 etapa (iii) y el producto de la etapa (ii) (8,6 g) para proporcionar el compuesto del subtítulo como un sólido incoloro (9,05 g), que se utilizó sin purificación adicional; <sup>1</sup>H NMR: 7,50 (s, 2H), 7,49 (d, 1H), 6,90 (s, 1H), 6,81 (d, 1H), 3,92 (s, 3H), 3,90 (s, 3H), 3,84 (s, 2H), 2,16 (s, 3H).

(iv) 4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo

Se agregó pentilamina (7,22 mL) a una solución del producto de la etapa (iii) (5 g) en NMP (80 mL) y la mezcla se agitó a 150°C durante 15 h. La mezcla de reacción se enfrió, se diluyó con EtOAc (200 mL), se lavó con agua (3 × 200 mL), salmuera (100 mL), se secó y concentró mediante evaporación. El residuo se suspendió en dietil éter (20 mL) y el sólido que se produjo se recogió por filtración para proporcionar el compuesto del título como un sólido incoloro (1,21 g); <sup>1</sup>H NMR 7,48 (d, 1H), 7,45 (dd, 1H), 6,81 (d, 1H), 6,07 (t, 1H), 5,68 (s, 2H), 3,92 (s, 3H), 3,83 (s, 3H), 3,68 (s, 2H), 3,25-3,20 (m, 2H), 1,93 (s, 3H), 1,47-1,38 (m, 2H), 1,27-1,08 (m, 4H), 0,81 (t, 3H); LC-MS *m/z* 373.

**Ejemplo 13: 4-((2-Amino-4-(1-hidroxipentan-2-ilamino)-6-metil-pirimidin-5-il)metil)-3-metoxibenzoato de (S)-metilo**

4-((2-Amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de (S)-metilo

Se agregó (S)-2-aminopentan-1-ol (0,769 g) a una solución del producto del Ejemplo 12 etapa (iii) (1,2 g) en NMP (20 mL) y la mezcla se agitó a 120°C durante 60 h. La mezcla de reacción se enfrió, se diluyó con EtOAc (50 mL), se lavó con NaHCO<sub>3</sub> sat. (2 × 50 mL), salmuera (50 mL), se secó y concentró mediante evaporación. El producto en bruto se purificó mediante FCC cluyendo con 20:1 a 10:1 DCM-MeOH para producir un aceite anaranjado (0,475 g). Una muestra de 100 mg se purificó adicionalmente mediante RPHPLC para proporcionar el compuesto del título como una goma anaranjada (15 mg); <sup>1</sup>H NMR: 7,48 (d, 1H), 7,46 (dd, 1H), 6,89 (d, 1H), 5,68 (s, 2H), 5,50 (d, 1H), 4,58-4,48

(m, 1H), 4.17-4.05 (m, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.70 (s, 2H), 3.39-3.20 (m, 2H), 1.99 (s, 3H), 1.54-1.39 (m, 1H), 1.33-1.20 (m, 1H), 1.16-1.02 (m, 2H), 0.76 (t, 3H); LC-MS  $m/z$  389.

5 **Ejemplo 14: 4-((2-Amino-4-(1-hidroxihexan-3-ilamino)-6-metil-pirimidin-5-il)metil)-3-metoxibenzoato de (S)-metilo**

**(i) Hept-2-enoato de (E)-terc-butilo**

A una solución de valeraldehído (5,81 g) en THF (100 mL) se agregó terc-butoxicarbonilmetilenotriphenilfosforano (25,4 g) y la mezcla se agitó durante 16 h a temperatura ambiente

10 Los solventes se eliminaron mediante evaporación y el residuo resultante se agregó a dietil éter y la mezcla se filtró. El filtrado se concentró mediante evaporación y el residuo se purificó mediante FCC eluyendo con 97:3 isohexano-EtOAc para proporcionar el compuesto del subtítulo (8,5 g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 6,86 (dt, 1H), 5,73 (dt, 1H), 2,25-2,09 (m, 2H), 1,47 (s, 9H), 1,47-1,27 (m, 4H), 0,90 (t, 3H).

15 **(ii) 3-(Bencil((S)-1-feniletil)amino)heptanoato de (S)-terc-butilo**

Se agregó *n*-Butyllitio (2,5 M en hexanos, 27,66 mL) a una solución agitada de (S)-*N*-bencil-1-feniletanamina (15,59 g) en THF (150 mL) a  $-78^\circ\text{C}$ . La mezcla de reacción se agitó durante 30 min, se agregó el producto de la etapa (i) (8,5 g) en THF (50 mL) y la mezcla de reacción se agitó durante 2h a  $-78^\circ\text{C}$ . La mezcla se inactivó con una solución de

20  $\text{NH}_4\text{Cl}$  sat. y se calentó a temperatura ambiente la mezcla se repartió entre EtOAc y agua, la fase orgánica se lavó con agua, se secó y concentró mediante evaporación. El residuo se purificó mediante FCC eluyendo con 95:5 isohexano-EtOAc para proporcionar el compuesto del subtítulo (12,7g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7,49-7,15 (m, 10H), 3,87-3,70 (m, 2H), 3,48 (d, 1H), 3,35-3,21 (m, 1H), 1,99-1,78 (m, 2H), 1,53 (s, 3H), 1,39 (s, 9H), 1,36-  
25 1,14 (m, 6H), 0,88 (t, 3H); LC-MS  $m/z$  396 ESI.

**(iii) Ácido (S)-3-(Bencil((S)-1-feniletil)amino)heptanoico**

El producto de la etapa (ii) (12 g) se disolvió en DCM (40 mL) y ácido trifluoroacético (2 mL) y la mezcla resultante se agitó durante 24 h. Los solventes se eliminaron mediante evaporación para proporcionar el compuesto del subtítulo (17 g); LC-MS  $m/z$  340 ESI.

30 **(iv) (S)-3-(Bencil((S)-1-feniletil)amino)heptan-1-ol**

El producto de la etapa (iii) (12 g) se disolvió en THF (120 mL) y se agregó por goteo complejo borano-THF (1 M en THF, 132,3 mL). La mezcla se agitó a temperatura

ambiente durante la noche y se agregó MeOH seguido de HCl 2M (20 mL). La mezcla se concentró mediante evaporación y el residuo resultante se disolvió en MeOH y se purificó mediante resina SCX. El residuo resultante se purificó adicionalmente mediante FCC eluyendo con 9:1 a 4:1 isohexano-EtOAc para proporcionar el compuesto del subtítulo (6 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7,45-7,13 (m, 10H), 4,00-3,91 (m, 1H), 3,85 (d, 1H), 3,69 (d, 1H), 3,56-3,43 (m, 1H), 3,27-3,15 (m, 1H), 2,84-2,71 (m, 1H), 2,61 (s, 1H), 1,77-1,63 (m, 1H), 1,55 (s, 2H), 1,47-1,20 (m, 8H), 0,93 (t, 3H); LC-MS *m/z* 326 ESI.

(v) (S)-3-Aminoheptan-1-ol

Una solución del producto de la etapa (iv) (5 g) y 5% de Pd/C (0,5 g) en EtOH (25 mL) se hidrogenó utilizando una presión de 5 bar a temperatura ambiente durante 5 días. Una porción adicional de 5% de Pd/C (1,50 g) se agregó y la mezcla se hidrogenó utilizando a presión de 5 bar a temperatura ambiente durante 1 día adicional. La mezcla de reacción se filtró y el solvente se eliminó mediante evaporación para proporcionar el compuesto del subtítulo (1,8 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3,89-3,74 (m, 2H), 2,94-2,84 (m, 1H), 2,79-2,41 (m, 3H), 1,70-1,60 (m, 1H), 1,55-1,38 (m, 2H), 1,39-1,19 (m, 5H), 0,96-0,83 (m, 3H).

(vi) 4-((2-Amino-4-(1-hidroxiheptan-3-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de (S)-metilo

El compuesto del título se preparó mediante el Método del Ejemplo 13 utilizando el producto del Ejemplo 12 etapa (iii) (0,1 g) y el producto de la etapa (v) (0,08 g). El producto en bruto se purificó mediante RPHPLC para proporcionar el compuesto del título como una goma incolora (9 mg); <sup>1</sup>H NMR: 7,49 (d, 1H), 7,46 (dd, 1H), 6,90 (d, 1H), 6,44-6,25 (m, 2H), 4,39-4,33 (m, 1H), 4,29-4,20 (m, 1H), 3,93 (s, 3H), 3,84 (s, 3H), 3,74 (s, 2H), 3,30-3,28 (m, 2H), 2,03 (s, 3H), 1,66-1,47 (m, 2H), 1,47-1,32 (m, 2H), 1,29-0,97 (m, 4H), 0,76 (t, 3H); LC-MS *m/z* 417.

**Ejemplo 15: Sal bencenosulfonato de 4-((2-amino-4-(1-hidroxipentan-2-il-amino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato (S)-4-(dimetilamino)butilo**

(i) Ácido (S)-4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoico

Se agregó (S)-2-amino-1-pentanol (192 mg) a una suspensión agitada del producto del Ejemplo 12 etapa (iii) (0,30 g) en butan-1-ol (2 mL) y la mezcla se calentó en un microondas a 180°C durante 2 h. Se agregó KOH 5M (0,5 mL) y la mezcla se calentó hasta 120°C durante un periodo de 1 h en un microondas. La mezcla se concentró mediante

evaporación y el residuo se diluyó con MeOH (2 mL). Se agregó por goteo ácido acético helado hasta que el pH fue ~ 7 y la mezcla se purificó mediante RPHPLC para proporcionar el compuesto del subtítulo como un sólido incoloro (53 mg); <sup>1</sup>H NMR: 7,47 (d, 1H), 7,41 (dd, 1H), 6,85 (d, 1H), 5,74 (s, 2H), 5,52 (d, 1H), 4.15-4.06 (m, 1H), 3,90 (s, 3H), 3,68 (s, 2H), 3,38-3,33 (m, 1H), 3,28-3,22 (m, 1H), 2,02 (s, 3H), 1,52-1,41 (m, 1H), 1,32-1,21 (m, 3H), 1,15-1,03 (m, 2H), 0,76 (t, 3H); LC-MS *m/z* 375.

(ii) Sulfonato de benceno 4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoato de (S)-4-(dimetilamino)butilo

Una solución de anhídrido cíclico del ácido 1-propanofosfónico (0,35 mL) (1,57 M en THF) se agregó una suspensión del producto de la etapa (i) (69 mg), trietilamina (0,077 mL), 4-(dimetilamino)-1-butanol (0,12 mL) y 4-dimetilaminopiridina (4.50 mg) en DMF (2 mL). La mezcla se agitó a temperatura ambiente durante 60 h y se diluyó con EtOAc (10 mL). La solución se lavó con agua (2 × 10 mL), se secó y concentró mediante evaporación. El producto en bruto se purificó mediante RPHPLC para producir una goma incolora que se disolvió en MeCN (0,5 mL). Se agregó ácido benzenosulfónico (7,9 mg) y el solvente se evaporó para proporcionar un residuo que se trituró con dietil éter para proporcionar el compuesto del título como un sólido incoloro (27,0 mg); <sup>1</sup>H NMR: 7,61-7,58 (m, 1H), 7,48-7,45 (m, 3H), 7,34-7,27 (m, 5H), 6,93 (d, 1H), 6,21-6,06 (m, 1H), 4.63-4.57 (m, 1H), 4.27 (t, 2H), 4.20-4.12 (m, 1H), 3,92 (s, 3H), 3,73 (s, 2H), 3,41-3,33 (m, 4H), 2,42 (s, 6H), 2,03 (s, 3H), 1,77-1,67 (m, 2H), 1,66-1,57 (m, 1H), 1,53-1,43 (m, 1H), 1,34-1,21 (m, 2H), 1,15-1,03 (m, 2H), 0,77 (t, 3H); LC-MS *m/z* 474.

**Ejemplo 16: 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-metoxibenzoato de metilo**

(i) 3-(Bromometil)-4-metoxibenzoato de metilo

Se disolvió 4-metoxi-3-metilbenzoato de metilo (16 g) en EtOAc (100 mL) y se agregaron *N*-bromosuccinimida (18,96 g) y 2,2'-azobisisobutironitrilo (1 g). La mezcla se calentó hasta 80°C durante 4 h. Después de enfriar a temperatura ambiente se agregó solución de tiosulfato de sodio sat., la fase orgánica se separó, se lavó con salmuera, se secó y los solventes se eliminaron mediante evaporación. El producto en bruto se disolvió en una mezcla de isohexano-EtOAc (9:1) y se produjo un sólido que se recogió para proporcionar el compuesto del subtítulo (11,82 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8,05-7,98 (m, 2H), 6,91 (d, 1H), 4,55 (s, 2H), 3,96 (s, 3H), 3,89 (s, 3H).

LC-MS *m/z* 260.

(ii) 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-metoxibenzoato de metilo

El compuesto del título se preparó utilizando el producto de la etapa (i) (11,82 g) y el

Método del Ejemplo 12 etapas (i)-(iv) para proporcionar un sólido producto (2,0 g); <sup>1</sup>H

5 NMR: 7,83 (d, 1H), 7,32 (s, 1H), 7,11 (d, 1H), 6,08 (s, 1H), 5,69 (s, 2H), 3,94 (s, 3H), 3,73 (s, 3H), 3,63 (s, 2H), 3,25-3,07 (m, 2H), 1,93 (s, 3H), 1,50-1,33 (m, 2H), 1,25-1,01 (m, 4H), 0,79 (t, 3H); LC-MS *m/z* 373.

**Ejemplo 17: 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-fluorobenzoato de metilo**

10 (i) 4-Fluoro-3-metilbenzoato de metilo

Se agregó por goteo SOCl<sub>2</sub> (5,68 mL) a una solución de ácido 4-fluoro-3-metilbenzoico (10 g) en MeOH (150 mL) a 0°C durante un periodo de 10 mins. bajo N<sub>2</sub>. La mezcla resultante se agitó a temperatura ambiente durante 24 h y el solvente se eliminó mediante evaporación. El residuo se disolvió en EtOAc, se lavó con NaHCO<sub>3</sub> sat., salmuera sat., se  
15 secó y se concentró mediante evaporación para proporcionar el compuesto del subtítulo (9,85 g); <sup>1</sup>H NMR: 7,93-7,83 (m, 2H), 7,04 (dd, 1H), 3,90 (s, 3H), 2,31 (s, 3H).

(ii) 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-4-fluorobenzoato de metilo

El compuesto del título se preparó utilizando el producto de la etapa (i) (12,8 g) y el

Método del Ejemplo 12 etapas (i)-(iv) para proporcionar un sólido incoloro (0,27 g); <sup>1</sup>H

20 NMR: 7,89-7,81 (m, 1H), 7,46 (dd, 1H), 7,32 (dd, 1H), 6,31 (t, 1H), 5,74 (s, 2H), 3,78 (s, 3H), 3,77 (s, 2H), 3,27-3,22 (m, 2H), 1,95 (s, 3H), 1,44 (qn, 2H), 1,27-1,07 (m, 4H), 0,79 (t, 3H); LC-MS *m/z* 361.

**Ejemplo 18: 4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo**

25 (i) 4-(Bromometil)-3-fluorobenzoato de metilo

El compuesto del subtítulo se preparó a partir de ácido 3-fluoro-4-metilbenzoico (15 g)

según el Método del Ejemplo 17 etapa (i) para proporcionar el producto (14,5 g) como un

aceite anaranjado; <sup>1</sup>H NMR: 7,70 (dd, 1H), 7,62 (dd, 1H), 7,45 (dd, 1H), 3,85 (s, 3H), 2,31 (d, 3H).

30 (ii) 4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo

El compuesto del título se preparó utilizando el producto de la etapa (i) (12,8 g) y el

Método del Ejemplo 12 etapas (i)-(iv) para proporcionar un sólido incoloro (40 mg); <sup>1</sup>H

NMR: 7,70-7,63 (m, 2H), 6,97 (dd, 1H), 6,53-6,41 (m, 1H), 6,00 (s, 2H), 3,84 (s, 3H), 3,81 (s, 2H), 3,28-3,21 (m, 2H), 1,97 (s, 3H), 1,44 (qn, 2H), 1,29-1,07 (m, 4H), 0,81 (t, 3H); LC-MS  $m/z$  361.

5 **Ejemplo 19: 5-(2-Metoxibencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 1 a partir de 2-metoxibenzaldehído (10 g) para proporcionar el producto como un sólido marrón claro (0,74 g);  $^1\text{H}$  NMR: 7,19 (1H, td), 7,00 (1H, d), 6,86-6,73 (2H, m), 6,03-5,90 (1H, m), 5,76 (2H, s), 3,86 (3H, s), 3,65 (2H, s), 3,29-3,16 (2H, m), 2,02 (3H, s), 1,51-1,39 (2H, m), 1,31-1,12 (4H, m), 0,84 (3H, t); LC-MS  $m/z$  315.

10 **Ejemplo 20: 2-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenol**

Se preparó mediante el Método del Ejemplo 2 utilizando el producto del Ejemplo 19 (0,6 g) para proporcionar el producto como un sólido incoloro (0,52 g);  $^1\text{H}$  NMR: 11,87 (1H, s), 7,89 (1H, t), 7,34 (2H, s), 7,05 (1H, t), 6,88-6,78 (2H, m), 6,74-6,68 (1H, m), 3,67 (2H, s), 3,37 (2H, q), 2,20 (3H, s), 1,49 (2H, qn), 1,29-1,11 (4H, m), 0,82 (3H, t); LC-MS  $m/z$  301.

15 **Ejemplo 21: 5-(2-Etoxibencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

Una suspensión del producto del Ejemplo 20 (0,1 g) y  $\text{Cs}_2\text{CO}_3$  (0,5 g) en DMF (2 mL) se agitó durante 30 mins. Se agregó bromoetano (0,03 mL) y la suspensión resultante se calentó a 80°C durante 1 h. La mezcla se enfrió, se filtró y se agregaron EtOAc (10 mL) y agua (5 mL). La fase orgánica se separó, se secó y se concentró para proporcionar un producto en bruto que se purificó mediante RPHPLC para proporcionar el compuesto del título como un sólido incoloro (27 mg);  $^1\text{H}$  NMR: 7,13 (1H, td), 6,96 (1H, d), 6,82-6,74 (2H, m), 5,93 (1H, t), 5,62 (2H, s), 4,09 (2H, q), 3,62 (2H, s), 3,23 (2H, q), 1,99 (3H, s), 1,41 (2H, qn), 1,39 (3H, t), 1,28-1,08 (4H, m), 0,82 (3H, t); LC-MS  $m/z$  329.

25 **Ejemplo 22: 5-(2-(3-(Dimetilamino)propoxi)bencil)-6-metil- $N^4$ -pentil-pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando el producto del Ejemplo 20 (0,1 g) e hidrocloreuro de  $N,N$ -dimetilaminopropilcloruro (0,105 g) para proporcionar un sólido incoloro (27 mg);  $^1\text{H}$  NMR: 7,14 (1H, td), 6,96 (1H, d), 6,81-6,74 (2H, m), 5,92 (1H, t), 5,63 (2H, s), 4,05 (2H, t), 3,63 (2H, s), 3,23 (2H, q), 2,41 (2H, t), 2,15 (6H, s), 1,99 (3H, s), 1,90 (2H, qn), 1,42 (2H, qn), 1,28-1,17 (2H, m), 1,17-1,07 (2H, m), 0,81 (3H, t); LC-MS  $m/z$  386.

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**Ejemplo 23: 5-(3-Metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 1 a partir de 3-metoxibenzaldehído (10 g) para proporcionar a sólido marrón claro (3,7 g); <sup>1</sup>H NMR: 7,16 (1H, dd), 6,75-6,66 (3H, m), 6,30 (1H, s), 5,82 (2H, s), 3,72 (2H, s), 3,70 (3H, s), 3,30-3,23 (2H, m), 2,03 (3H, s), 1,49-1,39 (2H, m), 1,29-1,08 (4H, m), 0,82 (3H, t); LC-MS *m/z* 315.

**Ejemplo 24: 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenol**

El compuesto del título se preparó mediante el Método del Ejemplo 2 utilizando el producto del Ejemplo 23 (0,9 g) para proporcionar a sólido marrón claro (0,72 g); <sup>1</sup>H NMR: 9,25 (1H, s), 7,20-6,93 (2H, m), 6,65 (2H, s), 6,60-6,53 (2H, m), 6,50 (1H, s), 3,71 (2H, s), 3,43-3,20 (2H, m), 2,10 (3H, s), 1,46 (2H, qn), 1,31-1,06 (4H, m), 0,82 (3H, t); LC-MS *m/z* 301.

**Ejemplo 25: 5-(3-(3-(Dimetilamino)propoxi)bencil)-6-metil-N<sup>4</sup>-pentil-pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando el producto del Ejemplo 24 (0,1 g) e hidrocloreto de *N,N*-dimetilaminopropilcloruro (0,105 g) para proporcionar un sólido incoloro (0,054 g); <sup>1</sup>H NMR: 7,14 (1H, dd), 6,72-6,64 (3H, m), 6,10 (1H, t), 5,63 (2H, s), 3,92 (2H, t), 3,69 (2H, s), 3,25 (2H, q), 2,31 (2H, t), 2,12 (6H, s), 2,01 (3H, s), 1,80 (2H, qn), 1,43 (2H, qn), 1,28-1,19 (2H, m), 1,18-1,09 (2H, m), 0,82 (3H, t); LC-MS *m/z* 386.

**Ejemplo 26: 6-Metil-N<sup>4</sup>-pentil-5-(3-(2-(piperidin-1-il)etoxi)bencil)pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando el producto del Ejemplo 24 (0,1 g) e hidrocloreto de *N*-2-cloroetilpiperidina (0,122 g) para proporcionar un aceite incoloro (0,045 g); <sup>1</sup>H NMR: 7,14 (1H, dd), 6,74-6,65 (3H, m), 6,09 (1H, t), 5,63 (2H, s), 3,98 (2H, t), 3,69 (2H, s), 3,24 (2H, q), 2,60 (2H, t), 2,42-2,37 (4H, m), 2,01 (3H, s), 1,51-1,33 (8H, m), 1,27-1,19 (2H, m), 1,17-1,10 (2H, m), 0,81 (3H, t); LC-MS *m/z* 412.

**Ejemplo 27: 5-(3-(2-(Dimetilamino)etoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando el producto del Ejemplo 24 (0,1 g) e hidrocloreto de *N*-2-dimetilaminocloruro (0,096 g) para

proporcionar a sólido marrón claro (0,022 g);  $^1\text{H}$  NMR: 7,15 (1H, dd), 6,72 (1H, d), 6,69-6,65 (2H, m), 6,10 (1H, t), 5,63 (2H, s), 3,97 (2H, t), 3,69 (2H, s), 3,25 (2H, q), 2,58 (2H, t), 2,19 (6H, s), 2,01 (3H, s), 1,43 (2H, qn), 1,29-1,09 (4H, m), 0,82 (3H, t); LC-MS  $m/z$  372.

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**Ejemplo 28: 6-Metil- $N^4$ -pentil-5-(3-(2-(pirrolidin-1-il)etoxi)bencil)pirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 3 utilizando el producto del Ejemplo 24 (0,1 g) e hidrocloreto de N-2-cloroetilpirrolidina (0,115 g) para proporcionar un aceite incoloro (0,036 g);  $^1\text{H}$  NMR: 7,15 (1H, dd), 6,74-6,65 (3H, m), 6,11 (1H, s), 5,65 (2H, s), 3,99 (2H, t), 3,70 (2H, s), 3,27-3,22 (2H, m), 2,74 (2H, t), 2,44-2,36 (4H, m), 2,02 (3H, s), 1,71-1,63 (4H, m), 1,44 (2H, qn), 1,30-1,19 (2H, m), 1,18-1,10 (2H, m), 0,82 (3H, t); LC-MS  $m/z$  398.

**Ejemplo 29: 5-(3-((Dimetilamino)metil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

(i) 2-(3-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenil)acetato de etilo

El Método del Ejemplo 12 utilizando 3-bromometilbenzoato de metilo (6 g) se usó para proporcionar el compuesto del subtítulo como un aceite anaranjado que se solidificó al reposar (0,7 g);  $^1\text{H}$  NMR: 7,79-7,71 (2H, m), 7,45-7,32 (2H, m), 6,36 (1H, s), 5,78 (2H, s), 4,29 (2H, q), 3,82 (2H, s), 3,29-3,22 (2H, m), 2,01 (3H, s), 1,49-1,38 (2H, m), 1,28-1,07 (7H, m), 0,79 (3H, t).

(ii) 3-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)fenil)metanol

Una solución del producto de la etapa (i) (0,21 g) en THF (2 mL) se agregó a una solución de  $\text{LiAlH}_4$  (1M en THF, 0,88 mL) en THF (2 mL) a  $0^\circ\text{C}$ . La mezcla se agitó a temperatura ambiente durante 2 h. Una porción adicional de  $\text{LiAlH}_4$  (0,88 mL) se agregó y la mezcla se agitó a temperatura ambiente durante 15 h. La mezcla se vertió cuidadosamente en NaOH 2M (20 mL) y la fase acuosa se extrajo con EtOAc ( $3 \times 20$  mL). Las fases orgánicas combinadas se secaron y concentraron mediante evaporación para proporcionar el compuesto del subtítulo como un sólido incoloro que se utilizó sin purificación adicional (0,176 g);  $^1\text{H}$  NMR: 7,19 (1H, dd), 7,09 (2H, d), 7,07 (2H, s), 6,97 (1H, d), 6,12 (1H, t), 5,10 (1H, t), 4,43 (2H, d), 3,72 (2H, s), 3,24 (2H, q), 2,01 (3H, s), 1,44 (2H, qn), 1,28-1,10 (4H, m), 0,82 (3H, t).

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(iii) 5-(3-(Clorometil)bencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina

Se agregó SOCl<sub>2</sub> (0,049 mL) a una solución agitada del producto de la etapa (ii) (0,176 g) en DCM (5 mL) a temperatura ambiente la mezcla se agitó durante 1 h, después El solvente se eliminó para proporcionar el compuesto del subtítulo como un aceite amarillo que se usó sin purificación adicional (0,182 g); <sup>1</sup>H NMR: 7,97 (1H, t), 7,34-7,25 (3H, m), 7,21 (2H, s), 7,15-7,09 (1H, m), 4,72 (2H, s), 3,86 (2H, s), 3,37 (2H, q), 2,19 (3H, s), 1,47 (2H, qn), 1,27-1,17 (2H, m), 1,15-1,06 (2H, m), 0,80 (3H, t).

(iv) 5-(3-((Dimetilamino)metil)bencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina

Se agregó una solución de dimetilamina 2M en EtOH (0,4 mL) a una solución del producto de la etapa (iii) (0,09 g) en DMF (2 mL) y la mezcla se agitó a temperatura ambiente durante 15 h. Se agregó NaHCO<sub>3</sub> sat y la fase acuosa se extrajo con EtOAc (2 × 10 mL). Las fases orgánicas combinadas se lavaron con agua (3 × 5 mL), se secaron y concentraron a un residuo que se purificó mediante RPHPLC para proporcionar el compuesto del título como un sólido blanquecino (44 mg); <sup>1</sup>H NMR: 7,19 (1H, dd), 7,07-7,03 (2H, m), 6,98 (1H, d), 6,13 (1H, s), 5,63 (2H, s), 3,72 (2H, s), 3,29 (2H, s), 3,24 (2H, q), 2,10 (6H, s), 2,00 (3H, s), 1,43 (2H, qn), 1,27-1,20 (2H, m), 1,18-1,10 (2H, m), 0,82 (3H, t); LC-MS *m/z* 342.

**Ejemplo 30: 5-(4-(3-(Dimetilamino)prop-1-inil)bencil)-6-metil-*N*<sup>4</sup>-pentil-pirimidina-2,4-diamina**

(i) 5-(4-Yodobencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina

Se usó el Método del Ejemplo 12 utilizando 4-yodobencilbromuro y etilacetoacetato para proporcionar el compuesto del subtítulo como un sólido (60mg); <sup>1</sup>H NMR: 7,59 (2H, d), 6,91 (2H, d), 6,16-6,09 (1H, m), 5,69-5,63 (2H, m), 3,69 (2H, s), 3,27-3,18 (2H, m), 1,99 (3H, s), 1,46-1,37 (2H, m), 1,28-1,06 (4H, m), 0,82 (3H, t); LC-MS *m/z* 411.

(ii) 5-(4-(3-(Dimetilamino)prop-1-inil)bencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina

Se disolvió 1-dimetilamino-2-propina (24 mg) en THF (2 mL) purgado con nitrógeno y se agregó CuI (4.64 mg). La mezcla se agitó durante 30 mins. y se agregó a una suspensión del producto de la etapa (i) (0,1 g) y Pd(PPh<sub>3</sub>)<sub>4</sub> (14.08 mg) en una mezcla 1:1 de THF y trietilamina (2 mL). La mezcla de reacción se calentó hasta 100°C durante 16 h, se enfrió y concentró mediante evaporación. El residuo se purificó mediante RPHPLC para proporcionar el compuesto del título como un sólido (9 mg); <sup>1</sup>H NMR: 7,31 (2H, d), 7,09

(2H, d), 6,16-6,11 (1H, m), 5,65 (2H, s), 3,74 (2H, s), 3,41 (2H, s), 2,22 (6H, s), 2,00 (3H, s), 1,46-1,40 (2H, m), 1,27-1,16 (4H, m), 1,14-1,06 (2H, m), 0,81 (3H, t); LC-MS  $m/z$  366.

**Ejemplo 31: 5-(4-(3-(Dimetilamino)propil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

El producto del Ejemplo 30 (8 mg) se disolvió en EtOH y se hidrogenó en un hidrogenador H-cube™ utilizando un cartucho de reacción de 10% de Pt/C (ofrecido por ThalesNano Nanotechnology, Hungría) utilizando el “modo H<sub>2</sub> completo”. El solvente se eliminó mediante evaporación y el residuo resultante se purificó mediante RPHPLC para proporcionar el compuesto del título como un sólido (1 mg); <sup>1</sup>H NMR: 7,06 (2H, d), 7,00 (2H, d), 6,09-6,03 (1H, m), 5,62 (2H, s), 3,68 (2H, s), 3,25-3,19 (2H, m), 2,19-2,13 (2H, m), 2,09 (6H, s), 2,00 (3H, s), 1,66-1,59 (2H, m), 1,46-1,38 (2H, m), 1,25-1,17 (4H, m), 1,16-1,08 (2H, m), 0,81 (3H, t); LC-MS  $m/z$  370.

**Ejemplo 32: 5-(3-(3-(Dimetilamino)propil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

(i) 5-(3-(3-(Dimetilamino)prop-1-inil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina  
Se usó el Método del Ejemplo 30 utilizando 3-yodobencil bromuro para proporcionar el compuesto del subtítulo (60 mg); LC-MS  $m/z$  366.

(ii) 5-(3-(3-(Dimetilamino)propil)bencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina  
Se siguió el Método del Ejemplo 31 utilizando el producto de la etapa (i) (0,06 g) para proporcionar el compuesto del subtítulo como un sólido (8 mg); <sup>1</sup>H NMR: 7,15 (1H, t), 7,00-6,89 (3H, m), 6,12-6,06 (1H, m), 5,62 (2H, s), 3,70 (2H, s), 3,29 (2H, s), 3,28-3,21 (2H, m), 2,18-2,13 (2H, m), 2,08 (6H, s), 2,01 (3H, s), 1,69-1,57 (2H, m), 1,49-1,38 (2H, m), 1,27-1,18 (2H, m), 1,18-1,07 (2H, m), 0,82 (3H, t); LC-MS  $m/z$  370.

**Ejemplo 33: 5-(4-(3-(Dimetilamino)propoxi)-2-metilbencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina**

(i) 5-(4-Metoxi-2-metilbencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina  
Se usó el Método del Ejemplo 1 utilizando 4-metoxi-2-metilbenzaldehído (10 g) para proporcionar el compuesto del subtítulo como un sólido color crema (0,67 g); <sup>1</sup>H NMR: 6,77 (d, 1H), 6,59 (dd, 1H), 6,49 (d, 1H), 5,97 (t, 1H), 5,63 (s, 2H), 3,68 (s, 3H), 3,52 (s, 2H), 3,22 (q, 2H), 2,32 (s, 3H), 1,90 (s, 3H), 1,42 (qn, 2H), 1,29-1,09 (m, 4H), 0,82 (t, 3H).  
(ii) 4-((2-Amino-4-(pentilamino)pirimidin-5-il)metil)-3-metilfenol

Se usó el Método del Ejemplo 2 utilizando el producto de la etapa (i) (0,5 g) para proporcionar el compuesto del subtítulo como un sólido incoloro que se usó sin purificación (0,350 g);  $^1\text{H}$  NMR: 8,96 (s, 1H), 6,58 (s, 1H), 6,48-6,30 (m, 2H), 5,95 (s, 1H), 5,62 (s, 2H), 3,48 (s, 2H), 3,22 (q, 2H), 2,25 (s, 3H), 1,90 (s, 3H), 1,41 (qn, 2H), 1,28-1,09 (m, 4H), 0,82 (t, 3H); LC-MS  $m/z$  313 (multimodo -).

(iii) 5-(4-(3-(Dimetilamino)propoxi)-2-metilbencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina

Se usó el Método del Ejemplo 3 utilizando el producto de la etapa (ii) (0,1 g) e hidrocloreuro de dimetilaminopropil-cloruro (0,075 g) para proporcionar el compuesto del título como un sólido incoloro (13 mg);  $^1\text{H}$  NMR: 6,76 (d, 1H), 6,57 (dd, 1H), 6,47 (d, 1H), 5,97 (t, 1H), 5,63 (s, 2H), 3,91 (t, 2H), 3,52 (s, 2H), 3,22 (q, 2H), 2,34-2,27 (m, 5H), 2,12 (s, 6H), 1,90 (s, 3H), 1,79 (qn, 2H), 1,46-1,36 (m, 2H), 1,27-1,06 (m, 4H), 0,81 (t, 3H); LC-MS  $m/z$  400.

**Ejemplo 34: 2-(3-(1-(2-Amino-5-(4-(3-(dimetilamino)propoxi)bencil)-6-metilpirimidin-4-ilamino)-3-hidroxi)propil)fenil)acetato de (R)-metilo**

(i) 4-((2-Amino-4-bromo-6-metilpirimidin-5-il)metil)fenol y 4-((2-amino-4-cloro-6-metilpirimidin-5-il)metil)fenol

Una solución de  $\text{BBr}_3$  (1 M en DCM, 15,2 mL) se agregó por porciones a una suspensión agitada del producto del Ejemplo 1 etapa (iii) (1 g) en DCM (20 mL) a 0 °C, durante un periodo de 10 mins. bajo  $\text{N}_2$ . La mezcla resultante se agitó a 0°C durante 1 h. La mezcla se diluyó con HCl 2M (30 mL) y MeOH (10 mL) y se agitó a temperatura ambiente durante 30 mins. La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (2 × 50 mL). Los extractos orgánicos combinados se secaron y concentraron mediante evaporación para proporcionar una mezcla 1:1 del compuesto del subtítulos (0,230 g) que se utilizó en la etapa siguiente sin purificación;  $^1\text{H}$  NMR: 6,90 (4H, d), 6,67 (4H, d), 3,89-3,79 (4H, m), 2,22 (3H, s), 2,20 (3H, s).

(ii) 4-Bromo-5-(4-(3-(dimetilamino)propoxi)bencil)-6-metilpirimidin-2-amina y 4-Cloro-5-(4-(3-(dimetilamino)propoxi)bencil)-6-metilpirimidin-2-amina

Se agregó hidrocloreuro de 3-(dimetilamino)propilcloruro (0,437 g) a una suspensión agitada del producto de la etapa (i) (0,23 g),  $\text{Cs}_2\text{CO}_3$  (2,401 g) y NaI (0,069 g) en DMF (10 mL). La suspensión resultante se agitó a 80°C durante 3 h., se enfrió y se diluyó con EtOAc (20 mL). La fase orgánica se lavó con agua (3 × 30 mL), salmuera (30 mL), se secó

y concentró mediante evaporación. El producto en bruto se purificó mediante FCC eluyendo con DCM y 10:2 DCM-MeOH para proporcionar una mezcla 1:1 de los compuestos del subtítulo (0,043 g) que se utilizaron en la etapa siguiente sin purificación ;  
<sup>1</sup>H NMR: 7,00 (d, 4H), 6,88-6,79 (m, 4H), 3,94 (t, 4H), 3,89 (s, 2H), 3,87 (s, 2H), 2,41 (t, 4H), 2,19 (s, 18H), 1,84 (qn, 4H).

(iii) 3-(3-(Hidroximetil)fenil)acrilato de (E)-terc-butilo

Una mezcla de (3-bromofenil)metanol (7,3 g), acrilato de terc-butilo (15 g), acetato de paladio (0,235g) y tri(o-tolil)fosfina (1,25 g) en MeCN (80 mL) se calentó a 90°C durante 2 h. La solución se enfrió y se concentró mediante evaporación. El residuo resultante se disolvió en EtOAc, se lavó con agua, se secó y concentró mediante evaporación. El producto en bruto se purificó mediante FCC eluyendo con 8:2 a 7:3 isohexano-EtOAc para proporcionar el compuesto del subtítulo (7,8 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7,58 (1H, d), 7,52 (1H, s), 7,45-7,33 (3H, m), 6,38 (1H, d), 4.72 ( 2H, s), 1,53 (9H, s).

(iv) 3-(Bencil((S)-1-feniletil)amino)-3-(3-((terc-butildimetil-sililoxi)metil)fenil)propanoato de (R)-terc-butilo

Una solución de butil litio (2,5 M en hexano, 34 mL) se agregó a una solución de (S)-(-)-N-bencil-α-metilbencilamina en THF (200 mL) a -78°C y la mezcla se agitó durante 45 mins. Una solución del producto de la etapa (iii) (7,8 g) en THF (20 mL) se agregó y se continuó agitando durante 3 h. El baño de enfriamiento se eliminó, se agregó solución de NH<sub>4</sub>Cl y la solución se dejó calentar a temperatura ambiente, se agregaron EtOAc y agua, la fase orgánica se separó, se secó y se concentró para proporcionar un residuo que se pasó a través de gel de sílice eluyendo con 4:1 isohexano-EtOAc. La eliminación del solvente mediante evaporación proporcionó un residuo que se disolvió en DMF (120 mL). Se agregaron imidazol (5 g) y terc-butil-dimetilsililcloruro y la solución se agitó a temperatura ambiente durante 2 h. Se agregaron EtOAc y agua, la fase orgánica se separó, se secó y se concentró para proporcionar el producto en bruto que se purificó mediante FCC eluyendo con 95:5 isohexano-EtOAc para proporcionar el compuesto del subtítulo (18 g); LC-MS *m/z* 560 (APCI +).

(v) (R)-3-(Bencil((S)-1-feniletil)amino)-3-(3-((terc-butildimetilsililoxi)-metil)fenil)propan-1-ol

El producto de la etapa (iv) (18 g) se disolvió en THF (120 mL) y se agregó una solución de LiAlH<sub>4</sub> (1M en THF, 45 mL). La mezcla se agitó a temperatura ambiente durante 4 h. y

se agregó agua. Se agregaron una solución de 45% de NaOH y agua y la mezcla se agitó durante 1 h. El solvente se eliminó mediante decantación para proporcionar un residuo que se disolvió en dietil éter. La solución orgánica se lavó con salmuera, se secó y concentró mediante evaporación para proporcionar el compuesto del subtítulo (15,5 g); LC-MS *m/z* 490 (APCI +).

(vi) 3-((*R*)-1-(Bencil(*S*)-1-feniletíl)amino)-3 (metoximetoxi)propil)-fenil)metanol

A una solución del producto de la etapa (v) y DIPEA (17 mL) en DCM (160 mL) a 0°C se agregó metiléter de clorometilo. La mezcla se calentó a temperatura ambiente y se agitó durante 18 h. Se agregó una porción adicional de metiléter de clorometilo (0,4 mL) y la mezcla se agitó adicionalmente durante 18 h. La mezcla se lavó con agua, se secó y concentró mediante evaporación. El residuo resultante se disolvió en THF (250 mL). Se agregó una solución de fluoruro de tetrabutilamonio (75 % p en agua, 10 mL) y la mezcla se agitó durante 4 h, se agregaron salmuera y EtOAc, la fase orgánica se separó, se lavó con salmuera, se secó y concentró mediante evaporación para proporcionar el producto en bruto que se purificó mediante FCC eluyendo con 7:3 isohexano-EtOAc para proporcionar el compuesto del subtítulo (10,9 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7,45-7,18 (10H, m), 4,71 (2H, d), 4,42 (2H, s), 4,15-4,08 (1H, m), 3,98-3,94 (1H, m), 3,84-3,64 (2H, m), 3,28-3,22 (5H, m), 2,20-2,10 (1H, m), 1,90-1,78 (1H, m), 1,69 (1H bs), 1,16 (3H, d).

(vii) Metanosulfonato de 3-((*R*)-1-(bencil(*S*)-1-feniletíl)amino)-3-

(metoximetoxi)propil)bencilo

Se agregó por goteo metano cloruro de sulfonilo (1,912 mL) a una solución del producto de la etapa (vi) (9,5 g) y trietilamina (4,8 mL) en DCM (100 mL) a 0-5°C bajo N<sub>2</sub>. La mezcla resultante se agitó durante 1 h y el solvente se eliminó para proporcionar el subcompuesto del título bruto que se utilizó en la siguiente etapa sin purificación adicional (11,27 g); LC-MS *m/z* 498 (APCI +).

(viii) 2-(3-((*R*)-1-(Bencil(*S*)-1-feniletíl)amino)-3-(metoximetoxi)propil)-fenil)acetonitrilo

Se agregó en una porción KCN (6 g) al producto de la etapa (vii) (11,27 g) en DMSO (30 mL) y DMF (30 mL) y la mezcla se calentó hasta 50°C bajo N<sub>2</sub>. La mezcla resultante se agitó a 50°C durante 18 h y se repartió entre EtOAc y agua. La fase orgánica se separó, se lavó con agua, se secó y concentró mediante evaporación para proporcionar el subcompuesto del título bruto que se utilizó en la siguiente etapa sin purificación adicional (7,69 g); LC-MS *m/z* 429 (APCI +).

(ix) 2-(3-((R)-1-(Bencil((S)-1-feniletil)amino)-3-hidroxi)propil)fenil)acetato de metilo

Se agregó una solución de KOH (2,81 g) disuelta en agua (10 mL) a una solución agitada del producto de la etapa (viii) (7,69 g, 17,94 mmol) en EtOH (50 mL) a temperatura ambiente la mezcla se agitó a reflujo durante 24 h. La mezcla se concentró mediante evaporación y el residuo resultante se hizo azeotrópico con tolueno. Se agregaron MeOH (100 mL) seguido de HCl conc. (3 mL) al residuo y la mezcla se agitó a temperatura ambiente durante 3 días. La mezcla se concentró mediante evaporación y el residuo resultante se repartió entre EtOAc y agua. La fase orgánica se separó, se lavó con agua, se secó y concentró mediante evaporación. El producto en bruto se purificó mediante FCC eluyendo con 7:3 isohexano-EtOAc para proporcionar el compuesto del subtítulo como un aceite (2,32 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7,43-7,19 (m, 14H); 4,14-4,08 (m, 1H); 3,96-3,92 (m, 2H); 3,70 (s, 3H); 3,66 (s, 2H); 3,62-3,53 (m, 2H); 3,41-3,35 (m, 1H); 2,24-2,15 (m, 1H); 1,84 (br s, 1H); 1,74-1,65 (m, 1H); 1,04 (d, 3H); LC-MS *m/z* 418 (APCI +).

(x) 2-(3-(1-Amino-3-hidroxi)propil)fenil)acetato de (R)-metilo

Una suspensión del producto de la etapa (ix) (2,3 g) y Pd/C (0,9 g) en MeOH (60 mL) se agitó bajo a H<sub>2</sub> presión de 45psi a temperatura ambiente durante 24 h. La mezcla se filtró a través tierra de diatomeas (Celite<sup>TM</sup>) y el solvente se evaporó para proporcionar un residuo que se purificó mediante FCC eluyendo con 84:16 DCM-MeOH para proporcionar el compuesto del subtítulo como un aceite (480 mg); <sup>1</sup>H NMR: 7,26-7,07 (m, 4H); 3,89 (t, 1H); 3,64 (s, 2H); 3,61 (s, 3H); 3,47-3,37 (m, 2H); 1,71-1,60 (m, 2H).

(xi) 2-(3-(1-(2-Amino-5-(4-(3-(dimetilamino)propoxi)bencil)-6-metilpirimidin-4-ilamino)-3-hidroxi)propil)fenil)acetato de (R)-metilo

Una solución del productos de la etapa (ii) (0,045 g) y el producto de la etapa (x) (0,107 g) en butan-1-ol (3 mL) se colocaron en un tubo para microondas cerrado y se calentaron hasta 170°C en el reactor de microondas durante 2,5 h. El solvente se eliminó mediante evaporación y el residuo resultante se repartió entre EtOAc (5 mL) y agua (5 mL). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (5 mL). Las fases orgánicas combinadas se secaron y concentraron mediante evaporación para proporcionar un residuo que se purificó mediante RPHPLC para proporcionar el compuesto del título como una goma incolora (11 mg); <sup>1</sup>H NMR: 7,20-7,13 (m, 1H), 7,10-7,00 (m, 5H), 6,82 (d, 2H), 6,41 (d, 1H), 5,60 (s, 2H), 5,36-5,26 (m, 1H), 4,52 (t, 1H), 3,94 (t, 2H), 3,78 (d, 1H), 3,69 (d,

1H), 3,60 (s, 3H), 3,57 (s, 4H), 2,37-2,31 (m, 2H), 2,14 (s, 6H), 2,02 (s, 3H), 1,91-1,77 (m, 4H); LC-MS  $m/z$  522.

**Ejemplo 35: 2-(3-(1-(2-Amino-5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metilpirimidin-4-ilamino)-3-hidroxiopropil)fenil)acetato de (R)-metilo**

**2-(3-(1-(2-Amino-5-(4-(3-(dimetilamino)propoxi)-2-metoxibencil)-6-metilpirimidin-4-ilamino)-3-hidroxiopropil)fenil)acetato de (R)-metilo**

Una solución del producto del Ejemplo 11 etapa (v) (0,15 g) y el producto del Ejemplo 34 etapa (x) (0,184 g) en butan-1-ol (3 mL) se colocaron en un tubo para microondas cerrado y se calentaron hasta 170°C en el reactor de microondas durante 2 h. El solvente se eliminó mediante evaporación y el residuo resultante se diluyó con MeOH (2 mL) y H<sub>2</sub>SO<sub>4</sub> conc. (0,5 mL). La mezcla se agitó a 65°C durante 2 h, se dejó enfriar, el pH se ajustó a 7 con NaHCO<sub>3</sub> sat. y se extrajo con EtOAc (3 × 10 mL). Las fases orgánicas combinadas se secaron y concentraron mediante evaporación para proporcionar un producto en bruto que se purificó mediante RPHPLC para proporcionar el compuesto del título como un sólido incoloro (43,0 mg); <sup>1</sup>H NMR: 7,16 (1H, dd), 7,09-7,00 (2H, m), 6,67 (1H, d), 6,55 (1H, d), 6,40 (1H, dd), 6,21 (1H, d), 5,58 (2H, s), 5,32-5,24 (1H, m), 4,47 (1H, s), 3,96 (2H, t), 3,82 (3H, s), 3,65-3,55 (9H, m), 2,34 (2H, t), 2,14 (6H, s), 2,01 (3H, s), 1,87-1,77 (4H, m); LC-MS  $m/z$  552.

**Ejemplo 36: 3-(4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxifenoxi)propan-1-ol**

**(i) 4-(3-(Terc-butildimetilsililoxi)propoxi)-2-metoxibenzaldehído**

Se agregaron (3-bromopropoxi)(terc-butil)dimetilsilano (6,85 mL) y K<sub>2</sub>CO<sub>3</sub> (4,09 g, 29,6 mmol) a una solución de 4-hidroxi-2-metoxibenzaldehído (3,00 g) en DMF (30 mL) y la mezcla se agitó durante 14 h a temperatura ambiente, se agregó salmuera y la mezcla se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron (MgSO<sub>4</sub>) y concentraron. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del subtítulo como un aceite incoloro (5,97 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 10,29 (1H, s), 7,80 (1H, d), 6,55 (1H, dd), 6,45 (1H, d), 4,15 (2H, t), 3,90 (3H, s), 3,81 (2H, t), 2,00 (2H, tt), 0,89 (9H, s), 0,05 (6H, s).

**(ii) 4-(3-(Terc-butildimetilsililoxi)propoxi)-2-metoxifenil)metanol**

Se agregó NaBH<sub>4</sub> (0,35 g) a una solución del producto de la etapa (i) (5,97 g) en THF/MeOH (30 mL / 3 mL) a 0°C y la mezcla se agitó durante 1 h. La reacción se inactivó con salmuera y se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (MgSO<sub>4</sub>) y concentraron. El residuo se purificó mediante FCC para proporcionar el subcompuesto del título como un aceite incoloro (5,76 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7,14 (1H, d), 6,46 (2H, m), 4,61 (2H, s), 4,06 (2H, t), 3,85 (3H, s), 3,81 (2H, t), 2,15 (1H, br s), 1,99 (2H, tt), 0,89 (9H, s), 0,05 (6H, s).

(iii) 2-(4-(3-(Terc-butildimetilsililoxi)propoxi)-2-metoxibencil)-3-oxobutanoato de metilo

Se agregó cloruro de metanosulfonilo (0,93 mL) a la mezcla del producto de la etapa (ii) (2,50 g) y DIPEA (2,09 mL) en THF (30 mL) a temperatura ambiente y la mezcla se agitó durante 2 h. El sólido resultante se eliminó por filtración. El filtrado se concentró al vacío, y se disolvió en DMF (20 mL). Se agregó acetoacetato de metilo (0,99 mL) a una suspensión de NaH (55% de dispersión de aceite, 0,37 g) en DMF (15 mL) a 0°C y la mezcla se agitó durante 15 min. La solución de DMF descrita anteriormente y KI (1,27 g) se agregaron a la mezcla y todo se agitó a 80°C durante 4 h. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc. La mezcla se lavó con NaHCO<sub>3</sub> sat. y salmuera. La capa orgánica se secó (MgSO<sub>4</sub>) y concentró. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del subtítulo como un aceite incoloro (1,80 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6,99 (1H, d), 6,42 (1H, d), 6,38 (1H, dd), 4,03 (2H, t), 3,89 (1H, t), 3,81 (3H, s), 3,80 (2H, t), 3,67 (3H, s), 3,09 (2H, m), 2,17 (3H, s), 1,97 (2H, tt), 0,88 (9H, s), 0,04 (6H, s).

(iv) 2-Amino-5-(4-(3-(terc-butildimetilsililoxi)propoxi)-2-metoxibencil)-6-metilpirimidin-4-ol

Se agregó carbonato de guanidinio (0,98 g) a una solución del producto de la etapa (iii) (1,78 g) en MeOH (50 mL) y la mezcla se calentó a 65°C durante 7 h. La mezcla se enfrió a temperatura ambiente y se agregó agua (50 mL). El sólido resultante se recogió por filtración y se lavó con EtOH/agua (50 mL / 50 mL), agua (50 mL), EtOH (50 mL) para proporcionar subcompuesto del título como un sólido blanco (1,53 g); <sup>1</sup>H NMR: 6,71 (1H, d), 6,41 (1H, d), 6,37 (1H, dd), 6,32 (2H, br s), 3,97 (2H, t), 3,79 (3H, s), 3,75 (2H, t), 3,45 (2H, s), 1,92 (3H, s), 1,85 (2H, tt), 0,85 (9H, s), 0,02 (6H, s); LC-MS *m/z* 433 ESI.

(v) 2-Amino-5-(4-(3-(terc-butildimetilsililoxi)propoxi)-2-metoxibencil)-6-metilpirimidin-4-il 2,4,6-trimetilbencenosulfonato

Se agregaron  $N^1, N^1, N^3, N^3$ -tetrametilpropano-1,3-diamina (0,88 mL) y cloruro de 2,4,6-trimetilbenceno-1-sulfonilo (1,15 g) a la solución del producto de la etapa (iv) (1,52 g) en THF (15 mL) y la mezcla se agitó a temperatura ambiente. Después de 22 h, se agregó HCl ac. 0,1N (45 mL) y la mezcla se extrajo dos veces con  $\text{CHCl}_3$ . La capa orgánica se secó  
 5 (MgSO<sub>4</sub>) y concentró. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del subtítulo como un aceite amarillo claro (1,92 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6,94 (2H, s), 6,71 (1H, d), 6,41 (1H, d), 6,33 (1H, dd), 4,72 (2H, br s), 4,02 (2H, t), 3,81 (2H, t), 3,79 (3H, s), 3,76 (2H, s), 2,61 (6H, s), 2,31 (3H, s), 2,26 (3H, s), 1,98 (2H, tt), 0,89 (9H, s), 0,05 (6H, s); LC-MS *m/z* 616 ESI.

10 (vi) 5-(4-(3-(Terc-butildimetilsililoxi)propoxi)-2-metoxibencil)-6-metil- $N^4$ -pentilpirimidina-2,4-diamina

Se agregaron ácido trifluoroacético (0,48 mL) y amilamina (1,78 mL) a la solución del producto de la etapa (v) (1,90 g) en propionitrilo (19 mL) y la mezcla se agitó a 100°C durante 3 h. El solvente se eliminó mediante evaporación y el residuo resultante se diluyó  
 15 con EtOAc (50 mL) y se lavó con una solución de 4% de NH<sub>3</sub> (20 mL × 4) y salmuera (20 mL). Se secó (MgSO<sub>4</sub>) y concentró. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del subtítulo as aceite amarillo claro (1,03 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6,82 (1H, d), 6,47 (1H, d), 6,40 (1H, dd), 5,10 (2H, br s), 4,03 (2H, t), 3,88 (3H, s), 3,79 (2H, t), 3,72 (1H, q), 3,60 (2H, s), 3,28 (2H, q), 2,36 (3H, s), 1,97 (2H, tt), 1,44  
 20 (2H, tt), 1,25 (2H, m), 1,15 (2H, m), 0,89 (9H, s), 0,86 (3H, t), 0,05 (6H, s); LC-MS *m/z* 502 ESI.

(vii) 3-(4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxifenoxi)propan-1-ol

Se agregó fluoruro de tetrabutilamonio (solución THF 1,0 M, 4.1 mL) a la solución del  
 25 producto de la etapa (vi) (1,03 g) en THF (6 mL) y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla se diluyó con EtOAc (30 mL) y se lavó con una solución de 4% de NH<sub>3</sub> (20 mL) y salmuera (20 mL). Se secó (Na<sub>2</sub>SO<sub>4</sub>) y concentró. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del título como un sólido blanco (0,51 g); <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6,82 (1H, d), 6,48 (1H, d), 6,38 (1H, dd), 4.87  
 30 (1H, br t), 4.69 (2H, br s), 4.10 (2H, t), 3,88 (3H, s), 3,86 (2H, t), 3,61 (2H, s), 3,28 (2H, dq), 2,32 (3H, s), 2,04 (2H, tt), 1,90 (1H, br s), 1,44 (2H, tt), 1,25 (2H, m), 1,15 (2H, m), 0,84 (3H, t); LC-MS *m/z* 388 ESI.

**Ejemplo 37: 5-(2-Metoxi-4-(3-morfolinopropoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

Se agregó cloruro de metanosulfonilo (0,030 mL) a la mezcla del producto del Ejemplo 36 (0,14 g) y trietilamina (0,053 mL) en THF (5 mL) a 0°C. La mezcla resultante se agitó durante 30 min. Se agregó NaHCO<sub>3</sub> sat. y la solución se extrajo dos veces con CHCl<sub>3</sub>. La capa orgánica se secó (MgSO<sub>4</sub>) y concentró. El residuo resultante se disolvió en DMF (5 mL). Se agregó morfolina (0,33 mL) y la mezcla se agitó a 60°C durante 5 h. Se agregó una solución de 4% de NH<sub>3</sub> y salmuera y la mezcla se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se lavaron dos veces con salmuera, se secaron (Na<sub>2</sub>SO<sub>4</sub>) y concentraron. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del título como un sólido blanco (0,13 g); <sup>1</sup>H NMR: 6,59 (1H, d), 6,52 (1H, d), 6,37 (1H, dd), 5,89 (1H, br t), 5,65 (2H, br s), 3,94 (2H, t), 3,82 (3H, s), 3,55 (4H, t), 3,51 (2H, s), 3,20 (2H, q), 2,39 (2H, t), 2,34 (4H, m), 1,98 (3H, s), 1,83 (2H, tt), 1,41 (2H, tt), 1,24 (2H, m), 1,14 (2H, m), 0,84 (3H, t); LC-MS *m/z* 457 ESI.

**Ejemplo 38: 5-(2-Metoxi-4-(3-(4-metilpiperazin-1-il)propoxi)bencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

El compuesto del título se preparó mediante el Método del Ejemplo 37 utilizando el producto del Ejemplo 36 (0,14 g) como un sólido blanco (0,13 g); <sup>1</sup>H NMR: 6,59 (1H, d), 6,52 (1H, d), 6,37 (1H, dd), 5,88 (1H, br t), 5,64 (2H, br s), 3,93 (2H, t), 3,82 (3H, s), 3,51 (2H, s), 3,21 (2H, q), 2,36 (2H, t), 2,29 (8H, m), 2,12 (3H, s), 1,98 (3H, s), 1,82 (2H, tt), 1,41 (2H, tt), 1,24 (2H, m), 1,14 (2H, m), 0,82 (3H, t); LC-MS *m/z* 470 ESI.

**Ejemplo 39: 5-(4-(4-(Dimetilamino)Butil)-2-metoxibencil)-6-metil-N<sup>4</sup>-pentilpirimidina-2,4-diamina**

**(i) 4-(4-(Terc-butildimetilsililoxi)but-1-inil)-2-metoxibenzoato de metilo**

Se disolvieron 4-(terc-butildimetilsililoxi)butina (3,7 g) y 4-bromo-2-metoxibenzoato de metilo (4,0 g) en THF (30 mL purgado con N<sub>2</sub>) y se agregaron CuI (0,61 g), Pd(PPh<sub>3</sub>)<sub>4</sub> (1,8 g) y trietilamina (4,1 mL). La mezcla se calentó hasta 100°C durante 6 h, se enfrió y se diluyó con EtOAc (10 mL). La solución se lavó con HCl 0,2N (2 × 10 mL), NaHCO<sub>3</sub> sat. (2 × 10 mL) y salmuera. La fase orgánica se secó y concentró mediante evaporación. El residuo resultante se purificó mediante FCC para proporcionar el compuesto del subtítulo como un aceite incoloro (5,6 g); <sup>1</sup>H NMR: 7,61 (1H, d), 7,08 (1H, d), 6,99 (1H, dd), 3,80-3,75 (8H, m), 2,63 (2H, t), 0,87 (9H, s), 0,06 (6H, s); ESI *m/z* 349 (M+1).

(ii) 4-(4-(Terc-butildimetilsililo)butil)-2-metoxibenzoato de metilo

El producto de la etapa (i) (5,6 g) se disolvió en MeOH. Se agregó 10% de Pd/C (50% húmedo) (1,0 g) y la mezcla se agitó bajo H<sub>2</sub> durante 7 h a temperatura ambiente. El Pd/C se filtró y el filtrado se concentró para proporcionar el compuesto del subtítulo como un  
5 aceite incoloro (5,6 g); <sup>1</sup>H NMR: 7,56 (1H, d), 6,95 (1H, d), 6,82 (1H, dd), 3,79 (3H, s), 3,74 (3H, s), 3,58 (2H, t), 3,58 (2H, t), 1,64-1,57 (2H, m), 1,50-1,44 (2H, m), 0,83 (9H, s), 0,01 (6H, s); MS:ESI 353 (M+1).

(iii) 4-(4-(Terc-butildimetilsililo)Butil)-2-metoxifenil)metanol

El producto de la etapa (ii) (5,6 g) en THF (30 mL) se agregó a la suspensión de LiAlH<sub>4</sub>  
10 (0,61 g) en THF (50 mL) y la mezcla se agitó durante 0,5 h a temperatura ambiente, se enfrió en un baño de hielo y se agregó lentamente Na<sub>2</sub>SO<sub>4</sub> (2 mL) sat. La mezcla se agitó durante 2 h a temperatura ambiente y la mezcla se secó (Na<sub>2</sub>SO<sub>4</sub>), el precipitado se filtró utilizando tierra de diatomeas (Celite<sup>TM</sup>) y el filtrado se concentró para proporcionar el  
15 compuesto del subtítulo como un aceite incoloro (4,4 g); <sup>1</sup>H NMR: 7,22 (1H, d), 6,73-6,71 (2H, m), 4,87 (1H, t), 4,42 (2H, d), 3,73 (3H, s), 3,60-3,56 (2H, m), 2,55 (2H, t), 1,61-1,57 (2H, m), 1,50-1,43 (2H, m), 0,84 (9H, s), 0,01 (6H, s).

(iv) Terc-butil(4-(4-(clorometil)-3-metoxifenil)butoxi)dimetilsilano

Se agregó cloruro de metanosulfonilo (54 µL) a la mezcla del producto de la etapa (iii) (195 mg) y DIPEA (155 µL) en THF (3 mL) a 0°C. Después de agitarse durante 10 mins,  
20 se agregó LiCl (42 mg) y la mezcla se agitó durante 2 h y se diluyó con EtOAc (10 mL). La solución se lavó con HCl 0,2N (2 × 10 mL), NaHCO<sub>3</sub> sat. (2 × 10 mL) y salmuera. La fase orgánica se secó y concentró para proporcionar el compuesto del subtítulo como un  
25 aceite incoloro (200 mg); <sup>1</sup>H NMR: 7,26 (1H, d), 6,84 (1H, d), 6,74 (1H, dd), 4,65 (2H, s), 3,80 (3H, s), 3,58 (2H, t), 2,57 (2H, t), 1,63-1,58 (2H, m), 1,48-1,34 (2H, m), 0,84 (9H, s), 0,00 (6H, s).

(v) 2-(4-(4-(Terc-butildimetilsililo)butil)-2-metoxibencil)-3-oxobutanoato de metilo

Se agregó acetoacetato de metilo (161 µL) a la suspensión de NaH (55% de dispersión de aceite, 43 mg) en THF (5 mL) a 0°C y la mezcla se agitó durante 0,5 h. Se agregaron el  
30 producto de la etapa (iv) (200 mg) en THF (5 mL) y KI (83 mg) y la mezcla se agitó a 80°C durante 2h. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (30 mL). La mezcla se lavó con HCl 0,1N (2 × 10 mL), NaHCO<sub>3</sub> sat. (2 × 10 mL) y salmuera. La fase orgánica se secó y concentró y el residuo se purificó mediante FCC para

proporcionar el compuesto del subtítulo como un aceite incoloro (200 mg); <sup>1</sup>H NMR: 6,93 (1H, d), 6,76 (1H, d), 6,64 (1H, dd), 3,89-3,85 (1H, m), 3,85 (3H, s), 3,62-3,55 (5H, m), 2,98-2,89 (2H, m), 2,54-2,50 (2H, m), 2,12 (3H, s), 1,59-1,56 (2H, m), 1,46-1,42 (2H, m), 0,84 (9H, s), 0,00 (6H, s); MS:ESI 423 (M+1).

5 (vi) 2-Amino-5-(4-(4-(terc-butildimetilsililo)butil)-2-metoxibencil)-6-metilpirimidin-4-ol

Se agregó carbonato de guanidinio (109 mg) a una solución del producto de la etapa (v) (200 mg) en MeOH (5 mL) y la mezcla se calentó a 65°C durante 12 h. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (30 mL). La mezcla se lavó con NaHCO<sub>3</sub> sat. (2 × 10 mL) y salmuera. La fase orgánica se secó y concentró y el residuo se purificó  
10 mediante FCC para proporcionar el compuesto del subtítulo como un aceite incoloro (147 mg); <sup>1</sup>H NMR: 6,73-6,69 (2H, m), 6,59 (1H, dd), 6,30 (2H, brs), 3,77 (3H, s), 3,57 (2H, t), 3,37 (2H, s), 2,52-2,50 (2H, m), 2,94 (3H, s), 1,59-1,56 (2H, m), 1,46-1,42 (2H, m), 0,84 (9H, s), 0,00 (6H, s).

(vii) 2-Amino-5-(4-(4-(terc-butildimetilsililo)butil)-2-metoxibencil)-6-metilpirimidin-4-il

15 2,4,6-trimetilbencenosulfonato

El compuesto del subtítulo se preparó mediante el Método del Ejemplo 35 etapa (v) utilizando el producto de la etapa (vi) (142 mg) para proporcionar un aceite incoloro (260 mg); <sup>1</sup>H NMR: 7,07 (2H, s), 6,75-6,72 (3H, m), 6,61-6,98 (2H, m), 3,72 (3H, s), 3,61-3,57 (4H, m), 2,55-2,51 (2H, m), 2,42 (6H, s), 2,28 (3H, s), 2,24 (3H, s), 1,61-1,54 (2H, m),  
20 1,53-1,42 (2H, m), 0,84 (9H, s), 0,00 (6H, s).

(viii) 5-(4-(4-(Terc-butildimetilsililo)Butil)-2-metoxibencil)-6-metil-N<sup>4</sup>pentilpirimidina-2,4-diamina

El compuesto del subtítulo se preparó mediante el Método del Ejemplo 36 etapa (vi) utilizando el producto de la etapa (vii) (260 mg) para proporcionar un aceite incoloro (101 mg); <sup>1</sup>H NMR: 6,78 (1H, s), 6,60 (2H, s), 6,01 (1H, br s), 5,72 (2H, br s), 3,81 (3H, s),  
25 3,58-3,54 (4H, m), 3,25-3,17 (2H, m), 2,53-2,49 (2H, m), 1,96 (3H, s), 1,63-1,51 (2H, m), 1,50-1,37 (4H, m), 1,30-1,08 (4H, m), 0,84-0,78 (12H, m), 0,00 (6H, s); MS:ESI 501 (M+1).

(ix) 4-(4-((2-Amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3

30 metoxifenil)butan-1-ol

El compuesto del subtítulo se preparó mediante el Método del Ejemplo 36 etapa (vii) utilizando el producto de la etapa (x) (100 mg) para proporcionar un aceite incoloro (71

mg); <sup>1</sup>H NMR: 6,79 (1H, s), 6,61-6,50 (2H, m), 5,95 (1H, t), 5,64 (2H, br s), 4,36 (1H, t), 3,82 (3H, s), 3,55 (2H, s), 3,39-3,33 (2H, m), 3,22-3,17 (2H, m), 2,52-2,49 (2H, m), 1,96 (3H, s), 1,57-1,53 (2H, m), 1,42-1,37 (4H, m), 1,22-1,10 (4H, m), 0,80 (3H, t); MS:ESI 387 (M+1).

5 (x) 5-(4-(4-(Dimetilamino)Butil)-2-metoxibencil)-6-metil-*N*<sup>4</sup>-pentilpirimidina-2,4-diamina

El compuesto del título se preparó mediante el Método del Ejemplo 37 utilizando el producto de la etapa (ix) para proporcionar un sólido blanco (58 mg); <sup>1</sup>H NMR: 6,79 (1H, s), 6,61-6,50 (2H, m), 5,94-5,92 (1H, m), 5,63 (2H, s), 3,82 (3H, s), 3,54 (2H, s), 3,22-3,17 (2H, m), 2,52-2,49 (2H, m), 2,18-2,14 (2H, m), 2,05 (6H, s), 1,95 (3H, s), 1,55-1,49 (2H, m), 1,44-1,32 (4H, m), 1,24-1,09 (4H, m), 0,81 (3H, t); MS:ESI 414 (M+1).

10 **Ejemplo 40: (S)-2-(2-Amino-5-(4-(hidroximetil)-2-metoxibencil)-6-metil-pirimidin-4-ilamino)pentan-1-ol**

(i) 4-((2-Amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)-metil)-3-metoxibenzoato de (S)-metilo

15 Se agregó (S)-2-aminopentan-1-ol (0,481 g) a una suspensión del producto del Ejemplo 12 etapa (iii) (0,5 g) en dioxano (5 mL) y la mezcla se calentó en un microondas CEM a 170°C durante 9 h. La mezcla se enfrió y el solvente se eliminó mediante evaporación. El residuo se purificó mediante FCC utilizando 5% de MeOH en DCM para proporcionar el compuesto del subtítulo (0,250 g) como una goma anaranjada; <sup>1</sup>H NMR: 7,53-7,42 (2H, m), 6,89 (1H, d), 5,75 (2H, d), 5,58 (1H, d), 4,61-4,54 (1H, m), 4,17-4,08 (1H, m), 3,92 (3H, s), 3,83 (3H, s), 3,69 (2H, d), 3,28-3,23 (m, 1H), 2,00 (3H, d), 1,53-1,40 (m, 1H), 1,35-1,19 (m, 2H), 1,16-1,02 (m, 2H), 0,77 (3H, t); LC-MS *m/z* 389.

(ii) Ácido (S)-4-((2-amino-4-(1-hidroxipentan-2-ilamino)-6-metilpirimidin-5-il)metil)-3-metoxibenzoico

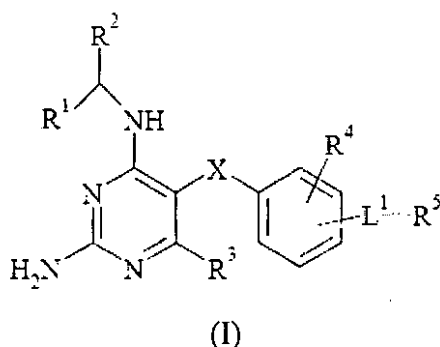
25 El producto de la etapa (i) (220 mg) se disolvió en THF (3 mL) y agua (3 mL) y se agregó solución de LiOH (3 M, 0,944 mL). La mezcla se calentó en un microondas CEM durante 6 h a 120°C. El solvente se eliminó mediante evaporación y el residuo resultante se disolvió en agua y se acidificó con HCl 2 M hasta un pH de 7. El precipitado sólido resultante se filtró y se secó bajo alto vacío durante la noche para proporcionar el subcompuesto del título (90 mg); <sup>1</sup>H NMR: 7,53-7,42 (2H, m), 6,92 (1H, d), 6,61 (2H, d), 4,21 (1H, d), 3,91 (3H, d), 3,75 (2H, s), 2,09 (3H, s), 1,53-1,42 (1H, m), 1,40-1,20 (2H, m), 1,09 (2H, q), 0,78 (3H, t); LC-MS *m/z* 375.

(iii) (S)-2-(2-Amino-5-(4-(hidroximetil)-2-metoxibencil)-6-metilpirimidin-4-ilamino)pentan-1-ol

Se agregó complejo borano-THF (1 M, 3 mL, 3,00 mmol) al producto de la etapa (ii) (85 mg) y la mezcla se calentó hasta 80°C durante 2 h. Se agregó cuidadosamente MeOH y la  
5 mezcla se calentó hasta 80°C durante 1 h. El solvente se eliminó mediante evaporación y el residuo resultante se disolvió en MeOH y se cargó en un cartucho SCX. El cartucho se lavó con MeOH y se eluyó con una solución de NH<sub>3</sub> 0,7 M en MeOH. Los solventes se evaporaron para proporcionar el compuesto del título como una goma incolora (40 mg); <sup>1</sup>H  
NMR: 6,94 (1H, s), 6,74 (2H, q), 5,66 (2H, s), 5,48 (1H, t), 5,14 (1H, s), 4,59 (1H, s), 4,45  
10 (2H, s), 4,15–4,04 (1H, m), 3,84 (3H, d), 3,59 (2H, d), 3,25 (1H, dd), 2,03 (3H, s), 1,54–  
1,44 (1H, m), 1,32–1,23 (2H, m), 1,11 (2H, m), 0,81–0,76 (3H, t); LC-MS *m/z* 361.

REIVINDICACIONES

1. Un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo:



donde

X representa  $-\text{CH}_2-$ ,  $-\text{NR}^8-$ ,  $-\text{O}-$  o  $-\text{S}(\text{O})_n-$ ;

$\text{R}^1$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{2-6}$ , alcóxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxialquilo $\text{C}_{1-6}$ , hidroxialcoxi $\text{C}_{1-6}$  o hidroxialcoxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ ;

- 15  $\text{R}^2$  representa hidrógeno, alquilo $\text{C}_{1-6}$  o fenilo donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^6$ ;

$\text{R}^3$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$  o  $-\text{S}-$ alquilo $\text{C}_{1-6}$ ;

$\text{R}^4$  representa hidrógeno, halógeno, alquilo $\text{C}_{1-6}$  o alcoxi $\text{C}_{1-6}$ ;

- 20  $\text{L}^1$  representa un enlace directo,  $-(\text{CR}^9\text{R}^{10})_m-$ ,  $-\text{CH}=\text{CH}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}\equiv\text{C}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{O}-(\text{CR}^9\text{R}^{10})_q-$ ,  $-\text{C}(\text{O})-\text{O}-(\text{CR}^9\text{R}^{10})_q-$  o  $-\text{O}-(\text{CH}_2)_q-\text{NR}^8-(\text{CH}_2)_q-$ ;

$\text{R}^5$  representa metilo, hidroxilo,  $-\text{NR}^{11}\text{R}^{12}$ , cicloalquilo $\text{C}_{3-6}$ , fenilo o un anillo monocíclico, o heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos seleccionados independientemente de O, N o S donde dichos fenilo y anillos heterocíclicos se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $\text{R}^7$ ;

- 25  $\text{R}^6$  representa alquilo $\text{C}_{1-6}$ , fluoroalquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , hidroxilo, halógeno, ciano,  $-\text{S}(\text{O})_n$ -alquilo $\text{C}_{1-6}$  o  $-\text{CH}_2-\text{C}(\text{O})-\text{O}-$ alquilo $\text{C}_{1-6}$ ;

$\text{R}^7$  representa alquilo $\text{C}_{1-6}$ , alcoxi $\text{C}_{1-6}$ , alcóxi $\text{C}_{1-6}$ alquilo $\text{C}_{1-6}$ , hidroxilo, hidroxialquilo $\text{C}_{1-6}$ , o  $-(\text{CH}_2)_q-\text{NR}^{11}\text{R}^{12}$ ;

$\text{R}^8$  representa hidrógeno o alquilo $\text{C}_{1-6}$ ;

- 30  $\text{R}^9$  y  $\text{R}^{10}$ , idéntica o diferentemente en cada caso, representa hidrógeno o metilo;

$\text{R}^{11}$  y  $\text{R}^{12}$  independientemente representan hidrógeno, alquilo $\text{C}_{1-4}$  o alcoxi $\text{C}_{1-4}$ alquilo $\text{C}_{2-4}$ ;

m representa 1, 2, 3, 4, 5 ó 6;

n representa 0, 1 ó 2; y

q representa 0, 1, 2, 3, 4, 5 ó 6;

con la condición de que el compuesto de la Fórmula (I) no sea:

etil éster del ácido [3-(2-amino-4-metil-6-pentilamino-pirimidin-5-ilmetil)]-benzoico;

5 4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-metoxibenzoato de metilo; o

4-((2-amino-4-metil-6-(pentilamino)pirimidin-5-il)metil)-3-fluorobenzoato de metilo.

2. Un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, donde X representa -CH<sub>2</sub>-.

10

3. Un compuesto de conformidad con la reivindicación 1 o la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, donde R<sup>1</sup> representa alquiloC<sub>1-6</sub>.

15

4. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, o una sal farmacéuticamente aceptable del mismo, donde R<sup>2</sup> representa hidrógeno.

5. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, o una sal farmacéuticamente aceptable del mismo, donde R<sup>2</sup> representa fenilo y donde dicho fenilo se sustituye opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de R<sup>6</sup>.

20

6. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable del mismo, donde R<sup>3</sup> representa metilo.

25

7. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable del mismo, donde R<sup>4</sup> representa alcoxiC<sub>1-6</sub>.

8. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable del mismo, donde R<sup>4</sup> representa hidrógeno.

30

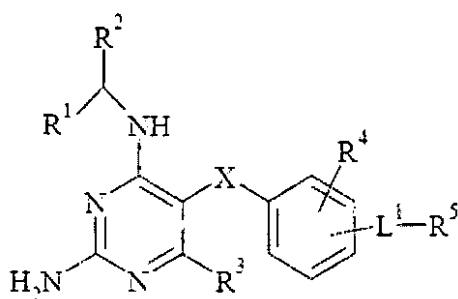
9. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo, donde R<sup>4</sup> está unido en la posición orto del anillo de fenilo, en relación al enlace -X-.

10. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 9, o una sal farmacéuticamente aceptable del mismo, donde q representa 1, 2 ó 3.
- 5 11. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, donde q representa 2 ó 3.
12. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 11, o una sal farmacéuticamente aceptable del mismo, donde  $L^1$  representa  $-(CR^9R^{10})_m-$ ,  $-CH=CH-$   
10  $(CR^9R^{10})_q-$  o  $-C\equiv C-(CR^9R^{10})_q-$ .
13. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 11, o una sal farmacéuticamente aceptable del mismo, donde  $L^1$  representa  $O-(CR^9R^{10})_q-$ .
- 15 14. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 13, o una sal farmacéuticamente aceptable del mismo, donde  $L^1$  está unido en la posición para del anillo de fenilo, en relación al enlace  $-X-$ .
15. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 13, o una  
20 sal farmacéuticamente aceptable del mismo, donde  $L^1$  está unido en la posición meta del anillo de fenilo, en relación al enlace  $-X-$ .
16. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8 ó 10 a 13, o una sal farmacéuticamente aceptable del mismo, donde  $L^1$  está unido en la posición  
25 orto del anillo de fenilo, en relación al enlace  $-X-$ .
17. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 16, o una sal farmacéuticamente aceptable del mismo, donde  $R^5$  representa  $NR^{11}R^{12}$  o un anillo monocíclico, o heterocíclico de 4, 5, 6 ó 7 miembros que comprende 1, 2 ó 3 heteroátomos  
30 seleccionados independientemente de O, N o S donde dicho anillo heterocíclico se sustituyen opcionalmente por 1, 2 ó 3 sustituyentes seleccionados de  $R^7$ .

18. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable del mismo, donde  $R^5$  representa  $NR^{11}R^{12}$  y  $R^{11}$  y  $R^{12}$  representan ambos metilo.
- 5 19. Una composición farmacéutica que comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, o una sal farmacéuticamente aceptable del mismo, asociada a un diluyente o vehículo farmacéuticamente aceptable.
- 10 20. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, o una sal farmacéuticamente aceptable de este, para uso como medicamento.
21. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, o una sal farmacéuticamente aceptable de este, para uso en el tratamiento del cáncer.
- 15 22. El uso de un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 18, o una sal farmacéuticamente aceptable de este, en la fabricación de un medicamento para uso en el tratamiento del cáncer.
- 20 23. Un método para tratar el cáncer en un animal de sangre caliente, como el hombre, que necesite dicho tratamiento y que comprende administrar a tal animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, según se define en cualquiera de las reivindicaciones 1 a 18.

**RESUMEN**

La invención se refiere a compuestos de Fórmula (I):



(I)

donde L<sup>1</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> y X son como se los define en la descripción. La presente invención también se refiere a procesos para la preparación de dichos compuestos, composiciones farmacéuticas que los contienen y su uso en el tratamiento de enfermedades, por ejemplo, cáncer.

From the INTERNATIONAL BUREAU

**PCT**NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

ASTRAZENECA INTELLECTUAL PROPERTY  
AstraZeneca AB  
S-151 85 Södertälje  
SUÈDE

Date of mailing (day/month/year)

21 November 2011 (21.11.2011)

Applicant's or agent's file reference

103757-1P WO

International application No.

PCT/GB2010/050825

## IMPORTANT NOTIFICATION

International filing date (day/month/year)

20 May 2010 (20.05.2010)

1. The following indications appeared on record concerning:

☒ the applicant☐ the inventor☐ the agent☐ the common representative

Name and Address

DAINIPPON SUMITOMO PHARMA CO., LTD  
2-6-8 Dosco-machi 2 chome  
Chuo-ku  
Osaka 5418524  
Japan

State of Nationality

JP

State of Residence

JP

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person☐ the name☒ the address☐ the nationality☐ the residence

Name and Address

DAINIPPON SUMITOMO PHARMA CO., LTD  
6-8, Dosho-machi 2-chome  
Chuo-ku  
Osaka 541-8524  
Japan

State of Nationality

JP

State of Residence

JP

Telephone No.

Facsimile No.

E-mail address

☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office☐ the International Searching Authority☐ the Authority(ies) specified for supplementary search☐ the International Preliminary Examining Authority☒ the designated Offices concerned☐ the elected Offices concerned☐ other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

Birchen Mireille

e-mail pt04.pct@wipo.int

Telephone No. +41 22 338 74 04

Facsimile No. +41 22 338 89 95

## PATENT COOPERATION TREATY

PCT/GB2010/050825

From the INTERNATIONAL BUREAU

**PCT**NOTIFICATION OF THE RECORDING  
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1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

BENNETT, Nicholas, James  
AstraZeneca R&D Charnwood  
Bakewell Road  
Loughborough  
Leicestershire LE11 5RH  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

BENNETT, Nicholas, James  
c/o AstraZeneca Intellectual Property  
AstraZeneca R&D Alderley  
Alderley Park  
Macclesfield  
Cheshire SK10 4TG  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

E-mail address

☐ Notifications by e-mail authorized

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- the Authority(ies) specified for supplementary search

- ☐
- the International Preliminary Examining Authority
- 
- ☒
- the designated Offices concerned
- 
- ☐
- the elected Offices concerned
- 
- ☐
- other:

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

Authorized officer

Birchen Mireille

e-mail pt04.pct@wipo.int

Telephone No. +41 22 338 74 04

Facsimile No. +41 22 338 89 95

Form PCT/IB/306 (January 2009)

1/TGREZ64EHRTXA0

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PATENT COOPERATION TREATY

PCT/GB2010/050825

From the INTERNATIONAL BUREAU

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S-151 85 Södertälje  
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IMPORTANT NOTIFICATION

International application No.

PCT/GB2010/050825

International filing date (day/month/year)

20 May 2010 (20.05.2010)

1. The following indications appeared on record concerning:

☒ the applicant

☒ the inventor

☐ the agent

☐ the common representative

Name and Address

MCINALLY, Thomas  
AstraZeneca R&D Chamwood  
Bakewell Road  
Loughborough  
Leicestershire LE11 5RH  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

E-mail address

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☐ the person

☐ the name

☒ the address

☐ the nationality

☐ the residence

Name and Address

MCINALLY, Thomas  
c/o AstraZeneca Intellectual Property  
AstraZeneca R&D Alderley  
Alderley Park  
Macclesfield  
Cheshire SK10 4TG  
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

E-mail address

☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☐ the receiving Office

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☐ the Authority(ies) specified for supplementary search

☐

the International Preliminary Examining Authority

☒

the designated Offices concerned

☐

the elected Offices concerned

☐

other:

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

Authorized officer

Birchen Mireille

Facsimile No. +41 22 338 89 95

e-mail [pt04.pct@wipo.int](mailto:pt04.pct@wipo.int)

Telephone No. +41 22 338 74 04

87

PATENT COOPERATION TREATY

PCT/GB2010/050825

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING  
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21 November 2011 (21.11.2011)

Applicant's or agent's file reference  
103757-1P WO

International application No.  
PCT/GB2010/050825

IMPORTANT NOTIFICATION

International filing date (day/month/year)  
20 May 2010 (20.05.2010)

1. The following indications appeared on record concerning:

☒ the applicant      ☒ the inventor      ☐ the agent      ☐ the common representative

|                                                                                                                                              |                            |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|--------------------------|
| Name and Address<br>THOM, Stephen<br>AstraZeneca R&D Charnwood<br>Bakewell Road<br>Loughborough<br>Leicestershire LE11 5RH<br>United Kingdom | State of Nationality<br>GB | State of Residence<br>GB |
|                                                                                                                                              | Telephone No.              |                          |
|                                                                                                                                              | Facsimile No.              |                          |
|                                                                                                                                              | E-mail address             |                          |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person      ☐ the name      ☒ the address      ☐ the nationality      ☐ the residence

|                                                                                                                                                                                |                                                                               |                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|
| Name and Address<br>THOM, Stephen<br>c/o AstraZeneca Intellectual Property<br>AstraZeneca R&D Alderley<br>Alderley Park<br>Macclesfield<br>Cheshire SK10 4TG<br>United Kingdom | State of Nationality<br>GB                                                    | State of Residence<br>GB |
|                                                                                                                                                                                | Telephone No.                                                                 |                          |
|                                                                                                                                                                                | Facsimile No.                                                                 |                          |
|                                                                                                                                                                                | E-mail address<br><input type="checkbox"/> Notifications by e-mail authorized |                          |

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

|                                                                                |                                                                            |
|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <input type="checkbox"/> the receiving Office                                  | <input type="checkbox"/> the International Preliminary Examining Authority |
| <input type="checkbox"/> the International Searching Authority                 | <input checked="" type="checkbox"/> the designated Offices concerned       |
| <input type="checkbox"/> the Authority(ies) specified for supplementary search | <input type="checkbox"/> the elected Offices concerned                     |
|                                                                                | <input type="checkbox"/> other:                                            |

|                                                                                               |                                                            |
|-----------------------------------------------------------------------------------------------|------------------------------------------------------------|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br><br>Birchen Mireille                 |
| Facsimile No. +41 22 338 89 95                                                                | e-mail pt04.pct@wipo.int<br>Telephone No. +41 22 338 74 04 |

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

|                                                                                                                                  |                                                                        |                                                            |                  |
|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------|------------------|
| Applicant's or agent's file reference<br>103757-1P WO                                                                            | FOR FURTHER ACTION                                                     |                                                            | See item 4 below |
| International application No.<br>PCT/GB2010/050825                                                                               | International filing date (day/month/year)<br>20 May 2010 (20.05.2010) | Priority date (day/month/year)<br>21 May 2009 (21.05.2009) |                  |
| International Patent Classification (8th edition unless older edition indicated)<br>See relevant information in Form PCT/ISA/237 |                                                                        |                                                            |                  |
| Applicant<br>ASTRAZENECA AB                                                                                                      |                                                                        |                                                            |                  |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

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

|                                     |              |                                                                                                                                                                 |
|-------------------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report                                                                                                                                             |
| <input type="checkbox"/>            | Box No. II   | Priority                                                                                                                                                        |
| <input type="checkbox"/>            | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability                                                                |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention                                                                                                                                      |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> | Box No. VI   | Certain documents cited                                                                                                                                         |
| <input checked="" type="checkbox"/> | Box No. VII  | Certain defects in the international application                                                                                                                |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application                                                                                                           |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

|                                                                                                                                     |                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland<br><br>Facsimile No. +41 22 338 82 70 | Date of issuance of this report<br>22 November 2011 (22.11.2011)                   |
|                                                                                                                                     | Authorized officer<br><br>Athina Nickitas-Etienne<br><br>e-mail: pt04.pct@wipo.int |

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/GB2010/050825

International filing date (day/month/year)  
20.05.2010

Priority date (day/month/year)  
21.05.2009

International Patent Classification (IPC) or both national classification and IPC  
INV. C07D239/49 C07D401/12 C07D403/12 C07D413/12 A61K31/505 A61K31/5377 A61P35/00

Applicant  
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office  
P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk - Pays Bas  
Tel. +31 70 340 - 2040  
Fax: +31 70 340 - 3016

Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

Mooren, Nicolai

Telephone No. +31 70 340-8054



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/GB2010/050825

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:
  - ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
  - a. (means)
    - ☐ on paper
    - ☐ in electronic form
  - b. (time)
    - ☐ in the international application as filed
    - ☐ together with the international application in electronic form
    - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |             |             |
|-------------------------------|-------------|-------------|
| Novelty (N)                   | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |
| Inventive step (IS)           | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |
| Industrial applicability (IA) | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/GB2010/050825

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

see separate sheet

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V.1 Subject-Matter under Rule 39.1(iv) PCT**

Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

**V.2 Documents**

Reference is made to the following documents:

- D1        WO 99/50249 A2 (DU PONT PHARM CO [US]) 7 October 1999  
            (1999-10-07)
- D2        US 2005/054590 A1 (AVERETT DEVRON R [US]) 10 March 2005  
            (2005-03-10)

**V.3 Novelty (Art. 33(2) PCT)**

**V.3.1** D1 discloses several 5-(2-phenylethyl)-6-methyl-pyrimidine-2,4-diamines wherein the phenyl ring carries different amide substituents (Ex. A-1091 to A-1104, see Table 1, p. 194) for use in the treatment of cancer metastasis (p. 1, l. 5-16).

The compounds of Formula (I) according to claim 1 of the present application differ from these compounds in that the phenyl ring is attached to the pyrimidyl ring via a -CH<sub>2</sub>-, -NR<sup>8</sup>-, -O- or -S(O)<sub>n</sub>- bridge and not an ethylene bridge, in that the amino group in the 4-position carries a - possibly substituted - alkyl substituent and in the substituents of the phenyl ring.

**V.3.2** D2 discloses several 5-bromo-6-phenyl-pyrimidine-2-amines (Ex. 3-5, see p. 40) for use as prodrugs of ligands of the TLR7 receptor (par. [0001], [0048]). The compounds according to claim 1 of the present application differ from these compounds in the substitution pattern of the pyrimidyl ring.

**V.3.3** Consequently, the subject-matter of claims 1-23 is novel.

**V.4 Inventive Step (Art. 33(3) PCT)**

**V.4.1** D1 is considered to be the prior art closest to the subject-matter of claims 1-23. The disclosure of D1 and the difference between this disclosure and the compounds according to claim 1 of the present application have been discussed above (section V. 3.1).

**V.4.2** The problem to be solved is considered to be the provision of alternative pyrimidine-2,4-diamine derivatives for use in the treatment of cancer, pharmaceutical compositions thereof and their uses.

The solution is given by the compounds, the compositions and the uses according to claims 1-23.

**V.4.3** The retrieved prior art does not contain any pointer to the possibility that the structure of the compounds known from D1 could be altered in such a way as to fall under claim 1 of the present application, i. e. that the ethylene bridge between the pyrimidyl and the phenyl ring might be exchanged against a -CH<sub>2</sub>-, -NR-, -O- or -S(O)<sub>n</sub>- bridge, the amino group in 4-position might be provided with a substituent and the substitution pattern of the phenyl ring might be modified.

**V.4.4** The ability of compounds according to claim 1 of the present application to activate the TLR7 receptor has been demonstrated in the application by means of experimental data (p. 23, l. 14 - p. 24, l. 6).

**V.4.5** The subject-matter of claims 1-23 therefore involves an inventive step.

**V.5 Industrial Applicability (Art. 33(4) PCT)**

Claims 1-23 meet the requirements of Art. 33(4) PCT.

**Re Item VI**

**Certain documents cited**

| Application No<br>Patent No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority dates<br>(day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|------------------------------------|
| WO 2009/067081 (D3)         | 28/05/2009                           | 21/11/2008                      | 22/11/2007<br>14/12/2007           |

**Re Item VII**

**Certain defects in the international application**

**VII.1** Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D2 is not mentioned in the description, nor is this document identified therein.

**VII.2** On p. 8, l. 26 and l. 31, there are two references to "said phenyl ... rings"; however, the preceding passages do not relate to phenyl rings.

**Re Item VIII**

**Certain observations on the international application**

**VIII.1** The proviso in claim 1 (p. 66, l. 3-7) refers to less compounds than the corresponding proviso in the description (p. 3, l. 21-29). This inconsistency between claim 1 and the description leads to a lack of clarity of claim 1 (Art. 6 PCT).

**VIII.2** According to several passages in the description, the invention is concerned with subject-matter which does not fall within the scope of the claims, for example methods for the preparation of the claimed compounds (cf. p. 1, l. 5-7). In particular, the passage on p. 12, l. 27 - p. 14, l. 9 of the description suggests that the invention relates to prodrugs of the claimed compounds which are not covered by the claims (it is also pointed out that the term "prodrug" is a functional term which does not give a specific technical guidance for the selection of suitable derivatives falling under this term and therefore has to be regarded as unclear).

These inconsistencies between the claims and the description lead to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Art. 6 PCT).

**VIII.3** It is noted that the expressions "optionally" and "such as" have no limiting effect on the claims (PCT-Guidelines 5.40).

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/GB2010/050825

International filing date (day/month/year)  
20.05.2010

Priority date (day/month/year)  
21.05.2009

International Patent Classification (IPC) or both national classification and IPC  
INV. C07D239/49 C07D401/12 C07D403/12 C07D413/12 A61K31/505 A61K31/5377 A61P35/00

Applicant  
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

## 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office  
P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk - Pays Bas  
Tel. +31 70 340 - 2040  
Fax: +31 70 340 - 3016

Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

Mooren, Nicolai

Telephone No. +31 70 340-8054



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/GB2010/050825

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:
  - ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
  - a. (means)
    - ☐ on paper
    - ☐ in electronic form
  - b. (time)
    - ☐ in the international application as filed
    - ☐ together with the international application in electronic form
    - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

|                               |             |             |
|-------------------------------|-------------|-------------|
| Novelty (N)                   | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |
| Inventive step (IS)           | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |
| Industrial applicability (IA) | Yes: Claims | <u>1-23</u> |
|                               | No: Claims  |             |

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/GB2010/050825

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)  
and / or
2. Non-written disclosures (Rules 43bis.1 and 70.9)  
see form 210

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**Box No. VII Certain defects in the international application**

---

The following defects in the form or contents of the international application have been noted:

see separate sheet

---

**Box No. VIII Certain observations on the international application**

---

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**V.1 Subject-Matter under Rule 39.1(iv) PCT**

Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

**V.2 Documents**

Reference is made to the following documents:

- D1 WO 99/50249 A2 (DU PONT PHARM CO [US]) 7 October 1999  
(1999-10-07)
- D2 US 2005/054590 A1 (AVERETT DEVRON R [US]) 10 March 2005  
(2005-03-10)

**V.3 Novelty (Art. 33(2) PCT)**

**V.3.1** D1 discloses several 5-(2-phenylethyl)-6-methyl-pyrimidine-2,4-diamines wherein the phenyl ring carries different amide substituents (Ex. A-1091 to A-1104, see Table 1, p. 194) for use in the treatment of cancer metastasis (p. 1, l. 5-16).

The compounds of Formula (I) according to claim 1 of the present application differ from these compounds in that the phenyl ring is attached to the pyrimidyl ring via a -CH<sub>2</sub>-, -NR<sup>B</sup>-, -O- or -S(O)<sub>n</sub>- bridge and not an ethylene bridge, in that the amino group in the 4-position carries a - possibly substituted - alkyl substituent and in the substituents of the phenyl ring.

**V.3.2** D2 discloses several 5-bromo-6-phenyl-pyrimidine-2-amines (Ex. 3-5, see p. 40) for use as prodrugs of ligands of the TLR7 receptor (par. [0001], [0048]). The compounds according to claim 1 of the present application differ from these compounds in the substitution pattern of the pyrimidyl ring.

**V.3.3** Consequently, the subject-matter of claims 1-23 is novel.

**V.4 Inventive Step (Art. 33(3) PCT)**

**V.4.1** D1 is considered to be the prior art closest to the subject-matter of claims 1-23. The disclosure of D1 and the difference between this disclosure and the compounds according to claim 1 of the present application have been discussed above (section V. 3.1).

**V.4.2** The problem to be solved is considered to be the provision of alternative pyrimidine-2,4-diamine derivatives for use in the treatment of cancer, pharmaceutical compositions thereof and their uses.

The solution is given by the compounds, the compositions and the uses according to claims 1-23.

**V.4.3** The retrieved prior art does not contain any pointer to the possibility that the structure of the compounds known from D1 could be altered in such a way as to fall under claim 1 of the present application, i. e. that the ethylene bridge between the pyrimidyl and the phenyl ring might be exchanged against a -CH<sub>2</sub>-, -NR-, -O- or -S(O)<sub>n</sub>- bridge, the amino group in 4-position might be provided with a substituent and the substitution pattern of the phenyl ring might be modified.

**V.4.4** The ability of compounds according to claim 1 of the present application to activate the TLR7 receptor has been demonstrated in the application by means of experimental data (p. 23, I.14 - p. 24, I. 6).

**V.4.5** The subject-matter of claims 1-23 therefore involves an inventive step.

**V.5 Industrial Applicability (Art. 33(4) PCT)**

Claims 1-23 meet the requirements of Art. 33(4) PCT.

**Re Item VI**

**Certain documents cited**

| Application No<br>Patent No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority dates<br>(day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|------------------------------------|
| WO 2009/067081 (D3)         | 28/05/2009                           | 21/11/2008                      | 22/11/2007<br>14/12/2007           |

**Re Item VII**

**Certain defects in the international application**

**VII.1** Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 and D2 is not mentioned in the description, nor is this document identified therein.

**VII.2** On p. 8, l. 26 and l. 31, there are two references to "said phenyl ... rings"; however, the preceding passages do not relate to phenyl rings.

**Re Item VIII**

**Certain observations on the international application**

**VIII.1** The proviso in claim 1 (p. 66, l. 3-7) refers to less compounds than the corresponding proviso in the description (p. 3, l. 21-29). This inconsistency between claim 1 and the description leads to a lack of clarity of claim 1 (Art. 6 PCT).

**VIII.2** According to several passages in the description, the invention is concerned with subject-matter which does not fall within the scope of the claims, for example methods for the preparation of the claimed compounds (cf. p. 1, l. 5-7). In particular, the passage on p. 12, l. 27 - p. 14, l. 9 of the description suggests that the invention relates to prodrugs of the claimed compounds which are not covered by the claims (it is also pointed out that the term "prodrug" is a functional term which does not give a specific technical guidance for the selection of suitable derivatives falling under this term and therefore has to be regarded as unclear).

These inconsistencies between the claims and the description lead to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Art. 6 PCT).

**VIII.3** It is noted that the expressions "optionally" and "such as" have no limiting effect on the claims (PCT-Guidelines 5.40).

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                       |                                                                                                  |                                                         |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Applicant's or agent's file reference<br>103757-1P WO | <b>FOR FURTHER ACTION</b><br>see Form PCT/ISA/220<br>as well as, where applicable, item 5 below. |                                                         |
| International application No.<br>PCT/GB2010/050825    | International filing date (day/month/year)<br>20/05/2010                                         | (Earliest) Priority Date (day/month/year)<br>21/05/2009 |
| Applicant<br><br>ASTRAZENECA AB                       |                                                                                                  |                                                         |

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

This international search report consists of a total of 3 sheets.

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

**1. Basis of the report**

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed  
☐ a translation of the international application into \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No III)

4. With regard to the title,

- ☐ the text is approved as submitted by the applicant  
☒ the text has been established by this Authority to read as follows:

NOVEL PYRIMIDINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF CANCER AND FURTHER DISEASES

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_  
☐ as suggested by the applicant  
☐ as selected by this Authority, because the applicant failed to suggest a figure  
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☒ none of the figures is to be published with the abstract

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2010/050825

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/49 C07D401/12 C07D403/12 C07D413/12 A61K31/505  
A61K31/5377 A61P35/00

ADD.

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN 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 99/50249 A2 (DU PONT PHARM CO [US])<br>7 October 1999 (1999-10-07)<br>page 1, line 5 - line 16; examples A-1091<br>- A-1104                                                                                                          | 1-23                  |
| A         | US 2005/054590 A1 (AVERETT DEVRON R [US])<br>10 March 2005 (2005-03-10)<br>paragraphs [0001], [0048]; examples 3-5                                                                                                                      | 1-23                  |
| X,P       | WO 2009/067081 A1 (ASTRAZENECA AB [SE];<br>DAINIPPON SUMITOMO PHARMA CO [JP]; BENNETT<br>NICHOL) 28 May 2009 (2009-05-28)<br>page 1, line 28 - line 30; claim 1;<br>examples<br>20(iv), 21(v), 22(v), 34(v), 40(v), 89(ii), 89(i<br>ii) | 1-23                  |

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

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

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

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

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

\*G\* document member of the same patent family

Date of the actual completion of the international search

30 July 2010

Date of mailing of the international search report

06/08/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Mooren, Nicolai

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/050825

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s) |    | Publication<br>date |
|-------------------------------------------|----|---------------------|----------------------------|----|---------------------|
| WO 9950249                                | A2 | 07-10-1999          | AU 3213799                 | A  | 18-10-1999          |
|                                           |    |                     | CA 2333927                 | A1 | 07-10-1999          |
|                                           |    |                     | EP 1054871                 | A2 | 29-11-2000          |
|                                           |    |                     | JP 2003504301              | T  | 04-02-2003          |
| US 2005054590                             | A1 | 10-03-2005          | US 2009298863              | A1 | 03-12-2009          |
| WO 2009067081                             | A1 | 28-05-2009          | AR 069412                  | A1 | 20-01-2010          |
|                                           |    |                     | AU 2008326863              | A1 | 28-05-2009          |
|                                           |    |                     | CA 2704214                 | A1 | 28-05-2009          |
|                                           |    |                     | PE 12362009                | A1 | 16-09-2009          |
|                                           |    |                     | US 2009209524              | A1 | 20-08-2009          |
|                                           |    |                     | UY 31481                   | A1 | 17-07-2009          |

PATENTE DE INVENCION ☐

MODELO DE

☐ Indicación que se solicita una patente.

☐ Datos de identificación del solicitante o de la persona que presenta la solicitud

☐ Descripción de la invención

☐ Dibujos de ser estos pertinentes

☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCION PCT ☒

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

☒ Indicación que se solicita una PCT

☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)

☐ Dibujos de ser estos pertinentes

☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

☐ Indicación que se solicita Diseño industrial

☐ Datos de identificación del solicitante o de la persona que presenta la solicitud

☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño

☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐ Indicación que se solicita un esquema de trazado

☐ Datos de identificación del solicitante o de la persona que presenta la solicitud

☐ Representación gráfica de un esquema de trazado

☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐