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Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
FOLIO
1

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-17881

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE 2-METILMORFOLINA PIRIDO,-PIRAZO- Y PIRIMID-PIRIDINA COMO INHIBIDORES DE mTOR

SOLICITANTE: KUDOS PHARMACEUTICALS LIMITED

DIRECCIÓN: 15 Stanhope Gate, Lodon, Greater London, W1K 1LN Gran Bretaña

APODERADO: J. IAN RAISBECK

BOGOTÁ: 23 de febrero de 2009

P2009/000017

OLARTE RAISBECK

OLARTE RAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017881- -00000-0000
Fecha: 2009-02-23 16:51:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 646

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000017**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: **KUDOS PHARMACEUTICALS LIMITED**
Dirección: 15 Stanhope Gate, London, Greater London, W1K 1LN
Nacionalidad o Domicilio: Gran Bretaña
Lugar de Constitución: Gran Bretaña
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: J. IAN RAISBECK
Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.376.996
TP 135.799

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2007/003179 Fecha Agosto 21, 2007

Publicación Internacional No. WO 2008/023161 Fecha Febrero 28, 2008

(6) **Título (54)** **DERIVADOS DE 2-METILMORFOLINA PIRIDO-, PIRAZO- Y PIRIMIDO- PIRIMIDINA COMO INHIBIDORES DE mTOR**

Clasificación Internacional (51) C07D 471/04, A61K 31/519

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 23, 2006	60/823,311
US	Mayo 18, 2007	60/938,776

(9) **Comprobante de pago No.** 09-14.146 **Fecha** Febrero 20, 2009

(10) **ANEXOS**

[X] 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 expediente No

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

[ ] Declaraciones.

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

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

[ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA). (IPRP)

[ ] Traducción del examen preliminar internacional efectuado por la IPEA.

[ ] De ser el caso, copia del contrato de acceso.

[ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

[ ] De ser el caso, certificado de depósito del material biológico.

[ ] Arte final 12 x 12.

[ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

[ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.

[X] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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

4

LISTA DE INVENTORES

PCT/GB2007/003179

1. **Heather Mary Ellen DUGGAN,**
   26 Foundry Lane, Horsham,
   Sussex, RH13 5PX
   Gran Bretaña
   Nacionalidad: Británica

2. **Frederic Georges Marie LEROUX,**
   26 Foundry Lane, Horsham,
   Sussex, RH13 5PX
   Gran Bretaña
   Nacionalidad: Francesa

3. **Karine MALAGU,**
   26 Foundry Lane, Horsham,
   Sussex, RH13 5PX
   Gran Bretaña
   Nacionalidad: Francesa

4. **Niall Morrisson Barr MARTIN,**
   410 Cambridge Science Park,
   Milton Road, Cambridge,
   Cambridgeshire CB4 0PE
   Nacionalidad: Británica

5. **Keith Allan MENEAR,**
   26 Foundry Lane, Horsham,
   Sussex, RH13 5PX
   Gran Bretaña
   Nacionalidad: Británica

6. **Graeme Cameron Murray SMITH,**
   410 Cambridge Science Park,
   Milton Road, Cambridge,
   Cambridgeshire CB4 0PE
   Nacionalidad: Británica

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 14,146
FECHA : FEBRERO 20 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017881- -00000-0000

Fecha: 2009-02-23 16:51:20 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 646

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105276172	18/02/2009	5,412,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

BOGOTA D.C. FEBRERO 04, 2009

TRADUCCION OFICIAL

(VERIFIQUE ANTES DE PROCEDER)

NOTA DE TRADUCCION: SE TRATA DE UNA SESION, EN IDIOMA INGLES Y EN CASTELLANO, (UNA PAGINA) POR DUGGAN HEATHER MARY Y OTROS, INVENTORES DE METHYLMORPHOLINE PYRIDO-, PYRAZO- Y DERIVADOS PYRIMIDO-PYRIMIDINE COMO mTOR INHIBIDORES, A FAVOR DE KuDOS PHARMACEUTICALS LIMITED; CON LEGALIZACION NOTARIAL Y APOSTILLA EN INGLES QUE SE TRADUCEN ASI:

DAWN A STALLWOOD, NOTARIO PUBLICO, THOMAS EGGAR LLP, BELMONT HOUSE, STATION WAY, (HAY FIRMA)

APOSTILLE

(Convención de la Haya, Octubre 5, 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. PAIS: Reino Unido de Gran Bretaña e irlanda del Norte
   ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR **DAWN ANN STALLWOOD**
3. ACTUANDO EN SU CALIDAD DE **NOTARIO PUBLICO**
4. LLEVA EL SELLO/ESTAMPILLA DE DICHO NOTARIO PUBLICO

CERTIFICADO

5. EN **LONDRES**
6. EL DIA **MARZO 31, 2008.**
7. POR EL SECRETARIO PRINCIPAL DE ESTADO DE SU MAJESTAD PARA ASUNTOS EXTERIORES Y DE LA COMUNIDAD.
8. NR. **H727582**
9. SELLO/ESTAMPILLA

10. FIRMADO

Fidel Murcia

TRADUCTOR E INTERPRETE OFICIAL RESOLUCION 488/94 MINJUSTICIA FIDEL ARTORIO MURCIA MURCIA

MINISTERIO DE
RELACIONES EXTERIORES

2009 FEB -6 P 12: 29

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

872692

SOLA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

MINISTERIO DE RELACIONES EXTERIORES

RECIBO LEGALIZACION

No. 181712 414

K. BEBBINGTON
(HAY FIRMA)

Si este documento va a ser usado en un país no miembro de la Convención de La Haya de Octubre 5, 1961,debe ser presentado ante la sección consular de la misión representante de ese país. Una apostilla o certificado de legalización solamente confirma que la firma, sello o estampilla en el documento es auténtica. No significa que el contenido del documento sea correcto o que la Oficina de Extranjería de la Comunidad apruebe el contenido.

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FIDEL ANTONO MURCIA MURCIA
Traductor e Interprete Oficial
Resolución No. 488/94 Ministerio de Justicia

Fidel Murcia

TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 488/94
MINJUSTICIA
FIDEL ANTONIO MURCIA MURCIA

P2009117 1

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ASSIGNMENT

The undersigned,

DUGGAN, Heather, Mary, Ellen; LEROUX, Frederic, Georges, Marie; MALAGU, Karine; MENEAR, Keith, Allan

domiciled in

KuDOS Horsham Limited, 26 Foundry Lane, Horsham, Sussex RH13 5PX, United Kingdom; and

jointly with
MARTIN, Niall, Morrisson, Barr and SMITH, Graeme, Cameron, Murray
domiciled in
KuDOS Pharmaceuticals Limited, 327 Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, United Kingdom

hereby state under oath to be the sole and true inventors of

2-METHYLMORPHOLINE PYRIDO-, PYRAZO- AND PYRIMIDO-PYRIMIDINE DERIVATIVES AS mTOR INHIBITORS

state as well that assign, without reservations or limitation, in favor of

KuDOS Pharmaceuticals Limited

a corporation organized and existing under the laws of

United Kingdon

domiciled in

15 Stanhope Gate, London, W1K 1LN, United Kingdom

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Heather Duggan
DUGGAN, Heather, Mary, Ellen

Malagu
MALAGU, Karine

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leves de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

LEROUX, Frederic, Georges, Marie

Keith Menear
MENEAR, Keith, Allan

Before me:
17/March/2009

Dawn A Stallwood
NOTARY PUBLIC
Thomas Eggar LLP
Belmont House, Station Way
Crawley West Sussex RH10 1
ENGLAND
My Commission is for Life

347627

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by **Dawn Ann Stallwood**
   a été signé par

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

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

Certified/Attesté

5. at London/à Londres
6. the/le **31 March 2008**

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

8. Number/sous No **H727582**

9. Stamp:
   timbre:

10. Signature: **K Bebbington**

KB

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

BOGOTA D.C. FEBRERO 04, 2009

TRADUCCION OFICIAL

(VERIFIQUE ANTES DE PROCEDER)

NOTA DE TRADUCCION: SE TRATA DE UNA SESION, EN IDIOMA INGLES Y EN CASTELLANO, (UNA PAGINA) POR MARTIN NIALL, MORRISON BARR Y OTROS, INVENTORES DE METHYLMORPHOLINE PYRIDO-, PYRAZO- Y DERIVADOS PYRIMIDO-PYRIMIDINE COMO mTOR INHIBIDORES, A FAVOR DE KuDOS PHARMACEUTICALS LIMITED; CON LEGALIZACION NOTARIAL Y APOSTILLA EN INGLES QUE SE TRADUCEN ASI:

CERTIFICACION SIMPLE DE LA FIRMA DEL COMPARECIENTE

SE INFORMA QUE YO, PAUL GITTINS DE ST ANDREW'S HOOUSE 59 ST. ANDREW'S STREET, CAMBRIDGE CB2 3DD UN NOTARIO PUBLICO DEBIDAMENTE ACREDITADO Y AUTORIZADO CERTIFICO (SOLAMENTE) QUE **GRAEME CAMERON MURRAY SMITH** DE 34 HUMPHRIES WAY MILTON CAMBRIDGE CBG24 6DI, IDENTIFICADO CON EL PASAPORTE DEL REINO UNIDO NR. 060303557 Y OTROS DOCUMENTOS PERSONALES, Y **NIALL MORRISON BARR MARTIN** DE HILL COTTAGE FORDHAM ROAD FRECKENHAM BURY ST EDMUNDS SULFOLK IP28 8JB IDENTIFICADO CON EL PASAPORTE DEL REINO UNIDO NR. 070777695 Y OTROS DOCUMENTOS PERSONALES, FIRMARON LA CESION ANEXA EN MI PRESENCIA.

FIRMADO Y SELLADO EN ANDREW'S HOUSE 59 ST. ANDREW'S STREET CAMBRIDGE CB2 3DD CON FECHA MARZO 17, 2008.

(HAY FIRMA)
PAUL GITTNS
NOTARIO PUBLICO
INGLATERRA Y GALES
(SELLO)
PAUL GITTINS
NOTARIO PUBLICO

TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 488/94
MINJUSTICIA
FIDEL ANTONIO MURCIA MURCIA

ST ANDREW'S HOUSE
29 ST ANDREW'S STREET
CAMBRIDGE CB2 3DD
MI COMISION NO EXPIRA. (HAY SELLO)

APOSTILLE

(Convención de la Haya, Octubre 5, 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. PAIS: Reino Unido de Gran Bretaña e irlanda del Norte

ESTE DOCUMENTO PUBLICO

2. HA SIDO FIRMADO POR **PAUL GITTINS**

3. ACTUANDO EN SU CALIDAD DE **NOTARIO PUBLICO**

4. LLEVA EL SELLO/ESTAMPILLA DE DICHO NOTARIO PUBLICO

CERTIFICADO

5. EN **LONDRES**

6. EL DIA **MARZO 31, 2008.**

7. POR EL SECRETARIO PRINCIPAL DE ESTADO DE SU MAJESTAD PARA ASUNTOS EXTERIORES Y DE LA COMUNIDAD.

8. NR. **H727579**

9. SELLO/ESTAMPILLA

10. FIRMADO

K. BEBBINGTON
(HAY FIRMA)

MINISTERIO DE RELACIONES EXTERIORES
2009 FEB -6 A 10: 20
JEFE DE LEGALIZACIONES BOGOTA D.C.
872501
NO SE ASUME RESPONSABILIDAD DEL TEXTO

Si este documento va a ser usado en un pais no miembro de la Convención de La Haya de Octubre 5, 1961,debe ser presentado ante la sección consular de la misión representante de ese pais. Una apostilla o certificado de legalización solamente confirma que la firma, sello o estampilla en el documento es auténtica. No significa que el contenido del documento sea correcto o que la Oficina de Extranjería de la Comunidad apruebe el contenido.

CERTIFICADO DE AUTENTICIDAD: El suscrito Traductor e Interprete Oficial juramentado, y debidamente registrado en el Ministerio de Relaciones Exteriores, con el presente certifica que esta es una traducción auténtica, verdadera, y precisa al Idioma Castellano, del documento en Inglés, **anexo.**

FIDEL ANTONO MURCIA MURCIA
Traductor e Interprete Oficial
Resolución No. 488/94 Ministerio de Justicia

TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 488/94
MINJUSTICIA
FIDEL ANTONIO MURCIA MURCIA

Simple attestation of the signature of the Appearer

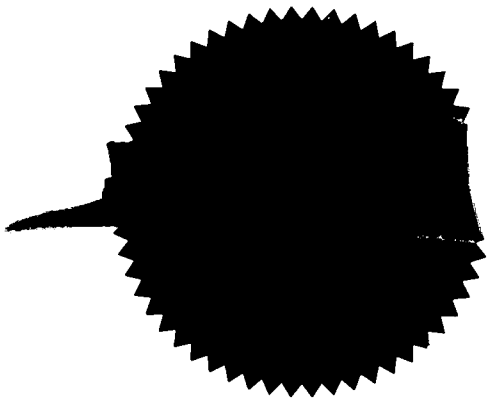
BE IT KNOWN that I, Paul Gittins of St Andrew's House 59 St Andrew's Street Cambridge CB2 3DD a duly authorised notary public CERTIFY (only) that Graeme Cameron Murray Smith of 34 Humphries Way Milton Cambridge CB24 6DL identified by UK passport number 060303557 and other personal papers and Niall Morrison Barr Martin of Hill Cottage Fordham Road Freckenham Bury St Edmunds Suffolk IP28 8JB identified by UK passport number 070777695 and other personal papers signed the annexed Assignment in my presence

SIGNED and sealed at St Andrew's House 59 St Andrew's Street Cambridge CB2 3DD on 17th March 2008

P. Gittins
.....
Paul Gittins
Notary Public
England and Wales

protocol number 456

PAUL GITTINS
NOTARY PUBLIC
ST ANDREW'S HOUSE
59 ST ANDREW'S STREET
CAMBRIDGE CB2 3DD
MY COMMISSION DOES NOT EXPIRE



APOSTILLE

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

Has been signed by **Paul Gittins**
a été signé par

'ing in the capacity of **Notary Public**
'ant en qualité de

'e seal/stamp of **The Said Notary Public**
du sceau/timbre de

ndres

Principal Secretary of State for Foreign and Commonwealth Affairs /
'iat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

6. Certified/Attesté
the/le **31 March 2008**

H727579

10. Signature: **K Bebbington**

KB

tary of State / Pour le Secrétaire d'Etat

party to the Hague Co
mission represen
ture, seal or s
correct

ASSIGNMENT

The undersigned,

MARTIN, Niall, Morrisson, Barr and SMITH, Graeme, Cameron, Murray

domiciled in

KuDOS Pharmaceuticals Limited, 327 Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, United Kingdom

jointly with
DUGGAN, Heather, Mary, Ellen; LEROUX, Frederic, Georges, Marie; MALAGU, Karine and MENEAR, Keith, Allan of KuDOS Horsham Limited, 26 Foundry Lane, Horsham, Sussex RH13 5PX, United Kingdom

hereby state under oath to be the sole and true inventors of

2-METHYLMORPHOLINE PYRIDO-, PYRAZO- AND PYRIMIDO-PYRIMIDINE DERIVATIVES AS mTOR INHIBITORS

state as well that assign, without reservations or limitation, in favor of

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a corporation organized and existing under the laws of

United Kingdon

domiciled in

15 Stanhope Gate, London, W1K 1LN, United Kingdom

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

.....
MARTIN, Niall, Morrisson, Barr

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leves de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

P.G.
GCMS

.....
SMITH, Graeme, Cameron, Murray

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 February 2008 (28.02.2008)

PCT

(10) International Publication Number
WO 2008/023161 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/519* (2006.01)

(21) International Application Number:
PCT/GB2007/003179

(22) International Filing Date: 21 August 2007 (21.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/823,311	23 August 2006 (23.08.2006)	US
60/938,776	18 May 2007 (18.05.2007)	US

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BH, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GT, GW, HN, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MC, MD, MG, MK, ML, MN, MR, MT, MW, MX, MY, MZ, NA, NE, NG, NI, NL, NO, NZ, OM only)*: **KUDOS PHARMACEUTICALS LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London, W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DUGGAN, Heather, Mary, Ellen** [GB/GB]; KuDOS Pharmaceuticals Limited, 26 Foundry Lane, Horsham, Sussex, RH13 5PX (GB). **LEROUX, Frederic, Georges, Marie** [FR/GB]; KuDOS Pharmaceuticals Limited, 26 Foundry Lane, Horsham, Sussex, RH13 5PX (GB). **MALAGU, Karine** [FR/GB]; KuDOS Pharmaceuticals Limited, 26 Foundry Lane, Horsham, Sussex, RH13 5PX (GB). **MARTIN, Niall, Morrisson, Barr** [GB/GB]; KuDOS Pharmaceuticals Limited, 410 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0PE (GB). **MENEAR, Keith, Allan** [GB/GB]; KuDOS Pharmaceuticals Limited, 26 Foundry Lane, Horsham, Sussex, RH13 5PX (GB). **SMITH, Graeme, Cameron, Murray** [GB/GB]; KuDOS Pharmaceuticals Limited, 410 Cambridge Science Park, Milton Road, Cambridge, Cambridgeshire CB4 0PE (GB).

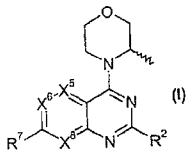
(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-SE-151 85 Södertälje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: 2-METHYLMORPHOLINE PYRIDO-, PYRAZO- AND PYRIMIDO-PYRIMIDINE DERIVATIVES AS MTOR INHIBITORS



(I)

(57) Abstract: There is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof. There are also provided processes for the manufacture of a compound of Formula (1), and the use of a compound of Formula (1) as a medicament and in the treatment of cancer.

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2-METHYLMORPHOLINE PYRIDO-, PYRAZO- AND PYRIMIDO-PYRIMIDINE DERIVATIVES AS MTOR INHIBITORS

The present invention relates to compounds which act as mTOR inhibitors, their use and their synthesis.

Background

Growth factor/mitogenic activation of the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway ultimately leads to the key cell cycle and growth control regulator mTOR, the mammalian target of rapamycin (alternatively referred to as FRAP (FKBP12 and rapamycin associated protein), RAFT1 (rapamycin and FKBP12 target 1), RAPT1 (rapamycin target 1) – all derived from the interaction with the FK-506-binding protein FKBP12, and SEP (sirolimus effector protein)). mTOR is a mammalian serine/threonine kinase of approximately 289 kDa in size and a member of the evolutionary conserved eukaryotic TOR kinases (refs. 1-4). The mTOR protein is a member of the PI3-kinase like kinase (PIKK) family of proteins due to its C-terminal homology (catalytic domain) with PI3-kinase and the other family members, e.g. DNA-PKcs (DNA dependent protein kinase), ATM (Ataxia-telangiectasia mutated). In addition to a catalytic domain in the C-terminus, mTOR contains a FKBP12/rapamycin complex binding domain (FRB). At the N-terminus up to 20 HEAT (Huntingtin, EF3, alpha regulatory subunit of PP2A and TOR) motifs are found whilst more C-terminal is a FAT (FRAP-ATM-TRRAP) domain, and at the extreme C-terminus of the protein an additional FAT domain is found (FAT-C) (refs. 5,6).

TOR has been identified as a central regulator of both cell growth (size) and proliferation, which is in part governed by translation initiation. TOR dependant phosphorylation of S6-kinase (S6K1) allows translation of ribosomal proteins involved in cell cycle progression (refs. 7-9). Cap-dependant translation is regulated by the phosphorylation of the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1 (PHAS-1)). This modification prevents PHAS-1 binding eIF4E, thereby permitting formation of an active eIF4F translation complex (reviewed in refs. 10,11,12). Activation of these signalling elements is dependant on insulin, other growth factors and nutrients suggesting a gatekeeper role for mTOR in the control of cell cycle progression only under favourable environmental conditions. The PI3K/AKT signalling cascade lies upstream of mTOR and this has been shown to be deregulated in certain cancers and results in growth factor independent activation in, for example, PTEN deficient cells. mTOR lies at the axis of control for this pathway and inhibitors of this kinase (e.g. sirolimus (rapamycin or Rapamune™) and everolimus (RAD001

or Certican™)) are already approved for immunosuppression and drug eluting stents (reviewed in refs. 13, 14), and are now receiving particular interest as novel agents for cancer treatment.

Tumour cell growth arises from the deregulation of normal growth control mechanisms such as the loss of tumour suppressor function(s). One such tumour suppressor is the phosphatase and tensin homologue deleted from chromosome ten (PTEN). This gene, also known as mutated in multiple advanced cancers (MMAC), has been shown to play a significant role in cell cycle arrest and is the most highly mutated tumour suppressor after p53. Up to 30% of glioblastoma, endometrial and prostate cancers have somatic mutations or deletions of this locus (refs. 15,16).

PI3K converts phosphatidylinositol 4,5, bisphosphate (PIP2) to phosphatidylinositol 3,4,5, triphosphate (PIP3) whilst PTEN is responsible for removing the 3' phosphate from PIP3 producing PIP2. PI3-K and PTEN act to maintain an appropriate level of PIP3 which recruits and thus activates AKT (also known as PKB) and the downstream signalling cascade that is then initiated. In the absence of PTEN, there is inappropriate regulation of this cascade, AKT becomes effectively constitutively activated and cell growth is deregulated. An alternative mechanism for the deregulation of this cell signalling process is the recent identification of a mutant form of the PI3K isoform, p110alpha (ref. 17). The apparent increased activity of this mutant is thought to result in increased PIP3 production, presumably in excess of that which the function of PTEN can counteract. Increased signalling from PI3K, thus results in increased signalling to mTOR and consequently, its downstream activators.

In addition to the evidence linking mTOR with cell cycle regulation (from G1 to S-phase) and that inhibition of mTOR results in inhibition of these regulatory events it has been shown that down regulation of mTOR activity results in cell growth inhibition (Reviewed in refs. 7,18,19). The known inhibitor of mTOR, rapamycin, potently inhibits proliferation or growth of cells derived from a range of tissue types such as smooth muscle, T-cells as well as cells derived from a diverse range of tumour types including rhabdomyosarcoma, neuroblastoma, glioblastoma and medulloblastoma, small cell lung cancer, osteosarcoma, pancreatic carcinoma and breast and prostate carcinoma (reviewed in ref. 20). Rapamycin has been approved and is in clinical use as an immunosuppressant, its prevention of organ rejection being successful and with fewer side effects than previous therapies (refs. 20, 21). Inhibition of mTOR by rapamycin and its analogues (RAD001, CCI-779) is brought about by

the prior interaction of the drug with the FK506 binding protein, FKBP12. Subsequently, the complex of FKBP12/rapamycin then binds to the FRB domain of mTOR and inhibits the downstream signalling from mTOR.

The potent but non-specific inhibitors of PI3K, LY294002 and wortmannin, also have been shown to inhibit the kinase function of mTOR but act through targeting the catalytic domain of the protein (ref. 21). Further to the inhibition of mTOR function by small molecules targeted to the kinase domain, it has been demonstrated that kinase dead mTOR cannot transmit the upstream activating signals to the downstream effectors of mTOR, PHAS-1 or p70S6 kinase (ref. 22). It is also shown that not all functions of mTOR are rapamycin sensitive and this may be related to the observation that rapamycin alters the substrate profile of mTOR rather than inhibiting its activity *per se* (ref. 23). Analysis of the interactions of mTOR with other cellular factors has revealed that in addition to the mTOR-Raptor complex, there is also an mTOR-Rictor complex representing a rapamycin insensitive activity of mTOR (B) (Sarbassov *et al.* Current Biology, 2004, 14, 1296-1302). This activity likely accounts for the discrepancy between kinase dead mTOR and the alteration of mTOR signalling by rapamycin and its derivatives. The discrepancy also identifies the possibility of a therapeutic advantage in inhibiting directly the catalytic activity of mTOR. It has been suggested that a catalytic inhibitor of mTOR may be a more effective antagonist of cancer cell proliferation and survival and that rapamycin may be more useful in combination with agents that can compensate for its failure to completely disrupt pathway signalling (Choo and Blenis, Cancer Cell, 2006, 9, 77-79; Hay, Cancer Cell, 2005, 8, 179-183). Therefore, it is proposed that a kinase domain directed inhibitor of mTOR may be a more effective inhibitor of mTOR.

In addition to rapamycin's ability to induce growth inhibition (cytostasis) in its own right, rapamycin and its derivatives have been shown to potentiate the cytotoxicity of a number of chemotherapies including cisplatin, camptothecin and doxorubicin (reviewed in ref. 20). Potentiation of ionising radiation induced cell killing has also been observed following inhibition of mTOR (ref. 24). Experimental and clinical evidence has shown that rapamycin analogues are showing evidence of efficacy in treating cancer, either alone or in combination with other therapies (see refs. 10, 18, 20). These findings suggest that pharmacological inhibitors of mTOR kinase should be of therapeutic value for treatment of the various forms of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In particular, inhibitors of mTOR kinase should

be of therapeutic value for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

Renal cell carcinoma in particular, has been identified as sensitive to the rapamycin derivative CCI-779, resulting from a loss of VHL expression (Thomas *et al.* Nature Medicine, 2006, 12, 122-127). Tumours that have lost the promyelocytic leukaemia (PML) tumour suppressor, have also been shown to be sensitive to inhibition of mTOR by rapamycin as a consequence of disruption of the regulation of the mTOR signalling pathway (Bernadi, Nature, 2006, 442, 779-785) and the use of an mTOR kinase inhibitor in these diseases should be of therapeutic value. These latter examples in addition to those of PTEN deficiency or PI3K mutation indicate where a targeted approach to the use of mTOR inihibitors may prove particularly effective due to an underlying genetic profile, but are not considered to be exclusive targets.

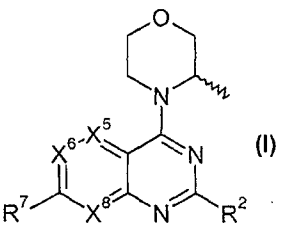
Recent studies have revealed a role for mTOR kinase in other diseases (Easton & Houghton, Expert Opinion on Therapeutic Targets, 2004, 8, 551-564). Rapamycin has been demonstrated to be a potent immunosuppressant by inhibiting antigen-induced proliferation of T cells, B cells and antibody production (Sehgal, Transplantation Proceedings, 2003, 35, 7S-14S) and thus mTOR kinase inhibitors may also be useful immunosuppressives. Inhibition of the kinase activity of mTOR may also be useful in the prevention of restenosis, that is the control of undesired proliferation of normal cells in the vasculature in response to the introduction of stents in the treatment of vasculature disease (Morice *et al.*, New England Journal of Medicine, 2002, 346, 1773-1780). Furthermore, the Rapamycin analogue, everolimus, can reduce the severity and incidence of cardiac allograft vasculopathy (Eisen *et al.*, New England Journal of Medicine, 2003, 349, 847-858). Elevated mTOR kinase activity has been associated with cardiac hypertrophy, which is of clinical importance as a major risk factor for heart failure and is a consequence of increased cellular size of cardiomyocytes (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Thus mTOR kinase inhibitors are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

The vast majority of mTOR pharmacology to date has focused on inhibition of mTOR via rapamycin or its analogues. However, as noted above, the only non-rapamycin agents that have been reported to inhibit mTOR's activity via a kinase domain targetted mechanism are the small molecule LY294002 and the natural product wortmannin (ref. 21).

Summary of the Invention

The present inventors have identified compounds which are ATP-competitive inhibitors of mTOR, and hence are non-rapamycin like in their mechanism of action.

Accordingly, the first aspect of the present invention provides a compound of formula I:



(I)

, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group, where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

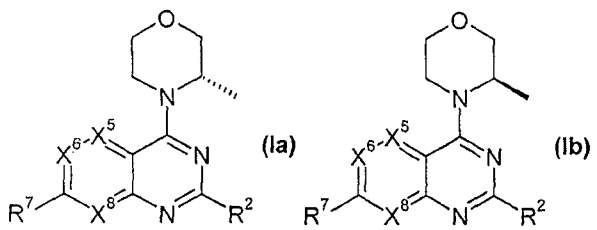
R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

According to a second aspect of the present invention there is provided a compound of formula Ia or Ib:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group, where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

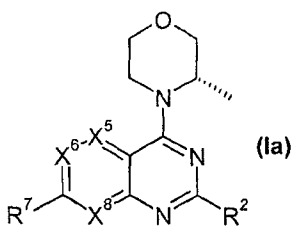
R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

According to a third aspect of the present invention there is provided a compound of formula Ia:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group,

where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

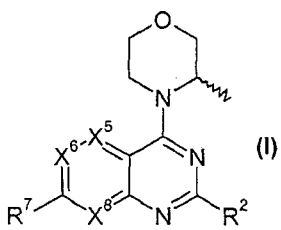
R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

According to a further aspect of the present invention there is provided a compound of formula I:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group,

where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted

C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

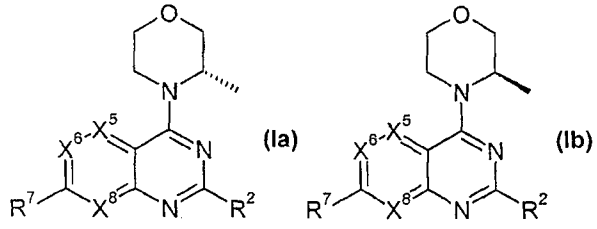
R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms.

According to a further aspect of the present invention there is provided a compound of formula Ia or Ib:



or a pharmaceutically acceptable salt thereof,wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group, where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl

group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

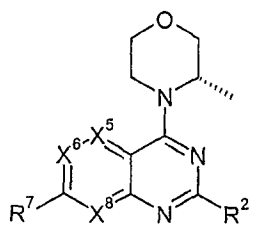
R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms.

According to a further aspect of the present invention there is provided a compound of formula Ia:



, or a pharmaceutically acceptable salt thereof,wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group,

where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$,

where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

According to a further aspect of the present invention there is provided a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof,for use in a method of treatment of the human or animal body.

According to a further aspect of the present invention there is provided the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof,in the preparation of a medicament for treating a disease ameliorated by the inhibition of mTOR.

The compounds of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, have activity as pharmaceuticals, in particular as modulators or inhibitors of mTOR activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

(1) carcinoma, including that of the bladder, brain, breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, cervix, colon, endometrium, thyroid and skin;

(2) hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukaemia, B-cell lymphoma and Burketts lymphoma;

(3) hematopoietic tumours of myeloid lineage, including acute and chronic myelogenous leukaemias and promyelocytic leukaemia;

(4) tumours of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and

(5) other tumours, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

Further aspects of the invention provide the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of: cancer, immuno-suppression, immune tolerance, autoimmune disease, inflammation, bone loss, bowel disorders, hepatic fibrosis, hepatic necrosis, rheumatoid arthritis, restinosis, cardiac allograft vasculopathy, psoriasis, beta-thalassaemia, and ocular conditions such as dry eye. mTOR inhibitors may also be effective as antifungal agents.

Another further aspect of the invention provides for the use of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use as an adjunct in cancer therapy or for potentiating tumour cells for treatment with ionizing radiation or chemotherapeutic agents.

Thus the compounds of the present invention provide a method for treating cancer characterised by inhibition of mTOR, i.e. the compounds may be used to produce an anti-cancer effect mediated alone or in part by the inhibition of mTOR.

Such a compound of the invention is expected to possess a wide range of anti-cancer properties as activating mutations in mTOR have been observed in many human cancers, including but not limited to, melanoma, papillary thyroid tumours, cholangiocarcinomas, colon, ovarian and lung cancers. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, bladder, prostate, endometrium, breast and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the skin, colon, thyroid, lungs, endometrium and ovaries. More particularly such compounds of the invention, or a pharmaceutically acceptable salt thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with mTOR, especially those tumours which are significantly dependent on mTOR

for their growth and spread, including for example, certain tumours of the skin, colon, thyroid, endometrium, lungs and ovaries. Particularly the compounds of the present invention are useful in the treatment of melanomas and gliomas.

Thus according to this aspect of the invention there is provided a compound of the formula I or 1(A), or a pharmaceutically acceptable salt thereof, as defined herein for use as a medicament.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in the treatment of melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of this aspect of the invention there is provided a method for producing a mTOR inhibitory effect 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), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer effect 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), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, 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), (Ia) or (Ib) or a pharmaceutically acceptable salt thereof as defined herein.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, 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), (Ia) or (Ib) or a pharmaceutically acceptable salt thereof as defined herein.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, glioma, papillary thyroid tumours,

cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

Other further aspects of the invention provide for the treatment of disease ameliorated by the inhibition of mTOR, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, preferably in the form of a pharmaceutical composition and the treatment of cancer, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in combination, preferably in the form of a pharmaceutical composition, simultaneously or sequentially with ionizing radiation or chemotherapeutic agents.

Definitions

The term "aromatic ring" is used herein in the conventional sense to refer to a cyclic aromatic structure, that is, a structure having delocalised π-electron orbitals.

Nitrogen-containing heterocyclic ring having from 3 to 8 ring atoms: The term "Nitrogen-containing heterocyclic ring having from 3 to 8 ring atoms" as used herein refers to a 3 to 8 membered heterocylic ring containing at least one nitrogen ring atom. The term "together with the nitrogen to which they are bound, form a heterocyclic ring containing between 3 and 8 ring atoms" as used herein refers to a 3 to 8 membered heterocylic ring containing at least one nitrogen ring atom. Examples of these groups include, but are not limited to:

N_1: aziridine (C_3 ie 3 membered), azetidine (C_4 ie 4 membered), pyrrolidine (tetrahydropyrrole) (C_5 ie 5 membered), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5 ie 5 membered), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5 ie 5 membered), piperidine (C_6 ie 6 membered), dihydropyridine (C_6 ie 6 membered), tetrahydropyridine (C_6 ie 6 membered), azepine (C_7 ie 7 membered);

N_2: imidazolidine (C_5 ie 5 membered), pyrazolidine (diazolidine) (C_5 ie 5 membered), imidazoline (C_5 ie 5 membered), pyrazoline (dihydropyrazole) (C_5 ie 5 membered), piperazine (C_6 ie 6 membered);

N_1O_1: tetrahydrooxazole (C_5 ie 5 membered), dihydrooxazole (C_5 ie 5 membered), tetrahydroisoxazole (C_5 ie 5 membered), dihydroisoxazole (C_5 ie 5 membered), morpholine (C_6 ie 6 membered), tetrahydrooxazine (C_6 ie 6 membered), dihydrooxazine (C_6 ie 6 membered), oxazine (C_6 ie 6 membered);

N_1S_1: thiazoline (C_5 ie 5 membered), thiazolidine (C_5 ie 5 membered), thiomorpholine (C_6 ie 6 membered);

N_2O_1: oxadiazine (C_6 ie 6 membered);

$N_1O_1S_1$: oxathiazine (C_6 ie 6 membered).

Alkyl: The term "alkyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated). Thus, the term "alkyl" includes the sub-classes saturated alkyl, alkenyl, alkynyl, saturated cycloalkyl, cycloalkyenyl, cylcoalkynyl, etc., discussed below. Unless otherwise specified, preferable "alkyl" groups are saturated alkyl or saturated cycloalkyl groups, more preferably saturated alkyl groups.

In the context of alkyl groups, the prefixes (e.g. C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C_{1-4} alkyl", as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups include C_{1-4} alkyl ("lower alkyl"), C_{1-7} alkyl, and C_{1-20} alkyl. Note that the first prefix may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic alkyl groups, the first prefix must be at least 3; etc.

The term saturated alkyl group includes saturated linear alkyl and saturated branched alkyl.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6), heptyl (C_7), octyl (C_8), nonyl (C_9), decyl (C_{10}), undecyl (C_{11}), dodecyl (C_{12}), tridecyl (C_{13}), tetradecyl (C_{14}), pentadecyl (C_{15}), and eicodecyl (C_{20}).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

Alkenyl: The term "alkenyl", as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds. Examples of groups of alkenyl groups include C_{2-4} alkenyl, C_{2-7} alkenyl, C_{2-20} alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH_2), 1-propenyl (-CH=CH-CH_3), 2-propenyl (allyl, -CH-CH=CH_2), isopropenyl (1-methylvinyl, -C(CH_3)=CH_2), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Alkynyl: The term "alkynyl", as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds. Examples of groups of alkynyl groups include C_{2-4} alkynyl, C_{2-7} alkynyl, C_{2-20} alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, -C≡CH) and 2-propynyl (propargyl, -CH_2-C≡CH).

Cycloalkyl: The term "cycloalkyl", as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or unsaturated (e.g. partially unsaturated, fully unsaturated), which moiety has from 3 to 20 carbon atoms (unless otherwise specified), including from 3 to 20 ring atoms. Thus, the term "cycloalkyl" includes the sub-classes saturated cycloalkyl, cycloalkenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring atoms. Examples of groups of cycloalkyl groups include C_{3-20} cycloalkyl, C_{3-15} cycloalkyl, C_{3-10} cycloalkyl, C_{3-7} cycloalkyl.

Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6), cycloheptane (C_7), methylcyclopropane (C_4), dimethylcyclopropane (C_5), methylcyclobutane (C_5), dimethylcyclobutane (C_6), methylcyclopentane (C_6), dimethylcyclopentane (C_7), methylcyclohexane (C_7), dimethylcyclohexane (C_8), menthane (C_{10});

unsaturated monocyclic hydrocarbon compounds: cyclopropene (C_3), cyclobutene (C_4), cyclopentene (C_5), cyclohexene (C_6), methylcyclopropene (C_4), dimethylcyclopropene (C_5), methylcyclobutene (C_5), dimethylcyclobutene (C_6),

methylcyclopentene (C_6), dimethylcyclopentene (C_7), methylcyclohexene (C_7), dimethylcyclohexene (C_8);

saturated polycyclic hydrocarbon compounds: thujane (C_{10}), carane (C_{10}), pinane (C_{10}), bornane (C_{10}), norcarane (C_7), norpinane (C_7), norbornane (C_7), adamantane (C_{10}), decalin (decahydronaphthalene) (C_{10});

unsaturated polycyclic hydrocarbon compounds: camphene (C_{10}), limonene (C_{10}), pinene (C_{10});

polycyclic hydrocarbon compounds having an aromatic ring: indene (C_9), indane (e.g., 2,3-dihydro-1H-indene) (C_9), tetraline (1,2,3,4-tetrahydronaphthalene) (C_{10}), acenaphthene (C_{12}), fluorene (C_{13}), phenalene (C_{13}), acephenanthrene (C_{15}), aceanthrene (C_{16}), cholanthrene (C_{20}).

Heterocyclyl: The term "heterocyclyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified), of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. Preferably the ring heteroatoms are selected from O, N and S. The heterocyclic ring may, unless otherwise specified, be carbon or nitrogen linked, and wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring sulphur atom may be optionally oxidised to form the S-oxides.

In this context, the prefixes (e.g. C_{3-20}, C_{3-7}, C_{5-6}, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}heterocyclyl" or "5 to 6 membered heterocyclyl", as used herein, pertains to a heterocyclyl group having 5 or 6 ring atoms. Examples of groups of heterocyclyl groups include C_{3-20} heterocyclyl (ie 3 to 20 membered heterocyclyl), C_{5-20} heterocyclyl (ie 5 to 20 membered heterocyclyl), C_{3-15} heterocyclyl (ie 3 to 15 membered heterocyclyl), C_{5-15} heterocyclyl (ie 5 to 15 membered heterocyclyl), C_{3-12} heterocyclyl (ie 3 to 12 membered heterocyclyl), C_{5-12} heterocyclyl (ie 5 to 12 membered heterocyclyl), C_{3-10} heterocyclyl (ie 3 to 10 membered heterocyclyl), C_{5-10} heterocyclyl (ie 5 to 10 membered heterocyclyl), C_{3-7} heterocyclyl (ie 3 to 7 membered heterocyclyl), C_{5-7} heterocyclyl (ie 5 to 7 membered heterocyclyl), and C_{5-6} heterocyclyl (ie 5 to 6 membered heterocyclyl).

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3 ie 3 memberd), azetidine (C_4 ie 4 membered), pyrrolidine (tetrahydropyrrole) (C_5 ie 5 membered), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5 ie 5 membered), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5 ie 5 membered), piperidine (C_6 ie 6 membered), dihydropyridine (C_6 ie 6 membered), tetrahydropyridine (C_6 ie 6 membered), azepine (C_7 ie 7 membered);

O_1: oxirane (C_3 ie 3 membered), oxetane (C_4 ie 4 membered), oxolane (tetrahydrofuran) (C_5 ie 5 membered), oxole (dihydrofuran) (C_5 ie 5 membered), oxane (tetrahydropyran) (C_6 ie 6 membered), dihydropyran (C_6 ie 6 membered), pyran (C_6 ie 6 membered), oxepin (C_7 ie 7membered);

S_1: thiirane (C_3 ie 3 membered), thietane (C_4 ie 4 membered), thiolane (tetrahydrothiophene) (C_5 ie 5 membered), thiane (tetrahydrothiopyran) (C_6 ie 6membered), thiepane (C_7 ie 7 membered);

O_2: dioxolane (C_5 ie 5 membered), dioxane (C_6 ie 6 membered), and dioxepane (C_7 ie 7 membered);

O_3: trioxane (C_6 ie 6 membered);

N_2: imidazolidine (C_5 ie 5 membered), pyrazolidine (diazolidine) (C_5 ie 5 membered), imidazoline (C_5 ie 5 membered), pyrazoline (dihydropyrazole) (C_5 ie 5 membered), piperazine (C_6 ie 6membered);

N_1O_1: tetrahydrooxazole (C_5 ie 5 membered), dihydrooxazole (C_5 ie 5 membered), tetrahydroisoxazole (C_5 ie 5 membered), dihydroisoxazole (C_5 ie 5 membered), morpholine (C_6 ie 6 membered), tetrahydrooxazine (C_6 ie 6 membered), dihydrooxazine (C_6 ie 6 membered), oxazine (C_6 ie 6 membered);

N_1S_1: thiazoline (C_5 ie 5 membered), thiazolidine (C_5 ie 5 membered), thiomorpholine (C_6 ie 6 membered);

N_2O_1: oxadiazine (C_6 ie 6 membered);

O_1S_1: oxathiole (C_5 ie 5 membered) and oxathiane (thioxane) (C_6 ie 6 membered); and,

$N_1O_1S_1$: oxathiazine (C_6 ie 6 membered).

Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include those derived from saccharides, in cyclic form, for example, furanoses (C_5 ie 5 membered), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C_6 ie 6

membered), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

Spiro-C_{3-7} cycloalkyl or heterocyclyl: The term "spiro C_{3-7} cycloalkyl or heterocyclyl" as used herein, refers to a C_{3-7} cycloalkyl or C_{3-7} heterocyclyl ring (3 to 7 membered) joined to another ring by a single atom common to both rings.

C_{5-20} aryl: The term "C_{5-20} aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of a C_{5-20} aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 ring atoms.

The ring atoms may be all carbon atoms, as in "carboaryl groups" in which case the group may conveniently be referred to as a "C_{5-20} carboaryl" group.

Examples of C_{5-20} aryl groups which do not have ring heteroatoms (i.e. C_{5-20} carboaryl groups) include, but are not limited to, those derived from benzene (i.e. phenyl) (C_6), naphthalene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), and pyrene (C_{16}).

Alternatively, the ring atoms may include one or more heteroatoms, including but not limited to oxygen, nitrogen, and sulfur, as in "heteroaryl groups". In this case, the group may conveniently be referred to as a "C_{5-20} heteroaryl" group, wherein "C_{5-20}" denotes ring atoms, whether carbon atoms or heteroatoms (or otherwise referred to as a 5 to membered heteroaryl group). Preferably, each ring has from 5 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. Commonly, heteroatoms are selected from oxygen, nitrogen or sulphur.

Examples of C_{5-20} heteroaryl groups include, but are not limited to, C_5 heteroaryl groups (5 membered heteroaryl groups) derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, tetrazole and oxatriazole; and C_6 heteroaryl groups (6 membered heteroaryl groups) derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine; e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) and triazine.

The heteroaryl group may be bonded via a carbon or hetero ring atom.

Examples of C_{5-20} heteroaryl groups which comprise fused rings, include, but are not limited to, C_9 heteroaryl groups (9 membered heteroaryl groups) derived from benzofuran, isobenzofuran, benzothiophene, indole, isoindole; C_{10} heteroaryl groups (10 membered

heteroaryl groups) derived from quinoline, isoquinoline, benzodiazine, pyridopyridine; C_{14} heteroaryl groups (14 membered heteroaryl groups) derived from acridine and xanthene.

The above alkyl, heterocyclyl, and aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkoxy group), a C_{3-20} heterocyclyl group (also referred to as a C_{3-20} heterocyclyloxy group), or a C_{5-20} aryl group (also referred to as a C_{5-20} aryloxy group), preferably a C_{1-7} alkyl group.

Nitro: $-NO_2$.

Cyano (nitrile, carbonitrile): -CN.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, H, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20} heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, $-C(=O)CH_3$ (acetyl), $-C(=O)CH_2CH_3$ (propionyl), $-C(=O)C(CH_3)_3$ (butyryl), and -C(=O)Ph (benzoyl, phenone).

Carboxy (carboxylic acid): -COOH.

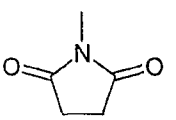
Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh.

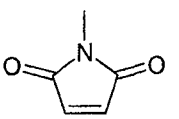
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinylcarbonyl.

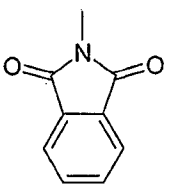
Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di-C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridinyl, azetidinyl, pyrrolidinyl, piperidino, piperazinyl, perhydrodiazepinyl, morpholino, and thiomorpholino. The cylic amino groups may be substituted on their ring by any of the substituents defined here, for example carboxy, carboxylate and amido.

Aminosulfonyl $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 each independently is an amino substituent, as defined for amino groups. Examples of aminosulfony groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NHCH_3$, $-S(=O)_2NHCH_2CH_3$ and $-S(=O)_2N(CH_3)_2$.

Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, most preferably H, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:


succinimidyl


maleimidyl


phthalimidyl

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R1 is a ureido substituent, for example, hydrogen, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, -NHCONHMe, -NHCONHEt, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, -NMeCONHMe, -NMeCONHEt, $-NMeCONMe_2$, $-NMeCONEt_2$ and -NHC(=O)NHPh.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl

group. Examples of acyloxy groups include, but are not limited to, -OC(=O)CH_3 (acetoxy), -OC(=O)CH_2CH_3, -OC(=O)$C(CH_3)_3$, -OC(=O)Ph, -OC(=O)C_6H_4F, and -OC(=O)CH_2Ph.

Thiol : -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkylthio group), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, -SCH_3 and -SCH_2CH_3.

Sulfoxide (sulfinyl): -S(=O)R, wherein R is a sulfoxide substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfoxide groups include, but are not limited to, -S(=O)CH_3 and -S(=O)CH_2CH_3.

Sulfonyl (sulfone): -S(=O)$_2$R, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)$_2CH_3$ (methanesulfonyl, mesyl), -S(=O)$_2CF_3$, -S(=O)$_2CH_2CH_3$, and 4-methylphenylsulfonyl (tosyl).

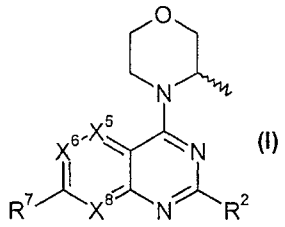
Thioamido (thiocarbamyl): -C(=S)NR^1R^2, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, -C(=S)NH_2, -C(=S)$NHCH_3$, -C(=S)$N(CH_3)_2$, and -C(=S)$NHCH_2CH_3$.

Sulfonamino: -NR^1S(=O)$_2$R, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7}alkyl group, a C_{3-20}heterocyclyl group, or a C_{5-20}aryl group, preferably a C_{1-7}alkyl group. Examples of sulfonamino groups include, but are not limited to, -NHS(=O)$_2CH_3$, -NHS(=O)$_2$Ph and -$N(CH_3)$S(=O)$_2C_6H_5$.

In addition, two or more adjacent substituents may be linked such that together with the atoms to which they are attached from a C_{3-7} cycloalkyl, C_{3-20} heterocyclyl or C_{5-20} aryl ring.

As mentioned above, the groups that form the above listed substituent groups, e.g. C_{1-7} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl, may themselves be substituted. Thus, the above definitions cover substituent groups which are substituted.

According to a further aspect of the present invention there is provided a compound of formula I:



(I)

, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

where $\mathbf{R^{O1}}$ and $\mathbf{R^{S1}}$ are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl, or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl,

ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{N1} and R^{N2} are independently H, a C_{1-7}alkyl group, a C_{5-20}heteroaryl group, a C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{C1} is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, a C_{1-7} alkyl group or $NR^{N8}R^{N9}$ where R^{N8} and R^{N9} are independently selected from H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{S2a} is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo,

hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

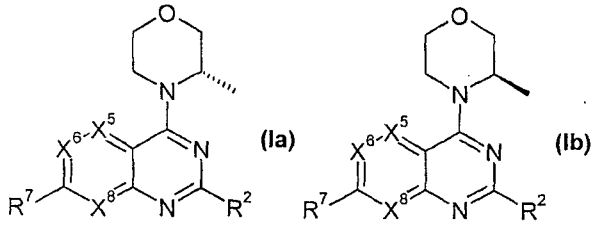
R^{N7a} and R^{N7b} are H or a C_{1-4} alkyl group;

R^2 is H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

wherein R^{O2} and R^{S2b} are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{N5} and R^{N6} are independently H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino).

According to a further aspect of the present invention there is provided a compound of formula Ia or Ib:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido,

ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

where $\mathbf{R^{O1}}$ and $\mathbf{R^{S1}}$ are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl, or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are independently H, a C_{1-7}alkyl group, a C_{5-20}heteroaryl group, a C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{C1}}$ is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, a C_{1-7} alkyl group or $NR^{N8}R^{N9}$ where $\mathbf{R^{N8}}$ and $\mathbf{R^{N9}}$ are independently selected from H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl,

C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{S2a} is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{N7a} and R^{N7b} are H or a C_{1-4} alkyl group;

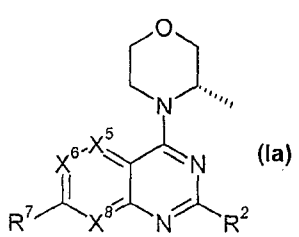
R^2 is H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl,

C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

wherein $\mathbf{R}^{O2}$ and $\mathbf{R}^{S2b}$ are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R}^{N5}$ and $\mathbf{R}^{N6}$ are independently H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino).

According to a further aspect of the present invention there is provided a compound of formula Ia:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

where $\mathbf{R^{O1}}$ and $\mathbf{R^{S1}}$ are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl, or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{N1}}$ and $\mathbf{R^{N2}}$ are independently H, a C_{1-7}alkyl group, a C_{5-20}heteroaryl group, a C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic is optionally substituted by one or more groups selected from halo, hydroxyl,

nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{C1}}$ is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, a C_{1-7} alkyl group or $NR^{N8}R^{N9}$ where $\mathbf{R^{N8}}$ and $\mathbf{R^{N9}}$ are independently selected from H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{S2a}}$ is H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

$\mathbf{R^{N7a}}$ and $\mathbf{R^{N7b}}$ are H or a C_{1-4} alkyl group;

R^2 is H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, a C_{5-20} heteroaryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino), or a C_{5-20} aryl group optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino),

wherein $\mathbf{R^{O2}}$ and $\mathbf{R^{S2b}}$ are H, a C_{5-20} aryl group, a C_{5-20} heteroaryl group, or a C_{1-7} alkyl group where each C_{1-7}alkyl, C_{5-20}heteroaryl or C_{5-20}aryl is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino);

R^{N5} and $\mathbf{R^{N6}}$ are independently H, a C_{1-7} alkyl group, a C_{5-20} heteroaryl group, a C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms where each C_{1-7}alkyl, C_{5-20}heteroaryl, C_{5-20}aryl or heterocyclic ring is optionally substituted by one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, and thiol, or C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl,

C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino (each optionally substituted with one or more groups selected from halo, hydroxyl, nitro, cyano, carboxy, thiol, C_{1-7}alkyl, C_{2-7}alkenyl, C_{2-7}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, C_{3-20}heterocyclyl, C_{5-20}aryl, C_{5-20}heteroaryl, ether, acyl, ester, amido, amino, acylamido, ureido, acyloxy, thioether, sulfoxide, sulfonyl, thioamido and sulfonamino).

Further Preferences

The following preferences can apply to each aspect of the present invention, where applicable. The preferences for each group may be combined with those for any or all of the other groups, as appropriate.

X^5, X^6, and X^8

When two of X^5, X^6 and X^8 are N, preferably X^5 and X^8 are N.

It is preferred that only one of X^5, X^6 and X^8 is N. More preferably one of X^5 and X^8 is N, and most preferably X^8 is N.

R^7

R^7 is preferably selected from an optionally substituted C_{5-20} aryl group, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$ and $NR^{N7b}SO_2R^{S2a}$, where R^{O1}, R^{S1}, R^{N1}, R^{N2}, R^{N7a}, R^{N7b}, R^{C1} and R^{S2a} are as previously defined. It is further preferred that R^7 is preferably selected from an optionally substituted C_{5-20} aryl group, OR^{O1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$ and $NR^{N7b}SO_2R^{S2a}$.

If R^7 is OR^{O1}, then preferably R^{O1} is a C_{1-7} alkyl group, which may be substituted.

If R^7 is $NR^{N1}R^{N2}$, then preferably R^{N2} is selected from H and C_{1-4} alkyl (e.g. methyl) and more preferably is H. If R^{N1} is C_{1-7} alkyl, it is preferably selected from C_{3-7} cycloalkyl. If R^{N1} is C_{5-20} aryl, it is preferably selected from C_{5-10} aryl (e.g. phenyl, pyrrolyl, pyridyl, pyrazolyl, furanyl, thiophenyl, pyrazinyl, pyrimidinyl, tetrazolyl, thiazolyl, indazolyl, imidazolyl, triazolyl, oxadiazolyl) and more preferably C_{5-6} aryl (e.g. phenyl, pyrrolyl, pyridyl, pyrazolyl, furanyl, thiophenyl, pyrazinyl, pyrimidinyl, tetrazolyl, thiazolyl, imidazolyl, triazolyl, oxadiazolyl). Particularly preferred groups include furyl, phenyl, pyridyl, pyrrolyl, pyrazolyl and thiophenyl. The aforementioned groups are optionally substituted, and in some embodiments are preferably substituted. Substituent groups may include, but are not limited to, C_{1-7} alkyl, C_{3-20} heterocyclyl, C_{5-20} aryl, carboxy, ester, ether

(eg C_{1-7}alkoxy), hydroxy, aryloxy, cyano, halo, nitro, amido, sulfonyl, sulfonylamino, amino sulfonyl and amino.

If R^7 is $NR^{N7a}C(O)R^{C1}$, then R^{N7a} is preferably H. R^{C1} may be an optionally substituted C_{5-20} aryl group (e.g. phenyl, imadazolyl, quinoxalinyl), C_{3-20} heterocyclyl, C_{1-7} alkyl (e.g. propenyl, methyl (substituted with thiophenyl)) or $NR^{N8}R^{N9}$. R^{N8} is preferably hydrogen, and R^{N9} is preferably C_{1-7} alkyl (e.g. ethyl).

If R^7 is $NR^{N7b}SO_2R^{S2a}$, then R^{N7b} is preferably H. R^{S2a} is preferably C_{1-7} alkyl (e.g. methyl).

If R^7 is a C_{5-20} aryl group, it is preferably an optionally substituted C_{5-10} aryl and more preferably an optionally substituted C_{5-6} aryl group. Most preferably it is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}arylamino and C_{1-7}alkylamino and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino and C_{1-7}alkylamino.

If R^7 is a 5 to 20 membered heteroaryl group, it is preferably an optionally substituted 5 to 10 membered heteroaryl and more preferably an optionally substituted 5 or 6 memebered heteroaryl group.

In one embodiment, R^7 is an optionally substituted C_{5-20} aryl group or an optionally substituted 5 to 20 membered heteroaryl group, wherein the optional substituents are preferably selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, sulfonamino (for example $-NHS(=O)_2C_{1-7}$alkyl) amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, $-NHS(=O)_2C_{1-7}$alkyl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

In one embodiment, R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, sulfonamino (for example $-NHS(=O)_2C_{1-7}$alkyl) amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl

groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, $-NHS(=O)_2C_{1-7}$alkyl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

In one embodiment, R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

In one embodiment, R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH(CH_3)_2$, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl.

In one embodiment, R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl.

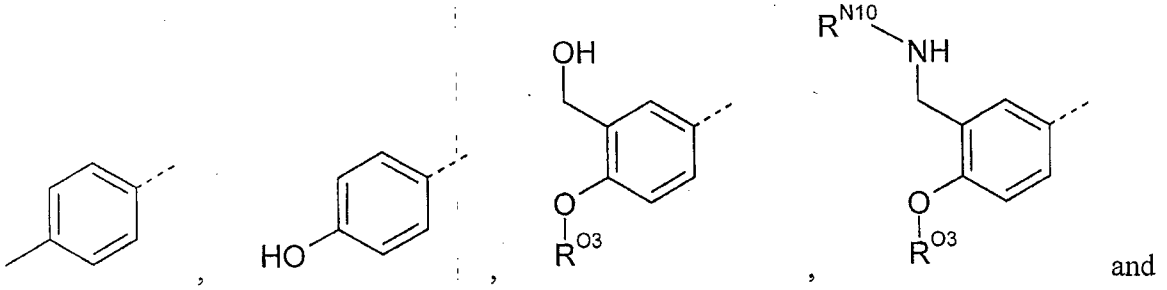
In one embodiment, R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CONH_2$, -CONHMe and $-CONHCH(CH_3)_2$.

In one embodiment R^7 is an optionally substituted 5 or 6 memebered nitrogen containing heteroaryl group such as a pyridine group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CO_2NH_2$, $-CO_2NHC_{1-7}$alkyl, $-CO_2N(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

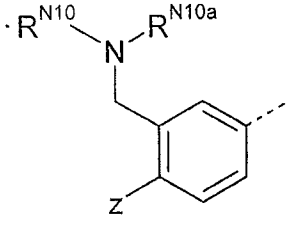
In one embodiment, R^7 is a pyridinyl group optionally substituted halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CO_2NH_2$, $-CO_2NHC_{1-7}$alkyl, $-CO_2N(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

In one embodiment, R^7 is a pyridinyl group optionally substituted with NH_2.

In one embodiment, R^7 is an optionally substituted phenyl group selected from



and



wherein

Z is H, F or OR^{O3};

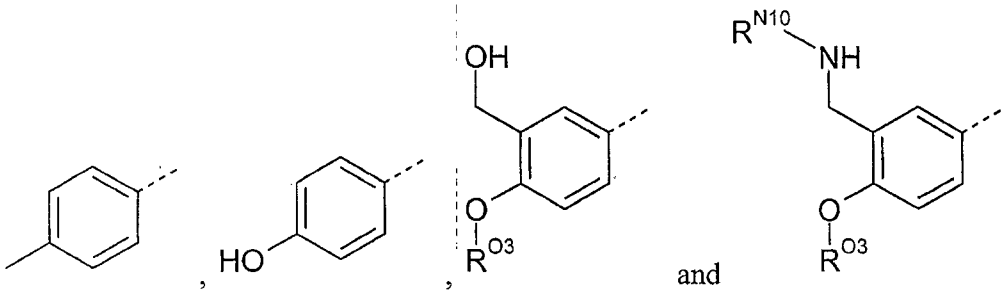
R^{O3} is selected from hydrogen or an optionally substituted C_{1-6} alkyl group;

R^{N10} is selected from hydrogen, $C(O)R^{C2}$, $C(S)R^{C3}$, SO_2R^{S3}, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} and R^{C3} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11} and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms; and R^{S3} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

In one embodiment, R^7 is an optionally substituted phenyl group selected from



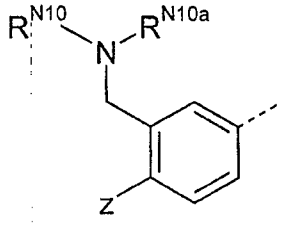
and

wherein

R^{O3} is selected from hydrogen or an optionally substituted C_{1-6} alkyl group; and

R^{N10} is selected from $C(O)R^{C2}$, $C(S)R^{C3}$, SO_2R^{S3}, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} and R^{C3} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11} and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms; and R^{S3} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heteroaryl group, or an optionally substituted C_{1-7} alkyl group.

In one embodiment, R^7 is



wherein

Z is H, F or OR^{O3};

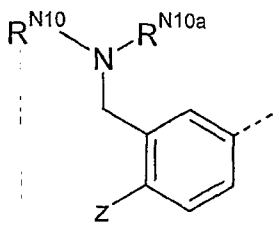
R^{N10} is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11}

and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heterocycly group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

In one embodiment, R^7 is



wherein

Z is H, F or OR^{O3};

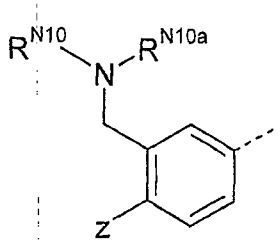
R^{N10} is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-6} heteroaryl group, an optionally substituted C_6 aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from CH_3 or CH_2OH;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

and where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino.

In one embodiment, R^7 is



wherein

Z is H, F or OR^{O3};

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$,

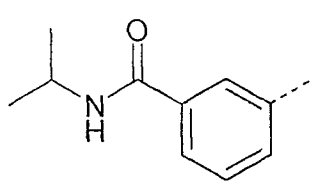
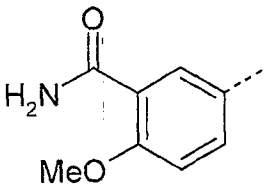
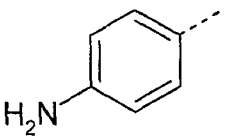
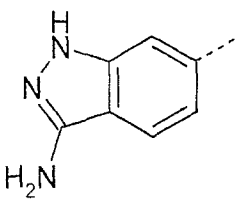
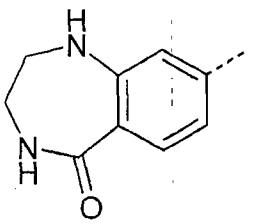
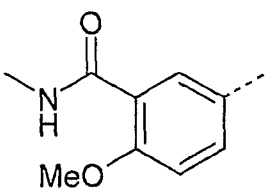
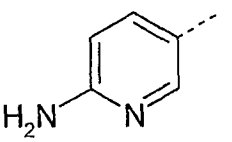
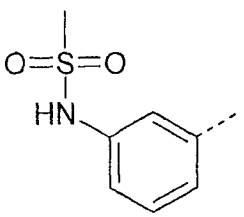
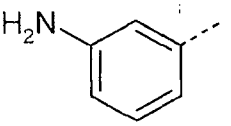
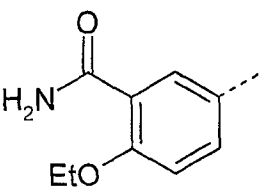
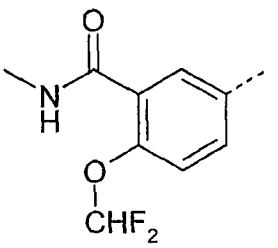
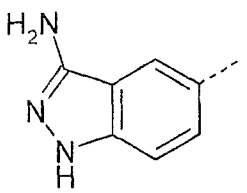
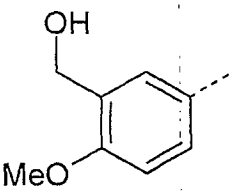
$-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

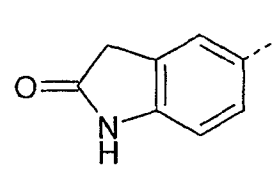
R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms;

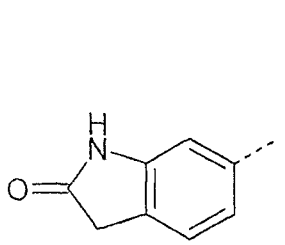
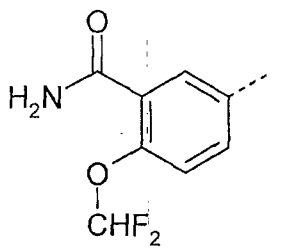
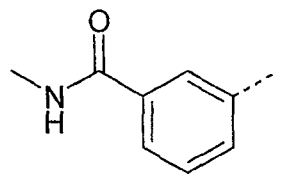
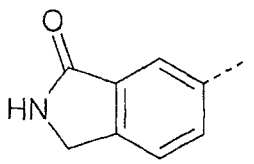
and where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy.

In a further embodiment of the invention R^7 is selected from


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and


R^2

In one embodiment R^2 is OR^{O2} where R^{O2} is an optionally substituted C_{1-7}alkyl group.

In one embodiment R^2 is OR^{O2} where R^{O2} is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, or $-CH(CH_3)CH_2N(CH_3)_2$.

Preferably R^2 is $NR^{N5}R^{N6}$, where R^{N5} and R^{N6} are as previously defined, and more preferably R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, which may optionally be substituted. The ring preferably has from 5 to 7 ring atoms. Preferred optionally substituted groups include, but are not limited, to imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) and pyrrolidinyl.

Preferred N-substituents for the piperazinyl and homopiperazinyl groups include esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$.

Preferred N-substituents for the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$.

Preferred C-substituents for the groups include C_{1-4} alkyl, preferably methyl. The groups may bear one or more substituents, for example one or two substituents.

Preferred C-substituents for the groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl,. The groups may bear one or more substituents, for example one or two substituents.

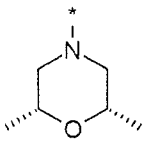
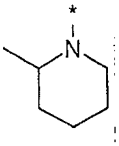
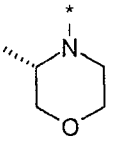
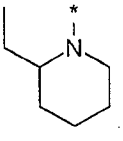
In one embodiment R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from amino, cyano, halo, hydroxyl, ester, a C_{3-7} cycloalkyl ring, a C_6carboaryl ring, a heterocyclic ring containing 5 to 7 ring atoms and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the heterocyclic ring, the cycloalkyl ring, the carboaryl ring, the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl)

In one embodiment R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl)

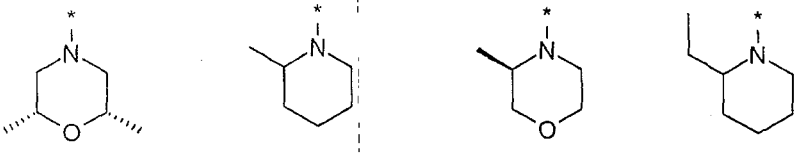
In one embodiment R^2 is $NR^{N5}R^{N6}$, where R^{N5} is an optionally substituted C_{1-7}alkyl group or an optionally substituted phenyl group, and R^{N6} is hydrogen.

In one embodiment R^2 is $NR^{N5}R^{N6}$, where R^{N5} is $-CH(CH_3)CH_2OCH_3$, cyclopentyl or a phenyl group, and R^{N6} is hydrogen.

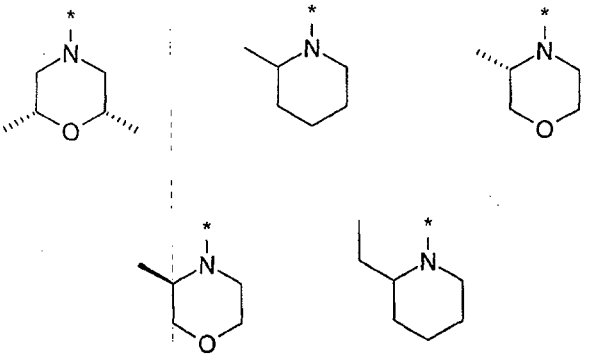
Preferred R^2 groups are pyrrolidinyl, morpholino, piperadinyl and homopiperadinyl groups. More preferred groups are morpholino and piperadinyl. These are preferably substituted with one or more alkyl substituents, for example methyl or ethyl substituents. More preferably these are substituted with one or two methyl substituents. If these groups bear two methyl substituents, these are preferably on separate carbon atoms. The alkyl substituents may also be optionally substituted. Examples of optional substituents of the alkyl substitutents include halo, hydroxy, ether or amino. Particularly preferred groups include methylmorpholino groups, dimethylmorpholino groups and methyl piperidinyl groups, for example:

More preferred groups are morpholino and piperadinyl. These are preferably substituted with one or more alkyl substituents, for example methyl or ethyl substituents. More preferably these are substituted with one or two methyl substituents. If these groups bear two methyl substituents, these are preferably on separate carbon atoms. Particularly preferred groups include methylmorpholino groups, dimethylmorpholino groups and methyl piperidinyl groups, for example:



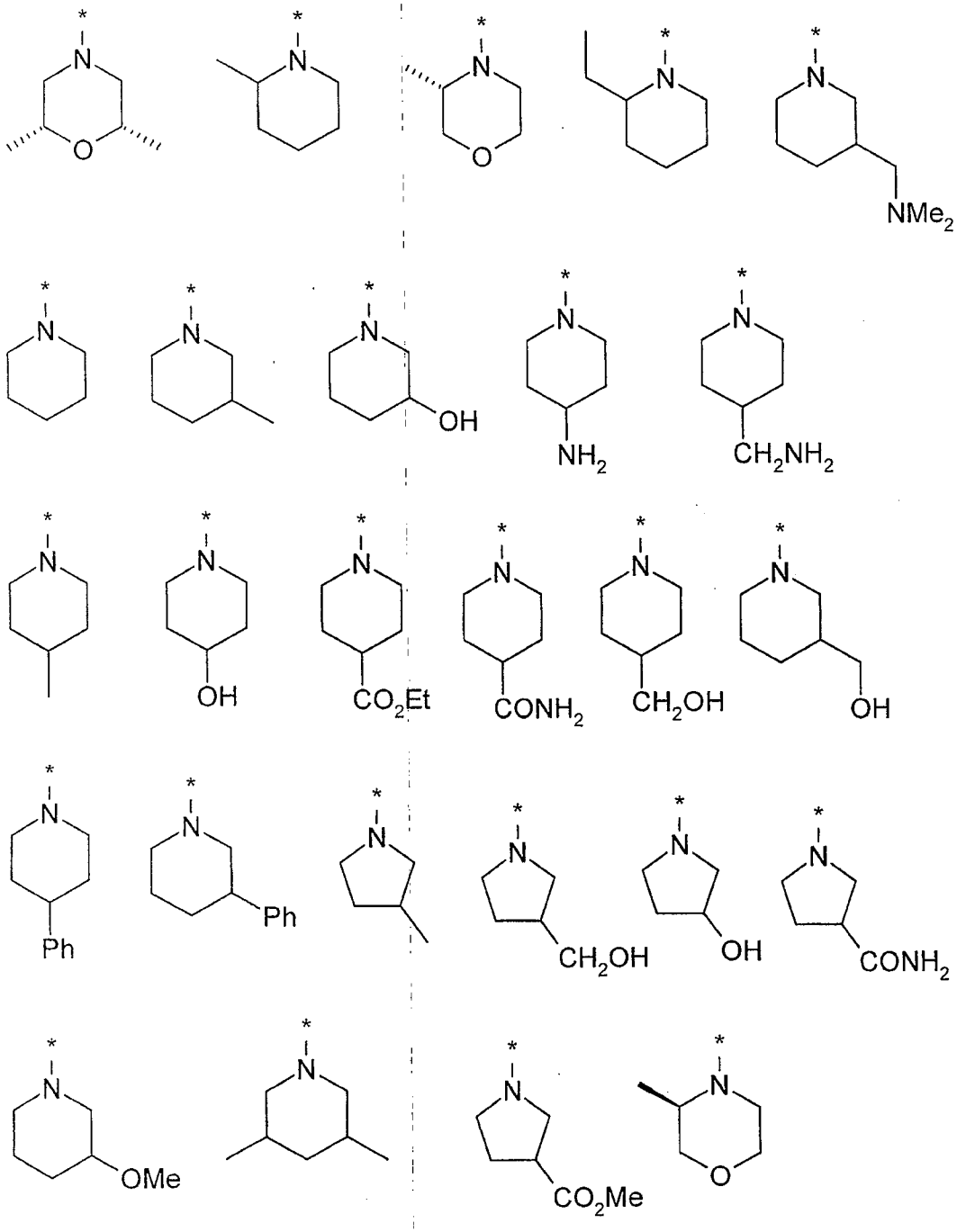
Preferred R^2 groups are pyrrolidinyl, morpholino, piperadinyl and homopiperadinyl groups. More preferred groups are morpholino and piperadinyl. These are preferably substituted with one or more alkyl substituents, for example methyl or ethyl substituents. More preferably these are substituted with one or two methyl substituents. If these groups bear two methyl substituents, these are preferably on separate carbon atoms. The alkyl substituents may also be optionally substituted. Examples of optional substituents of the alkyl substitutents include halo, hydroxy, ether or amino. Particularly preferred groups include methylmorpholino groups, dimethylmorpholino groups and methyl piperidinyl groups, for example:

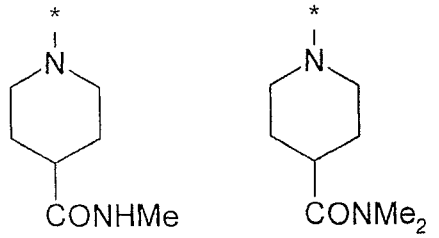


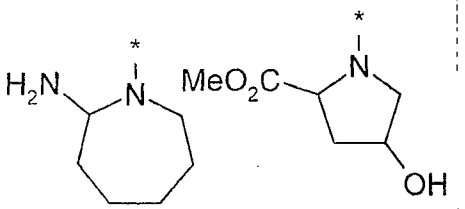
Further preferred R^2 groups are optionally substituted pyrrolidinyl, morpholino, piperadinyl and homopiperadinyl wherein the optional substituents are selected from hydroxyl, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}$alkyl$)_2$), ester (for example $-CO_2C_{1-7}$alkyl), C_6aryl and 3 to 7 membered heterocyclyl group and wherein the susbtitutent alkyl, alkoxy, aryl or heterocyclyl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, $-NH_2$,

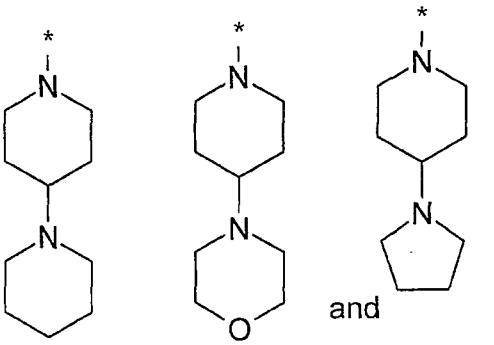
di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino. More preferred groups are morpholino, piperadinyl and homopiperadinyl which may be optionally substited by one or more groups selected from hydroxyl, methyl, ethyl, -CO_2Me, -CO_2Et, -CH_2OH, -CH_2Ome, -CH_2NMe_2, -$CONH_2$, -CONHMe, -$CONMe_2$, phenyl, pyrrolidinyl, morpholino and piperadinyl.

In a further embodiment of the invention R^2 is selected from

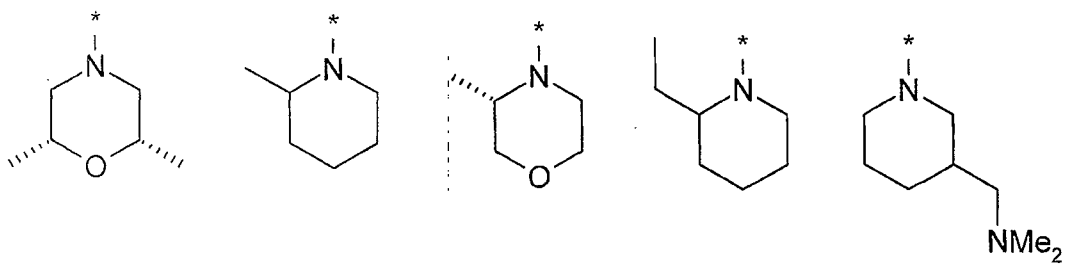


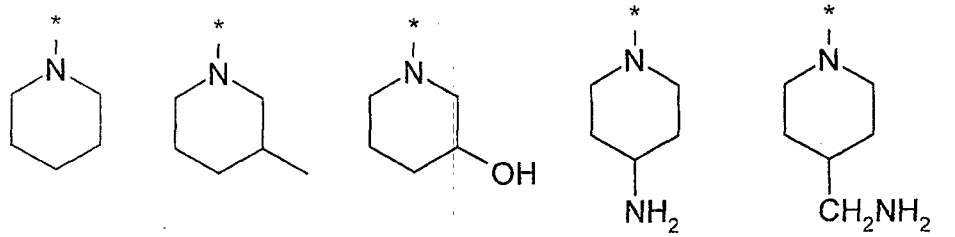


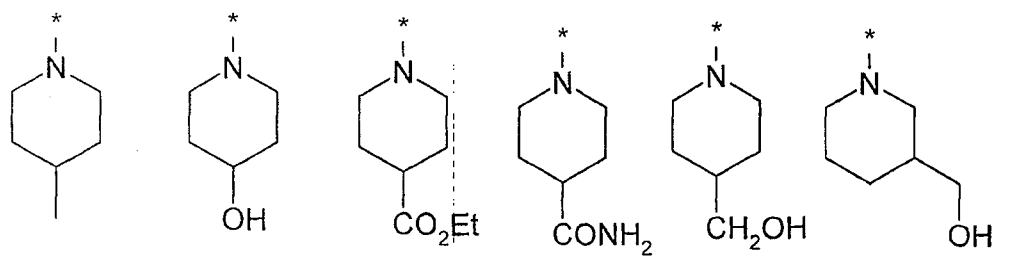




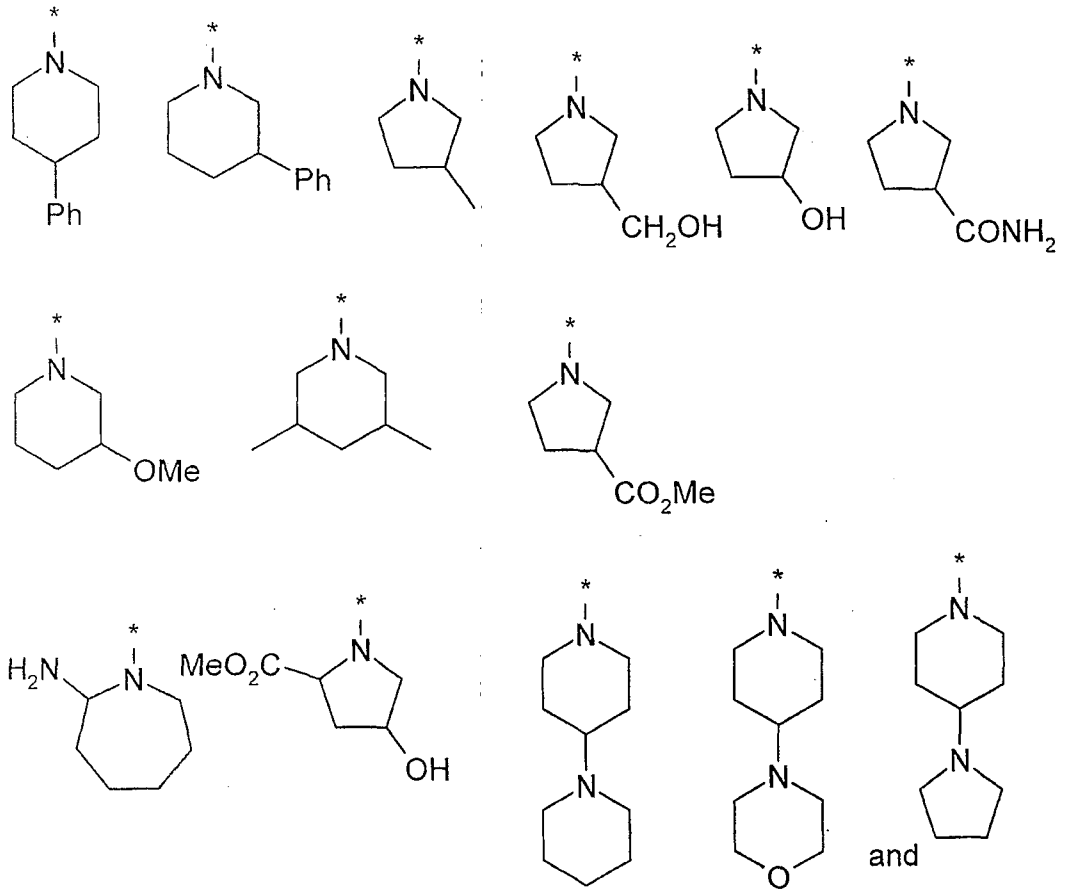
In a further embodiment of the invention R^2 is selected from



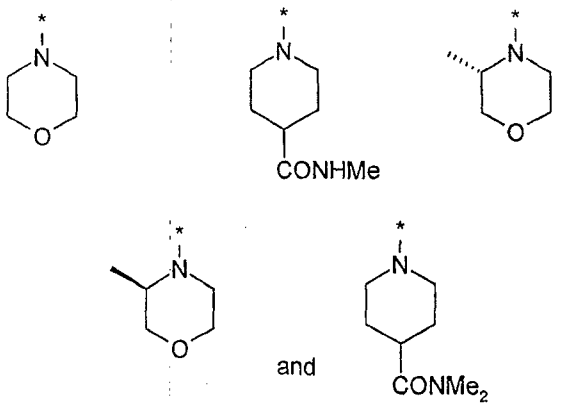




59.



In a further embodiment of the invention R^2 is selected from



In an embodiment of the invention, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is selected from an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteraryl group, OR^{O1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=O)R^{C1}$ and $NR^{N7b}SO_2R^{S2a}$; and

R^2 is selected from OR^{O2}, $NR^{N5}R^{N6}$, an optionally substituted C_{5-20} heteroaryl group, and an optionally substituted C_{5-20} aryl group.

In another embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is selected from OR^{O2}, $NR^{N5}R^{N6}$, an optionally substituted C_{5-6} heteroaryl group, and an optionally substituted C_6 aryl group.

In another embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from cyano,

halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is selected from an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteraryl group, OR^{O1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=O)R^{C1}$ and $NR^{N7b}SO_2R^{S2a}$; and

R^2 is selected from OR^{O2}, $NR^{N5}R^{N6}$, an optionally substituted C_{5-20} heteroaryl group, and an optionally substituted C_{5-20} aryl group.

In another embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is selected from OR^{O2}, $NR^{N5}R^{N6}$, an optionally substituted C_{5-6} heteroaryl group, and an optionally substituted C_6 aryl group.

In another embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N;

R^7 is an optionally substituted C_{5-6} aryl group or an optionally substituted 5 or 6 membered heteraryl group, wherein the optional substituents are selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}alkyl)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH(CH_3)_2$, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from amino, cyano, halo,

hydroxyl, ester, a C_{3-7} cycloalkyl ring, a C_6carboaryl ring, a heterocyclic ring containing 5 to 7 ring atoms and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the heterocyclic ring, the cycloalkyl ring, the carboaryl ring, the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH(CH_3)_2$, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In a further embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from $-NH_2$, fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH_2CH_2F$,

-$CONHCH_2CHF_2$, -$CONHCH_2CH_2OH$, -CONMeEt, -$CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. -$C(=O)OCH_3$, -$C(=O)OCH_2CH_3$ and -$C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from –NH_2, fluoro, hydroxyl, cyano, nitro, methyl, methoxy, -CH_2OH, -CO_2H, -$CONH_2$, -CONHMe, -CONHEt, -$CONHCH_2CH_2F$, -$CONHCH_2CHF_2$, -$CONHCH_2CH_2OH$, -CONMeEt, -$CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. -$C(=O)OCH_3$, -$C(=O)OCH_2CH_3$ and -$C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

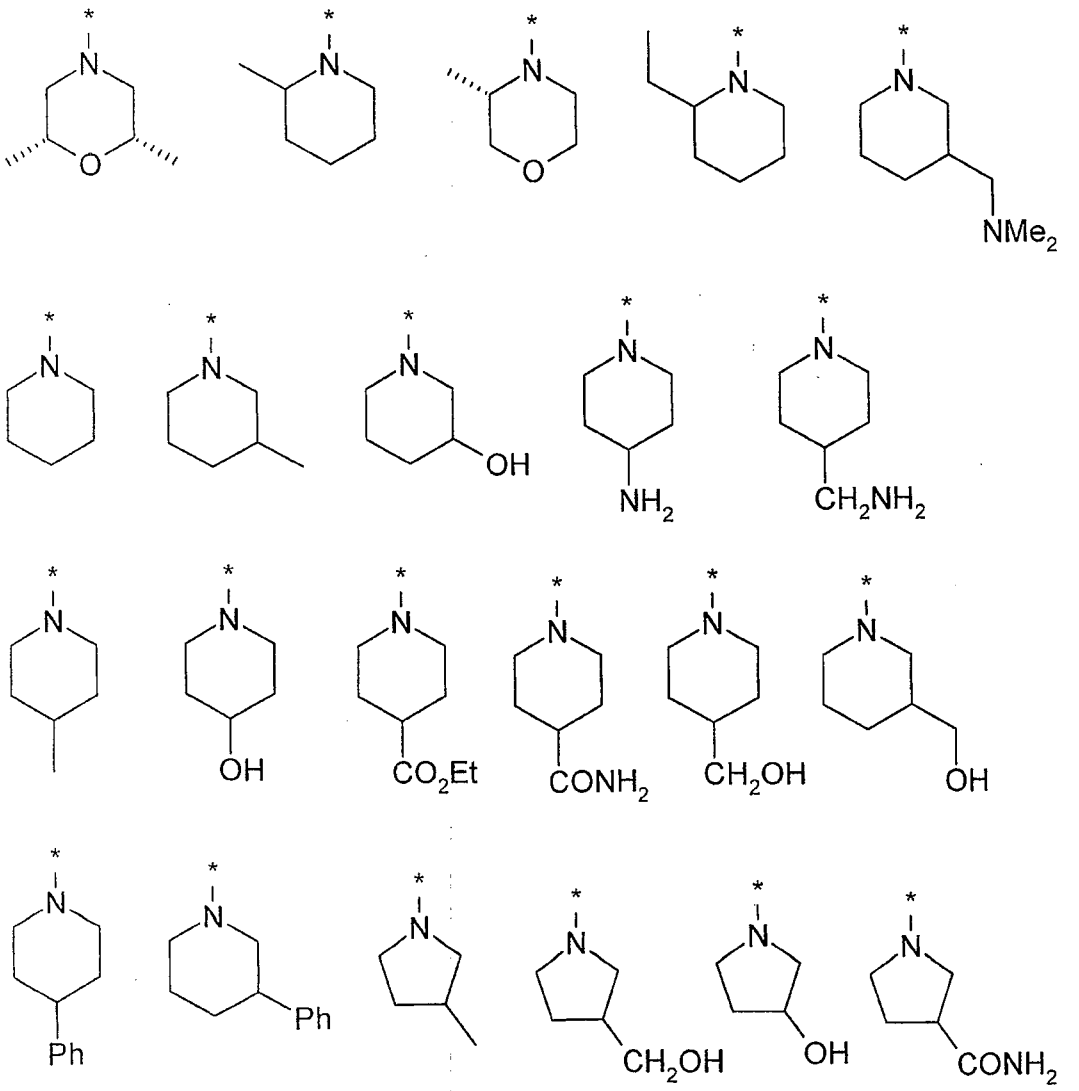
In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

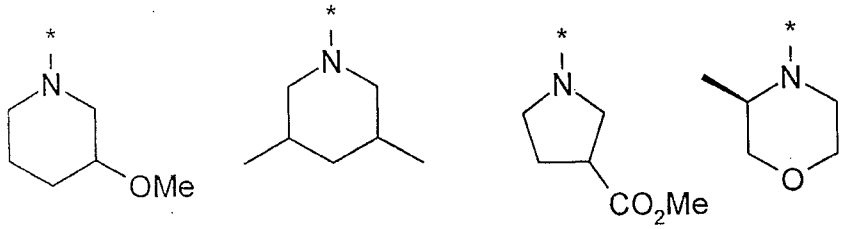
X^5 and X^6 are each CH;

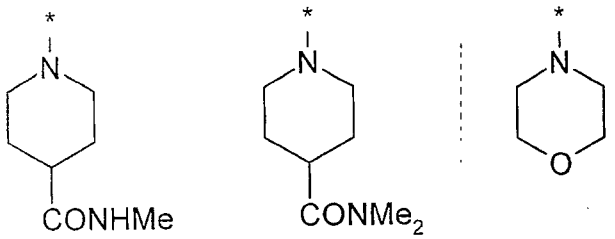
X^8 is N;

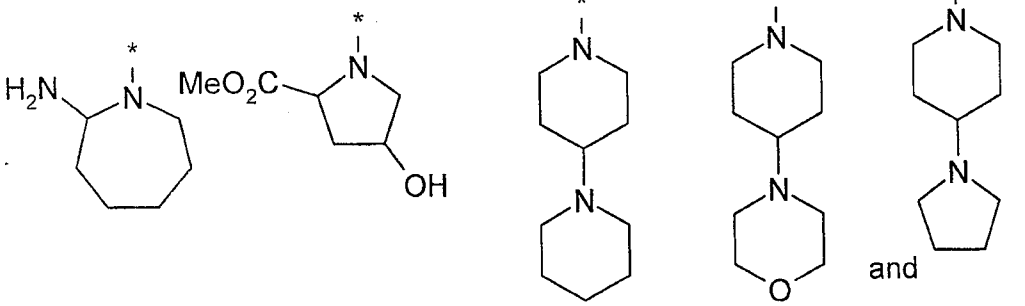
R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH(CH_3)_2$, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is a group selected from









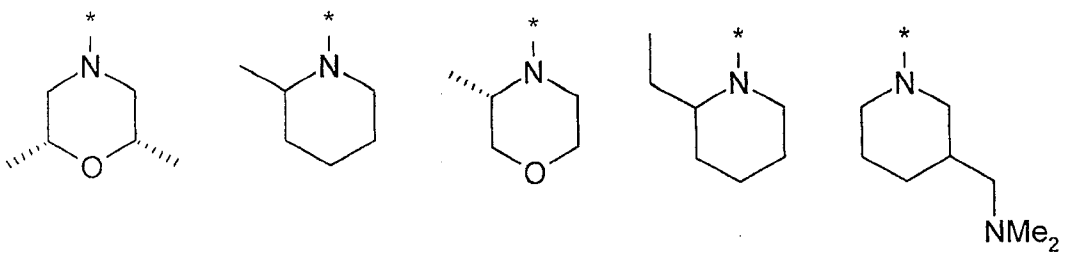
In a further embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

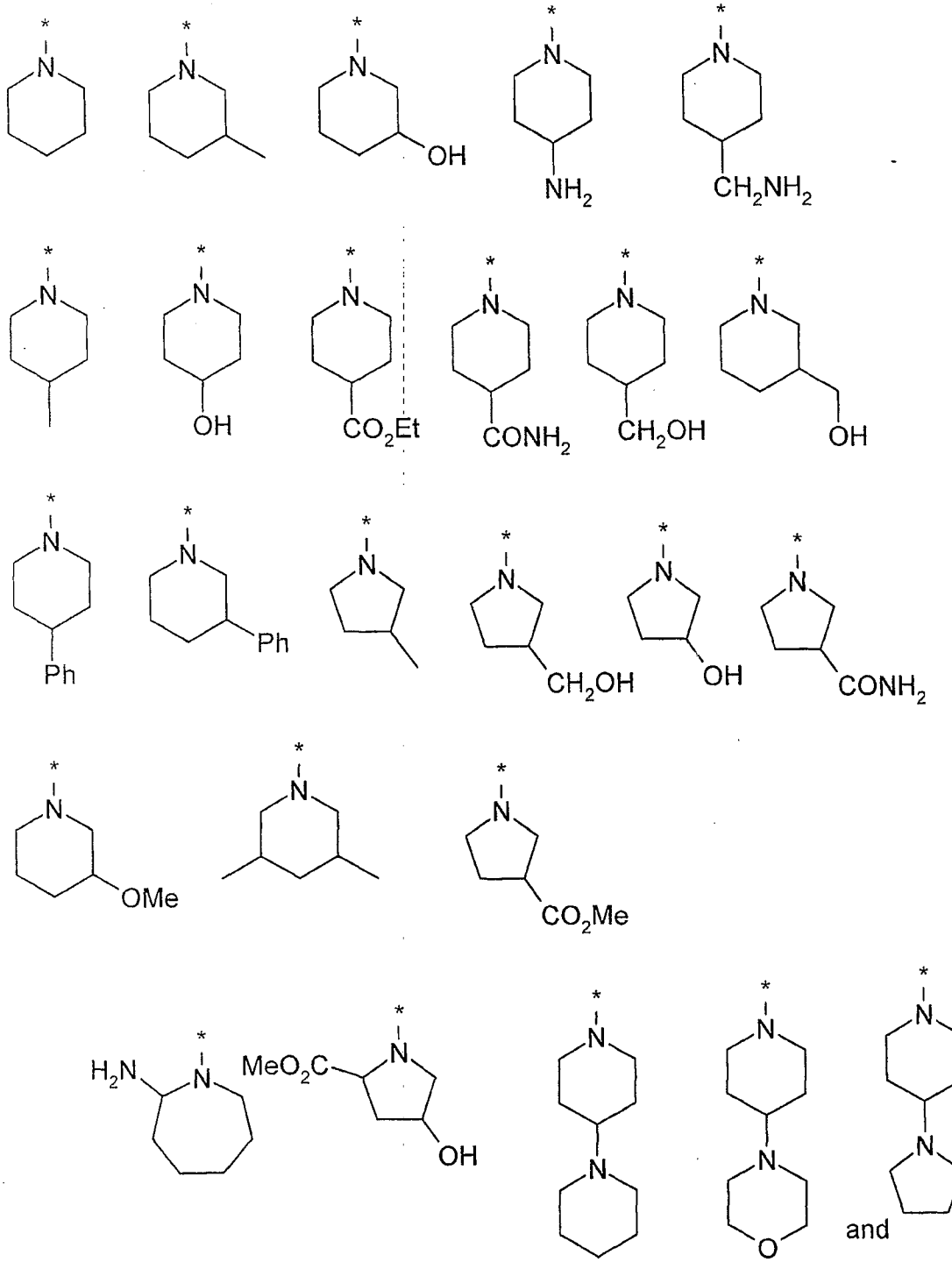
X^5 and X^6 are each CH;

X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from $-NH_2$, fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is a group selected from





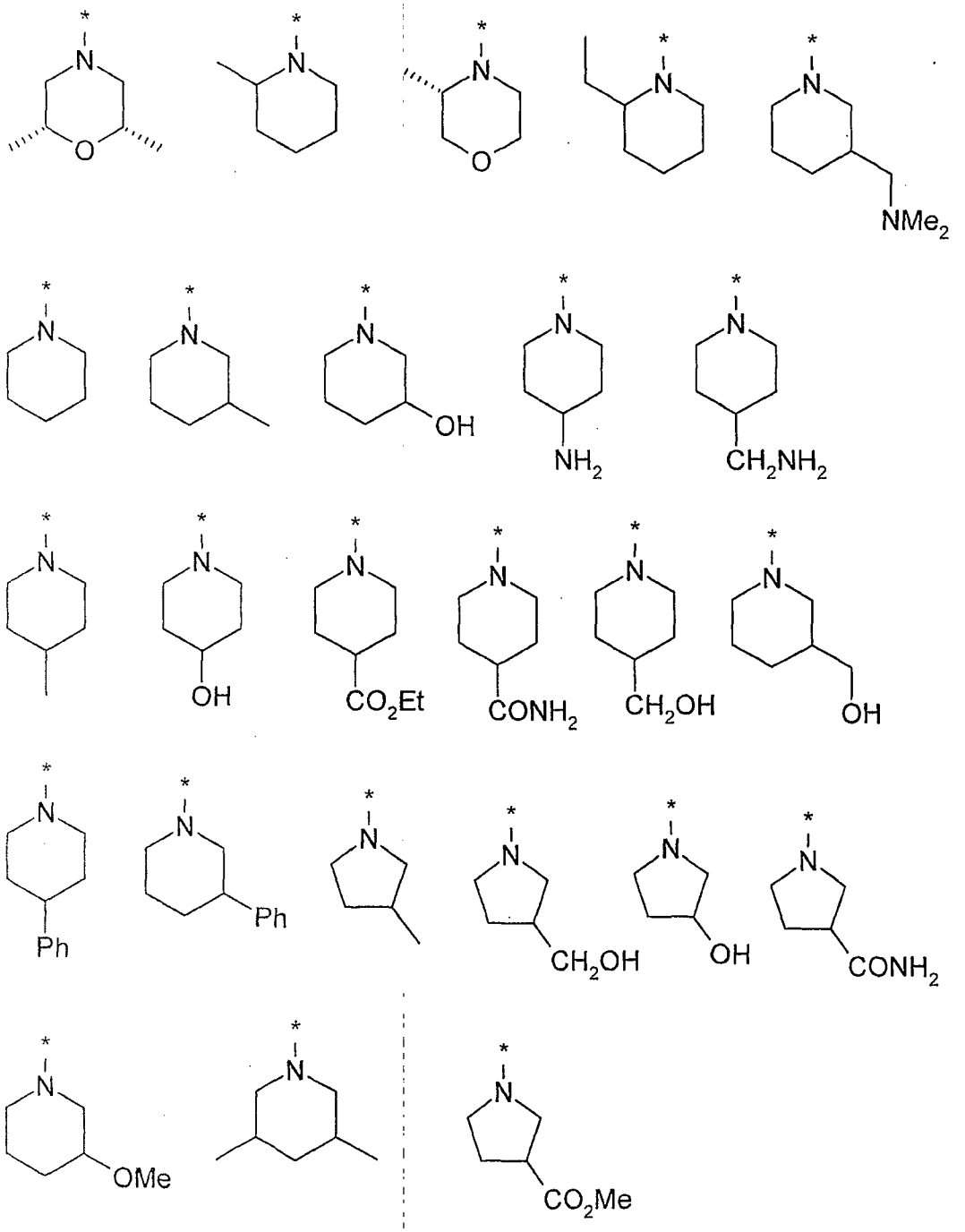
In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

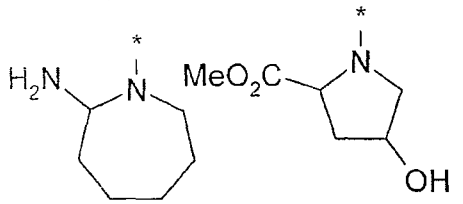
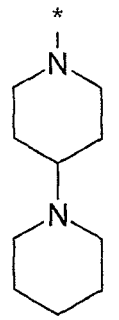
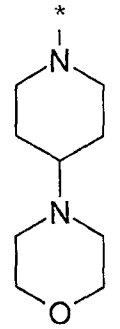
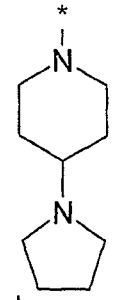
X^5 and X^6 are each CH;

X^8 is N;

R^7 is an optionally substituted phenyl or pyridinyl group, wherein the optional substituents are preferably selected from $-NH_2$, fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl; and

R^2 is a group selected from



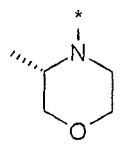
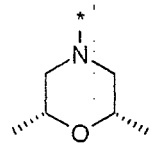
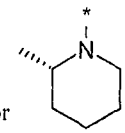
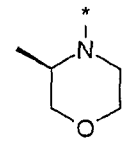




and

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

R^7 is a 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-hydroxymethyl-4-methoxy-phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 4-hydroxyphenyl, 3-hydroxyphenyl or a 3-hydroxymethylphenyl group; and

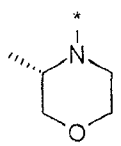
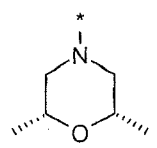
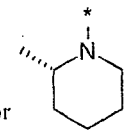
R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  or  or  or  group.

In a further embodiment, there is provided a subset of compounds of formula (I) or (Ia), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

R^7 is a 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-hydroxymethyl-4-methoxy-phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 4-hydroxyphenyl, 3-hydroxyphenyl or a 3-hydroxymethylphenyl group; and

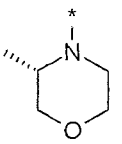
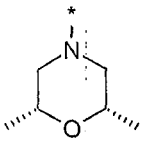
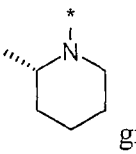
R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  or  or  group.

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

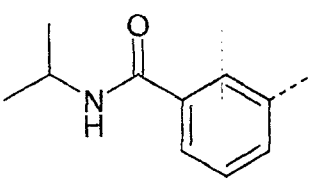
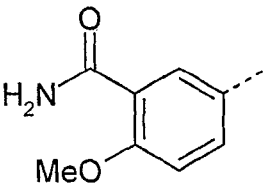
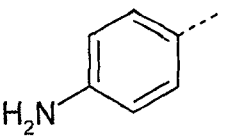
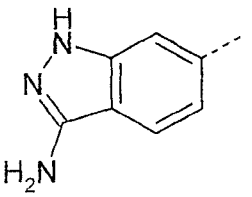
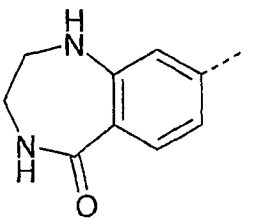
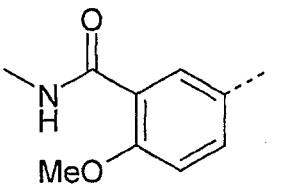
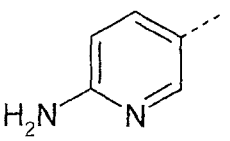
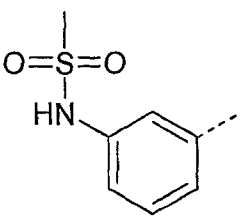
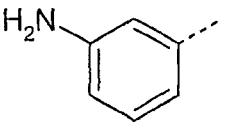
R^7 is a 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-hydroxymethyl-4-methoxy-phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 4-hydroxyphenyl, 3-hydroxyphenyl or a 3-hydroxymethylphenyl group; and

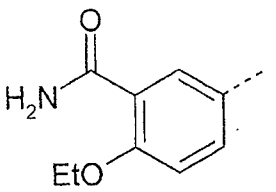
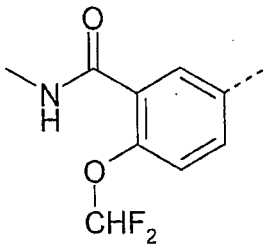
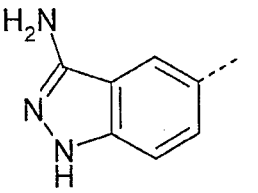
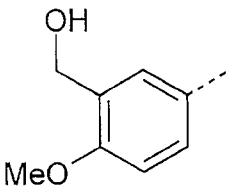
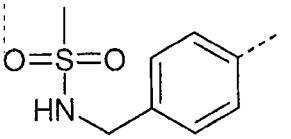
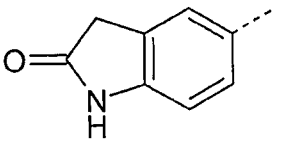
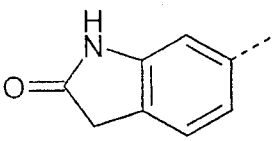
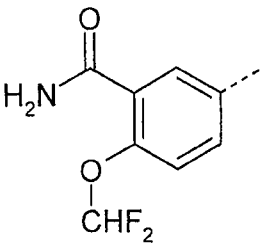
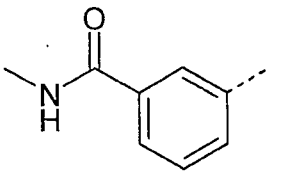
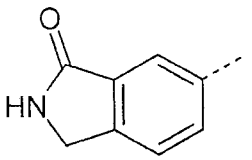
R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  or  or  group.

In a further embodiment, there is provided a subset of compounds of formula (I), (Ia) or (Ib), and pharmaceutically acceptable salts thereof, in which:

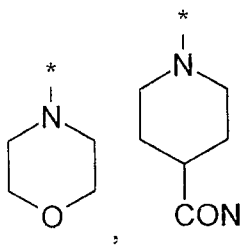
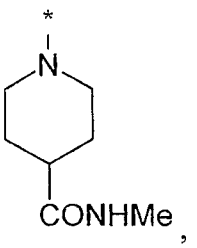
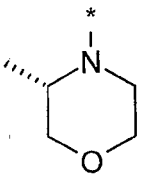
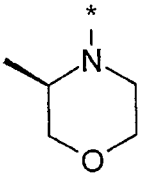
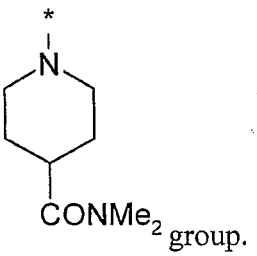
X^5 and X^6 are each CH;

X^8 is N;

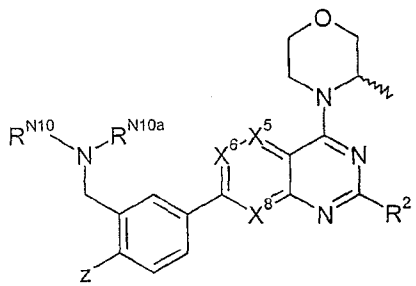
R^7 is a  ,  ,  ,  ,  ,  ,  ,  ,  ,

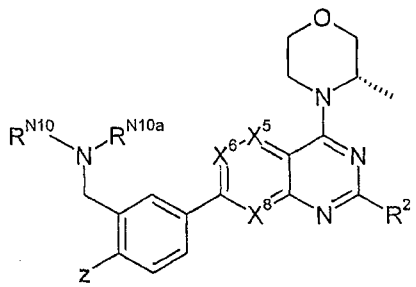

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or

group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a


,

,

,

or a

group.

In an embodiment of the invention, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof,


(II)


(IIa)

wherein:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3};

R^{N10} is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11} and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heterocycly group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{O3} is an optionally substituted C_{1-6} alkyl group; and

R^2 is selected from $NR^{N5}R^{N6}$, an optionally substituted C_{5-20} heteroaryl group, and an optionally substituted C_{5-20} aryl group.

In another embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is R^{N10} is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-6} heteroaryl group, an optionally substituted C_6 aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from CH_3 or CH_2OH where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms, where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino;

R^{O3} is an unsubstituted C_{1-3} alkyl group; and

R^2 is selected from $NR^{N5}R^{N6}$, an optionally substituted C_{5-6} heteroaryl group, and an optionally substituted C_6 aryl group.

In another embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In a further embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted morpholino, thiomorpholino, piperidinyl, homopiperidinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl group, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

Z is H, F or OR^{O3}

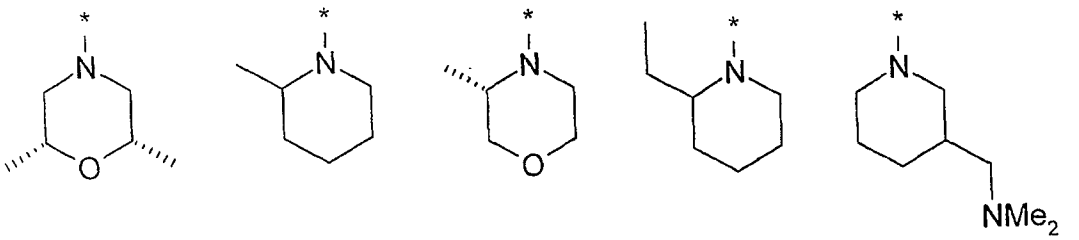
R^{N10} is a R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

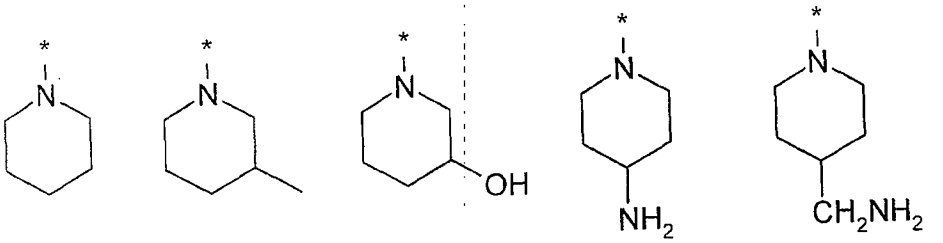
R^{N10a} is hydrogen; or

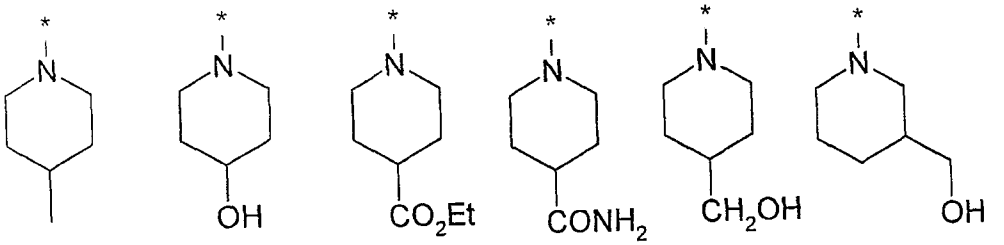
R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

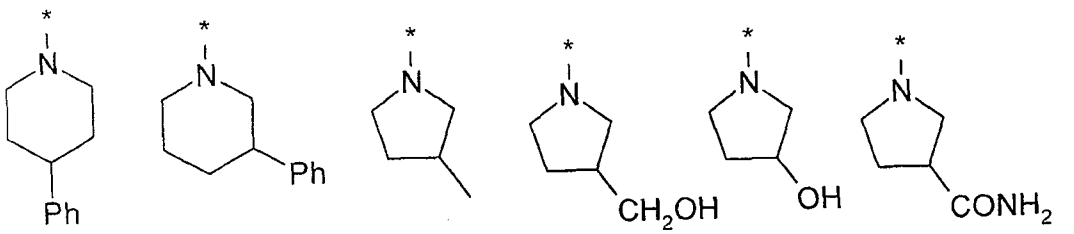
R^{O3} is a methyl group; and

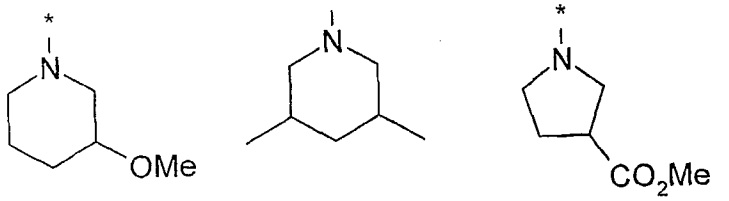
R^2 is a group selected from


NMe2

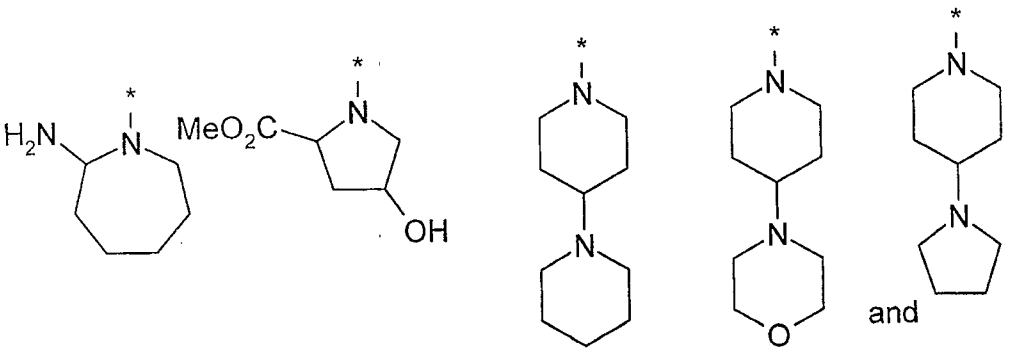

OH
NH2
CH2NH2


OH
CO2Et
CONH2
CH2OH
OH


Ph
Ph
CH2OH
OH
CONH2


OMe
CO2Me

5



In a further embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

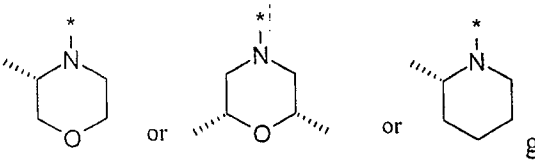
Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  group.

In a further embodiment, there is provided a subset of compounds of formula (**II**) or (**IIa**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

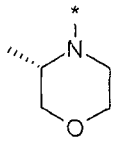
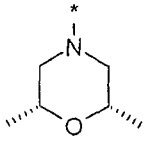
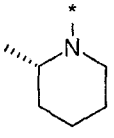
Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, -C(O)CH_3, -C(O)CH_2OH, -CH_3, -CH_2CH_3, -CH_2CH_2OH, -$CH(CH_3)_2$, -CH_2CH_2OMe, -$CH_2C(CH_3)_2$, -$CH_2CH_2C(CH_3)_2$, -$CH(CH_3)CH_2C(CH_3)_2$, -$CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, -CH_2cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, -CH_2imidazole ;

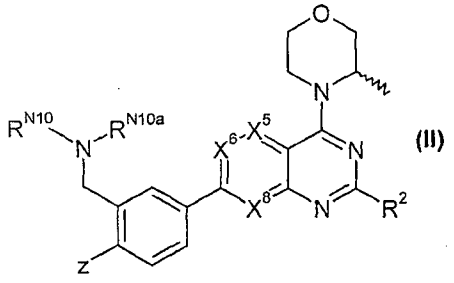
R^{N10a} is hydrogen; or

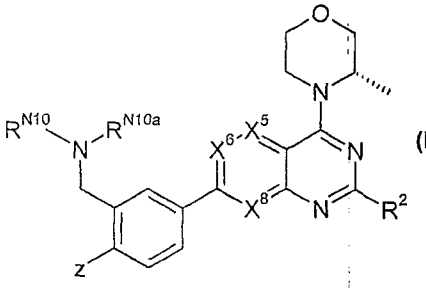
R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

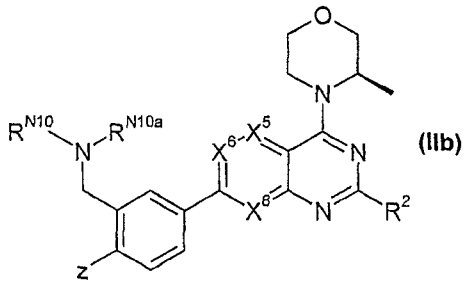
R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  or  or  group.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), (Ia) or (Ib) wherein the compound is a compound of formula (**II**), (IIa) or (**IIb**), and pharmaceutically acceptable salts thereof,


(II)


(IIa)


(IIb)

wherein:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3};

R^{N10} is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-20} heteroaryl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11} and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heterocycly group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{O3} is an optionally substituted C_{1-6} alkyl group; and

R^2 is selected from $NR^{N5}R^{N6}$, an optionally substituted C_{5-20} heteroaryl group, and an optionally substituted C_{5-20} aryl group.

In another embodiment, there is provided a subset of compounds of formula (**II**), (IIa) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is $R^{N10'}$ is selected from hydrogen, $C(O)R^{C2}$, an optionally substituted C_{5-6} heteroaryl group, an optionally substituted C_6 aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} are selected from CH_3 or CH_2OH where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms, where the optional subtsituents are selected from cyano, halo, hydroxyl, C_{1-7}alkyloxy, C_{1-7}alkylamino and di-C_{1-7}alkylamino;

R^{O3} is an unsubstituted C_{1-3} alkyl group; and

R^2 is selected from $NR^{N5}R^{N6}$, an optionally substituted C_{5-6} heteroaryl group, and an optionally substituted C_6 aryl group.

In another embodiment, there is provided a subset of compounds of formula (**II**), (IIa) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 5 to 7 ring atoms which may be optionally be substituted, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (**II**), (**IIa**) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

only one of X^5, X^6 and X^8 is N, and the others are CH;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably N-substituted) or pyrrolidinyl, wherein optional N-substituents on the piperazinyl and homopiperazinyl groups include C_{1-7}alkyl groups or esters, in particular, esters bearing a C_{1-7} alkyl group as an ester substituent, e.g. $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$ and $-C(=O)OC(CH_3)_3$, and optional C-substituents for the imidazolyl, morpholino, thiomorpholino, piperadinyl, homopiperadinyl, piperazinyl, homopiperazinyl or pyrrolidinyl groups include phenyl, ester, amide and C_{1-4} alkyl, preferably methyl, aminomethyl, hydroxymethyl or hydroxyethyl.

In a further embodiment, there is provided a subset of compounds of formula (**II**), (IIa) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted morpholino, thiomorpholino, piperidinyl, homopiperidinyl, piperazinyl (preferably N-substituted), homopiperazinyl (preferably

N-substituted) or pyrrolidinyl group, wherein the optional substituents are selected from cyano, halo, hydroxyl, and C_{1-7} saturated alkyl and C_{1-7} saturated alkoxy (wherein the saturated alkyl and alkoxy groups may be optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkoxy, amino and C_{5-6} aryl).

In a further embodiment, there is provided a subset of compounds of formula (**II**), (**IIa**) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

Z is H, F or OR^{O3}

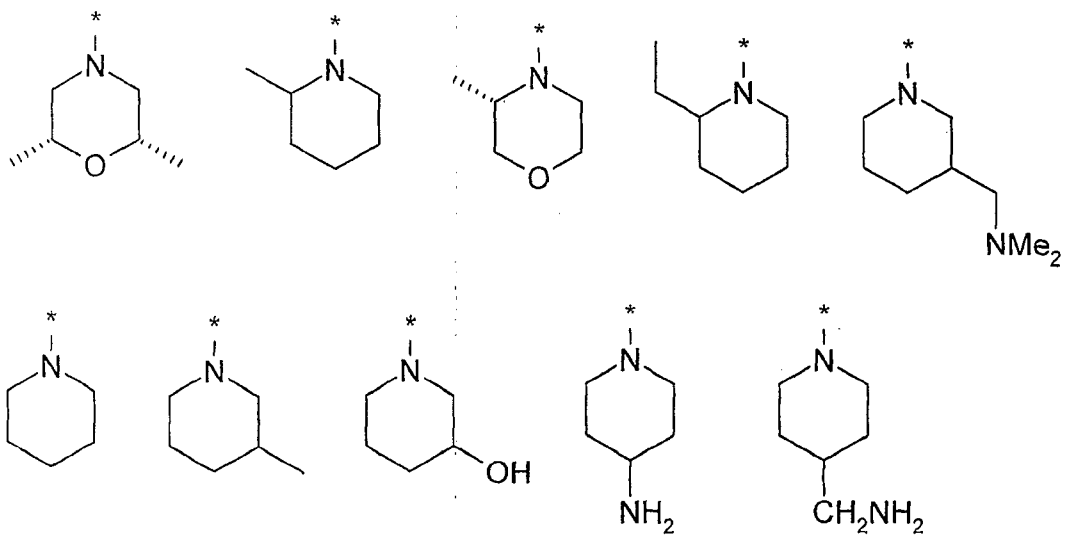
R^{N10} is a R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

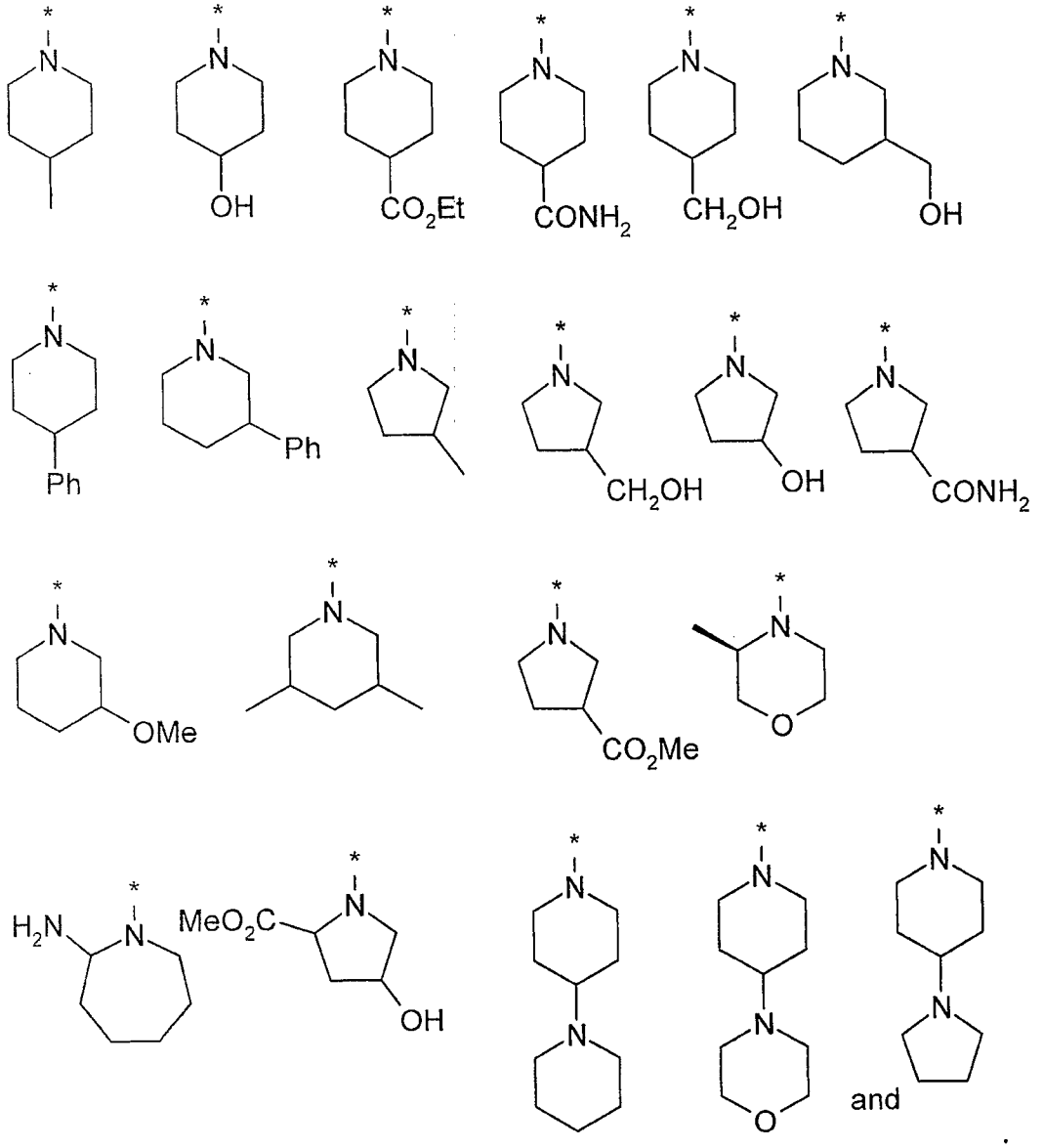
R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is a group selected from





In a further embodiment, there is provided a subset of compounds of formula **(II)**, (IIa) or **(IIb)**, and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

Z is H, F or OR^{O3}

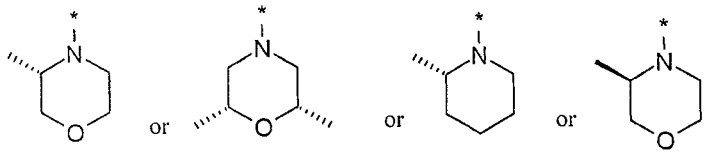
R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl,

cycloheptyl, -CH_2cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, -CH_2imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  group.

In a further embodiment, there is provided a subset of compounds of formula **(II)**, **(IIa)** or **(IIb)**, and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

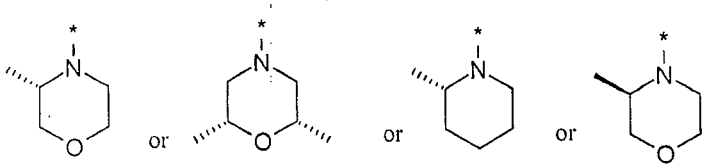
Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, -C(O)CH_3, -C(O)CH_2OH, -CH_3, -CH_2CH_3, -CH_2CH_2OH, -$CH(CH_3)_2$, -CH_2CH_2OMe, -$CH_2C(CH_3)_2$, -$CH_2CH_2C(CH_3)_2$, -$CH(CH_3)CH_2C(CH_3)_2$, -$CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, -CH_2cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, -CH_2imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  group.

In a further embodiment, there is provided a subset of compounds of formula (**II**), (**IIa**) or (**IIb**), and pharmaceutically acceptable salts thereof, in which:

X^5 and X^6 are each CH;

X^8 is N;

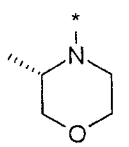
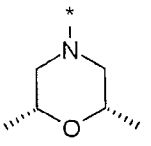
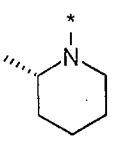
Z is H, F or OR^{O3}

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole ;

R^{N10a} is hydrogen; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms, where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy;

R^{O3} is a methyl group; and

R^2 is $NR^{N5}R^{N6}$ where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a  or  or  group.

In another aspect of the invention, there is provided a compound, or a pharmaceutical salt thereof, selected from any one of the Examples.

In a further aspect of the invention, there is provided a compound, or a pharmaceutical salt thereof, selected from Examples 1bu, 1ce, 12b, 18de, 18dg, 18j, 1ar, 19e, 19h, 19i, 19l, 19m, 19n, 19o, 18n, 18o, 18z, 18aa, 18ag, 18ai, 18al, 1v, 18az, 1ah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, 1aw, 3u, 1bf, 18ct, 19q, 19s, 19u, 19v, 19w, 1au, 5r, 4t, 18dj, 1cl, 2d, 2e, 1cs, 2h, 2j, 1cw, 1bo, 1bp, 1j, 1bx, 1by, 1cf, 1ci, 1cj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, 1n, 1p, 1q, 18e, 18h, 19b, 19c, 19f, 19k, 18p, 1bd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, 1ab, 4p, 9a, 1av, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, 1am, 1ao, 18cn, 18cx, 1bk, 13b, 4g, 5s, 4q, 18dd, 1cp, 1cq, 2f, 2g, 13g, 1cv, 1ct, 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g,

18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cr, 1cw, 1cy, 1dv, 15c, 1cl, 1cm, 1cn, 1cq, 1cv, 1cx, 1di, 1dj, 1eb, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

In a further aspect of the invention, there is provided a compound, or a pharmaceutical salt thereof, selected from Examples 1bo, 1bp, 1j, 1bx, 1by, 1cf, 1ci, 1cj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, 1n, 1p, 1q, 18e, 18h, 19b, 19c, 19f, 19k, 18p, 1bd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, 1ab, 4p, 9a, 1av, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, 1am, 1ao, 18cn, 18cx, 1bk, 13b, 4g, 5s, 4q, 18dd, 1cp, 1cq, 2f, 2g, 13g, 1cv, 1ct, 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cl, 1cm, 1cn, 1cq, 1cv, 1cx, 1di, 1dj, 1eb, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

In a further aspect of the invention, there is provided a compound, or a pharmaceutical salt thereof, selected from Examples 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x,

4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

In a further aspect of the invention, there is provided a compound, or a pharmaceutical salt thereof, selected from Examples 1a, 1u, 1al, 1ap, 1at, 1az, 1co, 1de, 1dg, 1dh, 1dk, 1dl, 1dp, 1dq, 1dr, 1ds, 1dt, 1du, 1dy, 1ec, 1ee, 12d, 14b, 18dn and 18do.

Includes Other Forms

Included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, *cis*- and *trans*-forms; *E*- and *Z*-forms; *c*-, *t*-, and *r*-forms; *endo*- and *exo*-forms; *R*-, *S*-, and *meso*-forms; *D*- and *L*-forms; *d*- and *l*-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

If the compound is in crystalline form, it may exist in a number of different polymorphic forms. For example, for Example 1a was isolated as Form A: 2-Theta° 6.9 (46%), 8.53 (100%), 10.1 (21%), 10.86 (24%), 11.65 (11%), 13.31 (14%), 13.75 (7%), 14.37 (54%), 15.21 (5%), 16.19 (13%), 16.81 (39%), 17.19 (40%), 17.97 (21%), 18.41 (65%), 18.78 (80%), 20.66 (8%), 21.07 (89%), 22.05 (19%), 22.36 (42%), 24 (7%), 24.36 (33%), 25.25 (31%), 25.54 (16%), 26.92 (18%), 27.26 (8%), 28.03 (8%), 28.39 (21%), 29 (8%), 29.91 (13%), 30.62 (23%), 31.48 (9%), 32.72 (5%), 33.27 (11%), 34.88 (4%), 35.48 (5%), 36.16 (4%), 36.88

(4%), 37.37 (4%), 37.91 (6%), 38.65 (4%) and 39.83 (4%). A less stable form, Form B, has also been isolated from water / THF: 2-Theta° 3.67 (7%), 7.28 (7%), 8.52 (7%), 9.22 (30%), 11.42 (78%), 12.69 (24%), 13 (15%), 13.41 (44%), 13.6 (26%), 14.51 (19%), 15.56 (13%), 16.25 (9%), 17.11 (13%), 17.55 (18%), 18.24 (64%), 18.59 (56%), 19.51 (33%), 19.85 (26%), 20.32 (13%), 21.49 (17%), 21.79 (13%), 22.23 (18%), 22.84 (26%), 23.72 (23%), 25.46 (74%), 26.1 (100%), 26.72 (43%), 27.94 (16%), 28.35 (8%), 34.74 (10%), 35.34 (6%), 36.72 (9%) and 38.55 (4%).

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers", as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7} alkyl includes *n*-propyl and *iso*-propyl; butyl includes *n*-, *iso*-, *sec*-, and *tert*-butyl; methoxyphenyl includes *ortho*-, *meta*-, and *para*-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol, imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, *N*-nitroso/hyroxyazo, and nitro/aci-nitro.

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g. fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below, as well as its different polymorphic forms.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in ref. 25.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: acetic, propionic, succinic, gycolic, stearic, palmitic, lactic, malic, pamoic, tartaric, citric, gluconic, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, cinnamic, pyruvic, salicyclic, sulfanilic, 2-acetyoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethanesulfonic, ethane disulfonic, oxalic, isethionic, valeric, and gluconic. Examples of suitable polymeric anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g. active compound, salt of active compound) and solvent.

If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form," as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, ref. 26.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a *t*-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or *t*-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide or a urethane, for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases, as an *N*-oxide (>NO•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g. a methyl ester; a *t*-butyl ester); a C_{1-7} haloalkyl ester (e.g. a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7} alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g. a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug", as used herein, pertains to a compound which, when metabolised (e.g. *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g. a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required. Examples of such metabolically labile esters include those wherein R is C_{1-20} alkyl (e.g. -Me, -Et); C_{1-7} aminoalkyl (e.g. aminoethyl; 2-(*N,N*-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-C_{1-7} alkyl (e.g. acyloxymethyl; acyloxyethyl; e.g. pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)carbonyloxyethyl).

Further suitable prodrug forms include phosphonate and glycolate salts. In particular, hydroxy groups (-OH), can be made into phosphonate prodrugs by reaction with chlorodibenzylphosphite, followed by hydrogenation, to form a phosphonate group -O-$P(=O)(OH)_2$. Such a group can be cleared by phosphotase enzymes during metabolism to yield the active drug with the hydroxy group.

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

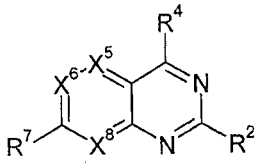
Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), *n*-propyl (nPr), *iso*-propyl (iPr), *n*-butyl (nBu), *tert*-butyl (tBu), *n*-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

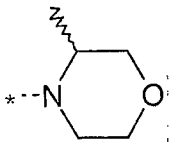
For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et_2O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

General Synthesis

Compounds of formula I can be represented by Formula 1:

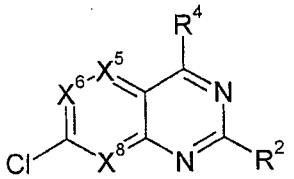


Formula 1



wherein R^4 represents .

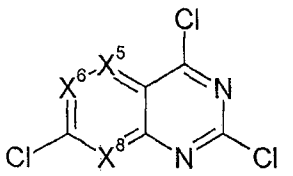
Compounds of Formula 1 can be synthesised from compounds of Formula 2:



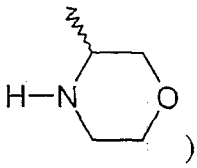
Formula 2

When R^7 is $NR^{N1}R^{N2}$, this is by reaction with R^7H. When R^7 is an amide, urea or sulfonamide group, this is by reaction with ammonia followed by reaction of the resulting primary amide with the appropriate acid chloride, isocyanate or sulfonyl chloride. When R^7 is OR^{O1} or SR^{S1}, this is by reaction with potassium carbonate in the appropriate alcohol or thiol solvent. When R^7 is an optionally substituted C_{3-20} heterocyclyl group or C_{5-20} aryl group, this is by reaction with $R^7B(OAlk)_2$, where each Alk is independently C_{1-7} alkyl or together with the oxygen to which they are attached form a C_{5-7} heterocyclyl group.

Compounds of Formula 2 can be synthesised from compounds of Formula 3:

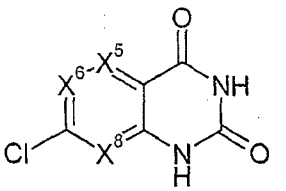


Formula 3



by reaction with HR^4 (eg.) followed by reaction with HR^2.

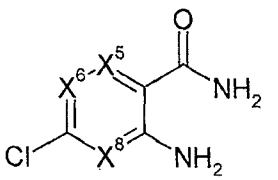
Compounds of Formula 3 can be synthesised from compounds of Formula 4:



Formula 4

by treatment with $POCl_3$ and N,N-diisopropylamine, for example.

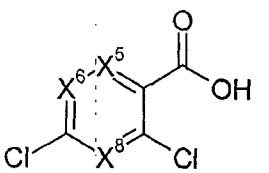
Compounds of Formula 4 can be synthesised from compounds of Formula 5:



Formula 5

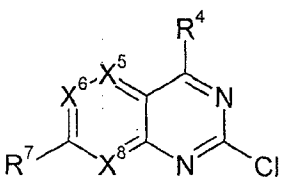
by treatment with oxalyl chloride, for example.

Compounds of Formula 5 can be synthesised from compounds of Formula 6, for example by reaction with liquid ammonia followed by reaction with thionyl chloride and ammonia gas:



Formula 6

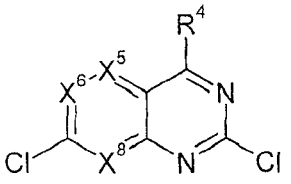
Alternatively compounds of Formula 1 can be synthesised from compounds of Formula 7:



Formula 7

by reaction with HR^2.

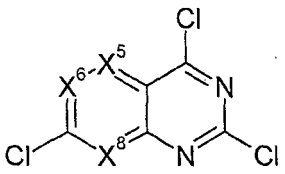
Compounds of Formula 7 can be synthesised from compounds of Formula 8:



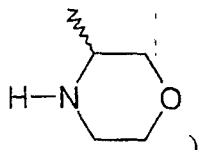
Formula 8

When R^7 is $NR^{N1}R^{N2}$, this is by reaction with R^7H. When R^7 is an amide, urea or sulfonamide group, this is by reaction with ammonia followed by reaction of the resulting primary amide with the appropriate acid chloride, isocyanate or sulfonyl chloride. When R^7 is OR^{O1} or SR^{S1}, this is by reaction with potassium carbonate in the appropriate alcohol or thiol solvent. When R^7 is an optionally substituted C_{3-20} heterocyclyl group or C_{5-20} aryl group, this is by reaction with $R^7B(OAlk)_2$, where each Alk is independently C_{1-7} alkyl or together with the oxygen to which they are attached form a C_{5-7} heterocyclyl group.

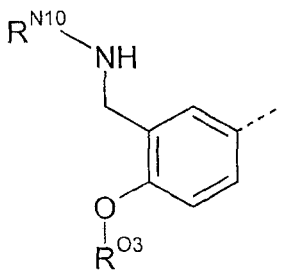
Compounds of Formula 8 can be synthesised from compounds of Formula 3:



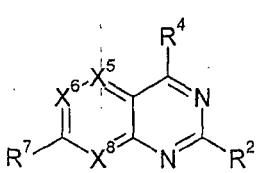
Formula 3

by reaction with HR^4 (eg. ).

When R^7 is

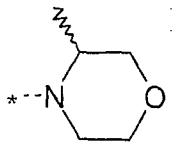


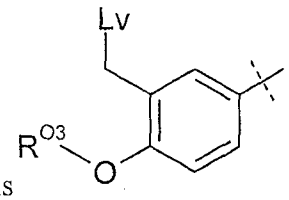
the Compound of Formula 1 can be prepared by reaction a compound of Formula 1a:



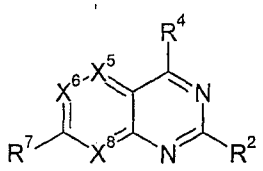
Formula 1a

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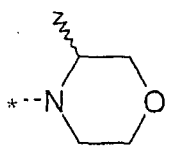
wherein R^4 represents  , and

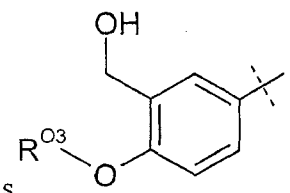
R^7 is  , wherein Lv is a leaving group, such as a halogen, for example chlorine, or a OSO_2 group, where R is alkyl or aryl, such as methyl, by reaction with $R^{N10}NH_2$.

Compounds of Formula 1a can be synthesised by reaction of a compound of Formula 1b



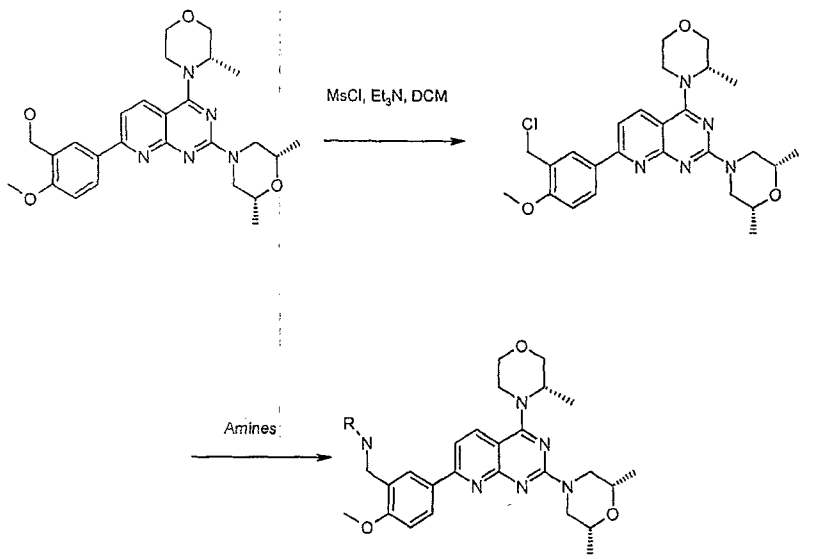
Formula 1b

wherein R^4 represents  , and

R^7 is  ,

with an alkyl or aryl sulphonyl chloride in the presence of a base.

For Example:



Compounds of Formula 1b can be prepared by reaction with $R^7B(OAlk)_2$, where each Alk is independently C_{1-7} alkyl or together with the oxygen to which they are attached form a C_{5-7} heterocyclyl group.

Use

The present invention provides active compounds, specifically, active in inhibiting the activity of mTOR.

The term "active" as used herein, pertains to compounds which are capable of inhibiting mTOR activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One assay which may conveniently be used in order to assess the mTOR inhibition offered by a particular compound is described in the examples below.

The present invention further provides a method of inhibiting the activity of mTOR in a cell, comprising contacting said cell with an effective amount of an active compound, preferably in the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

For example, a sample of cells may be grown *in vitro* and an active compound brought into contact with said cells, and the effect of the compound on those cells observed. As examples of "effect", the inhibition of cellular growth in a certain time or the accumulation of cells in the G1 phase of the cell cycle over a certain time may be determined. Where the active compound is found to exert an influence on the cells, this may be used as a prognostic

or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

The term "treatment", as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term "adjunct" as used herein relates to the use of active compounds in conjunction with known therapeutic means. Such means include cytotoxic regimes of drugs and/or ionising radiation as used in the treatment of different cancer types. Examples of adjunct anti-cancer agents that could be combined with compounds from the invention include, but are not limited to, the following: alkylating agents: nitrogen mustards, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil: Nitrosoureas: carmustine (BCNU), lomustine (CCNU), semustine (methyl-CCNU), ethylenimine/methylmelamine, thriethylenemelamine (TEM), triethylene thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine): Alkyl sufonates; busulfan; Triazines, dacarbazine (DTIC): Antimetabolites; folic acid analogs, methotrexate, trimetrexate, pyrimidine analogs, 5-fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2'-difluorodeoxycytidine: Purine analogs; 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin, erythrohydroxynonyladenine (EHNA), fludarabine phosphate, 2-Chlorodeoxyadenosine (cladribine, 2-CdA): Topoisomerase I inhibitors; camptothecin, topotecan, irinotecan, rubitecan: Natural products; antimitotic drugs, paclitaxel, vinca alkaloids, vinblastine (VLB), vincristine, vinorelbine, Taxotere™ (docetaxel), estramustine, estramustine phosphate; epipodophylotoxins, etoposide, teniposide: Antibiotics; actimomycin D, daunomycin (rubidomycin), doxorubicin (adriamycin), mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycin C, dactinomycin: Enzymes; L-asparaginase, RNAse A: Biological response modifiers; interferon-alpha, IL-2, G-CSF, GM-CSF: Differentiation Agents; retinoic acid derivatives: Radiosensitizers;, metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, RSU 1069, EO9, RB 6145, SR4233, nicotinamide, 5-bromodeozyuridine, 5-iododeoxyuridine, bromodeoxycytidine: Platinium coordination

complexes; cisplatin, carboplatin: Anthracenedione; mitoxantrone, AQ4N Substituted urea, hydroxyurea; Methylhydrazine derivatives, N-methylhydrazine (MIH), procarbazine; Adrenocortical suppressant, mitotane (*o.p'*-DDD), aminoglutethimide: Cytokines; interferon (α, β, γ), interleukin; Hormones and antagonists; adrenocorticosteroids/antagonists, prednisone and equivalents, dexamethasone, aminoglutethimide; Progestins, hydroxyprogesterone caproate, medroxyprogesterone acetate, megestrol acetate; Estrogens, diethylstilbestrol, ethynyl estradiol/equivalents; Antiestrogen, tamoxifen; Androgens, testosterone propionate, fluoxymesterone/equivalents; Antiandrogens, flutamide, gonadotropin-releasing hormone analogs, leuprolide; Nonsteroidal antiandrogens, flutamide; EGFR inhibitors, VEGF inhibitors; Proteasome inhibitors.

Active compounds may also be used as cell culture additives to inhibit mTOR, for example, in order to sensitize cells to known chemotherapeutic agents or ionising radiation treatments *in vitro*.

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

Cancer

The present invention provides active compounds which are anticancer agents or adjuncts for treating cancer. One of ordinary skill in the art is readily able to determine whether or not a candidate compound treats a cancerous condition for any particular cell type, either alone or in combination.

Examples of cancers include, but are not limited to, lung cancer, small cell lung cancer, gastrointestinal cancer, bowel cancer, colon cancer, breast carinoma, ovarian carcinoma, prostate cancer, testicular cancer, liver cancer, kidney cancer, bladder cancer, pancreas cancer, brain cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma and leukemias.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

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:-

(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, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5*-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) and N-(2-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 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 factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, 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 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), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl 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 growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), 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 avb3 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, WO 01/92224, WO 02/04434 and WO 02/08213;

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

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme 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

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines 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.

Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot, for example, subcutaneously or intramuscularly.

The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orangutang, gibbon), or a human.

Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g., formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least

one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts. See, for example, refs. 27 to 29.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g., by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g. compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica);

disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); and preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active compound in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as

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dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of

administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

In general, a suitable dose of the active compound is in the range of about 100 μg to about 250 mg per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

In addition to their use in therapeutic medicine, the compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of mTor in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

General Experimental Methods

Thin Layer chromatography was carried out using Merck Kieselgel 60 F_{254} glass backed plates. The plates were visualized by the use of a UV lamp (254 nm). Silica gel 60 (particle sizes 40-63 μm) supplied by E.M.Merck was employed for flash chromatography. ^1H NMR spectra were recorded at 300 MHz on a Bruker DPX-300 instrument. Chemical shifts were referenced relative to tetramethylsilane.

Purification of samples

The samples were purified on Gilson LC units. Mobile phase A – 0.1 % aqueous TFA, mobile phase B – Acetonitrile; flow rate 6 ml/min; Gradient – typically starting at 90 % A/10 % B for 1 minute, rising to 97 % after 15 minutes, holding for 2 minutes, then back to the starting conditions. Column: Jones Chromatography Genesis 4μm, C18 column, 10 mm X 250 mm. Peak acquisition based on UV detection at 254 nm.

Identification of samples

QC Method QC2-AQ

Mass spectra were recorded on a Waters ZQ instrument in Electrospray ionisation mode. Mobile phase A – 0.1 % aqueous formic acid. Mobile phase B – 0.1 % Formic acid in acetonitrile; Flowrate 2 ml/min; Gradient – starting at 100 % A/0 % B for 1 minute, rising to 95 % B after 7 minutes and holding for 2 minutes before returning to the starting conditions. Column: Varies, currently Genesis AQ 120A 4u 50mm X 4.6mm, Hichrom Ltd. PDA detection Waters 996, scan range 210-400 nm.

QC Method QC2-Long

Mass spectra were recorded on a Waters ZQ instrument in Electrospray ionisation mode. Mobile phase A – 0.1 % aqueous formic acid. Mobile phase B – 0.1 % Formic acid in acetonitrile; Flowrate 2 ml/min; Gradient – starting at 95 % A/5 % B, rising to 95 % B after 20 minutes and holding for 3 minutes before returning to the starting conditions. Column: Varies, but always C18 50 mm X 4.6 mm (currently Genesis C18 4u 50mm X 4.6mm, Hichrom Ltd). PDA detection Waters 996, scan range 210-400 nm.

QC Method QC2-QC

Mass spectra were recorded on a Waters ZQ instrument in Electrospray ionisation mode. Mobile phase A – 0.1 % aqueous formic acid. Mobile phase B – 0.1 % Formic acid in

acetonitrile; Flowrate 2 ml/min; Gradient – starting at 95 % A/5 % B, rising to 95 % B after 5 minutes and holding for 5 minutes before returning to the starting conditions. Column: Varies, but always C18 50 mm X 4.6 mm (currently Genesis C18 4µm 50 X 4.6 mm, Hichrom Ltd). PDA detection Waters 996, scan range 210-400 nm.

QC Method QC3-AQ-Long

Mass spectra were recorded on a Waters ZQ instrument in Electrospray ionisation mode. Mobile phase A – 0.1 % aqueous formic acid. Mobile phase B – 0.1 % Formic acid in acetonitrile; Flowrate 2 ml/min; Gradient – starting at 100 % A/0 % B for 1 minute, rising to 95 % B after 20 minutes and holding for 5 minutes before returning to the starting conditions. Column: Varies, currently Genesis AQ 4µm 50mm X 4.6mm, Hichrom Ltd. PDA detection Waters 996, scan range 210-400 nm.

Examples 1u, 9a, 18bs, 18bv, 18bw, 18bx, 18by, 18bz, 18ca, 18cb, 18cc, 18cd, 18ce, 18cf, 18cg, 18ch, 18ci, 18cj, 18ck, 18cl, 18cm, 18dk, 18dl and 18dm were analysed using the QC Method QC2-AQ.

Examples 12c, 12d, 13c, 13e, 13g, 14b, 15b, 18aa, 18ab, 18ac, 18ad, 18ae, 18af, 18ag, 18ah, 18ai, 18aj, 18ak, 18al, 18am, 18an, 18ao, 18ap, 18aq, 18ar, 18as, 18at, 18au, 18az, 18bc, 18bl, 18bm, 18bt, 18bu, 18cn, 18co, 18cp, 18cq, 18cr, 18cs, 18ct, 18cu, 18cv, 18cw, 18cx, 18cy, 18cz, 18da, 18db, 18dc, 18df, 18dj, 18l, 18o, 18q, 18r, 18s, 18t, 18u, 18v, 18w, 18x, 18y, 18z, 19a, 19b, 19c, 19d, 19e, 19f, 19g, 19h, 19i, 19j, 19k, 19l, 19m, 19n, 19o, 1a, 1aa, 1ab, 1ac, 1ad, 1ae, 1af, 1ag, 1ah, 1ai, 1ak, 1as, 1au, 1az, 1bb, 1cq, 1ct, 1dg, 1ec, 1g, 1i, 1m, 1w, 1x, 1y, 1z, 21a, 3a, 3ac, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3v, 3w, 3x, 3y, 3z, 4j, 4k, 4l, 4m, 4n, 4o, 4p, 6a, comparative of Example 1c, comparative of Example 1j and comparative of Example 1k were analysed using the QC Method QC2-Long.

Examples 10a, 11a, 12a, 12b, 12e, 13a, 13b, 13d, 13f, 14a, 15a, 15c, 16a, 17a, 18a, 18av, 18aw, 18ax, 18ay, 18b, 18ba, 18bb, 18bd, 18be, 18bf, 18bg, 18bh, 18bi, 18bj, 18bk, 18bn, 18bo, 18bp, 18bq, 18br, 18c, 18d, 18dd, 18de, 18dg, 18dh, 18di, 18dn, 18do, 18e, 18f, 18g, 18h, 18i, 18j, 18k, 18m, 18n, 19p, 19q, 19r, 19s, 19t, 19u, 19v, 19w, 19x, 1aj, 1al, 1am, 1an, 1ao, 1ap, 1aq, 1ar, 1at, 1av, 1aw, 1ax, 1ay, 1b, 1ba, 1bc, 1be, 1bf, 1bg, 1bh, 1bi, 1bj, 1bk, 1bl, 1bm, 1bn, 1bo, 1bp, 1bq, 1br, 1bs, 1bt, 1bu, 1bv, 1bw, 1bx, 1by, 1bz, 1c, 1ca, 1cb, 1cc, 1cd, 1ce, 1cf, 1cg, 1ch, 1ci, 1cj, 1ck, 1cl, 1cm, 1cn, 1co, 1cp, 1cr, 1cs, 1cu, 1cv, 1cw, 1cx,

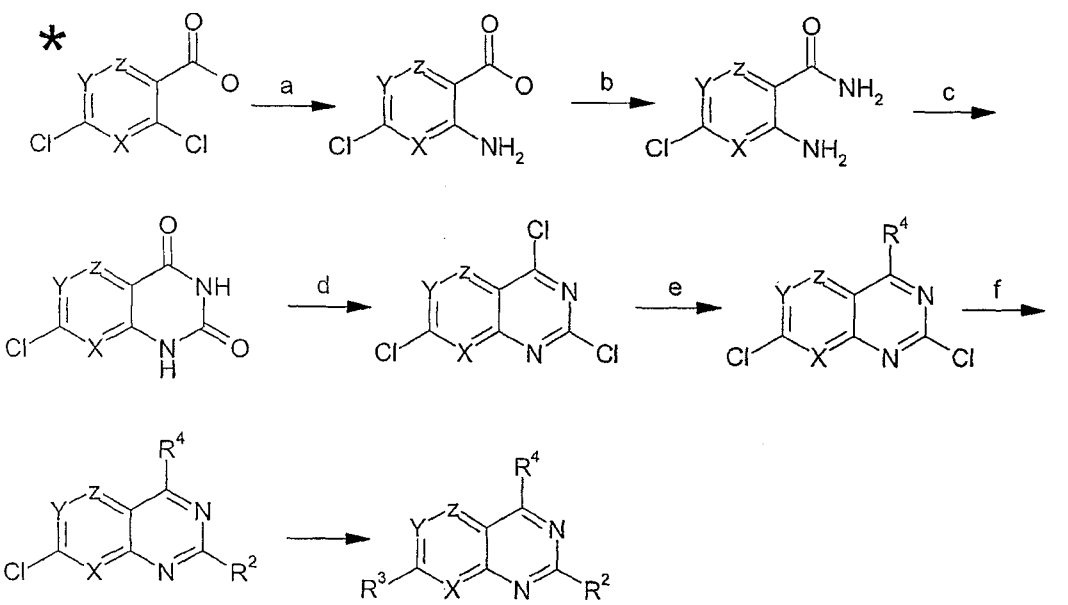
1cy, 1cz, 1d, 1da, 1db, 1dc, 1dd, 1de, 1df, 1dh, 1di, 1dj, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dr, 1ds, 1dt, 1du, 1dv, 1dw, 1dx, 1dy, 1dz, 1e, 1ea, 1eb, 1ed, 1ee, 1f, 1h, 1j, 1k, 1l, 1n, 1o, 1p, 1q, 1r, 1s, 1t, 1v, 20a, 20b, 20c, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 3aa, 3ab, 3ad, 3k, 3l, 3m, 3n, 3o, 3p, 3q, 3r, 3s, 3t, 3u, 4a, 4aa, 4ab, 4ac, 4ad, 4ae, 4af, 4ag, 4ah, 4ai, 4aj, 4ak, 4al, 4am, 4an, 4ao, 4ap, 4aq, 4ar, 4as, 4at, 4au, 4av, 4aw, 4ax, 4ay, 4az, 4b, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4q, 4r, 4s, 4t, 4u, 4v, 4w, 4x, 4y, 4z, 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l, 5m, 5n, 5o, 5p, 5q, 5r, 5s, 5t, 5u, 5v, 5w, 5x, 5y, 5z, 7a, 7b, 7c, 7d, 7e, 7f, 7g, 7h, 7i, 7j, 7k, 8a, 8b, 8c, 8d, comparative of Example 1a and comparative of Example 1b, were analysed using the QC Method QC2-QC.

Examples 18p and 1bd were analysed using the QC Method QC3-AQ-Long.

Microwave synthesis

Reactions were carried out using a Personal Chemistry™ Emrys Optimiser microwave synthesis unit with robotic arm. Power range between. 0-300 W at 2.45 GHz. Pressure range between 0-20 bar; temperature increase between 2-5°C/sec; temp range 60-250°C.

General procedure for the synthesis of 2,4,7-substituted pyridopyrimidine derivatives:

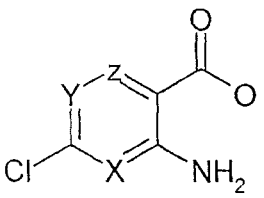


*2-amino-6- chloronicotinic acid – X=N, Y=C, Z=C

*3-amino-chloroisonicotinic acid – X=C, Y=N, Z=C

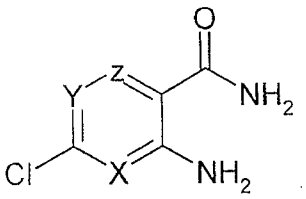
*3-Amino-chloropyridine-2-carboxylic acid – X=C, Y=C, Z=N

a) NH_3, 14 bar; b) (i) $SOCl_2$, THF, r.t., (ii) NH_3 c) Oxalyl chloride, Toluene, Δ; d) DIPEA, $POCl_3$, Toluene or Anisole, Δ;e) Appropriate amine, diisopropylethylamine, CH_2Cl_2 or Anisole; f) Appropriate amine, diiosopropylethyl amine, DMA, 70 °C;



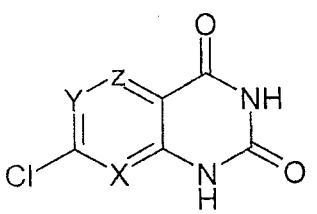
To the appropriate amino acid (1 equiv) was added liquid ammonia (sufficient to make a 0.6M solution of substrate in ammonia). The suspension was sealed in a pressure vessel which was then heated slowly to 130 °C. It was noted that at this temperature a pressure of 18 bar was observed. This temperature and pressure was maintained for a further 16 hours whereupon the mixture was cooled to room temperature. The pressure vessel was opened and the reaction poured into ice cold water (1 reaction volume). The resulting solution was acidified to pH 1-2 using concentrated HCl which caused a precipitate to form. The acidic mixture was allowed to warm to room temperature and was stirred like this for a further 30 min The suspension was then extracted with diethyl ether (3 X 400 ml). The combined organic extracts were then filtered and the filtrate concentrated *in vacuo* to give a white solid which was dried further over P_2O_5 to give the title compound (typically 80-90 % yield and 90 %+ pure) in suitably pure form to be used without any further purification.

2-amino-6-chloronicotinic acid - X=N, Y=C, Z=C: (90 % yield, 96 % purity) m/z (LC-MS, ESP): 173 $[M+H]^+$ R/T = 3.63 min



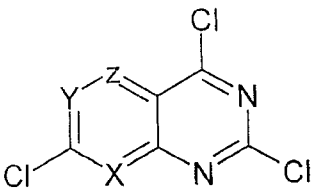
To a 0.3 M solution of amino acid (1 equiv) in anhydrous THF, under an inert atmosphere, was added thionyl chloride (3.3 equiv) in a dropwise fashion. The reaction mixture was stirred at room temperature for 2 hours. After this time the reaction was concentrated *in vacuo* to give a crude yellow solid residue. The crude solid was dissolved in THF (equal to initial reaction volume) and concentrated *in vacuo* again to give a yellow solid residue. The residue was dissolved once more in THF and concentrated as before to give a solid residue which was then dissolved in THF (to give a solution of 0.3M) and ammonia gas bubbled through the solution for 1 hour. The resultant precipitate was removed by filtration and the filtrate concentrated *in vacuo* to give a yellow precipitate which was triturated with water at 50 °C then dried to give the title compound (typically 90-95 %) yield and suitably clean enough to be used without any further purification.

2-Amino-6-chloronicotinamide - X=N, Y=C, Z=C: (92 % yield, 93 % purity) m/z (LC-MS, ESP): 172 $[M+H]^+$ R/T = 3.19 min



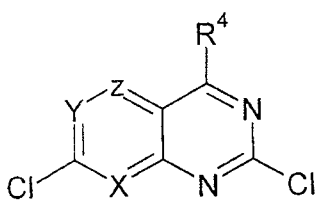
To a stirred solution (0.06 M) of substrate (1 equiv) in anhydrous toluene under an inert atmosphere was added oxalyl chloride (1.2 equiv) in a dropwise manner. The resulting mixture was then heated to reflux (115 °C) for 4 hours whereupon it was cooled and stirred for a further 16 hours. The crude reaction mixture was then concentrated to half its volume *in vacuo* and filtered to give the desired product in suitably pure form to be used without any further purification.

7-Chloro-1H-pyrido[2,3-d]pyrimidine-2,4-dione- X=N, Y=C, Z=C: (95 % yield, 96 % purity) m/z (LC-MS, ESP): 196 $[M-H]^-$ R/T = 3.22 min



To a stirred 0.5 M suspension of the appropriate dione (1 equiv) in anhydrous toluene under an inert atmosphere was slowly added diisopropylethylamine (3 equiv). The reaction mixture was then heated to 70 °C for 30 minutes and then cooled to room temperature prior to the addition of $POCl_3$ (3 equiv). The reaction was then heated to 100 °C for 2.5 hours before being cooled and concentrated *in vacuo* to give a crude slurry which was then suspended in EtOAc and filtered through a thin pad of Celite™. The filtrate was concentrated *in vacuo* to give a brown, oil which was dissolved in CH_2Cl_2 and stirred over silica gel for 30 minutes. After this time the silica was removed by filtration, the filtrate concentrated and the crude residue purified by flash chromatography (SiO_2) to give the title compound in analytically pure form.

2,4,7-Trichloro-pyrido[2,3-d]pyrimidine- X=N, Y=C, Z=C: (48 % yield, 96 % purity) m/z (LC-MS, ESP): 234 $[M+H]^+$ R/T = 4.21 min



To a cooled (0-5 °C) stirred solution (0.1 M) of the appropriate trichloro-substrate (1 equiv) in CH_2Cl_2 was added diisopropylethylamine (1 equiv) in a dropwise fashion. The appropriate amine (1 equiv) was then added to the reaction mixture portionwise over the period of 1 hour. The solution was maintained at room temperature with stirring for a further 1 hour before the mixture was washed with water (2x1 reaction volume). The aqueous extracts were combined

and extracted with CH_2Cl_2 (2x1 reaction volume). The organic extracts were then combined, dried (sodium sulphate), filtered and concentrated *in vacuo* to give an oily residue which solidified upon prolonged drying. The solid was triturated with diethylether and then filtered and the cake washed with cold diethyl ether to leave the title compound in suitable clean form to be used without any further purification.

2,7-Dichloro-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine - R1= morpholine, X=N, Y=C, Z=C: (92 % yield, 90 % purity) m/z (LC-MS, ESP): 285 $[M+H]^+$ R/T = 3.90 min

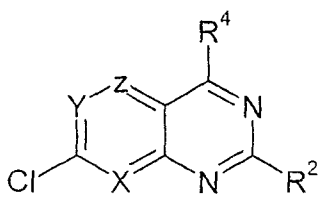
2,7-Dichloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine - R1= (S)-3-Methyl-morpholine, X=N, Y=C, Z=C: (87 % yield, 92 % purity) m/z (LC-MS, ESP): 301 $[M+H]^+$ R/T = 4.13 min

2,7-Dichloro-4-((R)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine - R1= (R)-3-Methyl-morpholine: (99 % yield, 94 % purity) m/z (LC-MS, ESP): 301 $[M+H]^+$ R/T = 3.49 min

Alternatively, to a stirred 0.47 M suspension of the appropriate dione (1 equiv) in anhydrous anisole under an inert atmosphere was added $POCl_3$ (2.6 equiv). The mixture was heated to 55 °C and then diisopropylethylamine (2.6 equiv) was slowly added. The reaction mixture was then heated to 85-90 °C for 30 minutes. Water was added in portions (0.15 equiv), and the reaction mixture was held at 85-90 °C for a further 30 minutes. The reaction was cooled to 50 °C, and then 15% of the anisole solvent was removed by vacuum distillation. The mixtutre was then cooled to -5 °C and diisopropylethylamine (1.1 equiv) was added. A 4.9M solution of the appropriate amine (1.05 equiv) in anisole was then added to the reaction mixture continuously over a period of 1 hour. The solution was then warmed to 30 °C and the reaction monitored by HPLC until reation completion.

One third of the resulting mixture from the above reaction was then added over 10min to a stirred mixture of 1.95M aqueous potassium hydroxide (3.9 equiv) and *i*-butanol (6.9 equiv) at 60 °C. The stirring was stoped, the phases were allowed to separate, and the aqueous phase was removed. Stirring was resumed, and 1.95M aqueous potassium hydroxide (3.9 equiv) was added to the retained organic phase. The second third of the resulting reaction mixture from the reaction above was then added over 10min at 60 °C. Again, stirring

was stoped, the phases were allowed to separate, and the aqueous phase was removed. Stirring was resumed, and 1.95M aqueous potassium hydroxide (3.9 equiv) was added to the retained organic phase. The remaining third of the resulting reaction mixture from the reaction above was then added over 10min at 60 °C. Again, stirring was stoped, the phases were allowed to separate, and the aqueous phase was removed. Water was then added to the organic phase with stirring, and the stirred mixture heated to 75 °C. Stirring was stoped, the phases were allowed to separate, and the aqueous phase was removed. The resulting organic phase was stirred and allowed to cool to 30 °C, and then as the mixture was heated to 60 °C heptane (11.5 equiv) was added over 20min when the mixture was around 40 °C. After being heated to 60 °C, the mixture was cooled over 2.5h to 10 °C. After 30min, the resulting slurry was filtered off, washed with a 10:1 heptane:anisole mixture (2 x 1.4equiv) and then washed with heptane (2 x 1.4equiv). The solid was then dried in a vacuum oven at 50 °C to leave the title compound in suitable clean form to be used without any further purification.



To a solution (0.2 M) of the appropriate dichloro-substrate (1 equiv) in anhydrous dimethyl acetamide under an inert atmosphere was added diisopropylethylamine (1 equiv) followed by the appropriate amine (1 equiv). The resulting mixture was heated for 48 hours at 70 °C before being cooled to ambient temperature. The reaction was diluted with CH_2Cl_2 (1 reaction volume) and then washed with water (3x1 reaction volumes). The organic extract was concentrated *in vacuo* to give a syrup which was dissolved in EtOAc (1 reaction volume) and washed with saturated brine solution before being dried (sodium sulphate) and concentrated *in vacuo* to give an oil. The crude residue was purified by flash chromatography (SiO_2, eluted with EtOAc:Hex (7:3) going to (1:1)) to give the title compound as a yellow solid that was suitably clean to be used without any further purification.

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7-Chloro-2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine - R1= morpholine, R2=cis-dimethylmorpholine, X=N, Y=C, Z=C: (45 % yield, 85 % purity) m/z (LC-MS, ESP): 348 $[M+H]^+$ R/T = 4.16 min

7-Chloro-4-((S)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine - R1= (S)-3-Methyl-morpholine, R2=(S)-3-Methyl-morpholine, X=N, Y=C, Z=C: (71 % yield, 90 % purity) m/z (LC-MS, ESP): 364 $[M+H]^+$ R/T = 3.52 min

7-Chloro-2-(2-ethyl-piperidin-1-yl)-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine - R1 = (S)-3-Methyl-morpholine, R2 = 2-Ethyl-piperidine, X=N, Y=C, Z=C: (51 % yield, 98 % purity) m/z (LC-MS, ESP): 376 $[M+H]^+$ R/T = 3.88 min

7-Chloro-4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidine, - R1 = (S)-3-Methyl-morpholine, R2 = morpholine, X=N, Y=C, Z=C: (72 % yield, 96 % purity) m/z (LC-MS, ESP): 350 $[M+H]^+$ R/T = 3.45 min

7-Chloro-2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)- 4-((S)-3-methyl-morpholin-4-yl-pyrido[2,3-d]pyrimidine - R1= (S)-3-Methyl-morpholine, R2=cis-dimethylmorpholine: (33 % yield) m/z (LC-MS, ESP): 378 $[M+H]^+$ R/T = 3.68 min

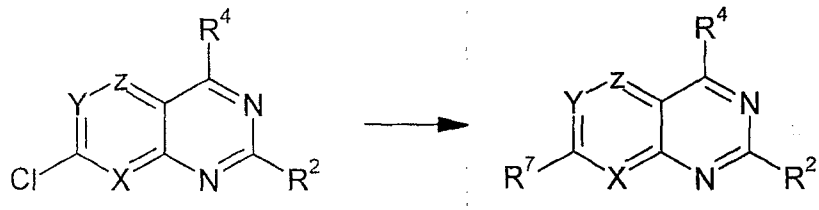
7-Chloro-4-((R)-3-methyl-morpholin-4-yl)-2-((R)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine, - R1 = R2 = (R)-3-Methyl-morpholine: (48 % yield, 100 % purity) m/z (LC-MS, ESP): 364 $[M+H]^+$ R/T = 2.80 min

To a 0.33 M solution of 2,7-dichloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine (1 equiv) in N,N-dimethylacetamide was added Hunig's base (1 equiv) followed by the appropriate amine (1.1 equiv). The reaction mixture was heated 40 °C for 1 hour. After this time the reaction was allowed to cool, diluted with EtOAc (1 reaction volume) and then washed with water (1 reaction volume). The aqueous fraction was removed and extracted further with EtOAc (2 X 1 reaction volume). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude oily residue which was purified

by flash chromatography (SiO_2) using EtOAc/Hexanes as eluent which furnished the desired products in a suitably clean form.

7-Chloro-4-((S)-3-methyl-morpholin-4-yl)-2-thiomorpholin-4-yl-pyrido[2,3-d]pyrimidine: (30 % yield, 100 % purity) m/z (LC-MS, ESP): 366.4$[M+H]^+$ R/T = 3.00 min

7-Chloro-4-((S)-3-methyl-morpholin-4-yl)-2-(4-methyl-piperazin-1-yl)-pyrido[2,3-d]pyrimidine:(32 % yield, 95 % purity) m/z (LC-MS, ESP): 363.4$[M+H]^+$ R/T = 2.37 min

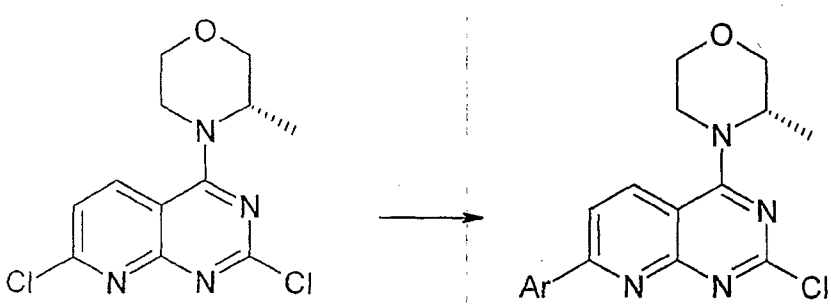


The appropriate chloro-substrate (1 equiv) was dissolved in a toluene/ethanol (1:1) solution (0.02 M). Sodium carbonate (2 equiv) and the appropriate pinacolate boron ester or boronic acid (1 equiv) were then added followed by tetrakis(triphenylphosphine) palladium^0 (0.1 equiv). The reaction vessel was sealed and the mixture exposed to microwave radiation (140 ^oC, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Example 1:

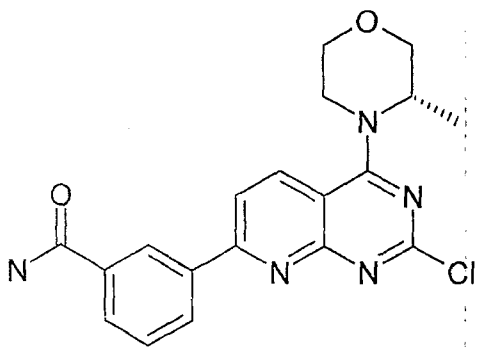
Preparation of 2,4,7-substituted pyridopyrimidine Intermediates:

Procedures for the synthesis of 2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-7-aryll-pyrido[2,3-d]pyrimidine derivatives

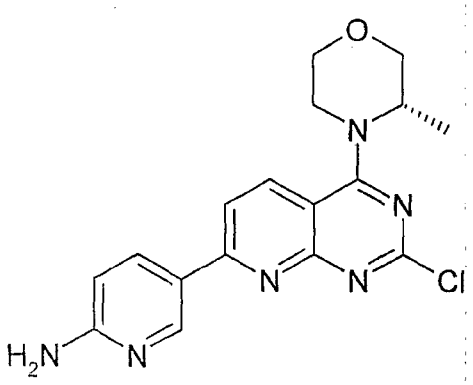


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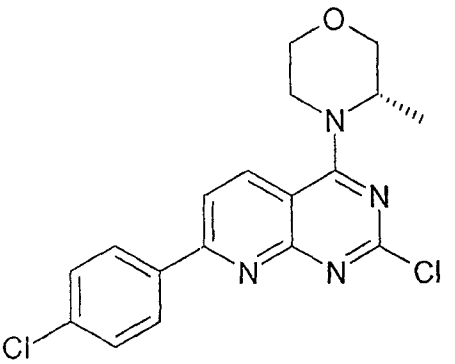
To a (0.1 M) solution of 2,7-dichloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine (1 equiv) in MeCN/H_2O (1:1 mixture) was added the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and potassium carbonate (3 equiv). The mixture was degassed with nitrogen for 20 minutes before the addition of tetrakis(triphenylphosphine)palladium^0 (0.05 equiv). The reaction was degassed for a further 5 minutes before being heated to reflux under an inert atmosphere for 3 hours. Whereupon, it was concentrated *in vacuo* and the crude residue partitioned between CH_2Cl_2/H_2O. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an oil which was further purified by flash chromatography (SiO_2) using 5 % MeOH in CH_2Cl_2 as eluent.



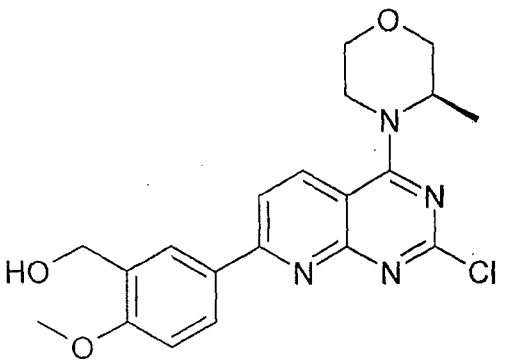
3-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzamide: (27 % yield, 99 % purity) m/z (LC-MS,ESP):384.3 $[M+H]^+$, R/T = 3.13 min)



5-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-ylamine: (93 % yield, 89 % purity) m/z (LC-MS,ESP):357 $[M+H]^+$, R/T = 2.53 min)

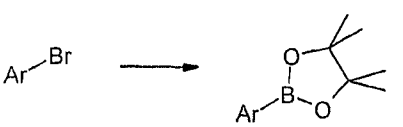


2-Chloro-7-(4-chloro-phenyl)-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine: (80 % yield, 85 % purity) m/z (LC-MS,ESP):357.5 $[M+H]^+$, R/T = 4.26 min)



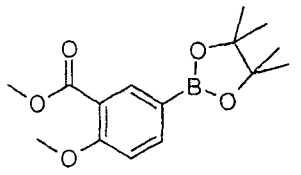
{5-[2-Chloro-4-((R)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-phenyl}-methanol: (97 % yield, 93 % purity) m/z (LC-MS,ESP):401 $[M+H]^+$, R/T = 3.42 min)

Procedures for the synthesis of boronic ester:



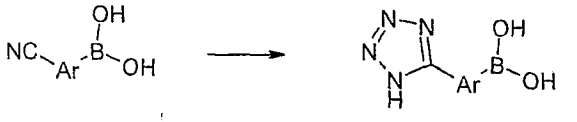
5-bromo-2-methoxybenzoic acid methyl ester (1 equiv) was dissolved in dioxane (0.1 M). Bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and dppf (0.05 equiv) were added and the mixture was degassed with nitrogen for 20 minutes. (1,1'-Bis(diphenylphosphino)ferrocene-dichloropalladium (0.05 equiv) was added and the mixture was degassed for a further 5 minutes. The reaction mixture was heated to 120 °C for 2 hours under nitrogen. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite™. The filtrate was concentrated *in vacuo* to give a dark oil. The residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate

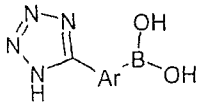
and the aqueous layer further extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to give a dark residue which was purified by flash column chromatography onto silica gel eluting with 0 to 30 % ethyl acetate in hexane.



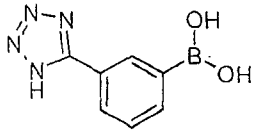
2-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester: (77 % yield, 100 % purity) m/z (LC-MS, ESP): 293.5 $[M+H]^+$ R/T = 4.24 min

Procedures for the synthesis of tetrazolyl boronic acids:



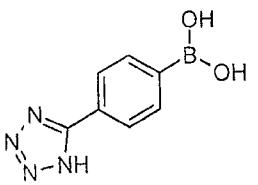


The appropriate cyanophenylpinacolate boron ester or boronic acid (1 equiv) was dissolved in DMF (0.67 M). Sodium azide (6 equiv) and ammonium chloride (6 equiv) were added. The reaction mixture was heated to 120°C for 2.5 hours. After cooling down, the reaction mixture was poured into a mixture of ice water and EtOAc. Sodium nitrite was added and the aqueous phase was acidified by 6N HCl until pH 2. The mixture was allowed to stir at room temperature for 30 min and then was extracted with EtOAc and n-butanol. Organic fractions were collected, dried over sodium sulphate, filtered off and concentrated *in vacuo*, to yield a crude residue which was further purified accordingly:



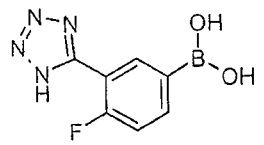
The crude residue was recrystallized from CH_2Cl_2 / hexane, obtaining the desired product as a white solid.

[3-(1H-tetrazol-5-yl)phenyl]boronic acid: (15 % yield, 100 % purity) m/z (LC-MS, ESP): 191 $[M+H]^+$ R/T = 2.49 min



The crude residue was recrystallized from CH_2Cl_2 / hexane, to give the desired product as a white solid.

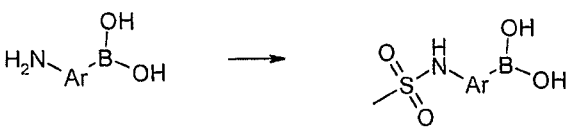
[4-(1H-tetrazol-5-yl)phenyl]boronic acid: (64 % yield, 100 % purity) m/z (LC-MS, ESP): 191 $[M+H]^+$ R/T = 2.49 min



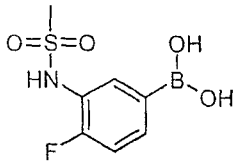
The residue was purified by reverse phase column using a gradient from 5 % to 20 % acetonitrile in 0.1 % formic acid/water solution, yielding the desired product.

[4-fluoro-3-(1H-tetrazol-5-yl)phenyl]boronic acid: (18 % yield, 100 % purity) m/z (LC-MS, ESP): 207 $[M-H]^-$ R/T = 2.51 min

Procedure for the synthesis of methanesulfonylamido boronic acid:

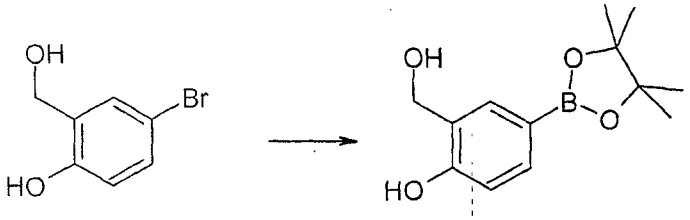


3-Amino-4-fluorophenylboronic acid (1 equiv) was dissolved in THF (0.1 M). Methane sulphonyl chloride (10 equiv) and pyridine (1 equiv) were added. The reaction mixture was heated to 70°C for 30 minutes. After cooling down, the reaction mixture was concentrated *in vacuo*, to yield a crude residue which was used without further purification.



3-(Methanesulfonylamino)-4-fluoro-phenylboronic acid: (51 % yield, 90 % purity) m/z (LC-MS, ESP): 232 $[M-H]^-$ R/T = 2.50 min

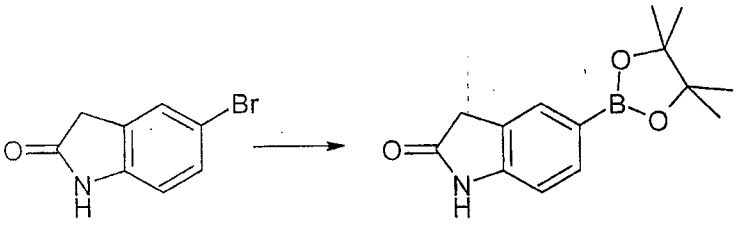
Procedure for the synthesis of 3-hydroxymethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ol



To a 0.18 M solution of 5-bromo-2-hydroxybenzyl alcohol (1 equiv) in dioxane was added bis(pinacolato)diboron (1.2 equiv) and potassium acetate (3.5 equiv) followed by 1,1'-bis(diphenylphosphino)ferrocene (0.05 equiv). The mixture was degassed with nitrogen for 20 minutes. $PdCl_2(dppf)$ (0.05 equiv) was added and the misxture degassed for a further 5 minutes. The reaction was then heated to reflux under an inert atmosphere for 2 hours. Upon completion, the reaction was cooled, filtered and concentrated *in vacuo* to give a crude residue which was purified by flash chromatography (SiO_2) using EtOAc/Hexanes – 1:1 as eluent to give the desired product.

3-Hydroxymethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ol 6-Bromo-3H-pyrido[2,3-d]pyrimidin-4-one: (67 % yield, 94 % purity) m/z (LC-MS,ESP):251 $[M-H]^-$ R/T = 3.32 minutes)

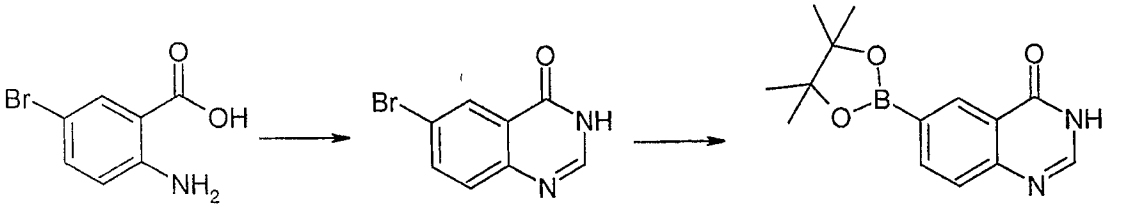
Procedure for the synthesis of 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one



To a 0.05 M solution of 5-bromo-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (1 equiv) in dioxane was added bis(pinacolato)diboron (1.2 eqiv) and potassium acetate (1.5 equiv) followed by 1,1'-bis(diphenylphosphino)ferrocene (0.05 equiv). The mixture was degassed with nitrogen for 20 minutes. $PdCl_2(dppf)$ (0.05 equiv) was added and the mixture degassed for a further 5 minutes. The reaction was then heated to 120 °C under an inert atmosphere for 8 hours. Upon completion, the reaction was cooled, filtered and concentrated *in vacuo* to give a crude residue which was purified by flash chromatography (SiO_2) using EtOAc/Hexanes – 4:1 as eluent to give the desired product.

5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one: (68 % yield, 92 % purity) m/z (LC-MS,ESP):260 $[M-H]^-$ R/T = 3.52 minutes)

Procedure for the synthesis of 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-pyrido[2,3-d]pyrimidin-4-one boronic ester



To a 1.2 M solution of 5-bromoanthranilic acid (1 equiv) in N,N-dimethylformamide was added formamidine acetate (1 equiv). The mixture was heated to reflux and stirred at this temperature for 16 hours. After this time, the reaction was cooled and $NaHCO_3$ solution (5 % in H_2O) (3 volumes) were carefully added and the mixture stirred vigorously. The resulting

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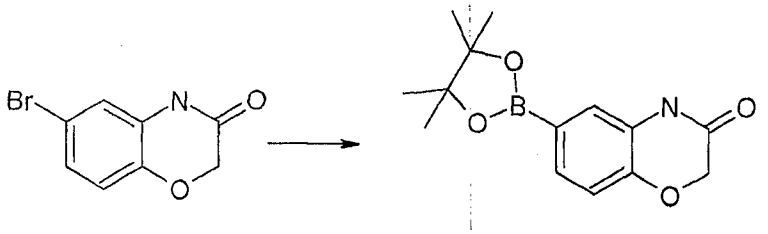
precipitate was collected by filtration and then washed with water (2 X 1 volume) and then t-butyl methylether (2 X 1 volume) before being dried in a vacuum oven to give the desired product which required no further purification.

6-Bromo-3H-pyrido[2,3-d]pyrimidin-4-one: (91 % yield, insert) m/z (LC-MS,ESP):225 [M-H]$^-$ R/T = 2.31 minutes)

To a (0.35M) solution of 6-bromo-3H-pyrido[2,3-d]pyrimidin-4-one (1 equiv) in dioxane was added bis(pinacolato)diboron (1.2 eqiv) and potassium acetate (1.5 equiv) followed by 1,1'-bis(diphenylphosphino)ferrocene (0.05 equiv). The mixture was degassed with nitrogen for 20 minutes. $PdCl_2$(dppf) (0.05 equiv) was added and the misxture degassed for a further 5 minutes. The reaction was then heated to reflux under an inert atmosphere for 16 hours. After this time, the mixture was cooled, filtered through Celite ™ and then partitioned between CH_2Cl_2/$NaHCO_{3(aq)}$. The organic fraction was removed, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2) 1:1-Hexanes:EtOAc going to neat EtOAc. The purified material was then dissolved in the minimum volume of CH_2Cl_2 and hexane added in order to precipitate the desired product as a whiter crystralline solid

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-pyrido[2,3-d]pyrimidin-4-one (15 % yield, 96 % purity) m/z (LC-MS,ESP):Mass ion not observable, R/T = 3.30 min)

Procedure for the synthesis of 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrido[2,3-b][1,4]oxazin-2-one



To a 0.3 M solution of 7-bromo-1H-pyrido[2,3-b][1,4]oxazin-2-one (1 equiv) were added bis(pinacolato)diboron (1.10 equiv), potassium acetate (3.5 equiv) and 1,1'-bis(diphenylphosphino)ferrocene (0.05 equiv). The mixture was degassed with nitrogen for 20 minutes before the addition of $PdCl_2$(dppf) (0.05 equiv) and degassing for a furthere 5

minutes. A condenser was attached to the reaction vessel and the mixture heated to reflux under an inert atmosphere for 16 hours. After this time, the reaction was cooled, filtered through Celite ™. The cake was washed CH_2Cl_2 and the filtrate concentrated *in vacuo* before being re-dissolved in EtOAc and washed with H_2O and then saturated brine. The organic fraction was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude residue which was further purified by flash chromatography (SiO_2) using 1:1- EtOAc:Hexanes going to neat EtOAc as eluent to give the desired product.

7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrido[2,3-b][1,4]oxazin-2-one: (97 % yield, 90 % purity) m/z (LC-MS,ESP):317 $[M+H+MeCN]^+$, R/T = 3.72 min)

Procedure for the synthesis of 2-Methoxynicotinonitrile-5-boronic acid

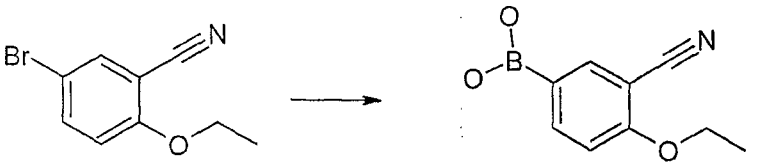


To a cooled (-78 °C) solution (0.25 M) of 5-bromo-2-methoxybenzonitrile in THF was added n-BuLi (1.10 equiv of a 2.5 M solution in hexanes) dropwise. The mixture was maintained at this temperature with stirring for 45 minutes before the addition of triisopropylborate (1.25 equiv). The reaction was then warmed to -20 °C before the addition of 1N HCl (0.5 reaction volumes). The mixture was allowed to warm to room temperature and stirred like this for a further 20 minutes. After this time the mixture was diluted with H_2O and then extracted with Et_2O (3 X 4 reaction volumes). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an off white solid which corresponded to the title compound

2-Methoxynicotinonitrile-5-boronic acid: (44 % yield, 90 % purity) m/z (LC-MS,ESP):177.0 $[M+H]^+$, R/T = 2.87 min)

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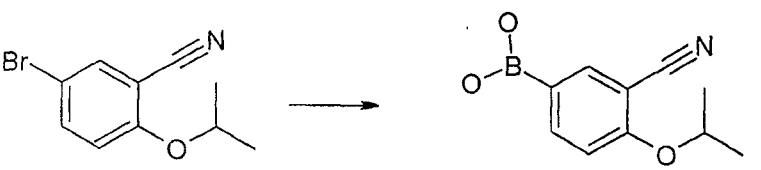
Procedure for the synthesis of 2-Ethoxynicotinonitrile-5-boronic acid



To a cooled (-78 °C) solution (0.25 M) of 5-bromo-2-ethoxybenzonitrile in THF was added n-BuLi (1.10 equiv of a 2.5 M solution in hexanes) dropwise. The mixture was maintained at this temperature with stirring for 45 minutes before the addition of triisopropylborate (1.25 equiv). The reaction was then warmed to -20 °C before the addition of 1N HCl (0.5 reaction volumes). The mixture was allowed to warm to room temperature and stirred like this for a further 20 minutes. After this time the mixture was diluted with H_2O and then extracted with Et_2O (3x4 reaction volumes). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an off white solid which corresponded to the title compound.

2-Ethoxynicotinonitrile-5-boronic acid: (23 % yield, 97 % purity) m/z (LC-MS,ESP):191.0 $[M+H]^+$, R/T = 3.09 min)

Procedure for the synthesis of 2-Isopropoxynicotinonitrile-5-boronic acid

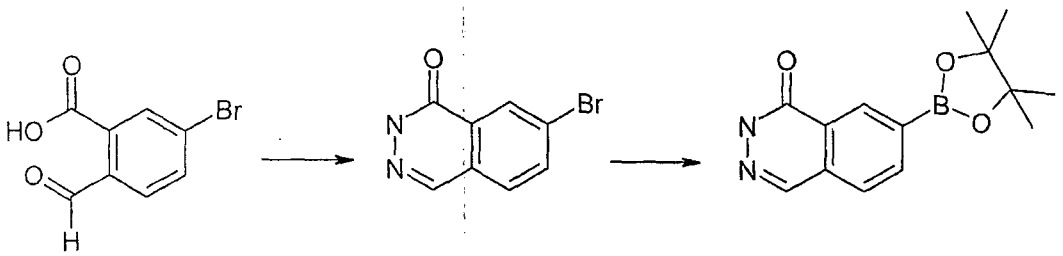


To a cooled (-78 °C) solution (0.25 M) of 5-bromo-2-isopropoxy-nicotinonitrile in THF was added n-BuLi (1.10 equiv of a 2.5 M solution in hexanes) dropwise. The mixture was maintained at this temperature with stirring for 45 minutes before the addition of triisopropylborate (1.25 equiv). The reaction was then warmed to -20 °C before the addition of 1N HCl (0.5 reaction volumes). The mixture was allowed to warm to room temperature and stirred like this for a further 20 minutes. After this time the mixture was diluted with H_2O and then extracted with Et_2O (3x4 reaction volumes). The combined organic fractions were then

dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an off white solid which which was triturated with CH_2Cl_2 to give the desired compound.

2-Isopropoxy-nicotinonitrile-5-boronic acid: (100 % yield, 97 % purity) m/z (LC-MS,ESP):204.2 $[M+H]^+$, R/T = 3.25 min)

Procedure for the synthesis of 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2H-phthalazin-1-one



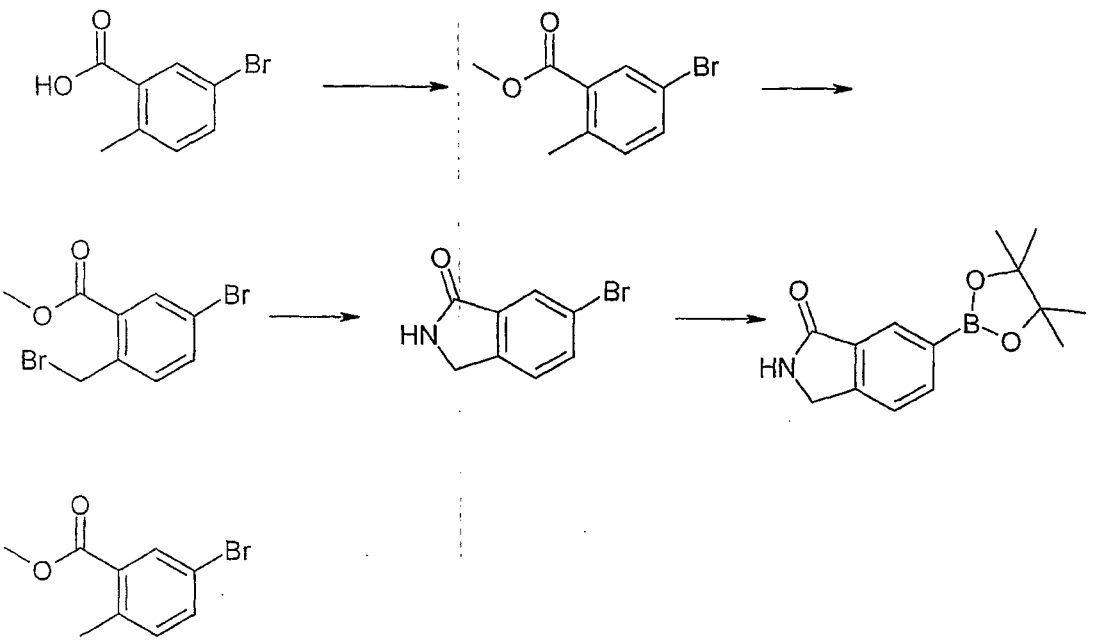
To a 3M solution of 5-bromo-2-formyl benzoic acid (1 equiv) in water was added hydrazine hydrate (5 equivs). The reaction was heated to 95 °C for 4 hours whereupon a white precipitate had formed in the mixture. The reaction was cooled, and filtered. The white solid material was washed with cold methanol and dried to give the desired product.

7-Bromo-2H-phthalazin-1-one: (73 % yield, 95 % purity) m/z (LC-MS,ESP):225.2 $[M+H]^+$, R/T = 2.99 min)

Bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and 1,1'-bis(diphenylphosphino)ferrocene (0.05 equiv) were dissolved in dioxane. The mixture was degassed with nitrogen for 20 minutes before the addition of $PdCl_2$(dppf) (0.05 equiv). The mixture was degassed for a further 5 minutes. The mixture was heated to reflux for 16 hours and then allowed to cool to room temperature. Water was added to the mixture before it was extracted with EtOAc (2 X 2 reaction volumes). The combined organic fractions were dried ($MgSO_4$), filtered aned concentrated *in vacuo* before being purified by flash chromatography (SiO_2) neat hexanes going to 1:1 - Hexanes:EtOAc then neat EtOAc to give the desire product as a white crystalline solid.

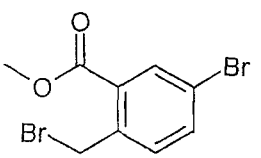
7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2H-phthalazin-1-one: (86 % yield, 92 % purity) m/z (LC-MS,ESP):191.3 $[M+H]^+$, R/T = 2.29 min)

Procedure for the synthesis of 6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one:



5-Bromo-2-methylbenzoic acid (1 equiv) was dissolved in a 1:9 MeOH/toluene mixture (0.1 M). The reaction mixture was cooled to 0°C and a trimethylsilyldiazomethane (1.05 equiv) solution in diethylether (2M) was added slowly until a persistent yellow tinge was observed. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The resulting residue was sonicated in hexane, collected by vacuum filtration over a sintered funnel, dried and used without further purification.

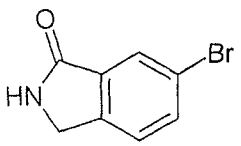
5-Bromo-2-methyl-benzoic acid methyl ester: (99 % yield, 100 % purity) m/z (LC-MS, ESP): no ionisation R/T = 4.43 min



To a solution of 5-Bromo-2-methyl-benzoic acid methyl ester (1 equiv) in chloroform (0.1 M) were added N-bromosuccinimide (1.2 equiv) and benzoyl peroxide (0.05 equiv). The reaction mixture was stirred at reflux for 16 hours. It was then diluted with chloroform and a precipitate was collected by vacuum filtration on a sintered funnel. The filtrate was concentrated *in vacuo*. The subsequent residue was purified by flash column chromatography

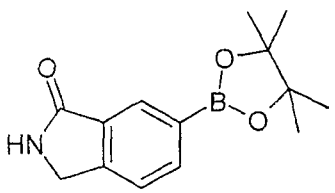
onto silica gel eluting with DCM in hexane (0 to 20 %) to yield the desired product as a clear colourless oil.

5-Bromo-2-bromomethyl-benzoic acid methyl ester: 80 % yield, 100 % purity) m/z (LC-MS, ESP): no ionisation R/T = 4.40 min



A solution of 5-bromo-2-bromomethyl-benzoic acid methyl ester (1 equiv) in a 1:1 THF/MeOH mixture was treated by gentle bubbling of ammonia gas for 40 minutes at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was sonicated in CH_2Cl_2 for 15 minutes then filtered to give the desired product as a white solid.

6-Bromo-2,3-dihydro-isoindol-1-one: (98 % yield, 90 % purity) m/z (LC-MS, ESP): 212.3/214.3 $[M+H]^+$ R/T = 2.98 min

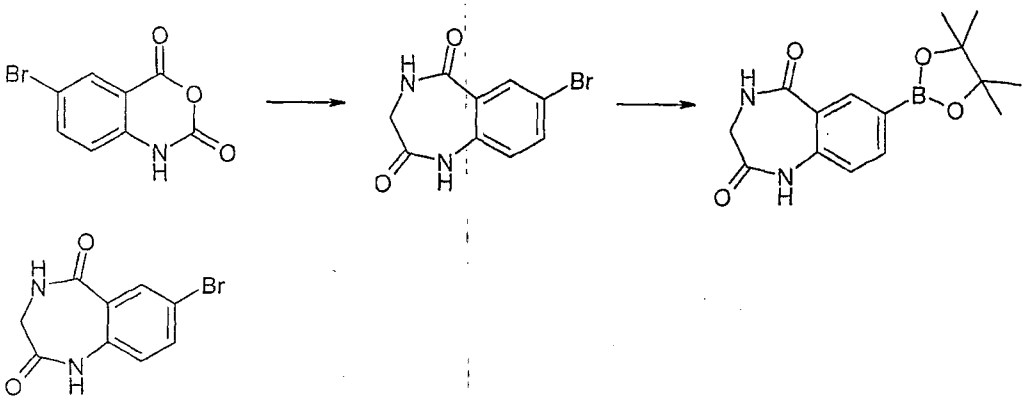


To a solution of 6-bromo-2,3-dihydro-isoindol-1-one (1 equiv) in dry dioxan (0.1 M) were added bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and dppf (0.05 equiv). The reaction mixture was degassed with nitrogen for 20 minutes. $PdCl_2(dppf)$ (0.05 equiv) was added to the reaction mixture, which was degassed for a further 5 minutes. The reaction mixture was heated to 70°C for 2 hours under nitrogen then heated to 120°C for 16 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was further extracted with EtOAc and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was sonicated in EtOAc, the suspension was filtered onto a sintered funnel and the collected grey solid was dried and used without further purification.

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one: (82 % yield, 29 % purity, main impurity being the boronic acid 43 %) m/z (LC-MS, ESP): 519.5 $[2M+H]^+$ R/T = 3.38 min

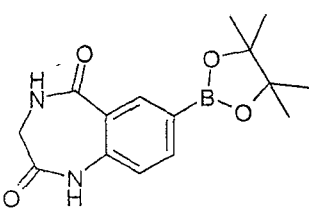
130

Procedure for the synthesis of 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione:



To a solution of 5-bromoisatoic anhydride (1 equiv) in water (1 M) was added glycine (1.4 equiv) and triethylamine (1 equiv) at room temperature. The reaction mixture was stirred at room temperature for 4 hours to give a cloudy solution. The reaction mixture was concentrated *in vacuo*. Acetic acid was added and the reaction mixture was stirred at 140°C for 4.5 hours. The reaction mixture was cooled down slowly to room temperature. A precipitate was formed. The reaction mixture was diluted with diethyl ether then filtered through a sintered funnel to yield the desired product.

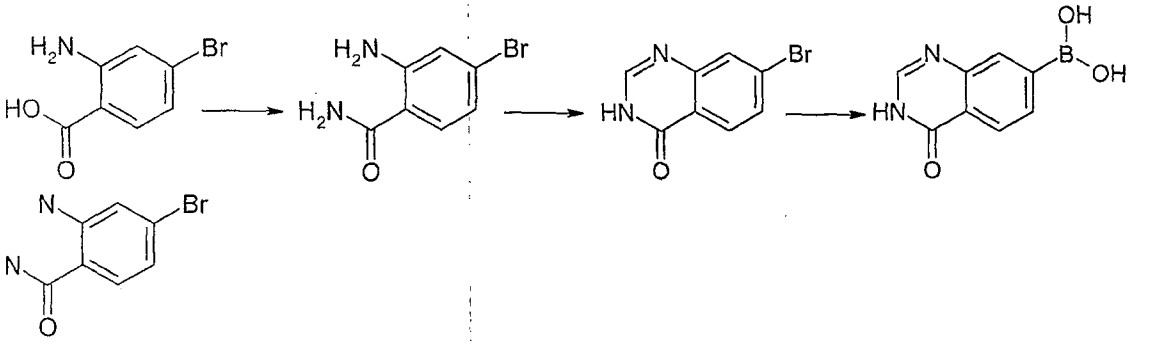
7-Bromo-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione: (75 % yield, 100 % purity) m/z (LC-MS, ESP): 255.2/257.2 $[M+H]^+$ R/T = 2.67 min



To a solution of 7-bromo-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (1 equiv) in dry dioxan (0.1 M) were added bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and dppf (0.05 equiv). The reaction mixture was degassed with nitrogen for 20 minutes. $PdCl_2$(dppf) (0.05 equiv) was added to the reaction mixture, which was degassed for a further 5 minutes. The reaction was heated to 120 °C for 16 hours under nitrogen. The reaction mixture was partitioned between CH_2Cl_2/MeOH and water. The aqueous phase was further extracted with CH_2Cl_2/MeOH. The combined organic phases were dried ($MgSO_4$), filtered

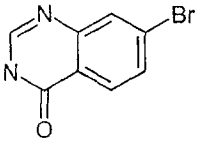
and concentrated *in vacuo*. The residue was sonicated in hexane/ CH_2Cl_2, filtered, sonicated in CH_2Cl_2 and filtered to yield the desired product.

7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione: (63 % yield, 85 % purity main impurity being the boronic acid 15 %) m/z (LC-MS, ESP): 303.4 $[M+H]^+$ R/T = 3.08 min



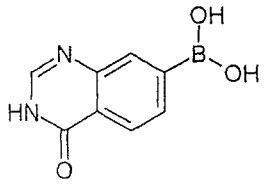
To a solution of 2-amino-4-bromobenzoic acid (1 equiv) in DMA (0.23 M), were added ammonium chloride (7 equiv), HBTU (1 equiv) and diisopropylethylamine (2 equiv). The reaction mixture was stirred for 24 hours at room temperature. DMA was evaporated and the residue was purified by flash column chromatography onto silica gel eluting with a gradient of TBME/hexane to yield the desired product as a white solid.

2-Amino-4-bromo-benzamide: 40 % yield, 100 % purity) m/z (LC-MS, ESP): 215 $[M+H]^+$ R/T = 3.00 min



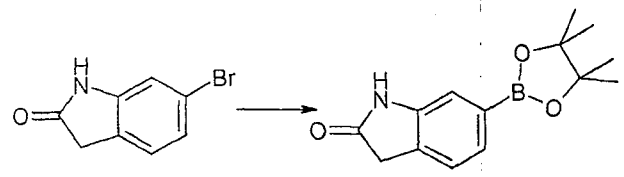
To a solution of 2-amino-4-bromo-benzamide (1 equiv) in DMA (0.14 M) were added triethyl orthoformate (10 equiv) and trifluoroacetic acid (1 equiv). The reaction vessel was sealed and exposed to microwave radiation (160 °C, medium absorption setting) for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue was filtered through a silica pad with 10 % methanol in ethyl acetate yielding the required product as a pale yellow solid.

7-Bromo-3H-quinazolin-4-one: (71 % yield, 100 % purity) m/z (LC-MS, ESP): 268 $[M+H]^+$ R/T = 2.94 min



To a solution of 7-bromo-3H-quinazolin-4-one (1 equiv) in dioxane (0.04 M) were added bispinacolato diboron (2.2 equiv), potassium acetate (1.5 equiv), dppf (0.1 equiv) and $PdCl_2$(dppf) (0.1 equiv). The reaction mixture was degassed with nitrogen for 5 minutes, sonicated and stirred at 120°C for 3 hours. The reaction mixture was concentrated *in vacuo*. The residue was filtered through a Celite™ pad topped with silica with ethyl acetate. The mother liquor was concentrated *in vacuo* yielding a brown solid which was further purified by flash column chromatography onto silica gel eluting with a gradient of methanol/diethyl ether (0 to 5 %) to yield the desired product as a white solid.

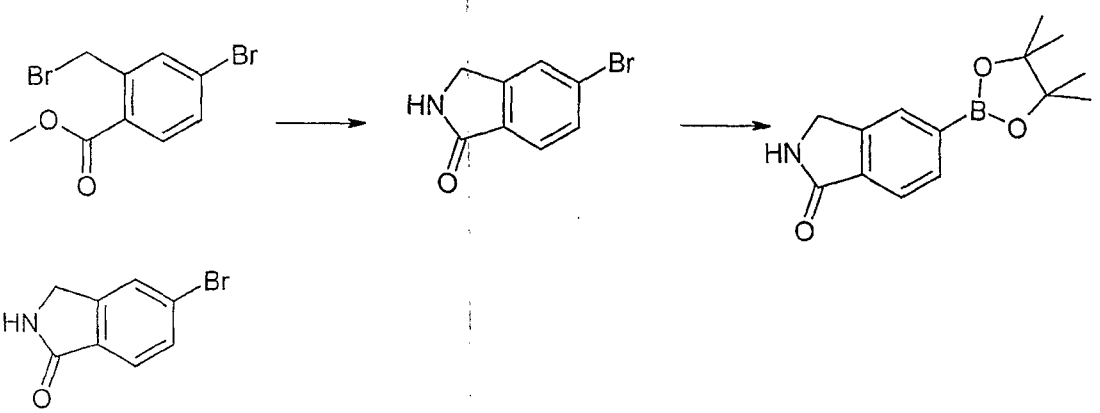
7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-quinazolin-4-one: (53 % yield, 61 % purity main impurity being the boronic acid 39 %) m/z (LC-MS, ESP): $[M+H]^+$ R/T = min



To a solution of 6-bromo-2-oxindole (1 equiv) in NMP (0.05 M) were added bispinacolato diboron (2.4 equiv), potassium acetate (1.5 equiv), dppf (0.05 equiv) and $PdCl_2$(dppf) (0.05 equiv). The reaction mixture was stirred at 130°C for 3 hours and then concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel eluting with EtOAc/hexane (9 / 1), yielding the desired product as a red solid.

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-dihydro-indol-2-one: (22 % yield, 51 % purity main impurity being the boronic acid 28 %) m/z (LC-MS, ESP): 260 $[M+H]^+$ R/T = 3.51 min

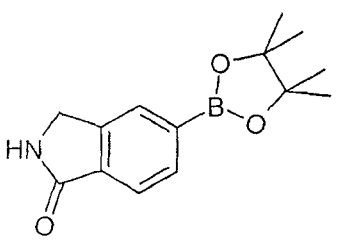
Procedure for the synthesis of 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one:



4-Bromo-2-bromomethyl-benzoic acid methyl ester was prepared according to literature.

A solution of 4-bromo-2-bromomethyl-benzoic acid methyl ester (1 equiv) in a 1:1 THF/MeOH mixture was treated by gentle bubbling of ammonia gas for 4 hours at room temperature. The reaction mixture was concentrated *in vacuo*. The residue was sonicated in water, filtered, then sonicated in diethylether and filtered to give the desired product as a white solid.

5-Bromo-2,3-dihydro-isoindol-1-one: (81 % yield, 100 % purity) m/z (LC-MS, ESP): 212.3/214.3 $[M+H]^+$ R/T = 3.06 min

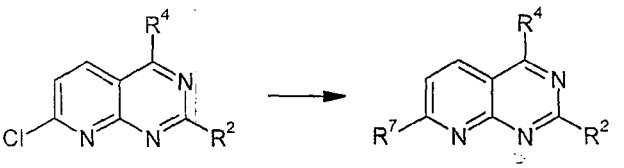


To a solution of 5-bromo-2,3-dihydro-isoindol-1-one (1 equiv) in dry dioxan (0.1 M) were added bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and dppf (0.05 equiv). The reaction mixture was degassed with nitrogen for 20 minutes. $PdCl_2$(dppf) (0.05 equiv) was added to the reaction mixture, which was degassed for a further 5 minutes. The reaction mixture was heated to 70°C for 2 hours under nitrogen then heated to 120°C for 16 hours. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was further extracted with EtOAc and the combined organic phases dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and hexane was added. The

resulting suspension was filtered and the collected brown powder was dried and used without further purification.

5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one: (94 % yield, 76 % purity, main impurity being the boronic acid 13 %) m/z (LC-MS, ESP): 260.4 $[2M+H]^+$ R/T = 3.51 min

Procedures for the preparation of Examples 1a to 1du



R^4 = (S)-3-methyl-morpholine
R^2 = (S)-3-methyl-morpholine or cis-dimethylmorpholine or 2-Ethyl-piperidine or morpholine or thiomorpholine or 4-methylpiperazine
R^7 = aryl or heteroaryl

Procedures for the Suzuki coupling:

The synthesis of the appropriate chloro-substrate has been described in the present document as intermediates. The appropriate pinacolate boron ester or boronic acids were prepared according to synthesis described in the present document (as intermediates) or commercially available, typically from the following suppliers:

Sigma-Aldrich, Lancaster, Frontier Scientific, Boron Molecular, Interchim, Asymchem, Combi-blocks, Apollo Scientific, Fluorochem, ABCR, Digital Speciality Chemicals.

Conditions A:

The appropriate chloro-substrate (1 equiv) was dissolved in a toluene/ethanol (1:1) solution (0.02 M). Sodium carbonate (2 equiv) and the appropriate pinacolate boron ester or boronic acid (1 equiv) were then added followed by tetrakis(triphenylphosphine) palladium^0 (0.1 equiv). The reaction vessel was sealed and the mixture exposed to microwave radiation (140 °C, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions B:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.4 equiv), the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in *n*-butanol (0.03 M of chloro-substrate) was stirred at 120 °C for 2 hours. Upon completion the samples were filtered through a silica cartridge, washed through with CH_2Cl_2 and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions C:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.4 equiv), and the appropriate pinacolate boron ester or boronic acid (1.1 equiv) in acetonitrile/water (1:1) (0.041 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (150 °C, medium absorption setting) for 30 minutes under nitrogen atmosphere. Upon completion the samples were filtered through a silica cartridge, washed with CH_2Cl_2 and methanol and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions D:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (1.2 equiv), and the appropriate pinacolate boron ester or boronic acid (1.2 equiv) in acetonitrile/water (1:1) (0.083 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 25 minutes under nitrogen atmosphere. Upon completion the sample was purified by column chromatography on silica gel using a gradient MeOH/ CH_2Cl_2 to afford the desired product which was recrystallised from diethyl ether.

Conditions E:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.4 equiv), and the appropriate pinacolate boron ester or boronic acid (1.3 equiv) in acetonitrile/water (1:1) (0.041 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and heated at 95 °C for 16 hours. Upon completion the reaction mixture was partitioned between aqueous HCl and CH_2Cl_2 and washed with aqueous HCl. Combined aqueous phase were extracted with CH_2Cl_2 (2 x), neutralised with aqueous NaOH (2N) to give a cloudy solution that was extracted with CH_2Cl_2. Combined organic

phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 4 % MeOH in CH_2Cl_2 to give the desired product.

Conditions F:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.0 equiv), and the appropriate pinacolate boron ester or boronic acid (1.5 equiv) in acetonitrile/water (1:1) (0.028 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and heated at 120 °C for 2 hours under nitrogen atmosphere. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 4 % MeOH in CH_2Cl_2 to give the desired product which was recrystallised from hexane/diethyl ether.

Conditions G:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), and the appropriate pinacolate boron ester or boronic acid (1.05 equiv) in acetonitrile/water (1:1) (0.068 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and heated at 100 °C for 5 hours under nitrogen atmosphere. Upon completion the reaction mixture was partitioned between brine and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 4 % MeOH in CH_2Cl_2 to give the desired products which were recrystallised from hexane/ CH_2Cl_2.

Conditions H:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 100 °C for 8 hours. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Conditions I:

Conditions I were similar to conditions H apart form the heating method: 100 °C for 2 hours.

Conditions J:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (1.2 equiv), the appropriate pinacolate boron ester or boronic acid (1.2 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.03 M of chloro-substrate) was stirred at 100 °C for 2 hours. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Conditions K:

Conditions K were similar to conditions G apart form the heating method: 100 °C for 16 hours.

Conditions L:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), and the appropriate pinacolate boron ester or boronic acid (1.10 equiv) in acetonitrile/water (1:1) (0.041 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (100 °C, medium absorption setting) for 90 minutes. Upon completion the reaction mixture was partly concentrated. The residue was partitioned between water and ethyl acetate and extracted with ethyl acetate and *n*-butanol. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 30 to 10 % hexane in ethyl acetate to give the desired product which was recrystallised from hexane/ CH_2Cl_2.

Conditions M:

A mixture of the appropriate chloro-substrate (1 equiv), cesium fluoride (3.0 equiv), the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.09 M of chloro-substrate) was stirred at 115 °C for 48 hours. Upon completion the sample was concentrated *in vacuo* to half original volume. The residue was partitioned between water and CH_2Cl_2. Organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 100 % ethyl acetate in hexane to give the desired product.

Conditions N:

A mixture of the appropriate chloro-substrate (1 equiv), tripotassium phosphate (1.5 equiv), the appropriate pinacolate boron ester or boronic acid (1.05 equiv) and bis(tri-t-butylphosphine) palladium (0.05 equiv) was suspended in dioxane (0.16 M of chloro-substrate). The reaction vessel was sealed and exposed to microwave radiation (170 °C, medium absorption setting) for 45 minutes. Upon completion the sample was concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 40 to 100 % ethyl acetate in hexane to give the desired product.

Conditions O:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in *n*-butanol (0.068 M of chloro-substrate) was stirred at 95 °C for 15 minutes. Upon completion, the residue was partitioned between ethyl acetate and brine. Organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 30 to 100 % ethyl acetate in hexane to give the desired product which was recrystallised from ethyl acetate/hexane.

Conditions P:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.0 equiv), and the appropriate pinacolate boron ester or boronic acid (2.0 equiv) in acetonitrile/water (1:1) (0.041 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (120 °C, medium absorption setting) for 10 minutes under nitrogen atmosphere. Upon completion the samples were filtered through a silica cartridge, washed through with CH_2Cl_2 and the concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Conditions Q:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), the appropriate pinacolate boron ester or boronic acid (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) were dissolved in *n*-butanol (0.056 M of chloro-substrate). The reaction vessel was sealed and exposed to microwave radiation (150

°C, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, washed with CH_2Cl_2 and methanol and then concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with ethyl acetate and then 5 % MeOH in CH_2Cl_2 to give the desired product.

Conditions R:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), the appropriate pinacolate boron ester or boronic acid (1.2 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.05 M of chloro-substrate) was stirred at 115 °C for 1.5 hours. Upon completion the crude reaction was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 5 to 20 % MeOH in CH_2Cl_2 to give the desired product.

Conditions S:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (10.0 equiv), the appropriate pinacolate boron ester or boronic acid (1.2 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 100 °C for 2 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product which was recrystallised from hexane/ CH_2Cl_2.

Conditions T:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.0 equiv), the appropriate pinacolate boron ester or boronic acid (2.0 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) was dissolved in acetonitrile/water (0.02 M of chloro-substrate). The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 30 minutes. Upon completion the sample was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product.

Conditions U:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), the appropriate pinacolate boron ester or boronic acid (1.0 equiv) and

tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 110 °C for 8 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 2 % MeOH in CH_2Cl_2 to give the desired product which was recrystallised from hexane/ CH_2Cl_2.

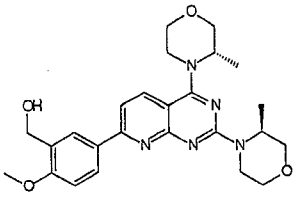
Conditions V:

A mixture of the appropriate chloro-substrate (1 equiv), cesium fluoride (3.0 equiv), the appropriate pinacolate boron ester or boronic acid (1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 100 °C for 16 hours. The reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product which was recrystallised from hexane/CH_2Cl_2.

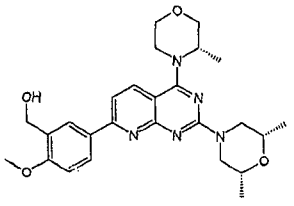
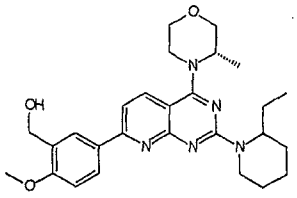
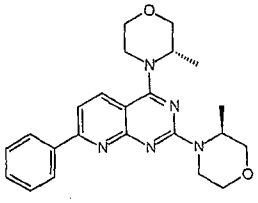
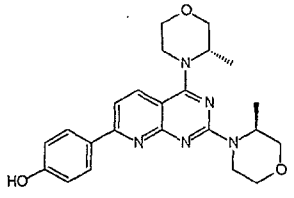
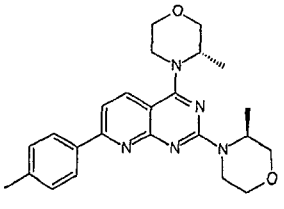
Conditions W:

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), the appropriate pinacolate boron ester or boronic acid (1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) was dissolved in acetonitrile/water (0.04 M of chloro-substrate). The reaction vessel was sealed and exposed to microwave radiation (110 °C, medium absorption setting) for 10 minutes. The crude residue was purified by column chromatography on silica gel eluting with 0 to 2 % MeOH in TBME to give the desired product.

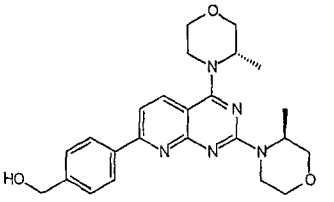
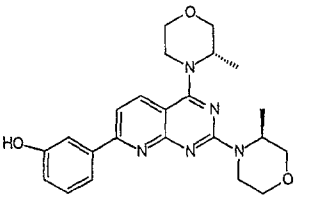
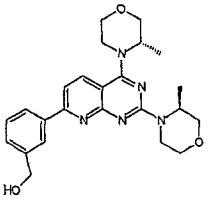
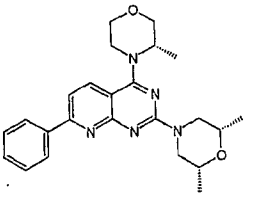
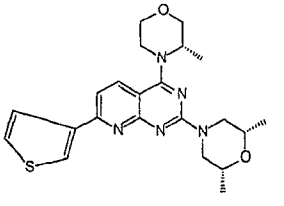
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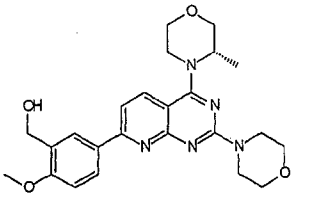
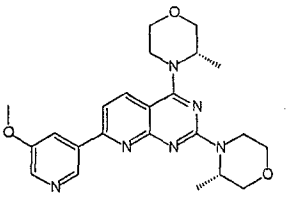
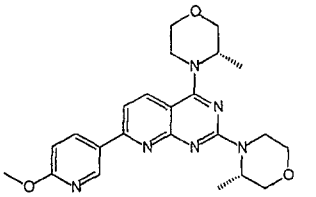
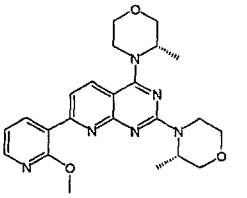
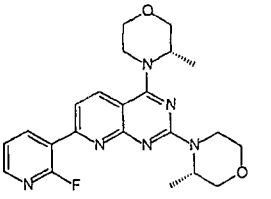
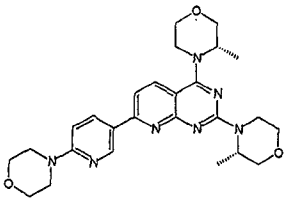
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1a	96	7.66	466.6	A	

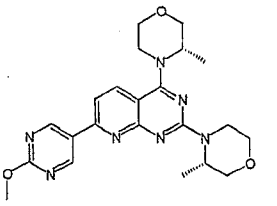
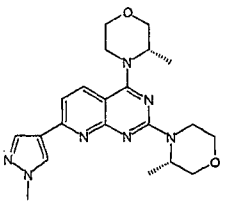
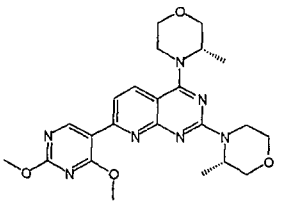
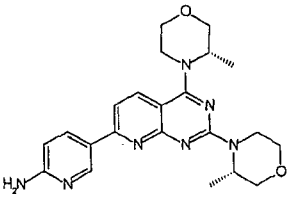
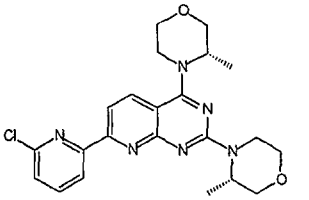
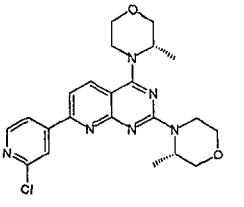
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	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1b	99	4.31	480.4	A	
1c	98	4.67	478.4	A	
1d	99	4.13	406.2	A	
1e	99	3.94	422.3	A	
1f	99	4.32	420.3	A	

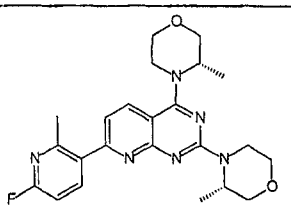
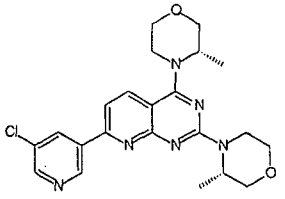
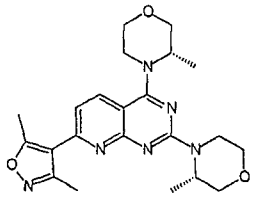
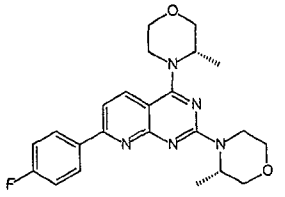
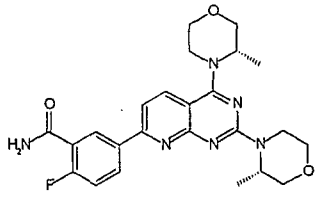
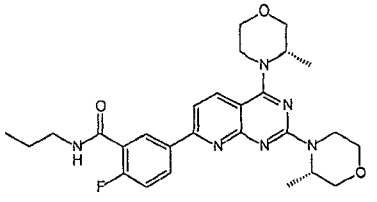
142

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1g	99	3.83	436.3	A	
1h	89	3.99	422.2	A	
1i	96	3.85	436.3	A	
1j	99	4.5	420.3	A	
1k	98	4.49	426.3	A	

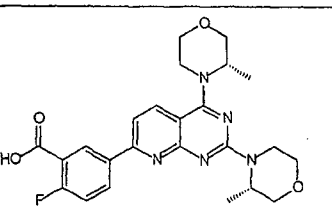
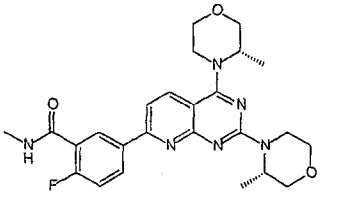
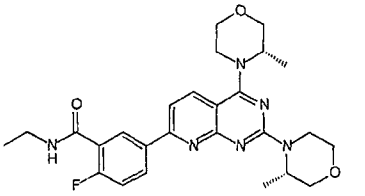
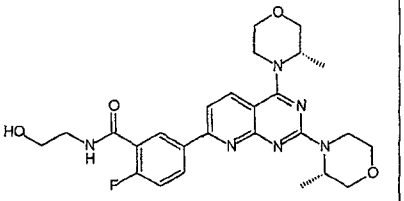
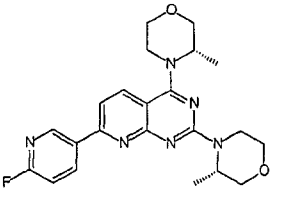
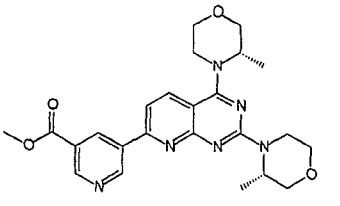
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1l	100	3.91	452.3	A	
1m	99	3.99	437.4	B	
1n	99	4.2	437.4	B	
1o	99	4.23	437.4	B	
1p	99	4.16	425.4	B	
1q	98	4.1	492.5	B	

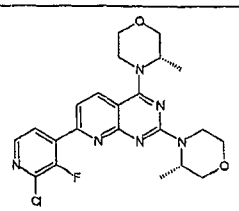
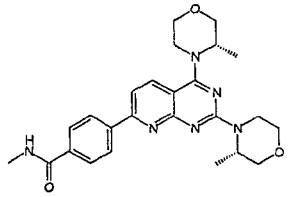
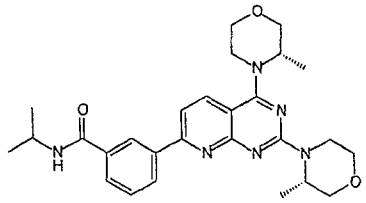
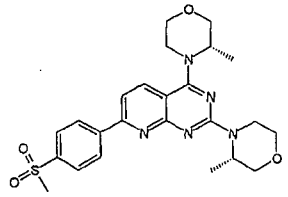
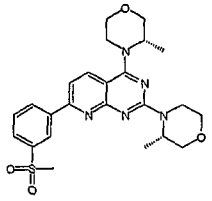
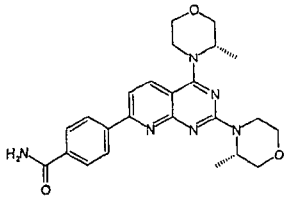
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1r	98	1.09	438.4	B	
1s	99	3.98	410.4	B	
1t	100	4.04	468.5	B	
1u	100	4.95	422.3	B	
1v	98	4.32	441.4	B	
1w	91	6.46	441.3	B	

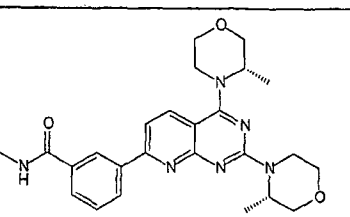
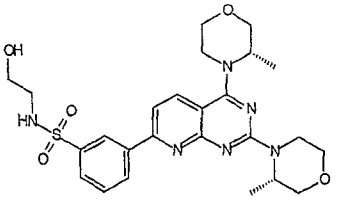
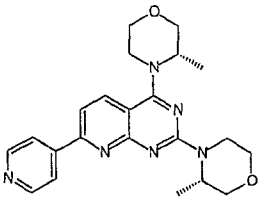
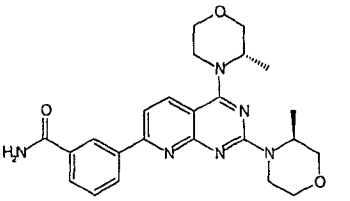
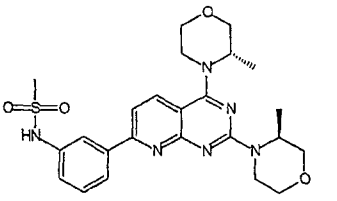
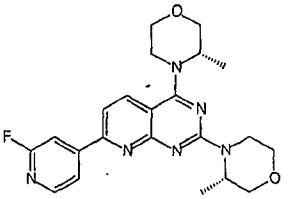
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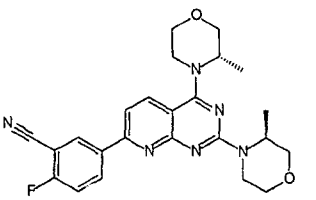
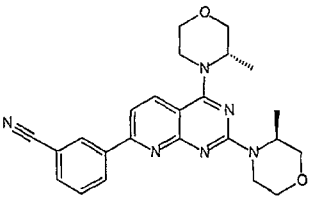
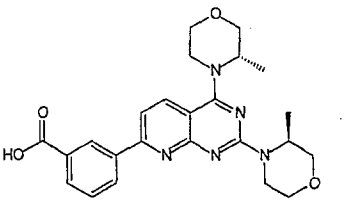
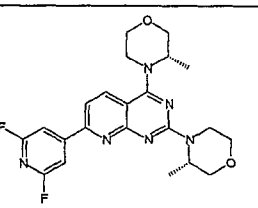
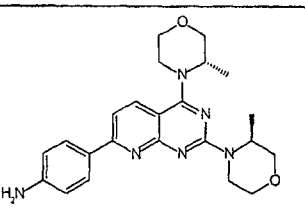
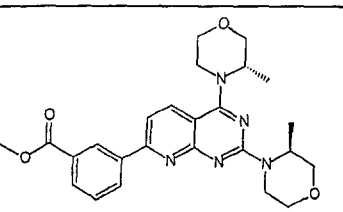
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1x	98	7.16	439.3	B	
1y	97	6.54	441.4	B	
1z	95	5.92	425.5	B	
1aa	100	8.28	424.4	B	
1ab	99	6.67	467.4	B	
1ac	100	8.01	509.5	B	

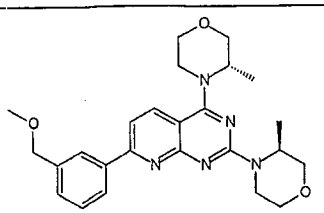
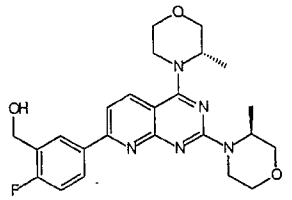
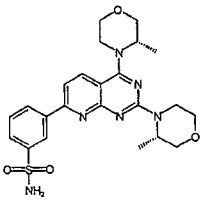
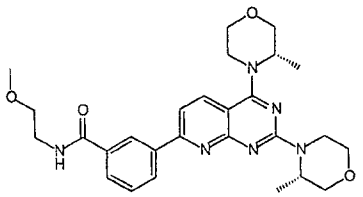
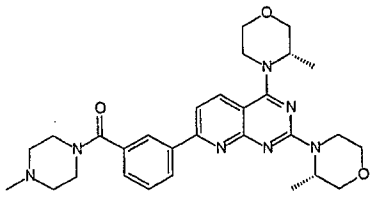
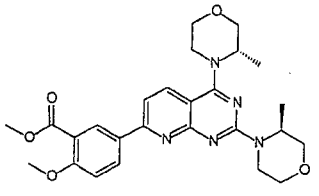
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	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1ad	100	7.23	468.4	B	
1ae	100	6.99	481.4	B	
1af	99	7.55	495.4	B	
1ag	100	6.51	511.4	B	
1ah	99	6.95	425.2	B	
1ai	89	7.52	465.2	B	

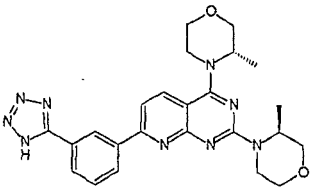
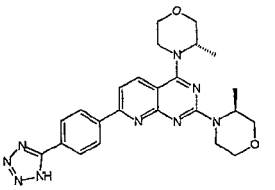
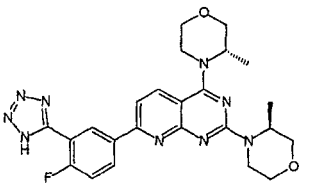
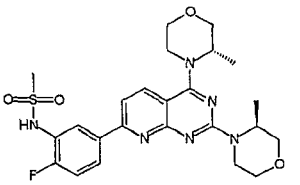
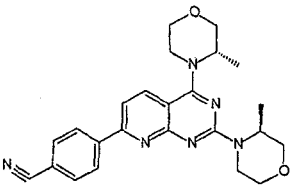
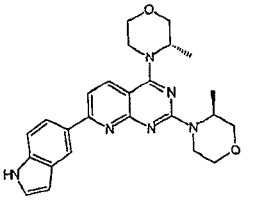
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1aj	80	4.5	459.3	B	
1ak	97	6.79	463.2	C	
1al	99	4.07	491.4	C	
1am	99	3.94	484.3	C	
1an	99	3.95	484.3	C	
1ao	97	3.75	449.3	C	

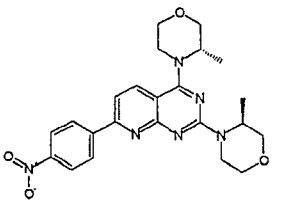
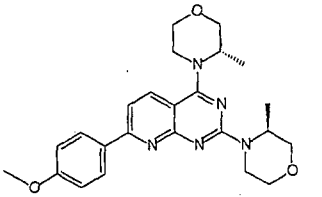
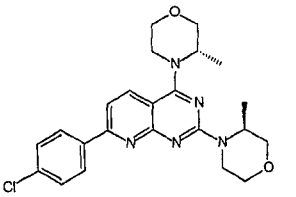
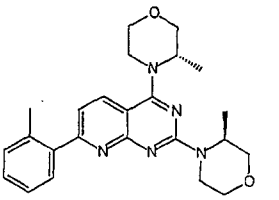
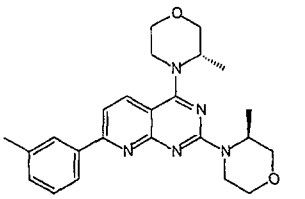
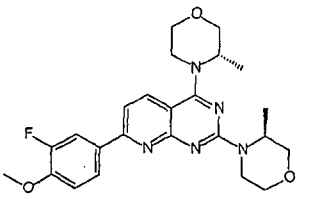
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1ap	99	3.86	463.3	C	
1aq	99	3.87	529.4	D	
1ar	99	3.41	407.3	E	
1as	98	6.59	449.4	F	
1at	97	4.05	499.3	G	
1au	96	7	425.3	G	

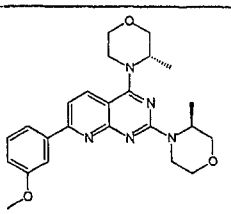
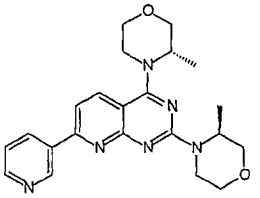
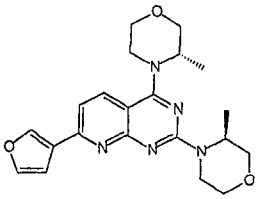
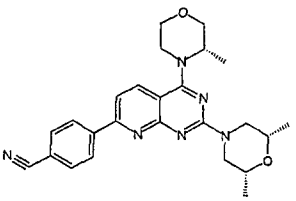
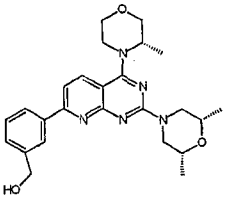
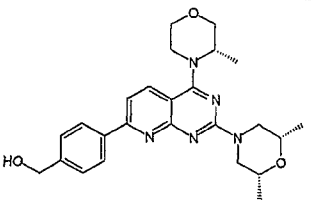
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1av	99	4.28	449.4	H	
1aw	97	4.33	431.3	I	
1ax	99	3.99	450.5	J	
1ay	98	4.19	443.3	K	
1az	100	8.94	421.2	L	
1ba	100	4.28	464.5	M	

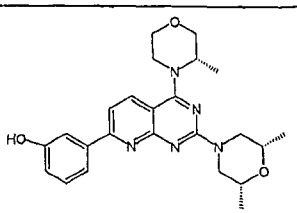
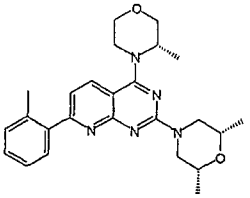
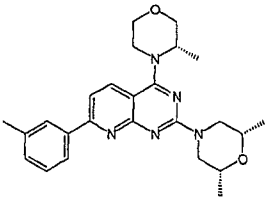
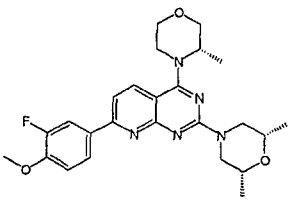
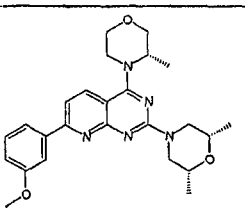
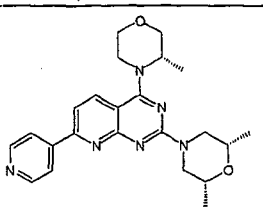
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1bb	98	8.16	450.3	N	
1bc	99	3.99	454.4	O	
1bd	90	8.4	485.3	P	
1be	99	3.91	507.4	C	
1bf	99	3.39	532.4	C	
1bg	97	4.19	494.4	M	

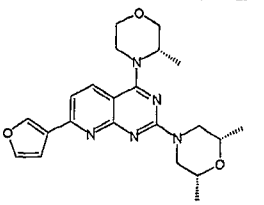
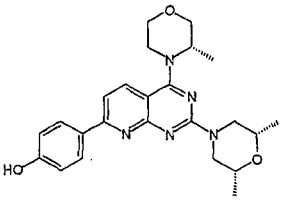
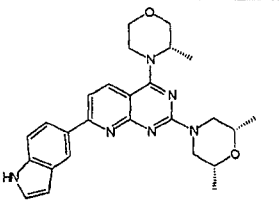
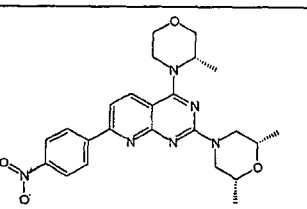
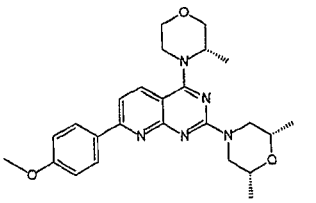
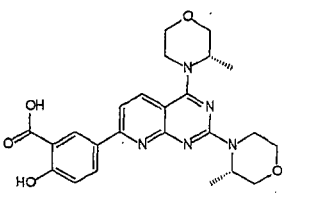
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	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1bh	98	4.15	474.3	Q	
1bi	96	4.13	474.4	R	
1bj	94	3.99	492.3	R	
1bk	98	4.04	517.4	S	
1bl	98	4.13	431.2	B	
1bm	98	4.27	445.3	B	

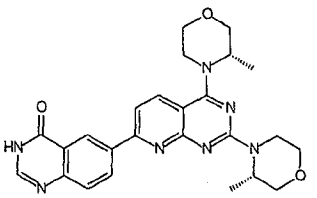
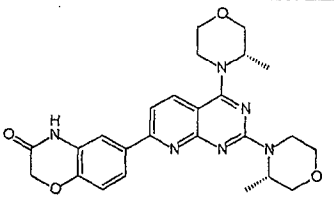
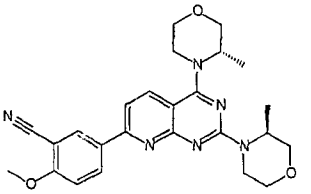
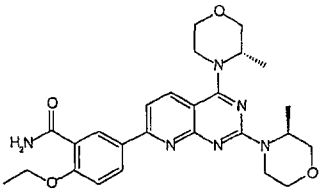
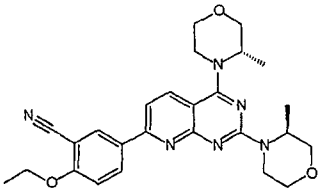
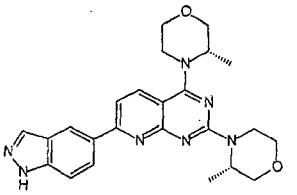
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1bn	97	4.27	451.2	B	
1bo	99	4.21	436.3	B	
1bp	99	4.40	440.2	B	
1bq	87	4.22	420.3	B	
1br	93	4.40	420.3	B	
1bs	94	4.30	454.2	B	

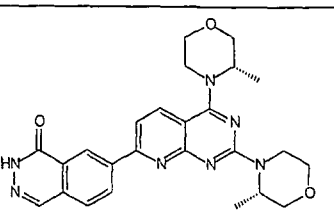
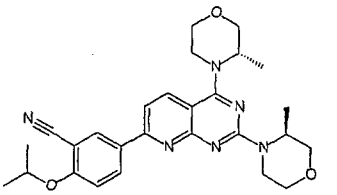
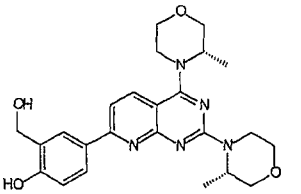
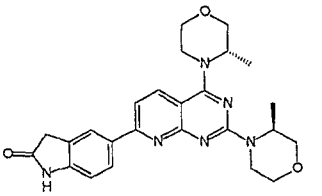
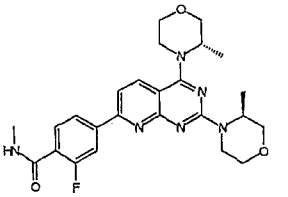
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1bt	95	4.32	436.3	B	
1bu	99	3.53	407.3	B	
1bv	99	3.94	396.3	B	
1bw	85	4.49	445.3	B	
1bx	99	4.59	450.3	B	
1by	98	4.20	450.3	B	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1bz	87	4.30	436.3	B	
1ca	99	4.62	434.4	B	
1cb	99	4.74	434.4	B	
1cc	92	4.67	463.0	B	
1cd	99	4.63	450.4	B	
1ce	85	3.71	421.3	B	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1cf	98	4.35	410.3	B	
1cg	97	4.34	436.3	B	
1ch	98	4.48	459.3	B	
1ci	87	4.49	465.3	B	
1cj	100	4.50	450.3	B	
1ck	99	4.14	466.5	T	

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	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1cl	100	3.8	474.4	P	
1cm	99	4.01	477.3	T	
1cn	99	4.73	474.3	E	
1co	99	4.08	477.3	D	
1cp	87	4.48	461.3	D	
1cq	84	7.44	493.4	L	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1cr	97	3.85	475.3	T	
1cs	100	4.63	450.4	D	
1ct	99		464.3	S	
1cu	100	3.89	436.2	B	
1cv	100	3.89		J	

Note:

The following examples were synthesized from the corresponding boronic acids: 1aa, 1ab, 1ac, 1ad, 1ae, 1af, 1ag, 1ah, 1ai, 1aj, 1ak, 1al, 1am, 1an, 1ao, 1ap, 1aq, 1as, 1at, 1au, 1av, 1aw, 1ax, 1ay, 1az, 1ba, 1bb, 1bd, 1be, 1bk, 1bl, 1bm, 1bn, 1bo, 1bp, 1bq, 1br, 1bs, 1bt, 1bu,

1bv, 1bw, 1bx, 1by, 1bz, 1ca, 1cb, 1cc, 1cd, 1cf, 1cg, 1ch, 1ci, 1cj, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1n, 1o, 1p, 1r, 1t, 1w, 1x, 1y 1cn, 1co, 1cp, 1cs, 1cv and 1z.

The following Examples were synthesized from the corresponding pinacolate boron esters: 1a-c, 1ck, 1cl, 1cm, 1cq, 1cr, 1ct, 1cu, 1ar, 1bf, 1ce, 1m, 1q, 1s, 1u and 1v.

NMR data for Example 1n

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.88 (ArH, d, J = 2.20 Hz, 1H), 8.55 (ArH, dd, J = 8.70, 2.45 Hz, 1H), 8.04 (ArH, d, J = 8.43 Hz, 1H), 7.42 (ArH, d, J = 8.44 Hz, 1H), 6.88 (ArH, d, J = 8.70 Hz, 1H), 5.01-4.90 (CH, m, 1H), 4.65 (CH, d, J = 13.12 Hz, 1H), 4.40 (CH, d, J = 6.68 Hz, 1H), 4.04 (OCH_3 + CH_2, s, 5H), 3.96-3.69 (CH_2, m, 7H), 3.60 (CH, dt, J = 11.86, 11.60, 2.67 Hz, 1H), 3.40 (CH, dt, J = 13.01, 12.73, 3.60 Hz, 1H), 1.50 (CH_3, d, J = 6.78 Hz, 3H), 1.39 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.41, 165.29, 162.98, 160.10, 160.01, 146.58, 138.51, 134.81, 128.05, 112.42, 110.84, 104.75, 71.29, 70.92, 67.26, 66.92, 53.75, 52.87, 46.94, 44.43, 39.33, 14.73 and 14.36.

NMR data for Example 1u

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.80 (ArH, d, J = 1.91 Hz, 1H), 8.39 (ArH, dd, J = 8.66, 2.39 Hz, 1H), 7.96 (ArH, d, J = 8.48 Hz, 1H), 7.35 (ArH, d, J = 8.49 Hz, 1H), 6.59 (ArH, d, J = 8.66 Hz, 1H), 4.91 (CH, dd, J = 4.15, 1.62 Hz, 1H), 4.78 (NH_2, s, 2H), 4.67-4.55 (CH, m, 1H), 4.34 (CH, d, J = 6.88 Hz, 1H), 4.04-3.91 (CH_2, m, 2H), 3.90-3.64 (CH_2, m, 7H), 3.62-3.49 (CH_2, m, 1H), 3.44-3.29 (CH_2, m, 1H), 1.45 (CH_3, d, J = 6.77 Hz, 3H), 1.34 (CH_3, d, J = 6.82 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.54, 163.10, 160.45, 160.13, 159.45, 148.10, 137.82, 134.76, 125.17, 112.16, 108.45, 104.59, 71.44, 71.06, 67.41, 67.07, 52.98, 47.05, 44.56, 36.46, 14.84 and 14.75.

NMR data for Example 1ag

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.59 (ArH, dd, J = 7.33, 2.43 Hz, 1H), 8.40 (ArH, ddd, J = 8.53, 5.03, 2.47 Hz, 1H), 7.97 (ArH, d, J = 8.42 Hz, 1H), 7.42 (ArH, d, J = 8.46 Hz, 1H), 7.20-7.10 (ArH, m, 1H), 4.84 (CH, dd, J = 3.67, 2.96 Hz, 1H), 4.53 (CH, d, J = 12.77 Hz, 1H), 4.33 (CH_2, d, J = 6.83 Hz, 1H), 3.99-3.89 (CH_2, m, 2H), 3.86-3.77 (CH_2, m, 4H), 3.75-

3.65 (CH_2, m, 5H), 3.67-3.32 (CH_2, m, 3H), 3.57-3.45 (CH_2, m, 1H), 3.36-3.26 (CH_2, m, 1H), 1.42 (CH_3, d, J = 6.78 Hz, 3H), 1.30 (CH_3, d, J = 6.82 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.26, 164.26, 162.74, 160.29, 159.93, 135.52, 135.11, 133.47, 133.34, 130.89, 116.84, 116.51, 113.11, 105.11, 71.26, 70.91, 67.11, 66.91, 62.20, 52.79, 47.02, 44.46, 43.02, 39.36, 14.77 and 14.37.

NMR data for Example 1aq

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.61 (ArH, t, J = 1.46, 1.46 Hz, 1H), 8.33 (ArH, d, J = 7.84 Hz, 1H), 8.06 (ArH, d, J = 8.37 Hz, 1H), 7.90 (ArH, s, 1H), 7.62 (ArH, d, J = 7.84 Hz, 1H), 7.44 (ArH, d, J = 8.38 Hz, 1H), 5.30 (CH_2, s, 1H), 4.97-4.84 (CH_2, m, 1H), 4.64-4.52 (CH_2, m, 1H), 4.45-4.34 (CH_2, m, 1H), 4.06-3.94 (CH_2, m, 2H), 3.93-3.64 (CH_2, m, 8H), 3.61-3.51 (CH_2, m, 1H), 3.45-3.30 (CH_2, m, 1H), 3.19 (CH_2, d, J = 4.84 Hz, 2H), 1.49 (CH_3, d, J = 6.78 Hz, 3H), 1.36 (CH_3, d, J = 6.82 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 160.22, 140.70, 140.01, 134.25, 131.82, 129.24, 128.02, 126.34, 113.12, 105.41, 104.65, 71.23, 70.87, 66.88, 61.03, 52.85, 47.04, 45.34, 44.42, 39.35, 14.78 and 14.38.

NMR data for Example 1ar

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.81-8.73 (ArH, m, 2H), 8.14-7.99 (ArH, m, 3H), 7.48 (ArH, d, J = 8.35 Hz, 1H), 5.02-4.89 (CH, m, 1H), 4.69-4.59 (CH_2, m, 1H), 4.41 (CH, d, J = 6.84 Hz, 1H), 4.08-3.96 (CH_2, m, 2H), 3.82 (H2, dddd, J = 19.69, 14.05, 6.26, 3.77 Hz, 7H), 3.65-3.53 (CH_2, m, 1H), 3.48-3.31 (CH_2, m, 1H), 1.51 (CH_3, d, J = 6.78 Hz, 3H), 1.38 (CH_3, d, J = 6.83 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.29, 162.96, 160.03, 159.82, 150.36, 145.80, 135.20, 121.83, 113.02, 105.93, 71.24, 70.87, 67.21, 66.87, 52.88, 46.99, 44.45, 39.35, 14.76 and 14.41.

NMR Data for Example 1as

^{1}H NMR (300 MHz,$CDCl_3$) δ ppm 8.67 (ArH, t, J = 1.54, 1.54 Hz, 1H), 8.29 (ArH, dd, J = 6.60, 1.28 Hz, 1H), 8.07 (ArH, d, J = 8.41 Hz, 1H), 8.03-7.98 (ArH, m, 2H), 7.62-7.49 (ArH, m, 2H), 4.98-4.89 (CH, m, br, 1H), 4.67-4.59 (CH, m, br, 1H), 4.41 (CH, d, J = 6.78 Hz, 1H),

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4.05-3.66 (CH_2, m, 10H), 3.64-3.34 (CH_2, m, 3H), 1.75 (s, 1.5H), 1.50 (CH_3, d, J = 6.78 Hz, 3H), 1.38 (CH_3, d, J = 6.82 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.86, 165.34, 162.90, 161.21, 160.01, 138 97, 135.00, 133.74, 131.09, 129.23, 128.98, 126.52, 113.20, 105.20, 100.00, 71.23, 70.89, 67.22, 66.90, 52.82, 46.97, 44.45, 39.34, 14.75 and 14.36

NMR data for Example 1at

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.06 (ArH, d, J = 2.05 Hz, 1H), 7.98 (ArH, d, J = 8.41 Hz, 1H), 7.86-7.79 (ArH, m, 1H), 7.46-7.33 (ArH, m, 3H), 7.23 (NH, s, 1H), 4.83 (CH, dd, J = 3.58, 2.50 Hz, 1H), 4.56-4.46 (CH, m, 1H), 4.32 (CH, d, J = 6.74 Hz, 1H), 3.93-3.89 (CH_2, m, 2H), 3.88-3.77 (CH_2, m, 2H), 3.76-3.58 (CH_2, m, 5H), 3.49 (CH_2, dt, J = 11.76, 11.38, 2.76 Hz, 1H), 3.35-3.20 (CH_2, m, 1H), 2.89 (SCH_3, s, 3H), 1.42 (CH_3, d, J = 6.78 Hz, 3H), 1.27 (CH_3, d, J = 5.25, Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.32, 162.87, 161.30, 159.96, 140.41, 137.57, 135.01, 129.92, 124.55, 122.25, 120.57, 113.32, 105.24, 71.25, 70.90, 67.22, 66.91, 52.86, 46.99, 44.42, 39.40, 31.60, 22.66, 14.77 and 14.12.

NMR data for Example 1ax

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.88 (ArH, t, J = 1.52, 1.52 Hz, 1H), 8.32-8.25 (ArH, m, 1H), 8.13-8.06 (ArH, m, 1H), 7.99 (ArH, d, J = 8.42 Hz, 1H), 7.53-7.39 (ArH, m, 2H), 4.90-4.80 (CH, m, 1H), 4.58-4.48 (CH, m, 1H), 4.33 (CH, d, J = 6.90 Hz, 1H), 3.95-3.65 (CH_2, + OH m, 8H), 3.64 (CH_2, d, J = 2.85 Hz, 2H), 3.56-3.45 (CH, m, 1H), 3.31 (CH, d, J = 3.67 Hz, 1H), 1.42 (CH_3, d, J = 6.79 Hz, 3H), 1.29 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.20, 165.22, 161.32, 159.85, 139.91, 135.01, 131.39, 129.70, 128.71, 113.31, 70.90, 67.10, 52.80, 47.07, 44.42, 39.36, 14.77 and 14.37.

NMR data for Example 1az

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.04-7.95 (ArH, m, 2H), 7.87 (ArH, d, J = 8.54 Hz, 1H), 7.32 (ArH, d, J = 8.55 Hz, 1H), 6.71-6.64 (ArH, m, 2H), 4.92-4.81 (CH, m, 1H), 4.57 (CH, d, br, 1H), 4.29 (CH_2, d, J = 7.10 Hz, 1H), 3.91 (CH_2, m, 2H), 3.82-3.58 (CH_2 + NH_2, m, 9H), 3.48 (CH_2, dd, J = 11.36, 2.76 Hz, 1H), 3.33 (CH_2, dd, J = 13.48, 3.61 Hz, 1H), 1.39 (CH_3, d, J = 6.78 Hz, 3H), 1.28 (CH_3, d, J = 6.82 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.28, 162.18, 148.68, 135.36, 129.54, 119.67, 114.75, 112.63, 104.43, 104.00, 71.29, 70.94, 67.27, 67.12, 66.95, 52.78, 44.45, 39.15, 14.74 and 14.37.

NMR data for Example 1ba

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.69 (ArH, t, J = 1.58, 1.58 Hz, 1H), 8.44-8.33 (ArH, m, 1H), 8.11-8.03 (ArH, m, 1H), 7.99 (ArH, d, J = 8.42 Hz, 1H), 7.57-7.38 (ArH, m, 2H), 4.87 (CH_2, dd, J = 4.84, 0.43 Hz, 1H), 4.57 (CH, d, J = 12.80 Hz, 1H), 4.31 (CH_2, t, J = 6.72, 6.72 Hz, 1H), 3.94 (CH_2, dd, J = 11.15, 3.26 Hz, 2H), 3.90 (OCH_3, d, J = 6.23 Hz, 3H), 3.83 – 3.62 (CH_2, m, 7H), 3.57-3.45 (CH_2, m, 1H), 3.39-3.24 (CH_2, m, 1H), 1.42 (CH_3, d, J = 6.78 Hz, 3H), 1.30 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.92, 165.41, 162.93, 161.43, 161.01, 139.13, 134.91, 132.51, 130.87, 130.57, 128.87, 113.26, 105.16, 71.29, 70.91, 67.25, 66.91, 52.86, 52.18, 46.96, 44.45, 14.77 and 14.37.

NMR data for Example 1bc

^{1}H NMR (300 MHz, DMSO) δ ppm 8.37 (ArH, dd, J = 7.40, 2.26 Hz, 1H), 8.20 (ArH, d, J = 8.50 Hz, 1H), 8.14-8.05 (ArH, m, 1H), 7.62 (ArH, d, J = 8.51 Hz, 1H), 7.29 (ArH, dd, J = 9.77, 8.71 Hz, 1H), 5.42 (CH, t, J = 5.76, 5.76 Hz, 1H), 4.77 (CH, dd, J = 6.57, 1.98 Hz, 1H), 4.65 (CH_2OH, d, J = 5.67 Hz, 2H), 4.51-4.37 (CH_2, m, 2H), 3.98-3.83 (CH_2, m, 3H), 3.80-3.70 (CH_2, m, 2H), 3.69-3.56 (CH_2, m, 4H), 3.45 (CH_2, dt, J = 11.86, 11.77, 2.75 Hz, 1H), 3.30- 3.16 (CH_2, m, 3H), 1.38 (CH_3, d, J = 6.75 Hz, 3H), 1.25 (CH_3, d, J = 6.75 Hz, 3H)

^{13}C NMR (75 MHz, DMSO) δ ppm 164.91, 162.60, 160.18, 159.82, 136.10, 134.86, 130.19, 129.99, 128.61, 128.27, 128.15, 115.85, 115.57, 113.00, 104.80, 70.89, 70.66, 66.84, 66.67, 52.29, 46.76, 44.34, 14.84 and 14.34.

NMR data for Example 1bd

^{1}H NMR (300 MHz, DMSO) δ ppm 8.63 (ArH, t, J = 1.49, 1.49 Hz, 1H), 8.26 (ArH, d, J = 7.95 Hz, 1H), 8.17 (ArH, d, J = 8.46 Hz, 1H), 7.91-7.80 (ArH, m, 1H), 7.62 (ArH, dd, J = 14.96, 8.10 Hz, 2H), 7.37 (NH_2, s, 2H), 4.69 (CH, dd, J = 6.21, 1.34 Hz, 1H), 4.35 (CH_2, d, J = 13.74 Hz, 2H), 3.91-3.74 (CH_2, m, 3H), 3.73-3.46 (CH_2, m, 6H), 3.36 (CH_2, dt, J = 11.82,

11.71, 2.49 Hz, 1H), 2.41 (CH_2, td, J = 3.46, 1.69, 1.69 Hz, 1H), 1.30 (CH_3, d, J = 6.74 Hz, 3H), 1.17 (CH_3, d, J = 6.75 Hz, 3H)

^{13}C NMR (75 MHz) δ ppm 164.85, 162.63, 159.86, 159.49, 145.34, 139.35, 136.44, 130.73, 129.98, 127.34, 124.96, 113.18, 105.38, 79.87, 79.43, 78.99, 70.89, 70.67, 66.85, 66.67, 52.29, 46.79, 44.37, 14.88 and 14.41.

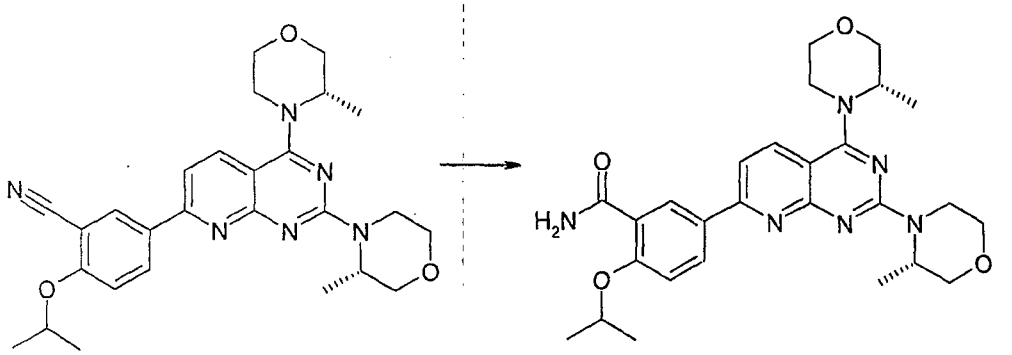
NMR data for Example 1bk

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (ArH, dd, J = 7.62, 2.22 Hz, 1H), 8.12 (ArH, ddd, J = 8.54, 5.03, 2.25 Hz, 1H), 8.01 (ArH, d, J = 8.41 Hz, 1H), 7.38 (ArH, d, J = 8.43 Hz, 1H), 7.24-7.19 (ArH, m, 1H), 6.83 (NH, s, br, 1H), 4.98-4.85 (CH, m, 1H), 4.67-4.55 (CH, m, 1H), 4.36 (CH_2, d, J = 6.95 Hz, 1H), 4.06-3.93 (CH_2, m, 2H), 3.91-3.65 (CH_2, m, 1H), 3.53 (CH_2, dd, J = 11.40, 2.69 Hz, 1H), 3.44-3.28 (CH_2, m, 1H), 3.07 (SCH3, s, 3H), 1.47 (CH_3, d, J = 6.77 Hz, 3H), 1.34 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.45, 162.93, 160.61, 160.12, 157.28, 153.99, 136.32, 135.15, 123.51, 116.31, 116.05, 113.26, 105.18, 71.39, 71.01, 67.36, 67.01, 53.00, 47.07, 44.51, 39.44, 31.71, 22.77 14.86, and 14.95.

Compounds were also synthesized according to the following procedures:

Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-isopropoxy-benzamide (Example 1cw)

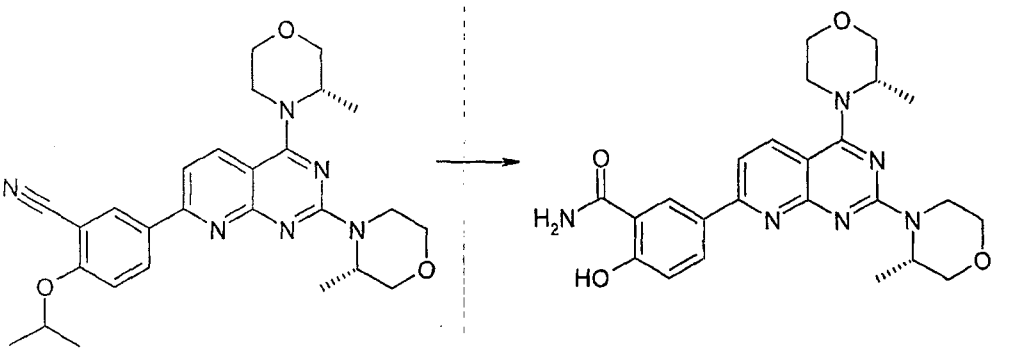


5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-isopropoxy-benzonitrile (1 equiv) was added portionwise to concentrated H_2SO_4 (0.1 M substrate in acid). The reaction was heated to 90 °C and maintained at this temperature until all starting material had dissolved to give a bright red solution. The mixture was cooled and water (2 reaction volumes) added dropwise, then the solution was neutralized by careful addition of

solid NaOH until pH 4-5 was attained. The mixture was cooled and neutralised by addition of 2N NaOH and then extracted using EtOAc (2 X 10 reaction volumes). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude residue which was purified by flash chromatography (SiO_2) using MeOH/DCM – 0:100 going to 5:95 as eluent to give the desire product as a yellow powder.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-isopropoxy-benzamide: (53 % yield, 100 % purity) m/z (LC-MS,ESP):507.5 $[M+H]^+$, R/T = 3.01 min)

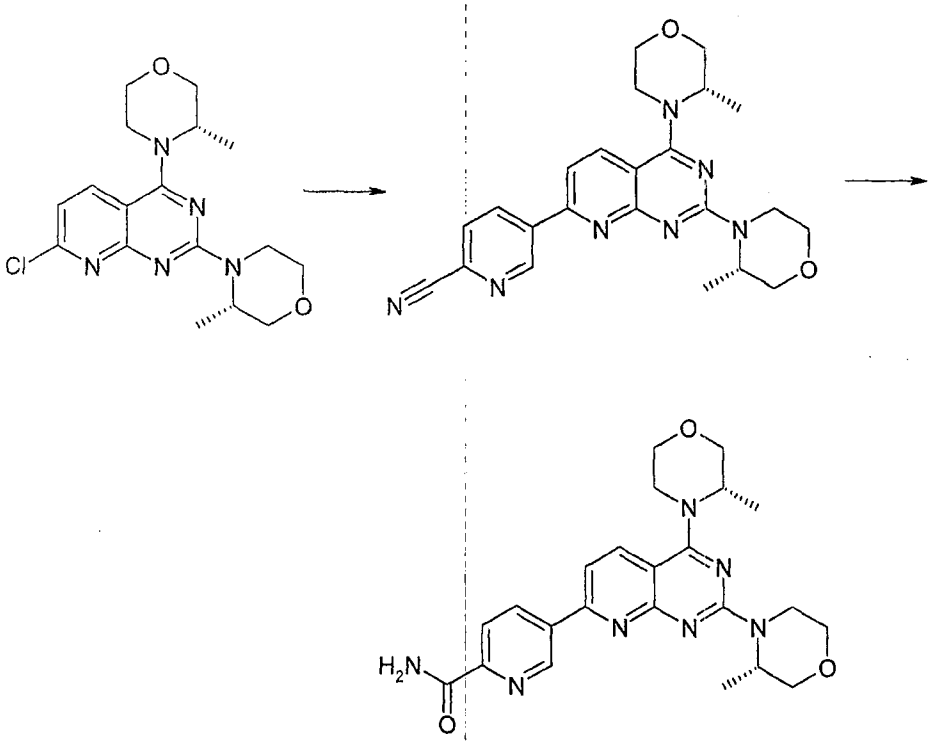
Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-hydroxy-benzamide (Example 1cx)



5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-isopropoxy-benzonitrile (1 equiv) was added portionwise to concentrated H_2SO_4 (0.1 M substrate in acid). The reaction was heated to 90 °C and maintained at this temperature until all starting material had dissolved to give a bright red solution. The mixture was cooled and water (2 reaction volumes) added dropwise, then the solution was neutralized by careful addition of solid NaOH until pH 4-5 was attained. The mixture was cooled and neutralised by addition of 2N NaOH and then extracted using EtOAc (2 X 10 reaction volumes). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude residue which was purified by flash chromatography (SiO_2) using MeOH/DCM – 0:100 going to 5:95 as eluent to give the desire product as a yellow powder.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-hydroxy-benzamide: (44 % yield, 100 % purity) m/z (LC-MS,ESP):465.4 $[M+H]^+$, R/T = 2.70 min)

Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridine-2-carboxylic acid amide (Example 1cy)



Synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridine-2-carbonitrile was carried out as follows:-

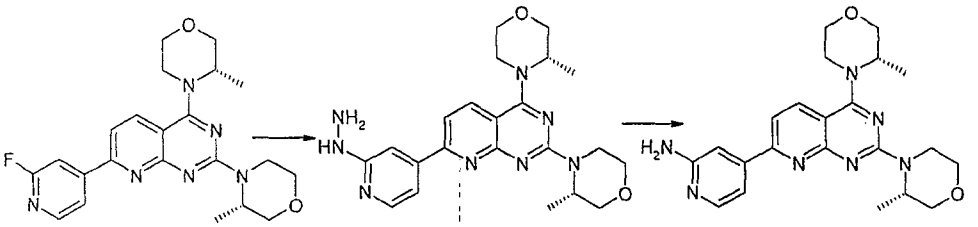
To the appropriate chloro-substrate (1 equiv), potassium carbonate (3 equiv) and the appropriate boronic acid or pinacolate boron ester (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) which were dissolved in N,N-dimethylacetamide (0.17 M of chloro-substrate). The mixture was degassed with nitrogen, sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 15 minutes. The mixture was concentrated *in vacuo* and then suspended in t-butylmethyl ether, filtered and dried to give the desired product.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridine-2-carbonitrile: (84 % yield, 93 % purity) m/z (LC-MS,ESP):191.3 $[M+H]^+$, R/T = 2.29 min)

To a suspension of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridine-2-carbonitrile (1 equiv) in concentrated H_2SO_4. The mixture was heated to 90 °C until a pale brown solution formed. The mixture was allowed to cool and then basified with 50 % w/w NaOH solution. The aqueous mixture was extracted using EtOAc (3 X 2 reaction volumes). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a pale yellow solid which was triturated with EtOAc to give the desire product.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridine-2-carboxylic acid amide: 93 % yield, 96 % purity) m/z (LC-MS,ESP):450.4 $[M+H]^+$, R/T = 3.72 min)

Procedure for the synthesis of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-ylamine (Example 1cz)



To a 1.2 M solution of compound 1au (1 equiv) in THF was added hydrazine hydrate (9 reaction volumes). The reaction vessel was sealed and exposed to microwave radiation (115 °C, medium absorption setting) for 2 hours. Upon completion, the reaction mixture was extracted with EtOAc (2 X 1 reaction volume). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired product in suitably clean form for use in subsequent reactions.

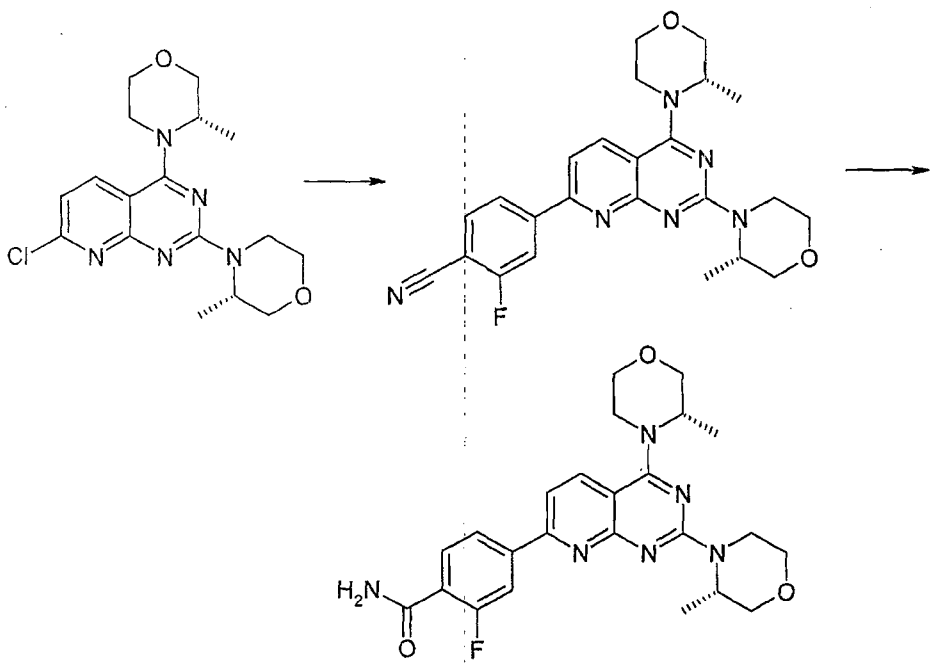
{4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-hydrazine 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2H-phthalazin-1-one: (77 % yield, 84 % purity) m/z (LC-MS,ESP):437.4 $[M+H]^+$, R/T = 2.23 min)

A 0.12 M solution of {4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-hydrazine 7-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2H-phthalazin-1-one (1 equiv) in EtOH was added to a a glass lined autoclave which contained activated Ra-Ni. The reaction was maintained under 5 bar H_2 for 30 hours. Upon completion, the mixture

was filtered through a pad of Celite™ and the filtrate concentrated *in vacuo*. The resulting crude residue was purified by reverse phase flash chromatography using 5:95 -0.1 % TFA/MeCN:0.1 % TFA/H_2O as eluent to give the desire product as a yellow powder.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-ylamine: (70 % yield, 100 % purity) m/z (LC-MS,ESP):422 $[M+H]^+$, R/T = 2.25 min)

Procedure for the synthesis of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzamide (Example 1da).



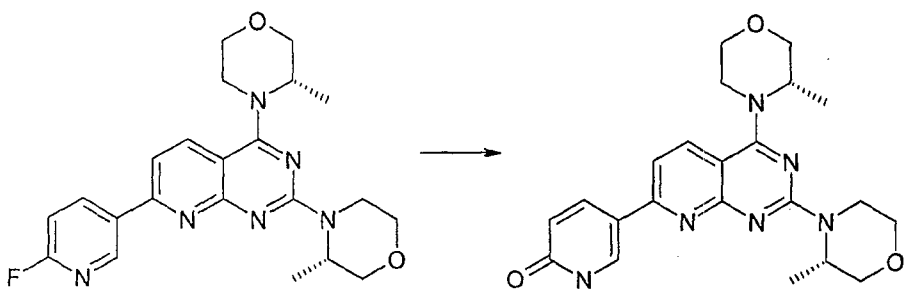
To the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv) and the appropriate boronic acid or pinacolate boron ester (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) which were dissolved in MeCN/H_2O (0.03 M of chloro-substrate). The mixture was degassed with nitrogen, sealed and exposed to microwave radiation (110 °C, medium absorption setting) for 25 minutes. The mixture filtered and the precipitate collected, and recrystallised from MeCN/H_2O to give the desired product.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzonitrile: (49 % yield, 87 % purity) m/z (LC-MS,ESP):449 $[M+H]^+$, R/T = 2.93 min)

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzonitrile (1 equiv) was dissolved concentrated sulfuric acid (0.15 M substrate in acid). The reaction was heated rapidly to 90 °C for 5 minutes before cooling the mixture and quenched, carefully, with solid NaOH until the solution was basic. The mixture was extracted with EtOAc/nBuOH (2 X 1 reaction volume – 1:1 ratio). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a residue which was further purified using flash chromatography (SiO_2) with TBME going to TBME/MeOH (95:5) as eluent, the give the title compound as a yellow solid.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzamide Synthesis: (71 % yield, 99 % purity) m/z (LC-MS,ESP):467 $[M+H]^+$, R/T = 2.60 min)

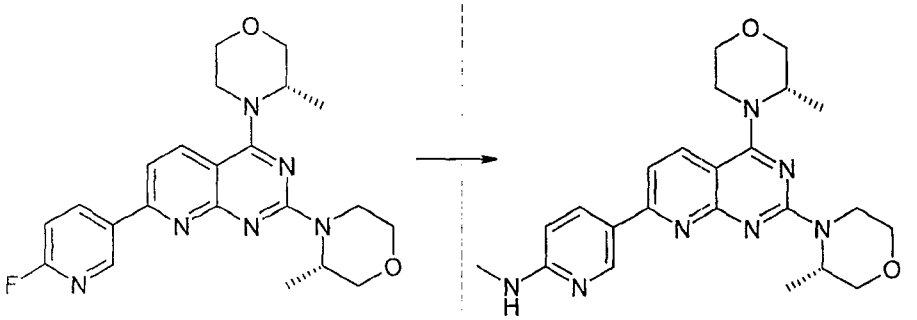
Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-pyridin-2-one (Example 1db).



To a 0.2 M solution of compound 1ah (1 equiv) in DMA was added a 1.6 M aqueous solution of sodium hydroxide (5 equiv). The reaction vessel was sealed and exposed to microwave radiation (110°C, medium absorption setting) for 10 minutes. The reaction mixture was concentrated *in vacuo*. The residue was suspended in water and sonicated to give a turbid solution, washed with TBME then cooled and neutralised with 2M HCl, forming a yellow precipitate. The precipitate was filtered and washed with water and TBME and dried to give the desired product.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-pyridin-2-one: (69 % yield, 96 % purity) m/z (LC-MS,ESP):423 $[M+H]^+$, R/T = 3.60 min)

Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-pyridin-2-one (Example 1dc).



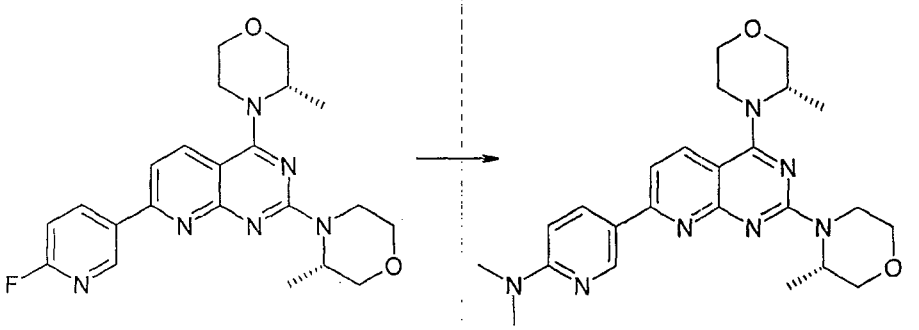
To the compound 1ah (1 equiv) was added a solution of 40 % methylamine in methanol (100 equiv). The reaction vessel was sealed and exposed to microwave radiation (115°C, medium absorption setting) for 30 minutes. The solution was concentrated *in vacuo* to yield a yellow solid. The crude residue was then purified by preparative HPLC to give the desired product. {5-[2,4-Bis-(3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-methyl-amine: (61 % yield, 99 % purity) m/z (LC-MS,ESP):436 $[M+H]^+$, R/T = 3.34 min)

NMR data for Example 1dc

^{1}H NMR (300 MHz, $CDCl_3$.δ ppm 8.69 (ArH, d, J = 2.06 Hz, 1H), 8.56 (ArH, dd, J = 9.02, 2.32 Hz, 1H), 7.97 (ArH, d, J = 8.47 Hz, 1H), 7.33 (ArH, d, J = 8.48 Hz, 1H), 6.59 (ArH, d, J = 9.03 Hz, 1H), 5.92 (NH, s, br, 1H), 4.90 (CH_2, dd, J = 5.85, 0.41 Hz, 1H), 4.59 (CH_2, d, J = 12.53 Hz, 1H), 4.41-4.29 (CH_2, m, 1H), 4.05-3.93 (CH_2, m, 2H), 3.90-3.62 (CH_2, m, 8H), 3.62-3.50 (CH_2, m, 1H), 3.43-3.31 (CH_2, m, 1H), 3.00 (NCH_3, s, 3H), 1.47 (CH_3, d, J = 6.78 Hz, 3H), 1.35 (CH_3, d, J = 6.82 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 167.59, 165.30, 162.90, 159.99, 158.84, 144.22, 139.19, 134.85, 123.35, 111.65, 106.51, 104.57, 71.28, 70.91, 67.24, 66.92, 52.83, 46.96, 44.42, 39.34, 29.05, 14.73 and 14.34.

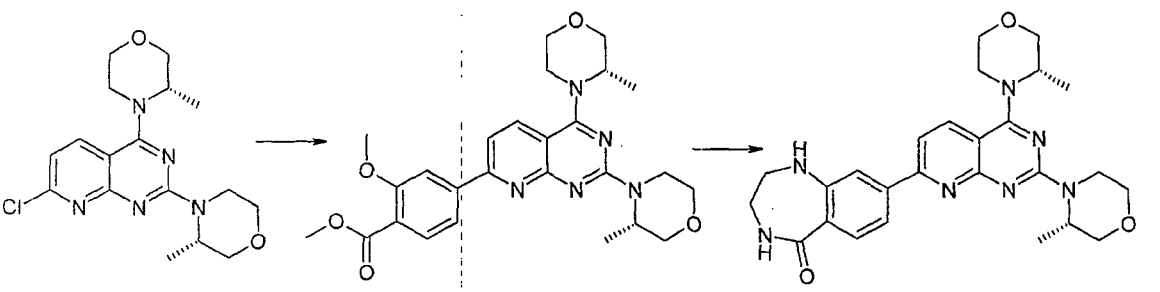
Procedure for the synthesis of {5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-dimethyl-amine (Example 1dd).



To a solution of compound 1ah (1 equiv) in THF (0.05 M) was added a solution of 33 % dimethylamine in ethanol (200 equiv). The reaction vessel was sealed and exposed to microwave radiation (130°C, medium absorption setting) for 40 minutes. The solution was concentrated *in vacuo* to yield a yellow solid. The crude residue was then purified by preparative HPLC to give the desired product.

{5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-dimethyl-amine: (54 % yield, 97 % purity) m/z (LC-MS,ESP):450 $[M+H]^+$, R/T = 3.52 min)

Procedure for the synthesis of 8-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one (Example 1de).



The appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), 3-methoxy-4-methoxycarbonylphenylboronic acid, pinacol ester (1.1 equiv) were suspended in (1:1) acetonitrile/water (0.1 M of chloro-substrate). The mixture was sonicated and degassed for 15 minutes with nitrogen. Tetrakistriphenylphosphine (0.05 equiv) was then added and the mixture was sonicated for a further 5 minutes with nitrogen. The mixture was heated to 100°C for 3 hours under nitrogen. The reaction was cooled and the insoluble residue was filtered off.

The filtrate was concentrated to half the original volume and the remaining water mixture was extracted with CH_2Cl_2. The organic layers were washed with water and brine, combined and dried with magnesium sulphate, filtered and concentrated *in vacuo* to yield an oil which was purified by flash column chromatography eluting with 50 % to 100 % EtOAc/Hexane.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid methyl ester: (67 % yield, 100 % purity) m/z (LC-MS,ESP):494 $[M+H]^+$, R/T = 2.86 min)

A solution of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid methyl ester (1 equiv) in ethylenediamine (0.35 M) was stirred at room temperature for 24 hours. DMA was added to the solution (ethylenediamine/DMA 1:1.25). The reaction vessel was sealed and exposed to microwave radiation (180°C, medium absorption setting) for 1 hour. The reaction mixture was diluted with CH_2Cl_2 and extracted with water and washed with brine. The organic layer was dried with magnesium sulphate, filtered and concentrated *in vacuo* to yield a yellow solid which was then purified by preparative HPLC to give the desired product.

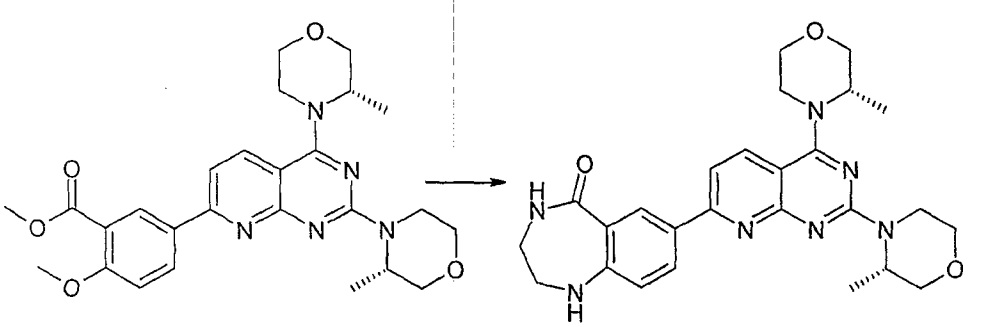
8-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one: (49 % yield, 99 % purity) m/z (LC-MS,ESP):490 $[M+H]^+$, R/T = 3.52 min)

NMR data for Example 1de

^1H NMR (300 MHz, $CDCl_3$ δ ppm 8.65 (NH, s, br, 1H), 8.01 (ArH, d, J = 8.38 Hz, 1H), 7.78 (ArH, s, 1H), 7.68 (ArH, s, 1H), 7.44 (ArH, dd, J = 18.50, 8.20 Hz, 2H), 4.93-4.77 (CH_2, m, 1H), 4.50 (CH_2, s, 1H), 4.46-4.32 (CH_2, m, 1H), 4.05-3.61 (CH_2, m, 14H), 3.53 (CH_2, d, J = 2.04 Hz, 1H), 3.41-3.26 (CH_2, m, 1H), 1.47 (CH_3, d, J = 6.76 Hz, 3H), 1.33 (CH_3, d, J = 6.78 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 165.11, 165.07, 165.00, 163.41, 162.64, 161.07, 159.90, 144.87, 135.18, 129.50, 118.02, 116.80, 113.87, 109.20, 105.45, 71.20, 70.89, 67.14, 66.89, 52.77, 47.04, 44.76, 44.40, 39.33, 14.78 and 13.32.

Procedure for the synthesis of 7-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one (Example 1df).



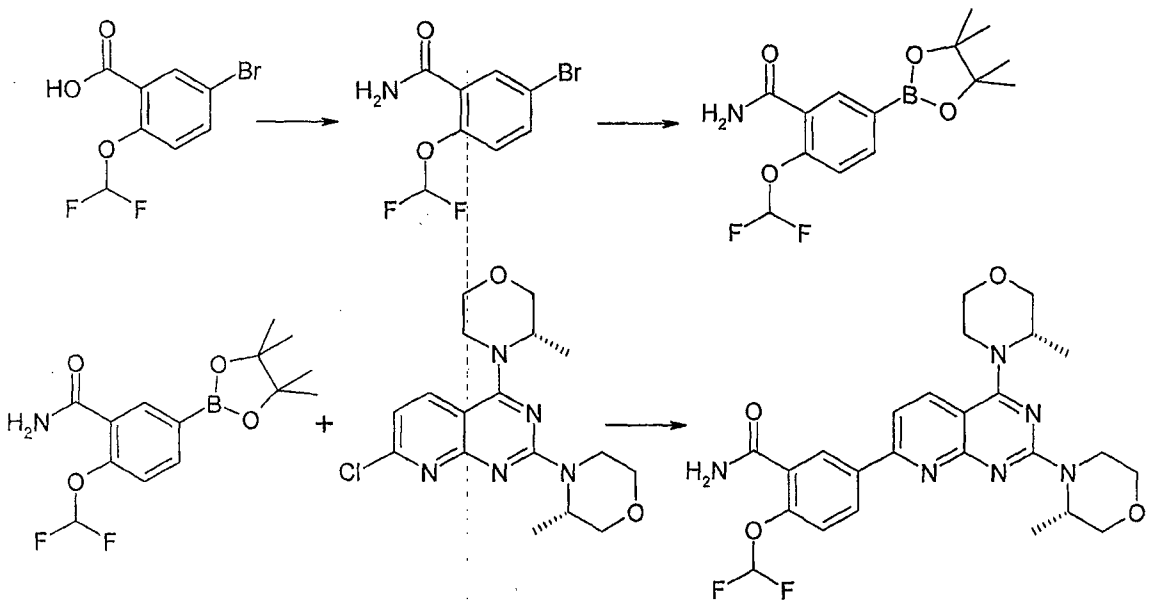
A solution of the compound 1bg (1 equiv) in ethylenediamine (0.35 M) was stirred at room temperature for 24 hours. DMA was added to the solution (ethylenediamine/DMA 1:1.25). The reaction vessel was sealed and exposed to microwave radiation (180°C, medium absorption setting) for 1 hour. The reaction mixture was diluted with ethyl acetate and extracted with water. The organic layer was dried with magnesium sulphate, filtered and concentrated *in vacuo* to yield a residue which was then purified by flash column chromatography eluting with 0 % to 20 % MeOH/ CH_2Cl_2.

8-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one: (40 % yield, 100 % purity) m/z (LC-MS,ESP):490 $[M+H]^+$, R/T = 3.49 min)

NMR data for Example 1df

^1H NMR (300 MHz, $CDCl_3$ δ ppm 8.60 (ArH, d, J = 2.23 Hz, 1H), 7.93-7.83 (ArH, m, 2H), 7.34 (ArH, d, J = 8.56 Hz, 1H), 6.89 (ArH, d, J = 8.97 Hz, 1H), 4.82-4.71 (CH_2, m, 1H), 4.47 (CH_2, dd, J = 7.28, 6.58 Hz, 1H), 4.30 (CH_2, d, J = 6.93 Hz, 1H), 3.95-3.55 (CH_2, m, 13H), 3.55-3.42 (CH_2, m, 1H), 3.35-3.21 (CH_2, m, 1H), 1.40 (CH_3, d, J = 6.77 Hz, 3H), 1.26 (CH_3, d, J = 6.80 Hz, 3H).

Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-difluoromethoxy-benzamide (Example 1dg).



To a solution of 5-bromo-2-difluoromethoxy-benzoic acid (1 equiv) in THF (0.1 M) was added dropwise thionyl chloride (5 equiv) at room temperature. The reaction mixture was stirred at 40°C for 2 hours. The reaction mixture was concentrated *in vacuo*. The residue was suspended in dry THF (0.04 M) and ammonia gas was slowly bubbled into the reaction mixture for 45 minutes. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in minimum CH_2Cl_2 and hexane was added to give a white precipitate that was collected by vacuum filtration in suitably clean form for use in subsequent reactions.
5-Bromo-2-difluoromethoxy-benzamide: (45 % yield, 73 % purity) m/z (LC-MS, ESP):266/268 $[M+H]^+$, R/T = 3.42 min)

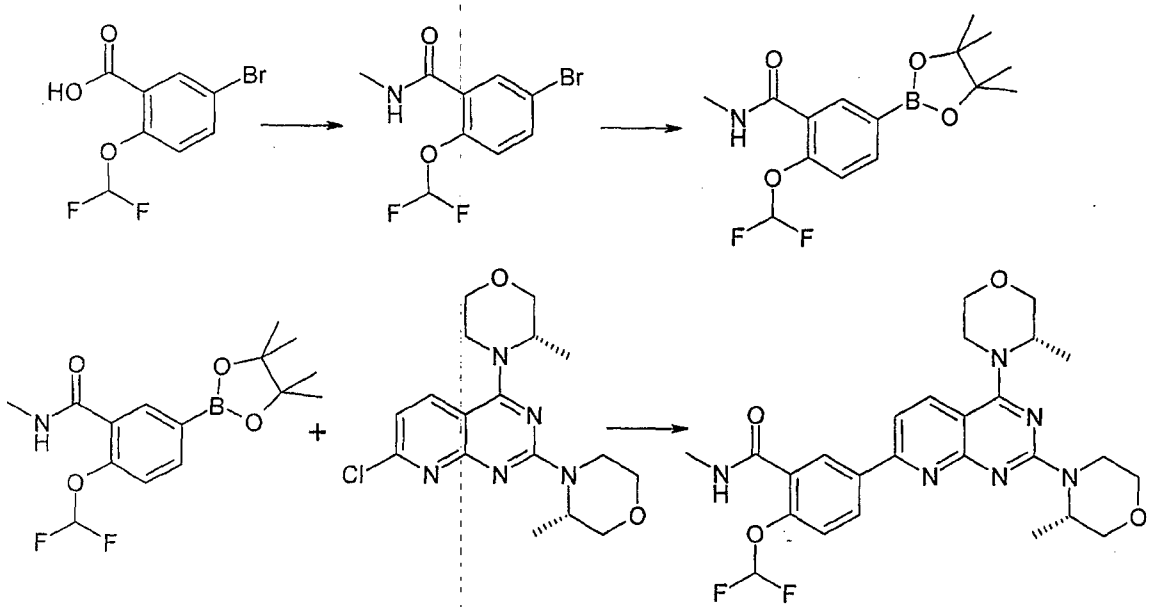
To a solution of 5-bromo-2-difluoromethoxy-benzamide (1 equiv) in dioxan (0.1 M) were added bis(pinacolato)diboron (1.1 equiv), potassium acetate (3.5 equiv) and dppf (0.05 equiv). The reaction mixture was degassed with nitrogen for 15 minutes. $PdCl_2$(dppf) (0.05 equiv) was added to the reaction mixture, which was degassed for a further 5 minutes. The reaction mixture was stirred at 110°C for 12 hours under nitrogen. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic phases were washed with water, dried with magnesium sulphate, filtered and concentrated *in vacuo* to give the desired product for use in subsequent reactions

2-Difluoromethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide: (71 % yield, crude taken forward without further analysis)

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), 2-difluoromethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 100 °C for 4 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC to give the desired product.

5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-difluoromethoxy-benzamide: (14 % yield, 100 % purity) m/z (LC-MS, ESP): 515 $[M+H]^+$, R/T = 7.40 min

Procedure for the synthesis of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-difluoromethoxy-N-methyl-benzamide (Example 1dh).



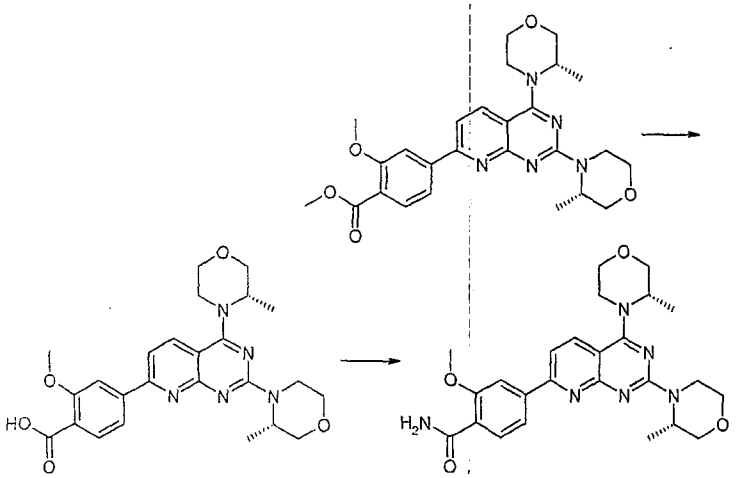
To a solution of 5-bromo-2-difluoromethoxy-benzoic acid (1 equiv) in DMF (0.1 M) was added triethylamine (4 equiv). The reaction mixture was cooled to 0°C and HBTU (1.2 equiv) was added. The reaction mixture was allowed to reach room temperature over 1 hour and methylamine hydrochloride (2 equiv) was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was partitioned between EtOAc and water and the aqueous phase was further extracted with EtOAc. The combined organic phases were

washed with water, dried with magnesium sulphate, filtered and concentrated under *in vacuo* to give the desired product in suitably clean form for use in subsequent reactions.
5-Bromo-2-difluoromethoxy-N-methyl-benzamide: (100 % yield, 75 % purity) m/z (LC-MS, ESP): 280/282 $[M+H]^+$, R/T = 3.55 min)

2-Difluoromethoxy-N-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide was prepared in a similar way as 2-Difluoromethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide using 5-bromo-2-difluoromethoxy- N-methyl-benzamide as the starting material.
2-Difluoromethoxy-N-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide: (100 % yield, crude taken forward without further analysis)

A mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), 2-difluoromethoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (1.1 equiv) and tetrakis(triphenylphosphine) palladium^0 (0.05 equiv) in acetonitrile/water (0.1 M of chloro-substrate) was stirred at 100 °C for 2 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC to give the desired product.
5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-difluoromethoxy-N-methyl-benzamide: (53 % yield, 87 % purity) m/z (LC-MS, ESP): 421 $[M+H]^+$, R/T = 4.06 min)

Procedure for the synthesis of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzamide (Example 1di).



4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid methyl ester (1 equiv) was dissolved in methanol (0.2 M). 1M Sodium hydroxide aqueous solution (5.0 equiv) was added. The reaction mixture was stirred at room temperature for 3 hours. Upon completion the reaction mixture was neutralised with 1M aqueous HCl and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 10 % MeOH in CH_2Cl_2 to give the desired product.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid: (100 % yield, 100 % purity) m/z (LC-MS, ESP): 480 $[M+H]^+$, R/T = 2.69 min)

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid (1 equiv) was suspended in THF (0.05 M). Thionyl chloride was added dropwise at 40°C. The reaction mixture was then heated for an hour at 40°C. Ammonia gas was then slowly bubbled into the reaction mixture. THF was then added for further dilution (0.025 M) and the reaction mixture was heated for an hour at 40°C. Upon completion the reaction mixture was cooled down and concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product.

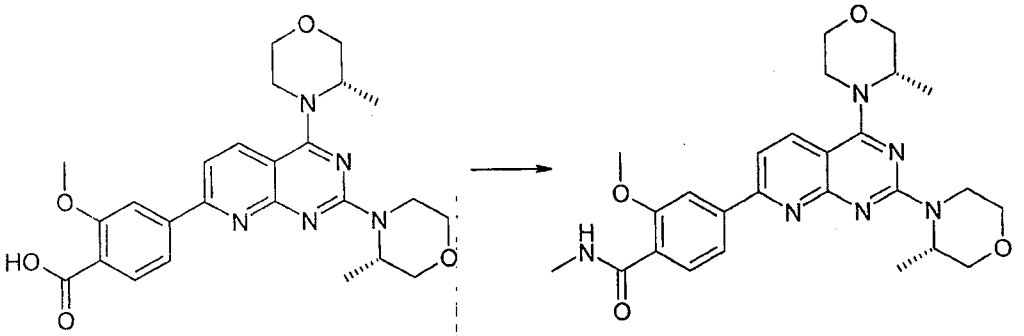
4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzamide: (88 % yield, 99 % purity) m/z (LC-MS, ESP): 479 $[M+H]^+$, R/T = 3.92 min)

NMR data for Example 1di

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.30 (ArH, d, J = 8.17 Hz, 1H), 8.04 (ArH, dd, J = 6.21, 4.98 Hz, 2H), 7.80 (NH, br, s, 1H), 7.67 (ArH, dd, J = 8.21, 1.49 Hz, 1H), 7.49 (ArH, d, J = 8.44 Hz, 1H), 5.96 (NH, s, br, 1H), 4.98-4.85 (CH_2, m, 1H), 4.61 (CH_2, d, J = 12.90 Hz, 1H), 4.39 (CH_2, d, J = 6.89 Hz, 1H), 4.13 (OCH_3, s, 3H), 4.05-3.64 (CH_2, m, 9H), 3.64-3.51 (CH_2, m, 1H), 3.41 (CH_2, dd, J = 13.34, 3.62 Hz, 1H), 1.49 (CH_3, d, J = 6.79 Hz, 3H), 1.36 (CH_3, d, J = 6.82 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.78, 165.32, 162.81, 160.99, 160.02, 158.15, 143.57, 134.98, 132.76, 121.80, 120.15, 113.62, 111.30, 105.44, 71.27, 70.89, 67.23, 66.90, 56.42, 52.88, 47.01, 44.41, 39.36, 14.77 and 14.40.

Procedure for the synthesis of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-N-methyl-benzamide (Example 1dj).



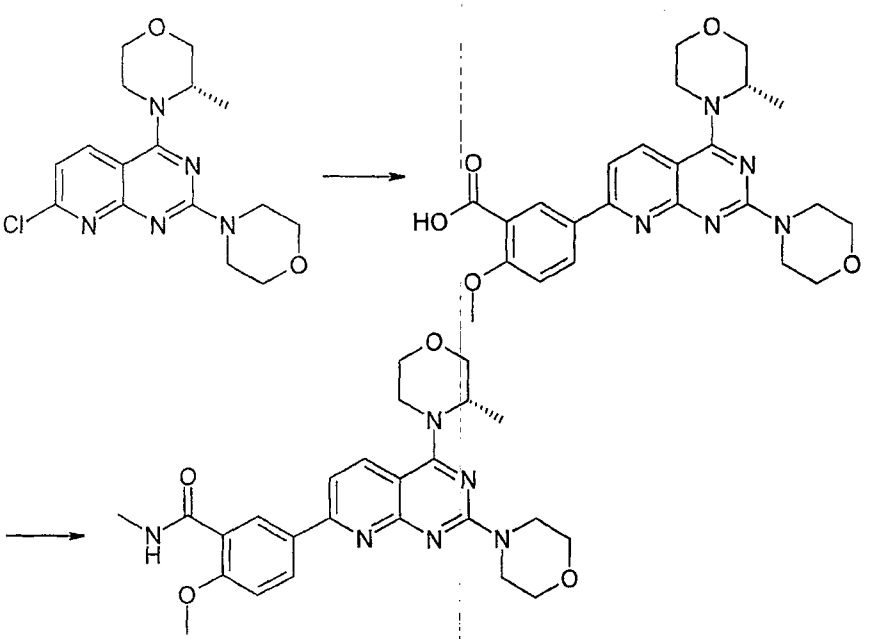
4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-benzoic acid (1 equiv) was dissolved in THF (0. 1 M) and HBTU (1.5 equiv) was added. Methylamine in THF (15 equiv) was added dropwise followed by triethylamine (1.5 equiv) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by preparative HPLC to give the desired product.

4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-N-methyl-benzamide: (56 % yield, 96 % purity) m/z (LC-MS, ESP): 493 $[M+H]^+$, R/T = 4.00 min)

NMR data for Example 1dj

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.26 (ArH, d, J = 8.16 Hz, 1H), 7.98 (ArH, dd, J = 8.74, 4.91 Hz, 2H), 7.91-7.81 (NH, m, br, 1H), 7.60 (ArH, dd, J = 8.21, 1.52 Hz, 1H), 7.43 (ArH, d, J = 8.45 Hz, 1H), 4.93-4.81 (CH_2, m, 1H), 4.62-4.51 (CH_2, m, 1H), 4.39-4.28 (CH_2, m, 1H), 4.07 (OCH_3, s, 3H), 4.00-3.58 (CH_2, m, 9H), 3.57-3.45 (CH_2, m, 1H), 3.40-3.27 (CH_2, m, 1H), 2.99 ($NHCH_3$, d, J = 4.82 Hz, 3H), 1.43 (CH_3, d, J = 6.78 Hz, 3H), 1.31 (CH_3, d, J = 6.81 Hz, 3H).

Procedure for the synthesis of 2-methoxy-N-methyl-5-[4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzamide (Example 1dk).



To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.0 equiv), and 2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester (1.05 equiv) in acetonitrile/water (1:1) (0.028 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (130°C, medium absorption setting) for 20 minutes. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in*

vacuo. The crude residue was purified by column chromatography on silica gel eluting with 0 to 20 % MeOH in CH_2Cl_2 to give the desired product.

2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid: (91 % yield, 100 % purity) m/z (LC-MS, ESP): 466.4 $[M+H]^+$, R/T = 2.68 min)

2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid (1 equiv) was dissolved in DMF (0.1 M) and DIPEA (8 equiv) was added. HBTU (1.2 equiv) was added at 0°C and the reaction mixture was stirred for 30 minutes. Methylamine hydrochloride (5 equiv) was added and the reaction mixture was stirred 0°C for 30 minutes and at room temperature for 1 hour. The reaction mixture was partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate. Combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography to give the desired product.

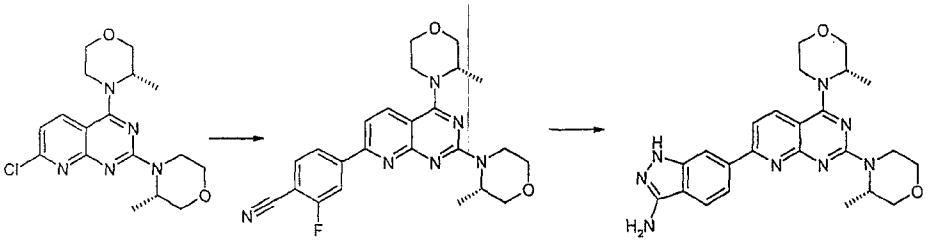
4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-N-methyl-benzamide: (73 % yield, 97 % purity) m/z (LC-MS, ESP): 479.2 $[M+H]^+$, R/T = 3.97 min)

NMR data for Example 1dk

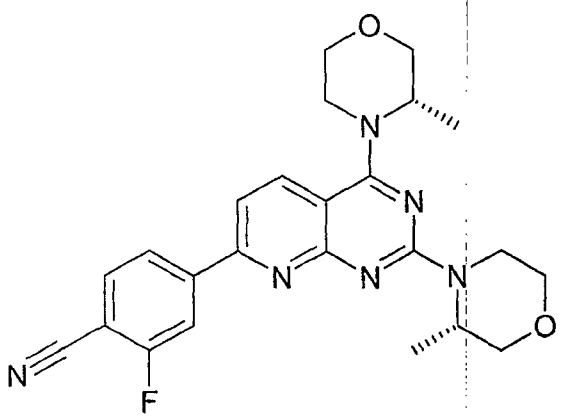
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.71 (ArH, d, J = 2.45 Hz, 1H), 8.45 (ArH, dd, J = 8.75, 2.48 Hz, 1H), 7.97 (ArH, d, J = 8.52 Hz, 1H), 7.78 (NH, s, br, 1H), 7.51 (ArH, d, J = 8.56 Hz, 1H), 7.01 (ArH, d, J = 8.84 Hz, 1H), 4.39 (CH_2, d, J = 6.69 Hz, 1H), 3.96 (OCH_3, s, 3H), 3.95-3.77 (CH_2, m, 7H), 3.76-3.58 (CH_2, m, 7H), 2.98 (NCH_3, d, J = 4.81 Hz, 3H), 1.42 (CH_3, d, J = 6.78 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.74, 164.71, 161.22, 160.99, 159.11, 159.04, 135.09, 132.93, 131.23, 131.16, 121.32, 119.02, 113.63, 111.84, 104.61, 70.90, 66.90, 56.27, 52.70, 44.70, 44.48, 26.70 and 14.85.

Procedure for the synthesis of 6-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-indazol-3-ylamine (Example 1dl).

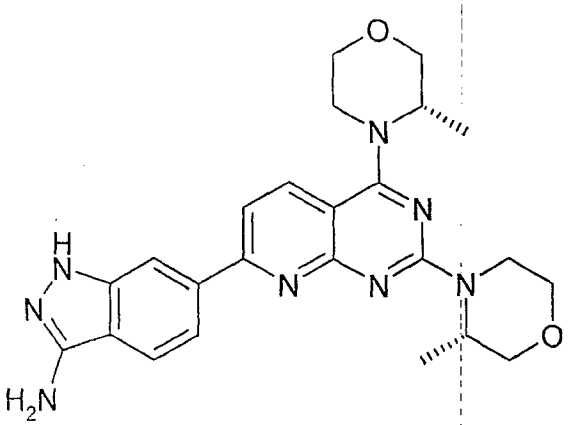


To a mixture of 7-chloro-4-((S)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine (1 equiv), potassium carbonate (2.5 equiv), and 4-cyano-3-fluorophenylboronic acid (1.2 equiv) in acetonitrile/water (1:1) (0.03 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (110 °C, medium absorption setting) for 25 minutes under nitrogen atmosphere. Upon completion the precipitate was collected by vacuum filtration, which was in suitably pure form to be used with no further purification.



4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzonitrile: (49 % yield, 96 % purity) m/z (LC-MS, ESP): 449.2 $[M+H]^+$ R/T = 2.93 min

To a 0.2 M solution of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzonitrile (1 equiv) in n-BuOH was added 0.2 reaction volumes of hydrazine hydrate. A reflux condenser was attached to the mixture which was then heated to 140 °C for 2 hours whereupon it was cooled, and concentrated *in vacuo* to give an orange residue which was purified by flash chromatography (SiO_2) using Et_2O:MeOH – 94:6 as eluent which allowed a yellow solid which was then recrystallised from CH_2Cl_2/Hexanes to furnish the title compound as a yellow solid.



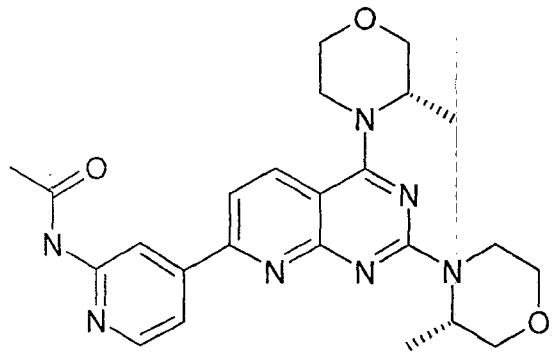
6-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-indazol-3-ylamine: (90 % yield, 97 % purity) m/z (LC-MS, ESP): 461.2 $[M+H]^+$ R/T = 3.77 min

NMR data for Example 1dl

(^{1}H NMR (300 MHz, CD_3SOCD_3 δ ppm 11.6 (1H, s, formate), 8.31-8.01 (ArH, m, 2H), 7.74 (ArH, ddd, J = 18.90, 15.23, 8.49 Hz, 3H), 5.42 (NH_2, s, 2H), 4.88-4.70 (NH, m, 1H), 4.44 (CH_2, d, J = 10.93 Hz, 2H), 3.91 (CH_2, m, 3H), 3.81-3.54 (CH_2, m, 6H), 3.46 (CH_2, dt, J = 11.82, 11.67, 2.52 Hz, 1H), 3.38-3.13 (CH_2, m, 1H), 2.51 (CH, td, J = 3.52, 1.73, 1.73 Hz, 1H), 1.38 (CH_3, d, J = 6.75 Hz, 3H), 1.26 (CH_3, d, J = 6.79 Hz, 3H).

13C NMR (75 MHz, CD_3SOCD_3) δ ppm 164.43, 162.05, 161.20, 159.29, 149.19, 141.79, 136.12, 135.32, 120.42, 116.81, 114.78, 113.13, 108.47, 104.30, 70.39, 70.15, 66.34, 66.15, 51.81, 46.24, 43.81, 30.89, 22.0, 14.31 and 13.89.

Procedure for the synthesis of N-{4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-acetamide (Example 1dm).



To a 0.1 M solution of 4-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-ylamine (example 1cz) (1 equiv) in pyridine was added acetic anhydride (3 equiv). A reflux condenser was attached to the reaction vessel which was then heated to 70 °C

for 2 days. Upon completion, the reaction was purified, in its crude for by preparative HPLC to give the title compound as a white solid.

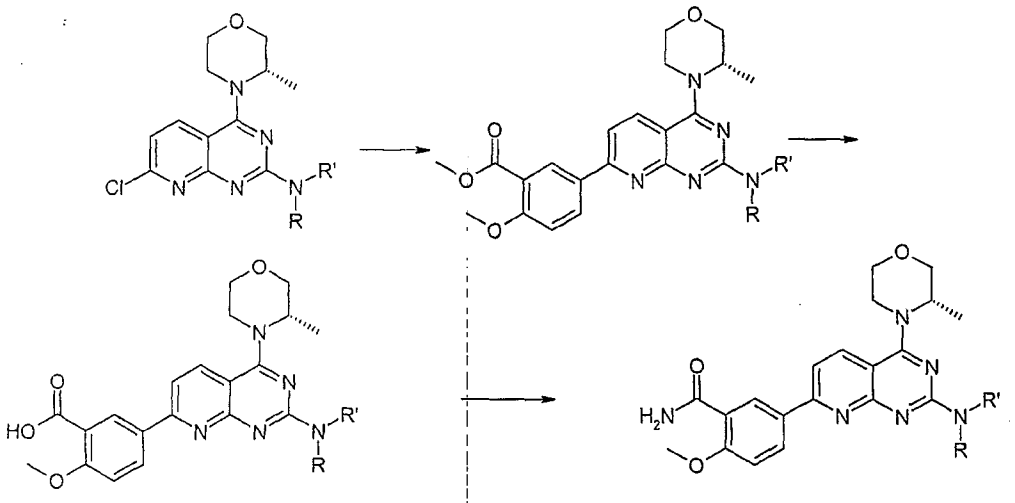
N-{4-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-yl}-acetamide :(95 % yield, 99 % purity) m/z (LC-MS, ESP): 464.1 $[M+H]^+$ R/T = 3.77 min

NMR data for Example 1dm

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm 8.70 (NH, s, 1H), 8.37-8.29 (ArH, m, 2H), 8.01 (ArH, d, J = 8.36 Hz, 1H), 7.94 (ArH, dd, J = 5.26, 1.54 Hz, 1H), 7.49 (ArH, d, J = 8.39 Hz, 1H), 4.87 (CH_2, ddd, J = 2.90, 1.56, 0.64 Hz, 1H), 4.56 (CH_2, d, J = 13.43 Hz, 1H), 4.33 (CH_2, d, J = 6.86 Hz, 1H), 3.99-3.58 (CH_2, m, 10H), 3.57-3.45 (CH_2, m, 1H), 3.39-3.25 (CH_2, m, 1H), 2.19 (CH_3, s, 3H), 1.43 (CH_3, d, J = 6.78 Hz, 3H), 1.31 (CH_3, d, J = 6.82 Hz, 3H)

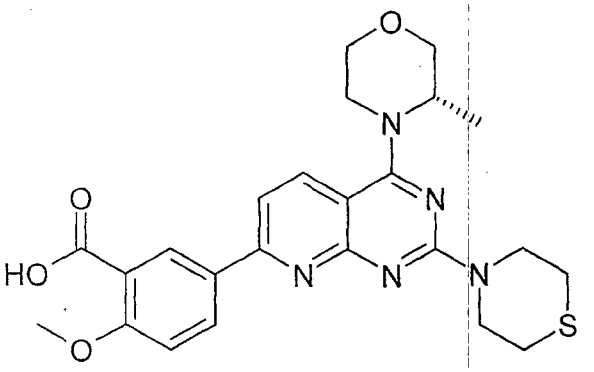
^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 168.79, 165.32, 162.82, 160.00, 159.87, 151.94, 148.64, 148.15, 135.18, 118.86, 113.66, 111.94, 106.03, 71.27, 70.89, 67.23, 66.89, 52.89, 46.98, 44.46, 39.35, 24.81, 14.77 and 14.41.

Procedure for the synthesis of Examples 1dn to 1dp

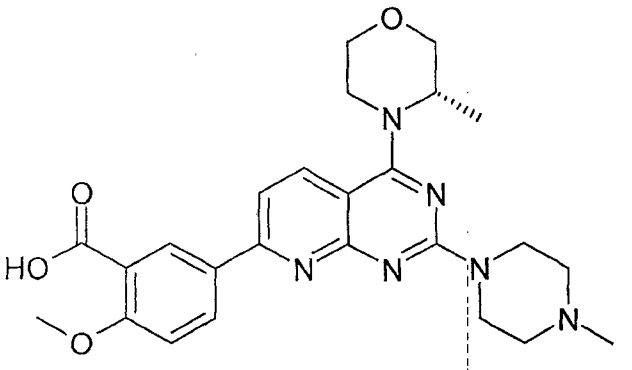


The appropriate 7-chloropyridopyrimidine was reacted with 2-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid methyl ester according to conditions E to give 2-methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-thiomorpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid methyl ester as the desired product (1 equiv) which was then diluted in MeOH to give a 0.03M solution. NaOH (5 equiv of 1 M solution) was then added and the resultant mixture stirred at room temperature for 5 days. After this time the reaction was filtered and neutralized with 1M HCl before being concentrated *in vacuo* to give a crude

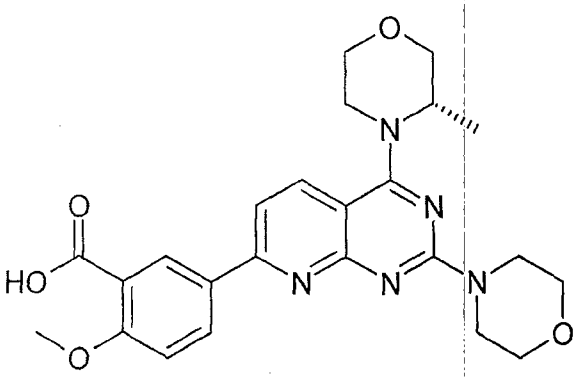
yellow residue which was diluted in CH_2Cl_2. The mixture was filtered and the resulting filtrate concentrated to give the desired product as an oil.



2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-thiomorpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid: (99 % yield, 95 % purity) m/z (LC-MS, ESP): 482.2$[M+H]^+$ R/T = 2.78 min

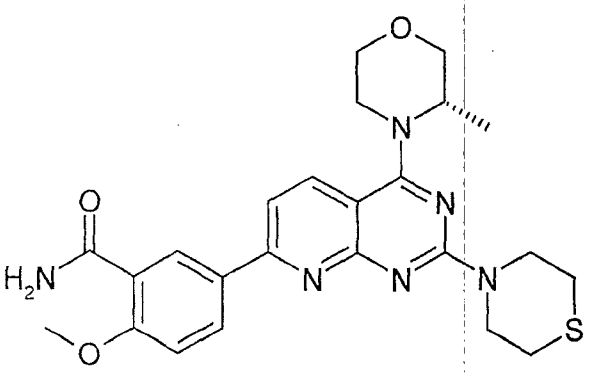


2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-(4-methyl-piperazin-1-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid: (88 % yield, 96 % purity) m/z (LC-MS, ESP): 479.5$[M+H]^+$ R/T = 2.26 min



2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzoic acid: (91 % yield, 100 % purity) m/z (LC-MS, ESP):466.4 $[M+H]^+$ R/T = 2.68 min

To a warmed (40 °C) 0.06 M solution of the appropriate benzoic acid derivative(1 equiv) in anhydrous THF was added thionyl chloride (2.5 equiv) in a dropwise fashion. The reaction was maintained at this temperature and stirred for a further 1 hour. After this time the mixture was evaporated to give a brown oil, which was diluted in dry THF (sufficient to make 0.06 M solution) before ammonia gas was bubble through the mixture, which was accompanied by an exotherm. Upon completion, addition of ammonia was stopped and the mixture concentrated *in vacuo* to give a a yellow oily residue which was dissolved in CH_2Cl_2 (1 reaction volume) and washed with water (2 X 1 reaction volume). The organic extract was removed, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound.

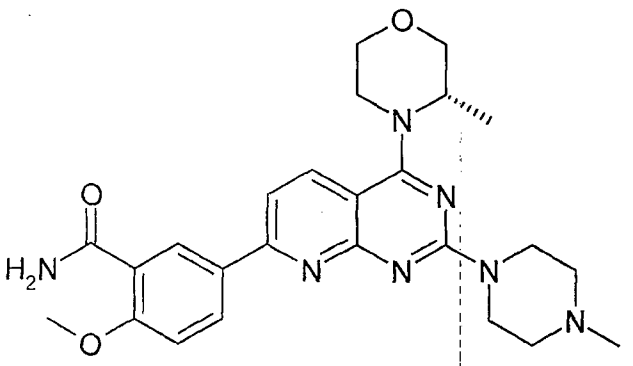


2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-thiomorpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzamide: (30 % yield, 97 % purity) m/z (LC-MS, ESP): 481.1$[M+H]^+$ R/T = 4.02 min

NMR data for Example 1dn

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.83 (ArH, d, J = 2.46 Hz, 1H), 8.61 (ArH, dd, J = 8.75, 2.48 Hz, 1H), 8.00 (ArH, d, J = 8.47 Hz, 1H), 7.72 (NH, d, J = 0.76 Hz, 1H), 7.56 (ArH, d, J = 8.50 Hz, 1H), 7.13 (ArH, d, J = 8.82 Hz, 1H), 5.88 (NH, d, J = 0.98 Hz, 1H), 4.42-4.23 (CH2, m,4), 4.05 (CH_3O, s, 3H), 4.03-3.94 (CH_2, m, 1H), 3.85 (CH_2, ddd, J = 14.51, 8.58, 5.82 Hz, 2H), 3.78-3.62 (CH_2, m, 3H), 2.75-2.65 (CH_2, m, 3H), 1.46 (CH_3, d, J = 6.76 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 166.60, 165.41, 162.87, 161.09, 159.89, 159.23, 134.73, 133.71, 131.82, 131.68, 120.56, 113.16, 111.89, 104.63, 70.95, 66.91, 56.29, 52.81, 46.70, 44.54, 27.45 and 14.70.

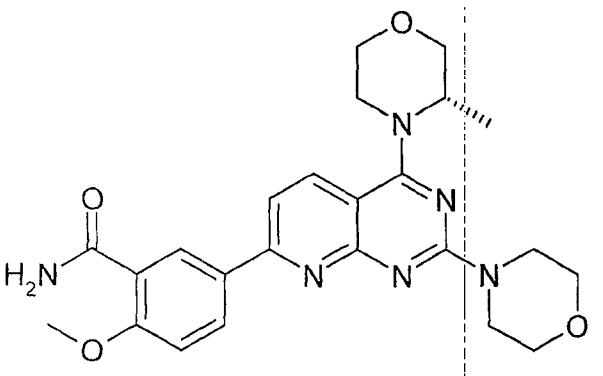


2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-(4-methyl-piperazin-1-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzamide: (12 % yield, 98 % purity) m/z (LC-MS, ESP): 481.1$[M+H]^+$ R/T = 43.28 min

NMR data for Example 1do

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.78 (ArH, d, J = 2.48 Hz, 1H), 8.57 (ArH, dd, J = 8.76, 2.52 Hz, 1H), 8.28 (NH, s, br, 1H), 7.96 (ArH, d, J = 8.50 Hz, 1H), 7.68 (NH, s, br, 1H), 7.54 (ArH, d, J = 8.55 Hz, 1H), 7.08 (ArH, d, J = 8.84 Hz, 1H), 4.42-4.28 (CH_2, m, 1H), 4.09

(CH_2, s, br, 2H), 4.01 (OCH_3, s, 3H), 3.77 (CH2, ddd, J = 36.04, 19.80, 10.87 Hz, 9H), 2.76 (CH_2, t, J = 5.05, 5.05 Hz, 4H), 2.47 (NCH_3, s, 3H), 1.42 (CH_3, d, J = 6.77 Hz, 3H).



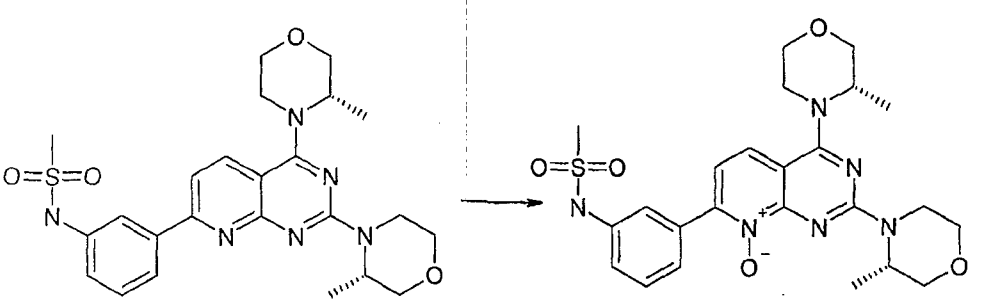
2-Methoxy-5-[4-((S)-3-methyl-morpholin-4-yl)-2-morpholin-4-yl-pyrido[2,3-d]pyrimidin-7-yl]-benzamide: (61 % yield, 97 % purity) m/z (LC-MS, ESP): 465.4 $[M+H]^+$ R/T = 2.69 min

(NMR data for Example 1dp

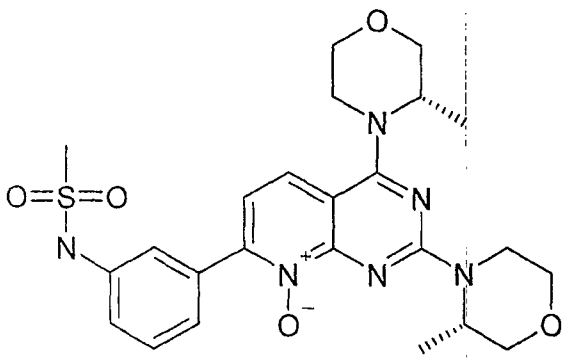
^1H NMR (300 MHz, , $CDCl_3$ δ ppm 8.77 (ArH, d, J = 2.44 Hz, 1H), 8.58 (ArH, dd, J = 8.76, 2.47 Hz, 1H), 7.94 (ArH, d, J = 8.48 Hz, 1H), 7.65 (NH, s, br, 1H), 7.51 (ArH, d, J = 8.53 Hz, 1H), 7.06 (ArH, d, J = 8.84 Hz, 1H), 5.91 (NH, s, br, 1H), 4.32 (CH_2, d, J = 6.79 Hz, 1H), 3.98 (OCH_3, s, 3H), 3.95-3.86 (CH_2, m, 5H), 3.84-3.55 (CH_2, m, 9H), 1.40 (CH_3, d, J = 6.77 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 166.63, 165.31, 162.78, 160.96, 160.31, 159.29, 134.76, 133.68, 131.69, 131.60, 120.56, 113.09, 111.88, 104.76, 70.94, 67.04, 66.91, 56.28, 52.76, 44.58, 44.45 and 14.75.

Procedure for the synthesis of Example 1dq



To a (0.1 M) solution of example 1at (1 equiv) in $CHCl_3$ was added m-CPBA (5.5 equiv). A reflux condenser was added to the apparatus and the mixture heated to 60 °C for 17 hours. After this time the reaction was concentrated *in vacuo* and purified by flash chromatography (SIO_2) using CH_2Cl_2:MeOH – 95:5 as eluent to furnish the desired product.



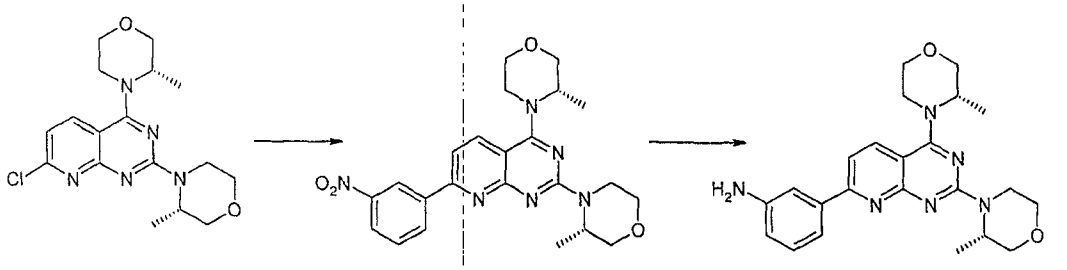
N-{3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-8-oxy-pyrido[2,3-d]pyrimidin-7-yl]-phenyl}-methanesulfonamide: (39 % yield, 100 % purity) m/z (LC-MS, ESP): 515.5$[M+H]^+$ R/T = 2.95min.

NMR data for Example 1dq

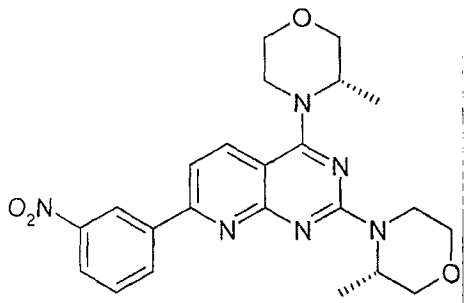
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 10.04 (NH, s, br, 1H), 8.42 (ArH, s, 1H), 7.55-7.25 (ArH, m, 4H), 6.96 (ArH, d, J = 8.67 Hz, 1H), 4.80 (CH_2, s, br, 1H), 4.51 (CH_2, s, br, 1H), 4.31 (CH_2, d, J = 6.71 Hz, 1H), 4.00-3.51 (CH_2, m, 9H), 3.49-3.34 (CH_2, m, 1H), 3.24 (CH_2, dd, J = 13.22, 3.30 Hz, 1H), 2.80 (SCH_3, s, 3H), 1.42 (CH_3, d, J = 6.78 Hz, 1H), 1.19 (CH_3, d, J = 6.69 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 165.58, 159.69, 158.28, 149.96, 138.59, 134.47, 129.53, 125.86, 123.35, 123.30, 116.17, 107.52, 71.33, 71.11, 67.32, 67.10, 53.39, 47.62, 44.87, 39.79, 38.68, 31.90, 22.97 and 15.16.

Procedure for the synthesis of Example 1dr

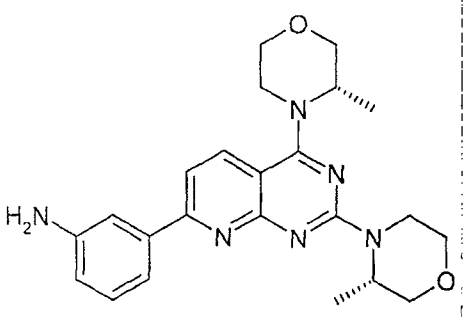


7-Chloro-2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine was couple with 3-nitrobenzoic acid using Suzuki conditions D to give the desire product as a yellow powder.



2,4-Bis-((S)-3-methyl-morpholin-4-yl)-7-(3-nitro-phenyl)-pyrido[2,3-d]pyrimidine: (90 % yield, 100 % purity) m/z (LC-MS, ESP): 451.6$[M+H]^+$ R/T = 3.41min

To a 0.1M solution of 2,4-bis-((S)-3-methyl-morpholin-4-yl)-7-(3-nitro-phenyl)-pyrido[2,3-d]pyrimidine (1 equiv) in EtOH/H_2O-1:1 was added ammonium chloride (8 equiv) and iron powder (8 equiv). The reaction mixture was heated to 100 °C for 1 hour before cooling and filtering through a thin Celite ™ pad. The cake was washed with EtOH (1 reaction volume). The filtrate was concentrated *in vacuo* and then partitioned between water and CH_2Cl_2 (1 reaction volume of each). The organic phase was removed, dried ($MgSO_4$) , filtered and concentrated *in vacuo* and then purified by flash chromatography (SiO_2) using MeOH:CH_2Cl_2 (0:100 – 5:95 – 10-90) as eluent to give the title compound as a yellow solid.



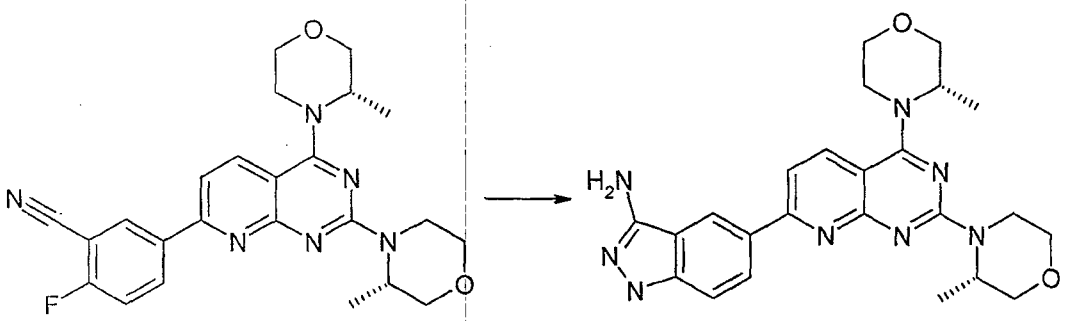
3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenylamine: (88 % yield, 98 % purity) m/z (LC-MS, ESP): 421.1$[M+H]^+$ R/T = 3.76min

NMR data for Example 1dr

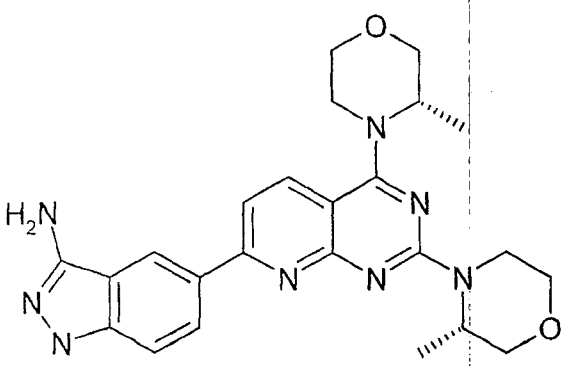
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 7.93 (ArH, d, J = 8.45 Hz, 1H), 7.62-7.55 (ArH, m, 1H), 7.41-7.32 (m, 1H), 7.20 (ArH, d, J = 7.32 Hz, 2H), 6.71 (ArH, ddd, J = 7.88, 2.40, 0.86 Hz, 1H), 4.87 (ArH, dd, J = 3.54, 1.66 Hz, 1H), 4.57 (NH, d, J = 13.25 Hz, 1H), 4.30 (NH, s, br, 1H), 3.98-3.56 (CH_2, m, 11H), 3.56-3.44 (CH_2, m, 1H), 3.37-3.24 (CH_2, m, 1H), 1.40 (CH_3, d, J = 6.77 Hz, 3H), 1.29 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 165.46, 162.87, 162.60, 159.96, 146.80, 139.75, 134.48, 129.35, 117.99, 116.69, 114.74, 113.48, 104.92, 71.32, 70.93, 67.28, 66.94, 52.80, 46.90, 44.49, 39.33, 14.71 and 14.33.

Procedure for the synthesis of Example 1ds



To a 0.3M solution of 5-[2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzonitrile (example 1av) (1 equiv) in EtOH was added hydrazine hydrate (5 equiv). The mixture was refluxed for 90 minutes wherepon it was cooled and partitioned between CH_2Cl_2 and water (1 reaction volume of each). The organic extract was removed. The aqueous phase was further extracted with CH_2Cl_2 (2 X 1 reaction volume). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow slurry which was further purified by flash chromatography (SiO_2) using EtOAC/Hexanes as eluent to give the title compound as a yellow powder.

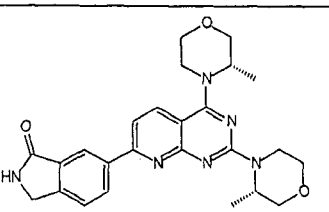
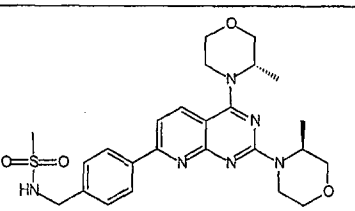
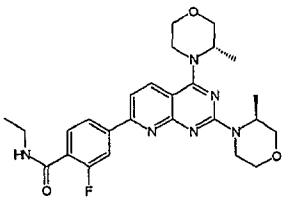
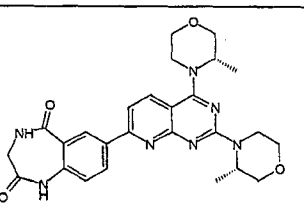
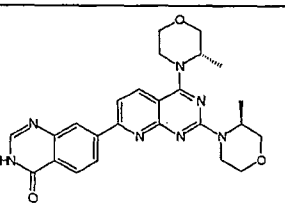


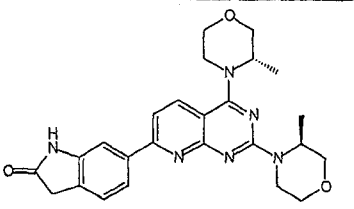
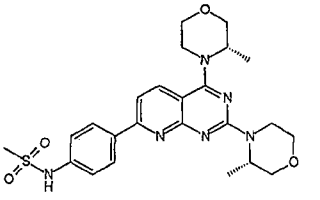
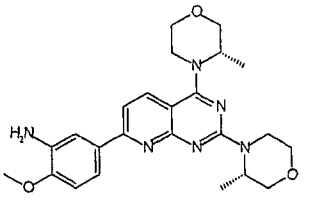
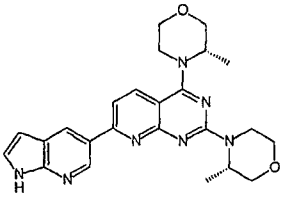
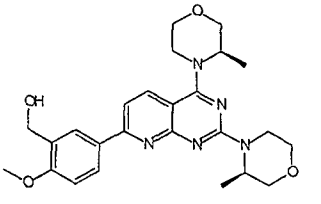
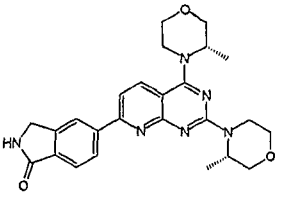
5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-1H-indazol-3-ylamine: (52 % yield, 100 % purity) m/z (LC-MS, ESP): 461.6$[M+H]^+$ R/T = 2.85min

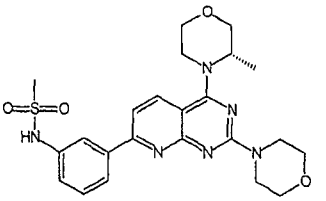
NMR data for Example 1ds

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.52 (ArH, s, 1H), 8.06 (ArH, dd, J = 8.84, 1.50 Hz, 1H), 7.94 (ArH, d, J = 8.49 Hz, 1H), 7.42 (ArH, d, J = 8.50 Hz, 1H), 7.29 (ArH, d, J = 8.79 Hz, 2H), 4.87 (CH_2, dd, J = 3.99, 1.99 Hz, 1H), 4.60 (CH_2, s, br, 1H), 4.32 (CH_2, d, J = 6.78 Hz, 1H), 3.98-3.58 (CH_2, m, 9H), 3.51 (CH_2, dt, J = 11.78, 11.46, 2.71 Hz, 1H), 3.39-3.25 (CH_2, m, 1H), 1.42 (CH_3, d, J = 6.77 Hz, 3H), 1.29 (CH_3, d, J = 6.81 Hz, 3H) (NH's not clearly seen)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 165.43, 162.97, 162.33, 160.01, 142.86, 134.62, 130.11, 127.06, 120.17, 115.21, 112.98, 109.71, 104.51, 71.32, 70.94, 67.28, 66.95, 52.80, 46.95, 44.48, 39.36, 27.01, 14.79 and 14.33.

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1dt	96	3.96	461.2	U	
1du	97	4.10	513.1	I	
1dv	99	4.04	495.0	J	
1dw	98	3.70	504.1	V	
1dx	99	3.79	474.1	I	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1dy	99	3.79	474.1	W	
1dz	99	4.06	499.2	D	
1ea	99	4.16	451.2	D	
1eb	98	3.96	446.2	P	
1ec	99	7.55	466.2	J	
1ed	98	3.86	461.2	D	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
1ee	98	4.04	485.2	D	

Note:

The following examples were synthesized from the corresponding boronic acids: 1du, 1dv, 1dz and 1ee.

The following examples were synthesized from the corresponding pinacolate boron esters: 1dw, 1dx, 1ea, 1eb and 1ec.

The following Examples were synthesized from a mixture of the corresponding boronic acids and pinacolate boron esters: 1dt, 1dy, and 1ed.

NMR data for Example 1ec

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.15 (ArH, d, J = 7.5 Hz, 2H), 7.97 (ArH, d, J = 8.46 Hz, 1H), 7.42 (ArH, d, J = 8.46 Hz, 1H), 6.98 (ArH, d, J = 9.24 Hz, 1H), 4.91 (CH_2, d, J = 5.55 Hz, 1H), 4.77 (CH_2OH, s, 2H), 4.61 (CH_2, d, J = 12.42 Hz, 1H), 4.36 – 4.34 (CH_2, m, 1H), 4.00 – 3.70 (OCH_3 + CH_2, m, 9H), 3.69 – 3.51 (CH_2, m, 1H), 3.41 – 3.31 (CH_2, m, 1H), 1.46 (CH_3, d, J = 6.69 Hz, 3H), 1.35 (CH_3, d, J = 6.87 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.42, 162.88, 161.87, 159.95, 159.16, 134.54, 131.13, 129.25, 128.89, 128.44, 112.85, 110.27, 104.49, 71.30, 70.92, 67.26, 66.93, 61.98, 55.56, 52.78, 46.91, 44.45, 39.32, 14.69 and 14.31.

NMR data for Example 1ed

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.34 (ArH, s, 1H), 8.11 (ArH, d, J = 8.02 Hz, 1H), 8.00 (ArH, d, J = 8.41 Hz, 1H), 7.90 (ArH, d, J = 7.98 Hz, 1H), 7.43 (ArH, d, J = 8.42 Hz, 1H), 7.10 (NH, br, s, 1H), 4.95-4.81 (CH_2, m, 1H), 4.57 (CH_2, d, J = 13.37 Hz, 1H), 4.47 ($NHCH_2$, s, 2H), 4.33 (CH_2, d, J = 6.68 Hz, 1H), 3.99-3.58 (CH_2, m, 9H), 3.51 (CH_2, dt, J = 11.81, 11.45, 2.72 Hz, 1H), 3.31 (CH_2, dt, J = 12.91, 12.52, 3.57 Hz, 1H), 1.42 (CH_3, d, J = 6.78 Hz, 3H), 1.30 (CH_3, d, J = 6.81 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 171.32, 165.36, 162.94, 161.42, 160.04, 144.06, 142.31, 135.01, 133.20, 127.63, 123.83, 123.08, 113.49, 105.35, 71.27, 70.91, 67.24, 66.91, 52.85, 46.96, 45.70, 44.48, 39.35, 14.76 and 14.39.

NMR data for Example 1ef

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.08 (ArH, d, J = 1.95 Hz, 1H), 8.01-7.94 (ArH, m, 1H), 7.82 (ArH, td, J = 6.63, 1.80, 1.80 Hz, 1H), 7.48 (NH, br, s, 1H), 7.39 (ArH, dd, J = 12.99, 5.20 Hz, 3H), 4.34 (CH_2, q, J = 6.63, 6.56, 6.56 Hz, 1H), 3.97-3.76 (CH_2, m, 7H), 3.75-3.57 (CH_2, m, 7H), 2.87 (SO_2CH_3, s, 3H), 1.42 (CH_3, d, J = 6.78 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.21, 162.77, 161.34, 160.28, 140.30, 137.69, 135.07, 129.91, 124.53, 122.37, 120.57, 113.44, 105.22, 70.91, 66.97, 66.89, 52.84, 44.58, 44.39, 39.32 and 14.79.

NMR data for Example 1dz

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.11-8.03 (ArH, m, 2H), 7.96 (ArH, d, J = 8.44 Hz, 1H), 7.38-7.31 (ArH, m, 1H), 7.32-7.24 (ArH, m, 2H), 4.85 (CH_2, d, J = 5.45 Hz, 1H), 4.54 (CH_2, d, J = 12.83 Hz, 1H), 4.32 (CH_2, d, J = 6.78 Hz, 1H), 3.97-3.57 (CH_2, m, 9H), 3.50 (CH_2, dt, J = 11.75, 11.35, 2.73 Hz, 1H), 3.37-3.24 (CH_2, m, 1H), 2.95 (SO2C<u>H</u>$_3$, s, 3H), 1.42 (CH_3, d, J = 6.78 Hz, 1H), 1.29 (CH_3, d, J = 6.81 Hz, 3H) (NH not seen).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.36, 162.93, 161.33, 160.00, 138.73, 135.29, 134.86, 129.34, 119.66, 112.95, 104.90, 71.27, 70.92, 67.24, 66.93, 52.82, 46.97, 44.45, 39.58, 33.35, 14.75 and 14.36.

NMR data for Example 1ea

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 7.87 (ArH, d, J = 8.55 Hz, 1H), 7.81 (ArH, d, J = 1.80 Hz, 1H), 7.47 (ArH, dd, J = 8.17, 1.85 Hz, 1H), 7.35 (ArH, d, J = 8.57 Hz, 1H), 6.69 (ArH, d, J = 8.14 Hz, 1H), 4.85 (CH_2, d, J = 5.96 Hz, 1H), 4.62-4.52 (CH_2, m, 1H), 4.28 (CH_2, d, J = 6.77 Hz, 1H), 4.02 (NH_2, s, br, 2H), 3.95 (d, J = 6.54 Hz, 1H), 3.93 (CH_3, s, 3H), 3.92-3.57 (CH_2, m, 9H), 3.55 -3.45 (CH_2, m, 1H), 3.38-3.25 (CH_2, m, 1H), 1.39 (CH_3, d, J = 6.77 Hz, 3H), 1.29 (CH_3, d, J = 6.81 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.48, 162.91, 162.45, 159.98, 147.22, 138.70, 134.14, 128.92, 121.24, 113.97, 112.74, 110.15, 104.11, 71.35, 70.95, 67.32, 66.96, 55.83, 52.79, 46.89, 44.44, 39.31, 31.60, 22.66 and 14.30.

NMR data for Example 1eb

^{1}H NMR (300 MHz, CD_3COCD_3 δ ppm 11.83 (ArH, s, 1H), 9.06 (ArH, d, J = 2.07 Hz, 1H), 8.75 (ArH, d, J = 2.09 Hz, 1H), 8.30-8.10 (ArH, m, 1H), 7.72 (ArH, d, J = 8.55 Hz, 1H), 7.54 (ArH, s, 1H), 6.59 (NH, s, 1H), 4.77 (CH_2, dd, J = 6.66, 1.89 Hz, 1H), 4.49-4.34 (CH_2, m, 2H), 4.03-3.83 (CH_2, m, 3H), 3.81-3.55 (CH_2, m, 6H), 3.54-3.38 (CH_2, m, 1H), 3.23 (CH_2, dd, J = 13.19, 3.46 Hz, 1H), 1.37 (CH_3, d, J = 6.74 Hz, 3H), 1.25 (CH_3, d, J = 6.75 Hz, 3H).
^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm 165.41, 163.09, 161.32, 160.22, 150.21, 143.45, 136.25, 128.14, 128.09, 126.99, 120.44, 113.54, 104.90, 101.82, 71.32, 71.09, 67.27, 67.09, 52.78, 47.17, 44.79 and 15.25.

NMR data for Example 1dy

1H NMR (300 MHz, CD_3SOCD_3 δ ppm 8.40 (ArH, d, J = 1.37 Hz, 1H), 8.33 (ArH, dd, J = 8.38, 1.63 Hz, 1H), 8.25 (ArH, d, J = 8.45 Hz, 2H), 8.17 (ArH, s, 1H), 7.79 (ArH, d, J = 8.48 Hz, 1H), 4.84-4.73 (CH, m, 1H), 4.45 (CH_2, d, J = 13.67 Hz, 2H), 4.00-3.84 (CH_2, m, 3H), 3.81-3.57 (CH_2, m, 6H), 3.46 (CH_2, dt, J = 11.84, 11.73, 2.61 Hz, 1H), 3.23 (CH_2, dt, J = 13.16, 12.92, 3.65 Hz, 1H), 1.39 (CH_3, d, J = 6.75 Hz, 3H), 1.26 (CH_3, d, J = 6.75 Hz, 3H)
13C NMR (75 MHz, CD_3SOCD_3 δ ppm 164.30, 162.06, 160.45, 159.32, 159.03, 149.10, 145.91, 143.53, 135.86, 126.40, 125.73, 125.30, 123.33, 113.30, 105.06, 70.35, 70.14, 66.31, 66.14, 51.79, 46.27, 43.81, 30.38, 14.35 and 13.89.

NMR data for Example 1dv

^{1}H NMR (300 MHz, CD_3SOCD_3 δ ppm 8.39 (ArH, dd, J = 5.45, 3.65 Hz, 1H), 8.23 (ArH, d, J = 8.47 Hz, 1H), 8.14-8.03 (ArH, m, 2H), 7.81-7.69 (ArH + NH, m, 2H), 4.77 (CH_2, dd, J = 6.52, 2.00 Hz, 1H), 4.43 (CH_2, d, J = 13.75 Hz, 2H), 3.99-3.83 (CH_2, m, 2H), 3.80-3.56 (CH_2, m, 6H), 3.52-3.15 (CH_2, m, 5H), 2.50 (CH_2, td, J = 3.67, 1.83, 1.83 Hz, 2H), 1.38 (CH_3, d, J = 6.75 Hz, 3H), 1.25 (CH_3, d, J = 6.75 Hz, 3H), 1.19-1.10 (CH_3, m, 3H).

^{13}C NMR (75 MHz, CD_3SOCD_3 δ ppm 164.80, 163.51, 162.52, 159.84, 158.73, 158.27, 142.53, 142.43, 136.38, 131.02, 125.84, 123.52, 123.48, 115.08, 114.76, 113.45, 105.57, 70.87, 70.64, 66.83, 66.65, 52.32, 46.79, 44.32, 34.59, 15.10, 14.87 and 14.42.

NMR data for Example 1dy

^{1}H NMR (300 MHz, , CD_3SOCD_3 δ ppm 10.52 (NH, s, 1H), 8.19 (ArH, d, J = 8.50 Hz, 1H), 7.79-7.68 (ArH, m, 2H), 7.61 (ArH, d, J = 8.52 Hz, 1H), 7.35 (ArH, d, J = 7.66 Hz, 1H), 4.84-4.69 (CH_2, m, 1H), 4.42 (CH_2, dd, J = 7.38, 5.30 Hz, 2H), 3.91 (CH_2, dd, J = 14.30, 7.97 Hz, 3H), 3.82-3.52 (CH_2, m, 8H), 3.45 (CH_2, d, J = 2.42 Hz, 1H), 3.26 – 3.15 (CH_2, m, 1H), 1.37 (CH_3, d, J = 6.74 Hz, 3H), 1.25 (CH_3, d, J = 6.76 Hz, 3H).

^{13}C NMR (75 MHz, CD_3SOCD_3 δ ppm 176.84, 164.89, 162.55, 160.83, 159.82, 144.90, 138.19, 135.98, 128.66, 125.02, 120.94, 113.09, 108.05, 104.92, 70.90, 70.67, 66.84, 66.67, 52.32, 46.76, 44.30, 36.29, 14.85 and 14.35.

NMR data for Example 1dt

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.58 (ArH, d, J = 7.97 Hz, 1H), 8.49 (ArH, d, J = 45.95 Hz, 1H), 7.99 (ArH, d, J = 8.42 Hz, 1H), 7.50 (ArH, dd, J = 17.31, 8.21 Hz, 1H), 7.24 (ArH, d, J = 17.82 Hz, 1H), 5.01-4.86 (CH_2, s, br, 1H), 4.65-4.39 (CH_2, m, 3H), 4.33 (CH_2, d, J = 6.25 Hz, 1H), 4.04-3.58 (CH_2, m, 8H), 3.49 (CH_2, d, J = 11.36 Hz, 1H), 3.31 (CH_2, d, J = 2.99 Hz, 1H), 1.41 (CH_3, d, J = 6.72 Hz, 3H), 1.29 (CH_3, d, J = 6.76 Hz, 3H) (1 proton missing, lots of overlap seen, NH not seen either)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 171.52, 165.39, 162.90, 161.33, 160.01, 145.14, 139.06, 135.02, 132.17, 123.57, 122.56, 113.20, 105.21, 71.29, 70.92, 67.25, 66.93, 52.78, 46.95, 45.68, 44.51, 39.34, 27.00, 14.74 and 14.35.

NMR data for Example 1du

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.12 (ArH, d, J = 8.32 Hz, 2H), 8.03 (ArH, d, J = 8.43 Hz, 1H), 7.51-7.39 (ArH, m, 3H), 5.08 (CH_2, br, s, 1H), 4.89 (CH_2, d, J = 4.91 Hz, 1H), 4.58 (CH_2, d, J = 12.59 Hz, 1H), 4.40 (CH_2NH, br, s, 2H), 4.22 (NH, br, s, 1H), 4.04-3.64 (CH_2, m, 9H), 3.56 (CH_2, dt, J = 11.80, 11.45, 2.75 Hz, 1H), 3.44-3.30 (CH_2, m, 1H), 2.87 (SO_2CH_3s, 3H), 1.48 (CH_3, d, J = 6.78 Hz, 3H), 1.35 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$ δ ppm 165.16, 163.70, 162.51, 159.71, 138.71, 138.33, 134.99, 128.40, 128.15, 113.45, 105.20, 71.23, 70.89, 67.18, 66.90, 52.82, 47.07, 46.90, 44.21, 41.25, 39.41, 14.78 and 14.38.

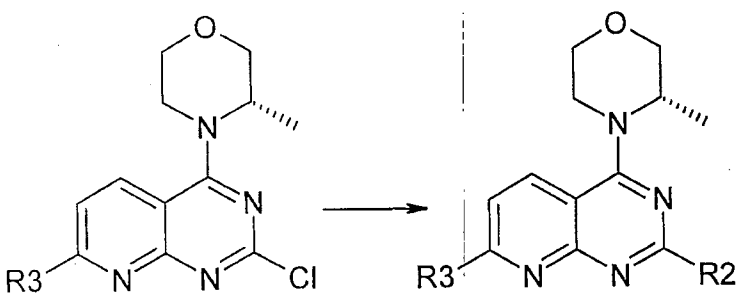
Tested in the Biological Assay: Ex. (1b) 0.00185μM; Ex. (1c) 0.00184μM Ex. (1d) 0.00245μM; Ex. (1az) 0.006865μM.

Tested in Alternative Enzyme Assay: Ex. (1a) 0.0089μM; Ex. (1e) 0.0044μM; Ex. (1f) 0.005μM; Ex. (1g) 0.011μM; Ex. (1h) 0.0021μM; Ex. (1i) 0.0056μM; Ex. (1j) 0.035μM; Ex. (1k) 0.015μM; Ex. (1l) 0.0057μM; Ex. (1m) 0.31μM; Ex. (1n) 0.085μM; Ex. (1o) 0.14μM; Ex. (1p) 0.038μM; Ex. (1q) 0.39μM; Ex. (1r) 0.23μM; Ex. (1s) 0.028μM; Ex. (1t) 0.34μM; Ex. (1u) 0.015μM; Ex. (1v) 0.18μM; Ex. (1w) 0.26μM; Ex. (1x) 0.53μM; Ex. (1y) 0.33μM; Ex. (1z) 0.37μM; Ex. (1aa) 0.025μM; Ex. (1ab) 0.029μM; Ex. (1ac) 0.14μM; Ex. (1ad) 0.0069μM; Ex. (1ae) 0.38μM; Ex. (1af) 0.054μM; Ex. (1ag) 0.029μM; Ex. (1ah) 0.012μM; Ex. (1ai) 1.1μM; Ex. (1aj) 0.49μM; Ex. (1ak) 0.017μM; Ex. (1al) 0.23μM; Ex. (1am) 0.21μM; Ex. (1an) 0.14μM; Ex. (1ao) 0.0083μM; Ex. (1ap) 0.02μM; Ex. (1aq) 0.084μM; Ex. (1ar) 0.006μM; Ex. (1as) 0.013μM; Ex. (1at) 0.031μM; Ex. (1au) 0.09μM; Ex. (1av) 0.29μM; Ex. (1aw) 0.062μM; Ex. (1ax) 0.0092μM; Ex. (1ay) 0.15μM; Ex. (1ba) 0.44μM; Ex. (1bb) 0.14μM; Ex. (1bc) 0.083μM; Ex. (1bd) 0.011μM; Ex. (1be) 0.18μM; Ex. (1bf) 0.06μM; Ex. (1bg) 0.17μM; Ex. (1bh) 0.014μM; Ex. (1bi) 0.032μM; Ex. (1bj) 0.035μM; Ex. (1bk) 0.039μM; Ex. (1bl) 0.0027μM; Ex. (1bm) 0.055μM; Ex. (1bn) 0.04μM; Ex. (1bo) 0.018μM; Ex. (1bp) 0.11μM; Ex. (1bq) 0.14μM; Ex. (1br) 0.056μM; Ex. (1bs) 0.039μM; Ex. (1bt) 0.11μM; Ex. (1bu) 0.016μM; Ex. (1bv) 0.0051μM; Ex. (1bw) 0.036μM; Ex. (1bx) 0.038μM; Ex. (1by) 0.0046μM; Ex. (1bz) 0.018μM; Ex. (1ca) 0.35μM; Ex. (1cb) 0.5μM; Ex. (1cc) 0.0064μM; Ex. (1cd) 0.46μM; Ex. (1ce) 0.091μM; Ex. (1cf) 0.073μM; Ex. (1cg) 0.00026μM; Ex. (1ch) 0.22μM; Ex. (1ci) 0.15μM; Ex. (1cj) 0.091μM; Ex. (1ck) 0.065μM; Ex. (1cl) 0.2μM; Ex. (1cm) 0.16μM; Ex. (1cn) 0.31μM; Ex. (1co) 2.5μM; Ex. (1cp) 1μM; Ex. (1cq) 0.25μM; Ex. (1cr) 0.69μM; Ex. (1cs) 7.5μM; Ex. (1ct) 0.024μM; Ex. (1cu) 0.042μM; Ex. (1cv) 0.3μM; Ex. (1cw) 0.49μM; Ex. (1cx) 0.12μM; Ex. (1cy) 0.72μM; Ex. (1cz) 0.066μM; Ex. (1da) 1.8μM; Ex. (1db) 0.031μM; Ex. (1dc) 0.02μM; Ex. (1dd) 0.073μM; Ex. (1de) 0.0049μM; Ex. (1dg) 0.014μM; Ex. (1dh) 0.041μM; Ex. (1di) 0.23μM; Ex. (1dj) 0.25μM; Ex. (1dk) 0.02μM; Ex. (1dl) 0.018μM; Ex. (1dm) 0.0075μM; Ex. (1dn) 0.0055μM; Ex. (1do) 0.03μM; Ex. (1dp) 0.0067μM; Ex. (1dq) 0.037μM; Ex. (1dt) 0.0026μM; Ex. (1du)

0.00039μM; Ex. (1dv) 0.72μM; Ex. (1dw) 0.021μM; Ex. (1dx) 0.035μM; Ex. (1dy) 0.0035μM; Ex. (1dz) 0.099μM; Ex. (1ea) 0.057μM; Ex. (1eb) 0.17μM; Ex. (1ec) 0.013μM; Ex. (1ed) 0.016μM; Ex. (1ee) 0.0048μM.

Tested in phospho-Ser473 Akt assay: Ex. (1df) 0.3813μM; Ex. (1dr) 0.01415μM; Ex. (1ds) 0.06066μM.

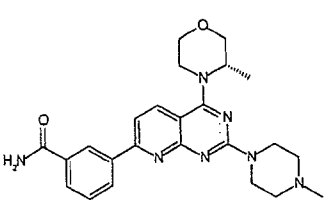
Example 2

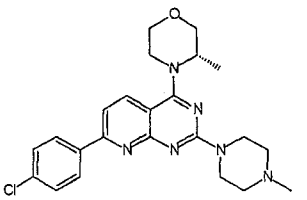
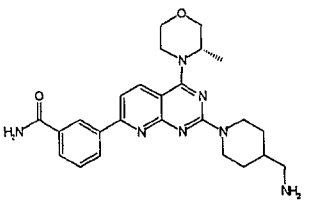
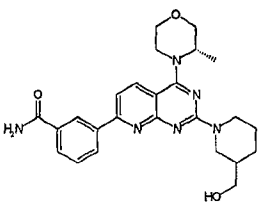
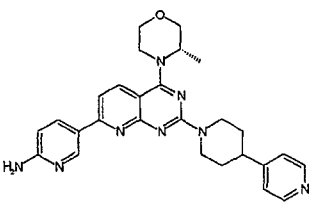
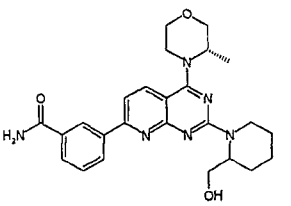


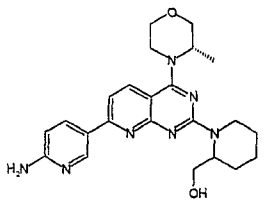
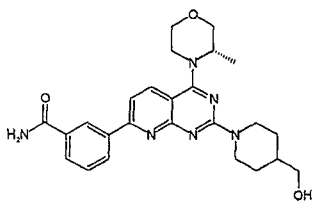
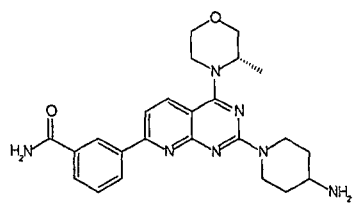
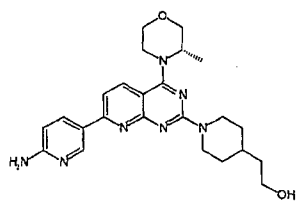
R2= Amino

R3= Aryl or hetero aryl

To a solution (0.2 M) of the appropriate chloro-substrate (1 equiv) in dioxane was added diisopropylethylamine (2 equiv). To this mixture was then added the appropriate amine (2 equiv). The reaction was then heated under the influence of microwave radiation (120 °C, medium absorption setting) for 10 minutes. Upon completion the sample was concentrated *in vacuo* and the resulting residue dissolved in CH_2Cl_2 and washed with H_2O. The organic fraction was removed, dried ($MgSO_4$). The crude residue was purified by flash chromatography (SiO_2) to give the desired products.

	Purity (%)	Retention time (min)	M/z $[M+H]^+$	Example Structure
2a	97	3.28	448.3	

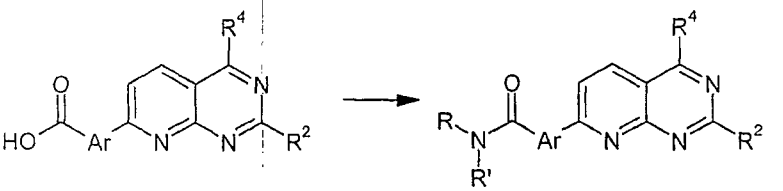
	Purity (%)	Retention time (min)	M/z $[M+H]^+$	Example Structure
2b	99	3.78	439.3	
2c	99	3.31	462.4	
2d	100	3.76	463.3	
2e	99	3.11	483.3	
2f	99	3.82	463.4	

	Purity (%)	Retention time (min)	M/z $[M+H]^+$	Example Structure
2g	100	3.39	436.5	
2h	100	3.68	463.4	
2i	98	3.26	448.4	
2j	100	3.38	450.3	

Tested in Alternative Enzyme Assay: Ex. (2a) 0.7μM; Ex. (2b) 0.56μM; Ex. (2c) 0.6μM; Ex. (2d) 0.27μM; Ex. (2e) 0.35μM; Ex. (2f) 0.17μM; Ex. (2g) 0.064μM; Ex. (2h) 0.29μM; Ex. (2i) 0.64μM; Ex. (2j) 0.2μM.

Example 3:

(Compounds 3a to 3ab)
R^4 = (S)-3-methyl-morpholine
R^2 = (S)-3-methyl-morpholine
Ar = aryl



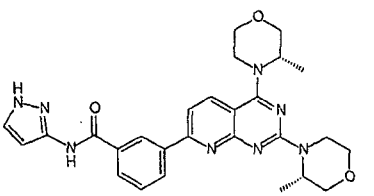
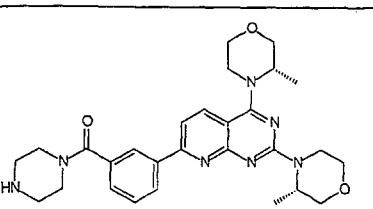
Carboxy-substrates are reported in Example 1.

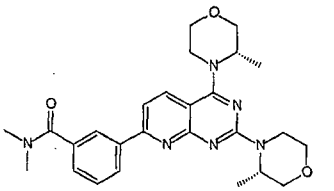
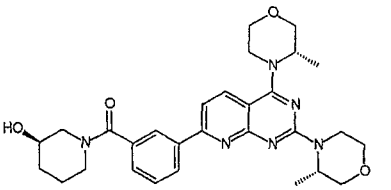
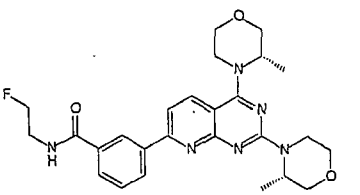
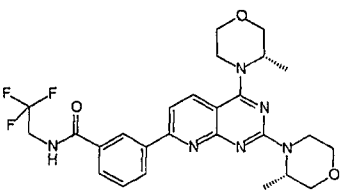
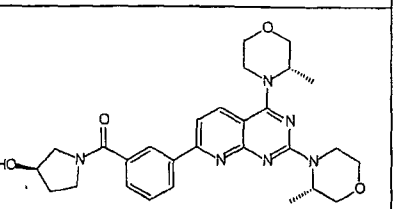
Method: Amide Formation

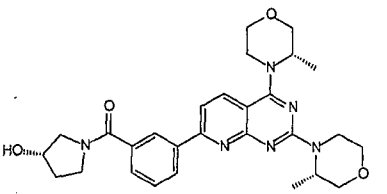
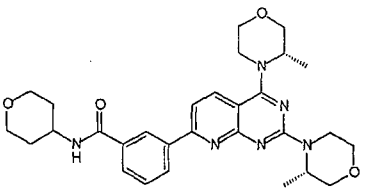
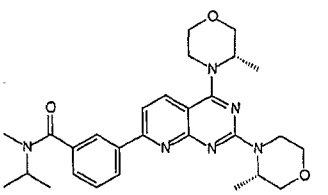
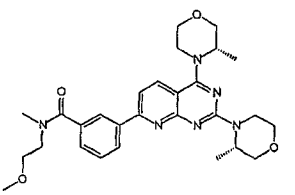
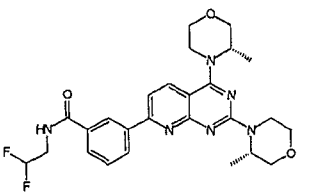
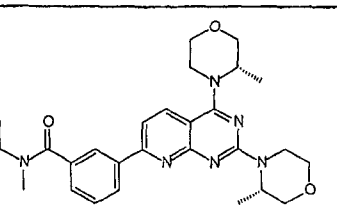
Conditions A:

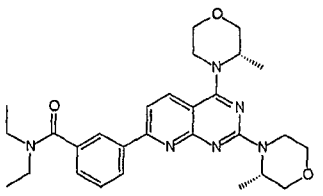
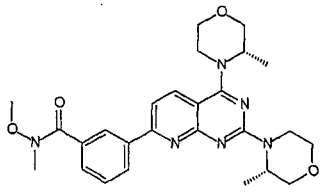
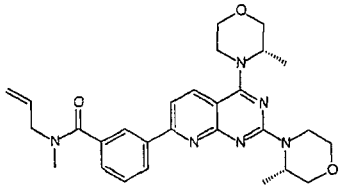
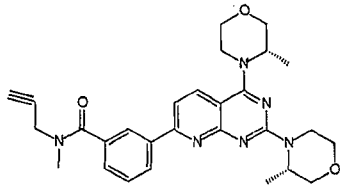
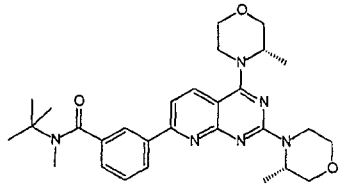
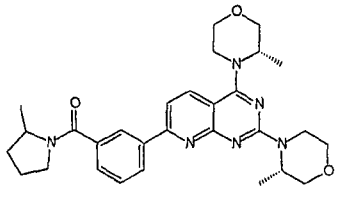
The appropriate carboxy-substrate (1 equiv) was dissolved in DMF (0.067 M). HBTU (1.2 equiv) and appropriate amines (1.05 equiv) were added along with 3 drops of triethylamine at 0°C. The reaction vessels were sealed and the mixtures were stirred between 1 and 12 hours at room temperature. Upon completion the samples were concentrated *in vacuo*. The crude residues were then purified by preparative HPLC to give the desired products.

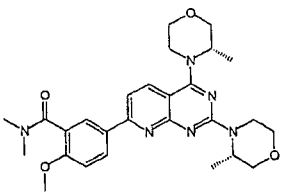
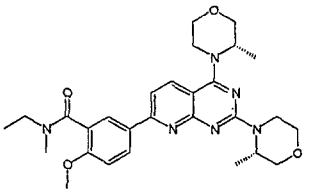
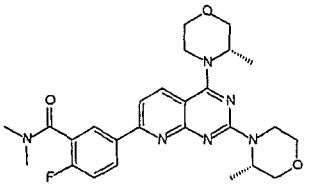
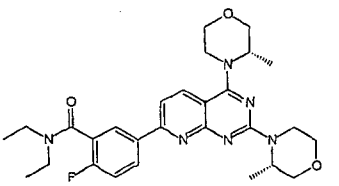
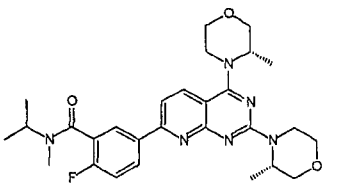
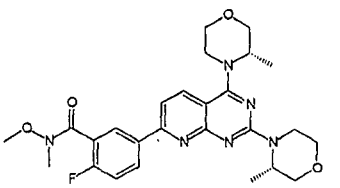
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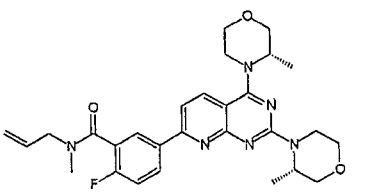
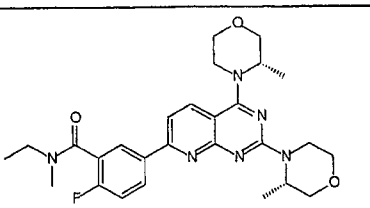
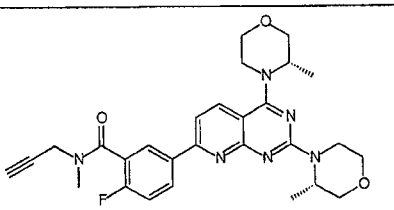
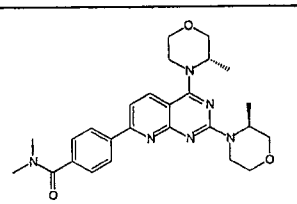
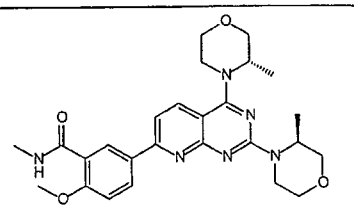
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3a	98	7.36	515.3	A	
3b	82	5.31	518.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3c	96	7.2	477.3	A	
3d	96	6.95	533.4	A	
3e	95	7.33	495.3	A	
3f	95	8.34	531.3	A	
3g	98	6.61	519.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3h	98	6.64	519.4	A	
3i	99	7.32	533.4	A	
3j	99	8.19	505.4	A	
3k	98	4.15	521.5	A	
3l	99	4.27	513.4	A	
3m	90	4.22	491.3	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3n	98	4.35	505.5	A	
3o	95	4.2	493.4	A	
3p	98	4.36	503.4	A	
3q	98	4.31	501.4	A	
3r	95	4.62	519.5	A	
3s	99	4.19	517.3	A	

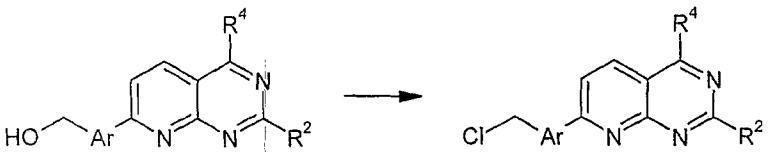
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3t	99	3.97	507.4	A	
3u	99	4.07	521.4	A	
3v	96	7.38	495.4	A	
3w	91	8.42	523.3	A	
3x	97	8.44	523.4	A	
3y	97	7.69	511.3	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
3z	92	8.33	521.3	A	
3aa	86	4.12	509.3	A	
3ab	83	4.19	519.3	A	
3ac	100	7.13	477.4	A	
3ad	100	4.00	493.4	A	

Tested in Alternative Enzyme Assay: Ex. (3a) 0.048μM; Ex. (3b) 0.32μM; Ex. (3c) 0.09μM; Ex. (3d) 0.28μM; Ex. (3e) 0.0047μM; Ex. (3f) 0.28μM; Ex. (3g) 0.0052μM; Ex. (3h) 0.18μM; Ex. (3i) 0.14μM; Ex. (3j) 0.17μM; Ex. (3k) 0.23μM; Ex. (3l) 0.044μM; Ex. (3m) 0.32μM; Ex. (3n) 0.23μM; Ex. (3o) 0.37μM; Ex. (3p) 0.56μM; Ex. (3q) 0.12μM; Ex. (3r)

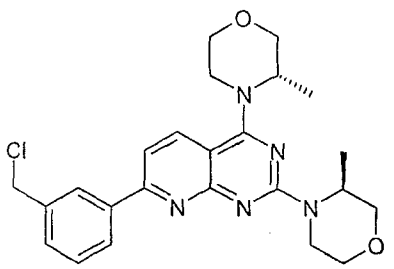
0.5μM; Ex. (3s) 0.38μM; Ex. (3t) 0.042μM; Ex. (3u) 0.13μM; Ex. (3v) 0.16μM; Ex. (3w) 0.5μM; Ex. (3x) 0.24μM; Ex. (3y) 0.74μM; Ex. (3z) 0.34μM; Ex. (3aa) 0.026μM; Ex. (3ab) 0.14μM; Ex. (3ac) 1.6μM; Ex. (3ad) 0.066μM.

Example 4

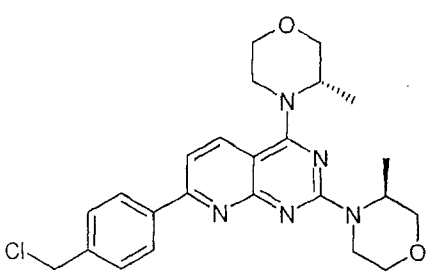


Benzyl alcohol substrates are reported in Example 1.

The appropriate benzyl alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.08 M). Triethylamine (1 equiv) was added at room temperature, followed by the addition of thionyl chloride (2 equiv). The reaction mixture was stirred at 30°C for 45 minutes. Upon completion the reaction mixture was partitioned between brine and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 10 to 70 % ethyl acetate in hexane.

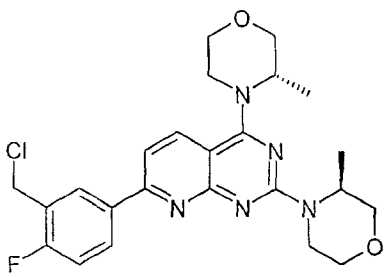


7-(3-Chloromethyl-phenyl)-2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine: (72 % yield, 90 % purity) m/z (LC-MS, ESP): 454 $[M+H]^+$ R/T = 3.15 min



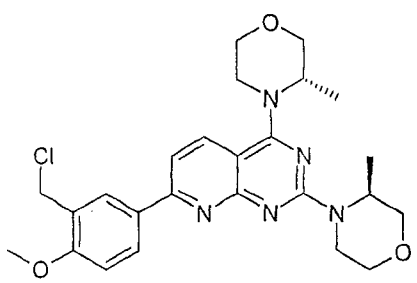
The appropriate benzyl alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.052 M). Thionyl chloride (3.3 equiv) was added. The reaction mixture was heated up to 55°C and a solution of triethylamine (1.7 equiv) in CH_2Cl_2 (0.044 M) was added dropwise over 10 minutes. The reaction mixture was allowed to stir at 30°C for 10 minutes. Upon completion the reaction mixture was partitioned between brine and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 10 to 50 % ethyl acetate in hexane.

7-(4-Chloromethyl-phenyl)-2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine: (65 % yield, 90 % purity) m/z (LC-MS, ESP): 454 $[M+H]^+$ R/T = 3.15 min



The appropriate benzyl alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.044 M). Thionyl chloride (3.3 equiv) was added. The reaction mixture was heated up to 55°C and a solution of triethylamine (1.7 equiv) in CH_2Cl_2 (0.044 M) was added dropwise over 10 minutes. The reaction mixture was allowed to stir at 30°C for 30 minutes. Upon completion the reaction mixture was partitioned between brine and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was used without further purification.

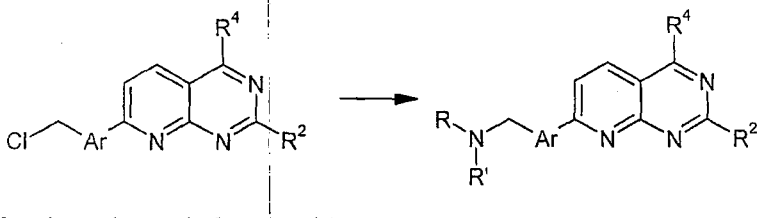
7-(3-Chloromethyl-4-fluoro-phenyl)-2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine: (96 % yield, 90 % purity) m/z (LC-MS, ESP): 472 $[M+H]^+$ R/T = 3.96 min



The appropriate benzyl alcohol (1 equiv) was dissolved in CH_2Cl_2 (0.086 M). Triethylamine (2.5 equiv) and thionyl chloride (2.5 equiv) were added. The reaction mixture was heated up to 45°C afor 3 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 10 to 50 % ethyl acetate in hexane.

7-(3-Chloromethyl-4-methoxy-phenyl)-2,4-bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine: (37 % yield, 90 % purity) m/z (LC-MS, ESP): 484 $[M+H]^+$ R/T = 3.21 min

(Compounds 4a to 4ak)
R^4 = (S)-3-methyl-morpholine
R^2 = (S)-3-methyl-morpholine
Ar = aryl



Method: Benzylamines, benzylethers and benzylsulfones formation

Conditions A:

The appropriate chlorobenzyl-substrate (1 equiv) was dissolved in THF (0.067 M). The appropriate amine (80 equiv) as well as triethylamine (1 equiv) was added. The reaction vessels were sealed and the mixtures were stirred for 3 to 5 hours at 95°C. Upon completion the samples were concentrated *in vacuo*. The crude residues were then purified by preparative HPLC to give the desired products.

Conditions B:

The appropriate chlorobenzyl-substrate (1 equiv) was dissolved in an aqueous ammonia/n-butanol (1.5:1) solution (0.011 M). The reaction vessel was sealed and the mixture was stirred for 10 minutes at 140°C. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions C:

The appropriate chlorobenzyl-substrate (1 equiv) and sodium hydroxide (1 equiv) were dissolved in ethanol (0.011 M). The reaction vessel was sealed and the mixture was stirred for 3 hours at 50°C. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions D:

The appropriate chlorobenzyl-substrate (1 equiv) was dissolved in DMF (0.022 M). Imidazole (3 equiv) and potassium *tert*-butoxide (3 equiv) were added. The reaction vessel was sealed and the mixture was stirred for 2 hours at room temperature. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

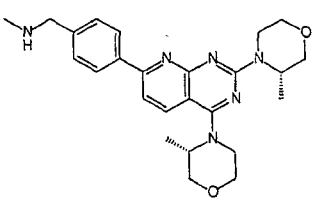
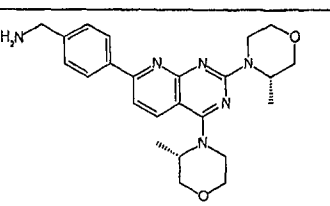
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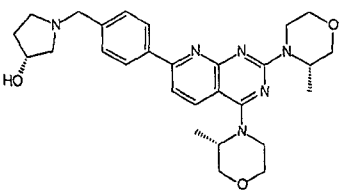
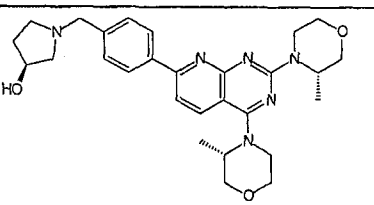
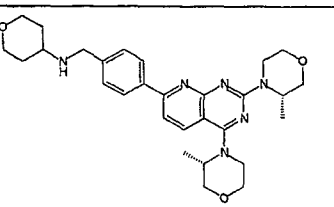
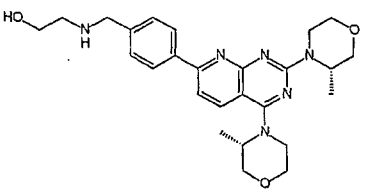
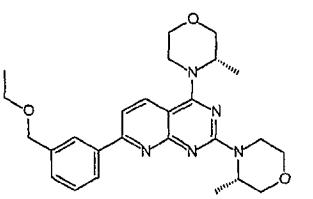
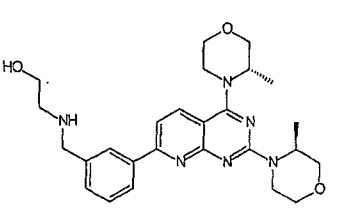
The appropriate chlorobenzyl-substrate (1 equiv) was dissolved in DMF (0.066 M). Sodium sulfinate (1.3 equiv) was added. The mixture was stirred for 2 hours at 125°C. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

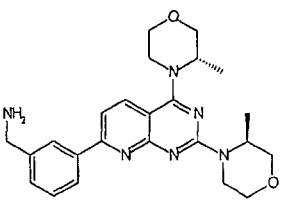
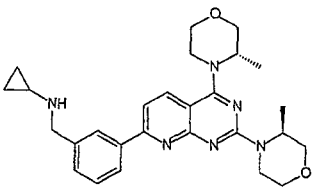
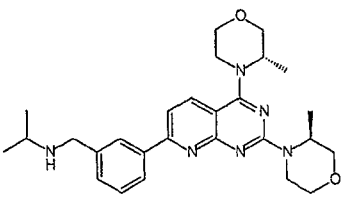
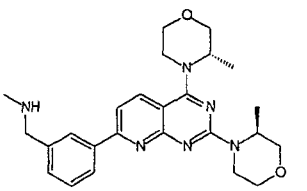
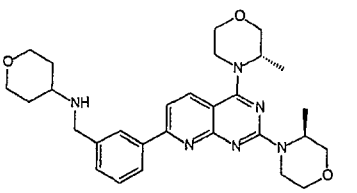
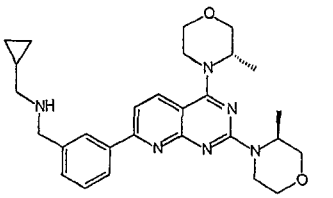
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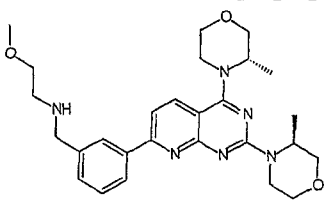
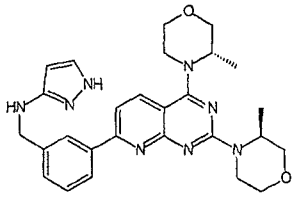
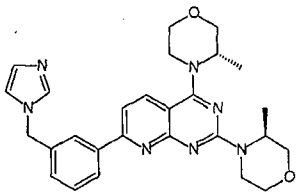
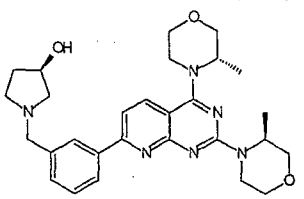
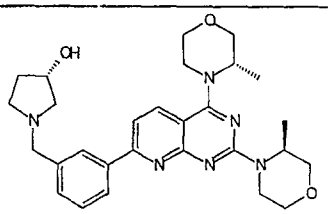
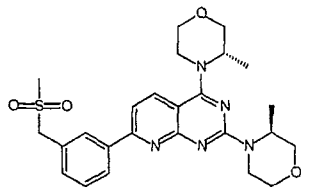
The appropriate chlorobenzyl-substrate (1 equiv), potassium carbonate (2.6 equiv) triethylamine (1 equiv) and the appropriate amine (1.1 equiv) were suspended in DMF (0.028 M). The reaction vessel was sealed and the mixture was stirred for 16 hours at 40°C. Upon completion the sample was filtered through a silica cartridge, washed with CH_2Cl_2 and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

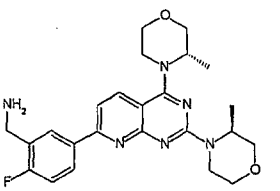
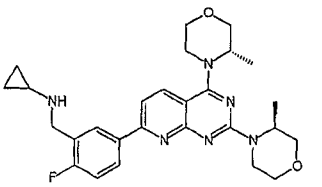
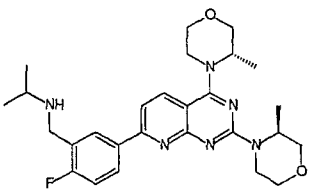
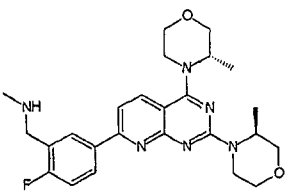
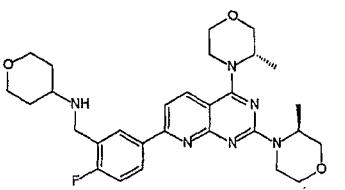
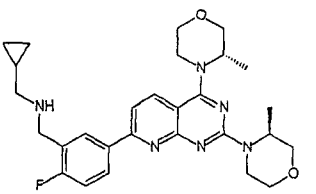
Table 4:

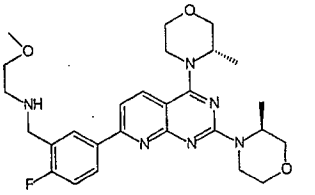
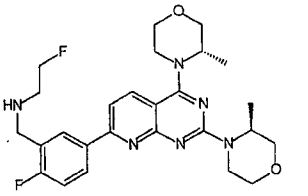
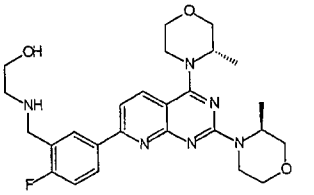
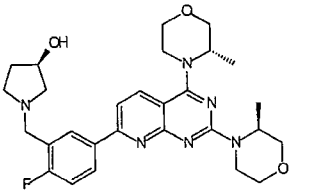
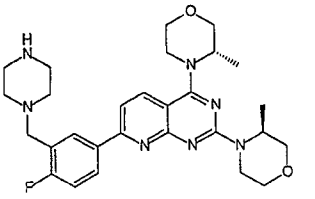
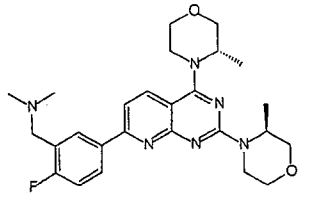
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4a	87	3.61	449.3	A	
4b	95	3.41	435.2	B	

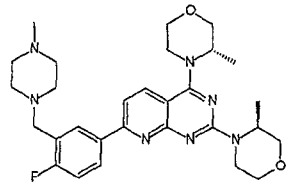
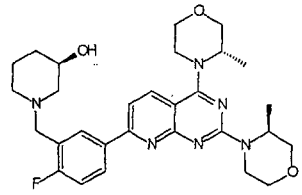
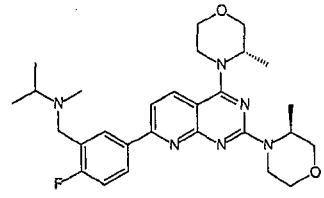
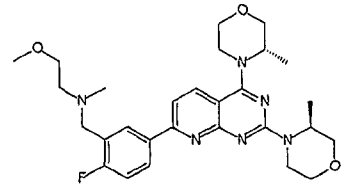
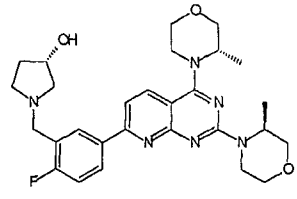
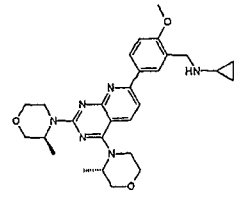
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4c	99	3.4	505.5	A	
4d	100	3.42	505.5	A	
4e	100	3.44	519.5	A	
4f	100	3.39	479.4	A	
4g	95	4.36	464.4	C	
4h	96	3.4	479.4	A	

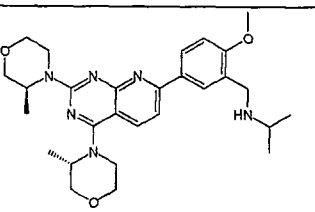
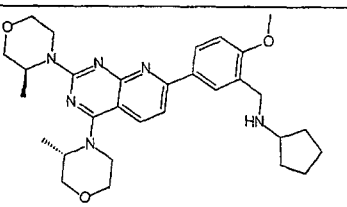
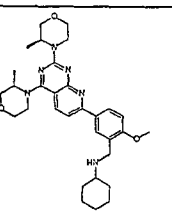
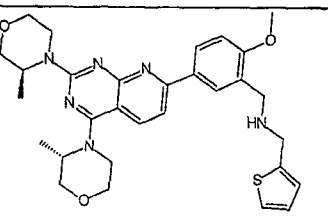
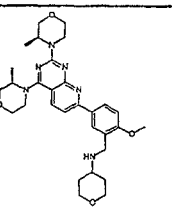
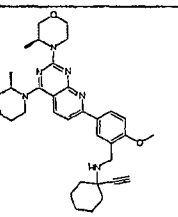
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4i	95	3.4	435.4	B	
4j	92	5.6	475.4	A	
4k	94	5.65	477.4	A	
4l	97	5.39	449.4	A	
4m	90	5.6	519.5	A	
4n	96	5.83	489.5	A	

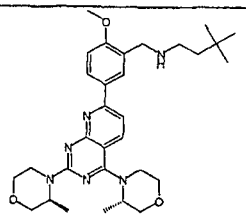
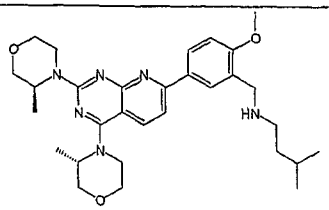
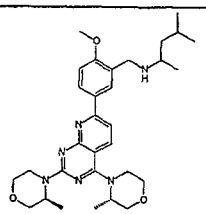
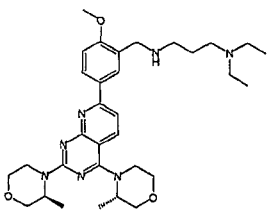
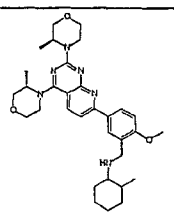
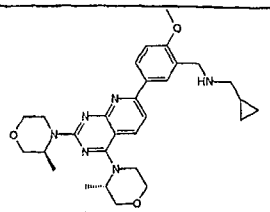
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4o	95	5.56	493.4	A	
4p	26, 69	6.63, 6.78	501.4	A	
4q	99	3.43	486.4	D	
4r	94	3.44	505.5	A	
4s	97	3.44	505.3	A	
4t	94	6.06	498.7	E	

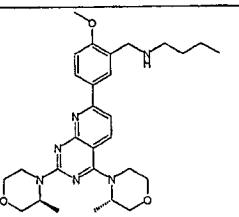
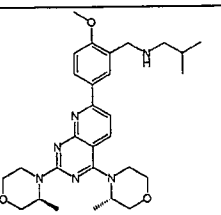
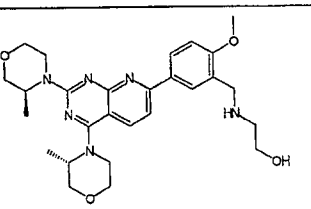
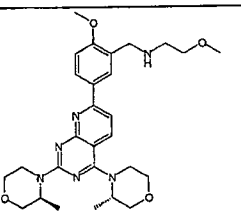
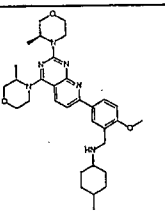
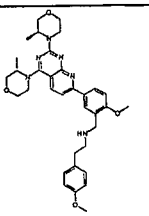
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4u	98	3.42	453.4	B	
4v	99	3.63	493.4	A	
4w	99	3.62	495.4	A	
4x	96	3.55	467.4	A	
4y	99	3.6	537.4	A	
4z	99	3.67	507.4	A	

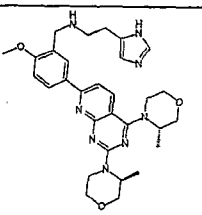
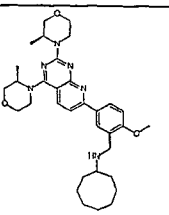
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4aa	97	3.59	511.4	A	
4ab	91	3.58	499.4	A	
4ac	99	3.55	497.4	A	
4ad	99	3.4	523.4	A	
4ae	99	3.47	522.4	A	
4af	99	3.42	481.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4ag	99	3.49	536.4	A	
4ah	98	3.43	537.5	A	
4ai	99	3.48	509.4	A	
4aj	99	3.46	525.5	A	
4ak	99	3.42	523.5	A	
4al	99	3.55	505.4	F	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4am	99	3.60	507.4	F	
4an	99	3.66	533.4	F	
4ao	99	3.77	547.5	F	
4ap	99	3.70	561.4	F	
4aq	99	3.52	549.5	F	
4ar	99	3.85	571.5	F	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4as	99	3.85	549.5	F	
4at	99	3.76	535.5	F	
4au	99	3.83	549.5	F	
4av	96	3.32	578.5	F	
4aw	99	3.82	561.5	F	
4ax	99	3.59	519.4	F	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4ay	99	3.66	521.4	F	
4az	99	3.65	521.4	F	
4ba	99	3.46	509.4	F	
4bb	99	3.52	523.4	F	
4bc	99	3.84	561.5	F	
4bd	99	3.81	599.5	F	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
4be	93	3.29	559.4	F	
4bf	99	3.91	575.5	F	

NMR data for example 4h

^{1}H NMR (300 MHz, DMSO) δ ppm 8.21 (ArH, d, J = 8.39 Hz, 2H), 8.08-8.01 (ArH, m, 1H), 7.65 (ArH, d, J = 8.49 Hz, 1H), 7.49 (ArH, d, J = 4.85 Hz, 2H), 4.82-4.72 (CH_2, m, 1H), 4.45 (CH_2,+ NH m, 3H), 3.99-3.82 (CH_2, m, 7H), 3.69 (CH_2, ddd, J = 19.97, 8.86, 5.32 Hz, 8H), 3.53 (CH_2, t, J = 5.65, 5.65 Hz, 2H), 3.29-3.15 (CH_2, m, 2H), 1.38 (CH_3, d, J = 6.75 Hz, 3H), 1.25 (CH_3, d, J = 6.75 Hz, 3H)

NMR data for Example 4r

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.19 (ArH, s, 1H), 8.03 (ArH, ddd, J = 8.43, 5.31, 3.28 Hz, 2H), 7.54-7.37 (ArH, m, 3H), 5.00-4.85 (CH, m, 1H), 4.68-4.56 (CH_2, m, 1H), 4.36 (CH_2, ddd, J = 6.83, 4.79, 2.16 Hz, 2H), 4.07-3.92 (CH_2, m, 2H), 3.91-3.66 (CH_2, m, 11H), 3.63-3.49 (CH_2, m, 1H), 3.39 (CH_2, dd, J = 13.37, 3.58 Hz, 1H), 3.04-2.92 (CH_2, m, 1H), 2.80 (CH_2, d, J = 10.30 Hz, 1H), 2.65 (CH_2, dd, J = 10.23, 4.92 Hz, 1H), 2.52-2.39 (CH_2, m, 1H), 2.21 (CH_2, d, J = 7.02 Hz, 1H), 1.89-1.73 (CH_2, m, 1H), 1.46 (CH_3, d, J = 6.77 Hz, 3H), 1.35 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.57, 163.03, 162.50, 160.11, 139.06, 134.83, 130.62, 128.81, 127.10, 113.70, 105.06, 71.44, 71.06, 67.41, 67.25, 67.07, 62.87, 60.08, 52.98, 52.49, 47.07, 44.58, 39.47, 35.02, 14.86 and 14.90.

NMR data for Example 4s

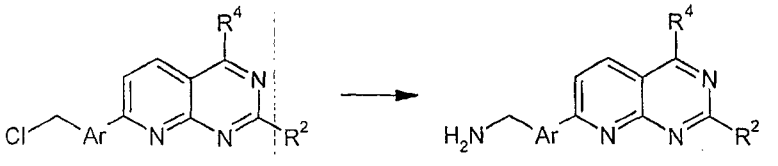
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.22 (ArH, s, 1H), 8.11-7.96 (ArH, m, 2H), 7.48 (ArH, dd, J = 10.85, 7.98 Hz, 3H), 4.99-4.86 (CH, m, 1H), 4.68-4.55 (CH, m, 1H), 4.44-4.30 (CH_2, m, 2H), 4.06-3.92 (CH_2, m, 2H), 3.93-3.65 (CH_2, m, 10H), 3.62-3.50 (CH_2, m, 1H), 3.39 (CH_2, dd, J = 13.39, 3.57 Hz, 1H), 3.14-3.01 (CH_2, m, 1H), 2.88 (CH_2, d, J = 10.59 Hz, 1H), 2.77-2.67 (CH_2, m, 1H), 2.63-2.43 (CH_2, m, 1H), 2.31-2.14 (CH_2, m, 1H), 1.92-1.79 (CH_2, m, 1H), 1.47 (CH_3, d, J = 6.77 Hz, 3H), 1.35 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$)) δ ppm 165.56, 163.03, 162.34, 160.12, 139.16, 134.89, 130.80, 128.94, 128.91, 127.39, 113.69, 105.11, 71.44, 71.21, 71.06, 67.40, 67.06, 62.61, 59.93, 52.98, 52.42, 47.08, 44.58, 39.47, 34.88, 31.73, 22.80, 14.86 and 14.91.

Tested in the Biological Assay: Ex. (4f) 0.001967μM.

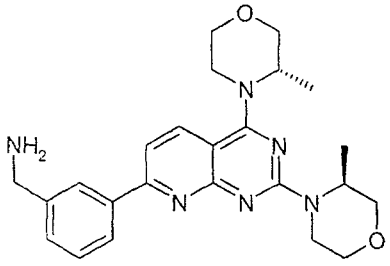
Tested in Alternative Enzyme Assay: Ex. (4a) 0.0016μM; Ex. (4b) 0.025μM; Ex. (4c) 0.093μM; Ex. (4d) 0.013μM; Ex. (4e) 0.0019μM; Ex. (4f) <0.0027μM; Ex. (4g) 0.13μM; Ex. (4h) 0.031μM; Ex. (4i) 0.027μM; Ex. (4j) 0.054μM; Ex. (4k) 0.016μM; Ex. (4l) 0.0091μM; Ex. (4m) 0.015μM; Ex. (4n) 0.0071μM; Ex. (4o) 0.021μM; Ex. (4p) 0.17μM; Ex. (4q) 0.13μM; Ex. (4r) 0.04μM; Ex. (4s) 0.029μM; Ex. (4t) 0.09μM; Ex. (4u) 0.027μM; Ex. (4v) 0.14μM; Ex. (4w) 0.028μM; Ex. (4x) 0.12μM; Ex. (4y) 0.13μM; Ex. (4z) 0.13μM; Ex. (4aa) 0.21μM; Ex. (4ab) 1.1μM; Ex. (4ac) 0.087μM; Ex. (4ad) 0.081μM; Ex. (4ae) 0.16μM; Ex. (4af) 0.58μM; Ex. (4ag) 0.54μM; Ex. (4ah) 0.2μM; Ex. (4ai) 0.22μM; Ex. (4aj) 0.46μM; Ex. (4ak) 0.015μM; Ex. (4al) 0.064μM; Ex. (4am) 0.024μM; Ex. (4an) 0.095μM; Ex. (4ao) 0.064μM; Ex. (4ap) 0.11μM; Ex. (4aq) 0.012μM; Ex. (4ar) 0.06μM; Ex. (4as) 0.091μM; Ex. (4at) 0.12μM; Ex. (4au) 0.096μM; Ex. (4av) 0.0038μM; Ex. (4aw) 0.11μM; Ex. (4ax) 0.1μM; Ex. (4ay) 0.14μM; Ex. (4az) 0.038μM; Ex. (4ba) 0.013μM; Ex. (4bb) 0.032μM; Ex. (4bc) 0.076μM; Ex. (4bd) 0.12μM; Ex. (4be) 0.049μM; Ex. (4bf) 0.059μM.

Example 5

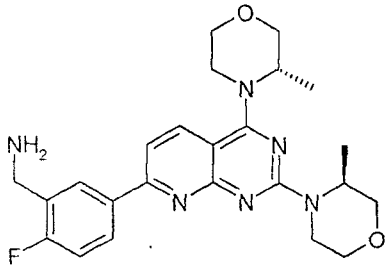


Benzyl chloride substrates are reported in Example 4.

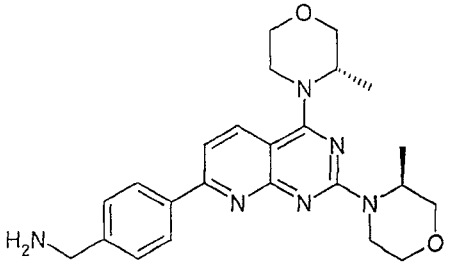
The appropriate benzyl chloride (1 equiv) was dissolved in an ammonium hydroxide and n-butanol (1.5:1) solution (0.01 M). The reaction vessel was sealed and the mixture exposed to microwave radiation (140 °C, medium absorption setting) for 10 minutes. Upon completion the reaction mixture was partitioned between brine and ethyl acetate and extracted with ethyl acetate. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % methanol in CH_2Cl_2.



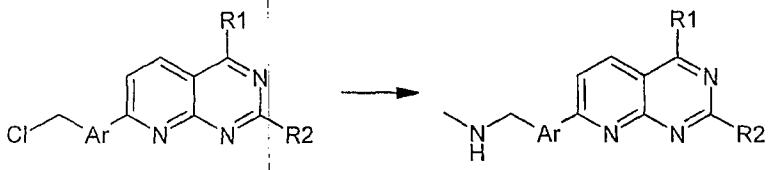
3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzylamine: (81 % yield, 100 % purity) m/z (LC-MS, ESP): 435 $[M+H]^+$ R/T = 2.44 min



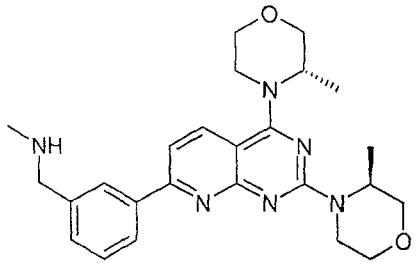
5-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-fluoro-benzylamine: (85 % yield, 98 % purity) m/z (LC-MS, ESP): 453 $[M+H]^+$ R/T = 3.21 min



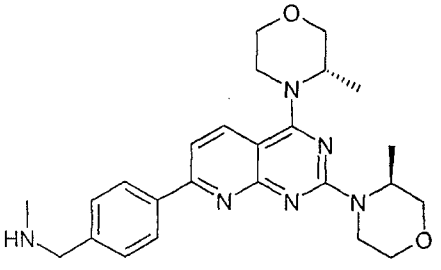
4-[2,4-Bis-(3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzylamine: (95 % yield, 97 % purity) m/z (LC-MS, ESP): 435 $[M+H]^+$ R/T = 2.36 min



The appropriate benzyl chloride (1 equiv) was dissolved in a 2 M solution of methylamine in THF (80 equiv). Triethylamine (1 equiv) was added. The reaction mixture was stirred at 95°C for 2.5 hours. Upon completion the reaction mixture was concentrated *in vacuo* and the residue was diluted with ethyl acetate and n-butanol and the organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 7 % methanol in CH_2Cl_2.



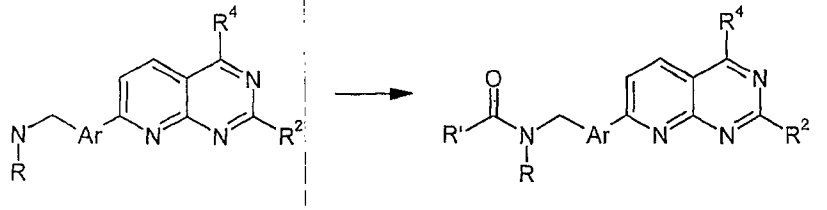
{3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzyl}-methyl-amine: (77 % yield, 94 % purity) m/z (LC-MS, ESP): 449 $[M+H]^+$ R/T = 2.44 min



{4-[2,4-Bis-(3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-benzyl}-methyl-amine: (93 % yield, 87 % purity) m/z (LC-MS, ESP): 449 $[M+H]^+$ R/T = 2.40 min

Procedures for the synthesis of Examples 5a to 5z

R^4 = (S)-3-methyl-morpholine
R^2 = (S)-3-methyl-morpholine



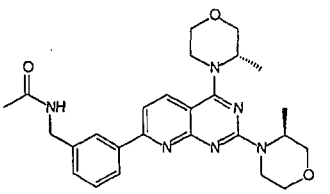
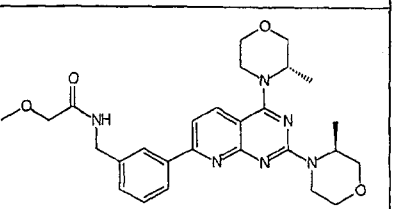
Conditions A:

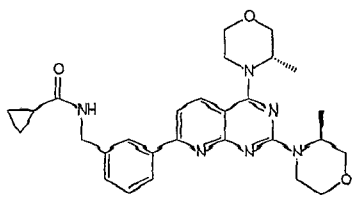
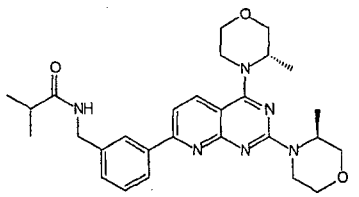
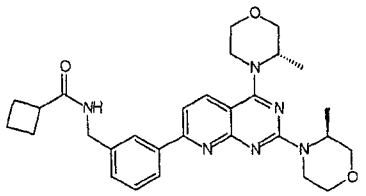
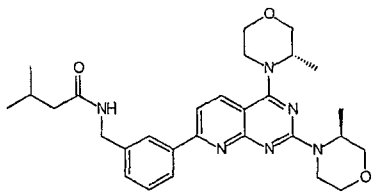
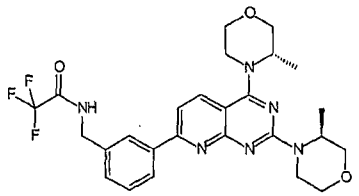
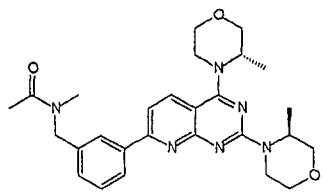
The appropriate aminobenzyl-substrate (1 equiv) was dissolved in CH_2Cl_2 (0.035 M). The appropriate acyl chloride or acid anhydride (2 equiv) as well as triethylamine (1 equiv) was then added. The mixtures were stirred for 2 hours at room temperature. Upon completion the samples were concentrated *in vacuo*. The crude residues were then purified by preparative HPLC to give the desired products.

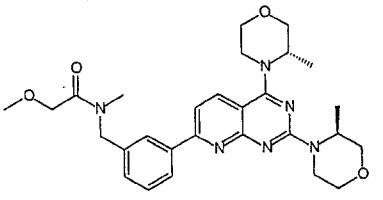
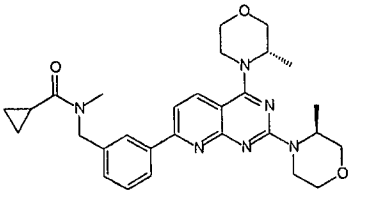
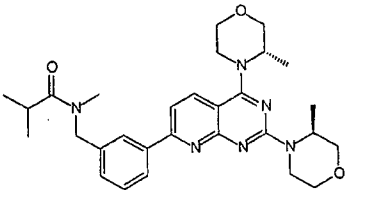
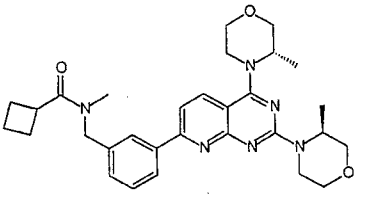
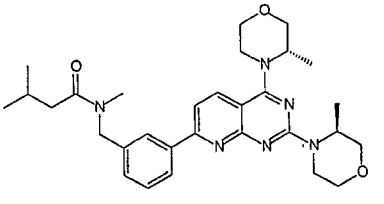
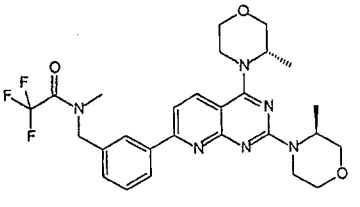
Conditions B:

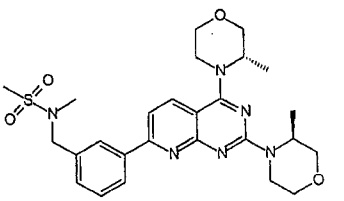
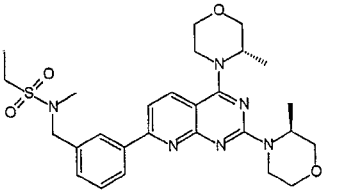
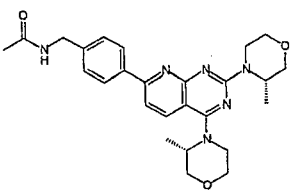
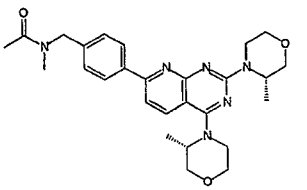
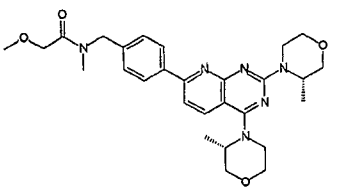
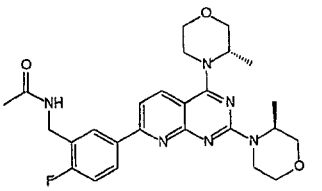
The appropriate methylaminobenzyl-substrate (1 equiv) was dissolved in CH_2Cl_2 (0.035 M). The appropriate acyl chloride or acid anhydride (2 equiv) as well as triethylamine (1 equiv) were added. The mixtures were stirred for 12 hours at 95°C. Upon completion the samples were concentrated *in vacuo*. The crude residues were then purified by preparative HPLC to give the desired products.

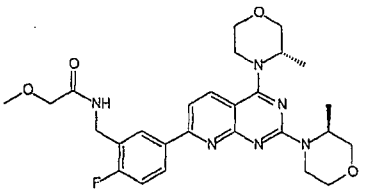
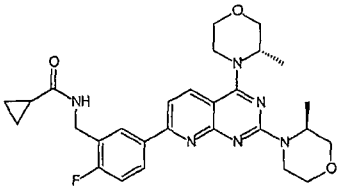
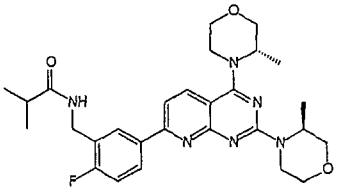
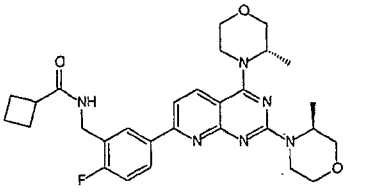
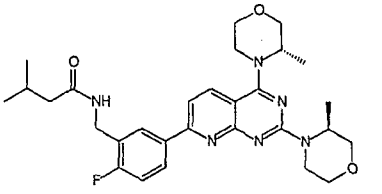
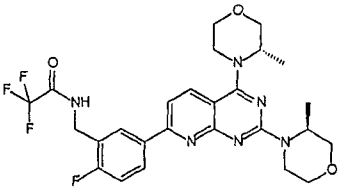
Table 5:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
5a	98	4.02	477.4	A	
5b	99	4.12	507.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
5c	99	4.22	503.4	A	
5d	99	4.27	505.4	A	
5e	99	4.34	517.4	A	
5f	99	4.41	519.4	A	
5g	99	4.51	531.3	A	
5h	98	4.17	491.4	B	

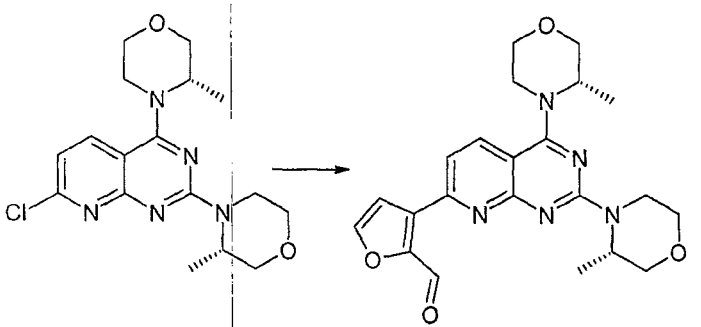
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
5i	99	4.17	521.5	B	
5j	98	4.39	517.4	B	
5k	98	4.48	519.5	B	
5l	99	4.58	531.5	B	
5m	99	4.64	533.5	B	
5n	98	4.73	545.4	B	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
5o	100	4.38	527.4	C	
5p	99	4.51	541.4	C	
5q	99	3.8	477.4	A	
5r	98	3.93	491.4	B	
5s	99	3.93	521.4	B	
5t	100	3.94	495.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
5u	100	4.02	525.4	A	
5v	100	4.16	521.4	A	
5w	100	4.19	523.4	A	
5x	100	4.27	535.4	A	
5y	100	4.32	537.5	A	
5z	98	4.38	549.5	A	

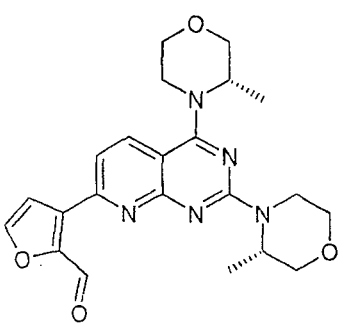
Tested in Alternative Enzyme Assay: Ex. (5a) 0.023μM; Ex. (5b) 0.054μM; Ex. (5c) 0.12μM; Ex. (5d) 0.12μM; Ex. (5e) 0.12μM; Ex. (5f) 0.37μM; Ex. (5g) 0.12μM; Ex. (5h) 0.19μM; Ex. (5i) 0.2μM; Ex. (5j) 0.31μM; Ex. (5k) 0.89μM; Ex. (5l) 0.049μM; Ex. (5m) 1.4μM; Ex. (5n) 0.64μM; Ex. (5o) 0.12μM; Ex. (5p) 0.5μM; Ex. (5q) 0.091μM; Ex. (5r) 0.56μM; Ex. (5s) 0.67μM; Ex. (5t) 0.057μM; Ex. (5u) 0.16μM; Ex. (5v) 0.14μM; Ex. (5w) 0.16μM; Ex. (5x) 0.29μM; Ex. (5y) 0.44μM; Ex. (5z) 1.4μM.

Example 6



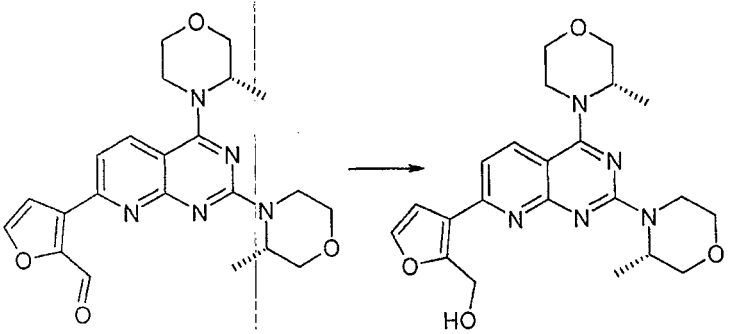
The chloro-substrate was reported in Example 1.

The appropriate chloro-substrate (1 equiv) was dissolved in n-butanol (0.055 M). 2-formylfuran-3-boronic acid (1.0 equiv), potassium carbonate (1.2 equiv), and tetrakis(triphenylphosphine)palladium^0 (0.05 equiv) were added. The reaction vessel was sealed and exposed to microwave radiation (110 °C, medium absorption setting) for 15 minutes. Upon completion the reaction mixture was filtered through a silica cartridge and the filtrate was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 40 % ethyl acetate in hexane to give the desired product.



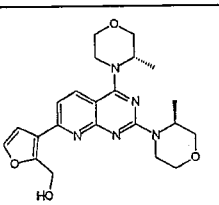
3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-furan-2-carbaldehyde: (26 % yield, 90 % purity) m/z (LC-MS, ESP): 424 $[M+H]^+$ R/T = 2.81 min

(Compound 6a)



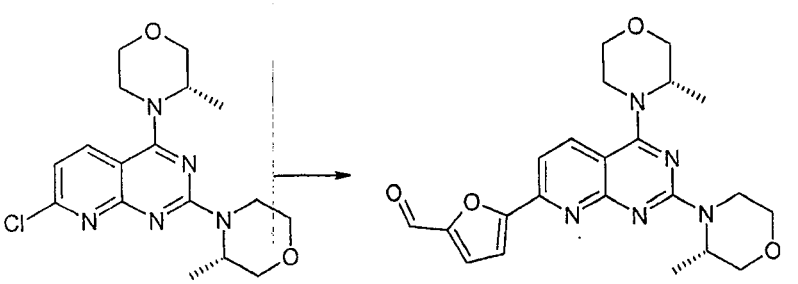
The above product was dissolved in THF (0.018 M) and sodium borohydride (2 equiv) was added. This mixture was allowed to stir at room temperature for 5 minutes. Upon completion the reaction mixture was filtered through a silica cartridge and the filtrate was concentrated *in vacuo*. The crude residue was purified by preparative HPLC to give the desired product.

Table 6:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
6a	96	6.89	426.3	

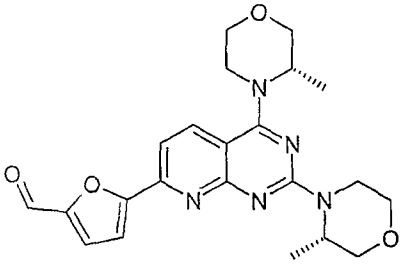
Tested in Alternative Enzyme Assay: Ex. (6a) 0.013μM.

Example 7



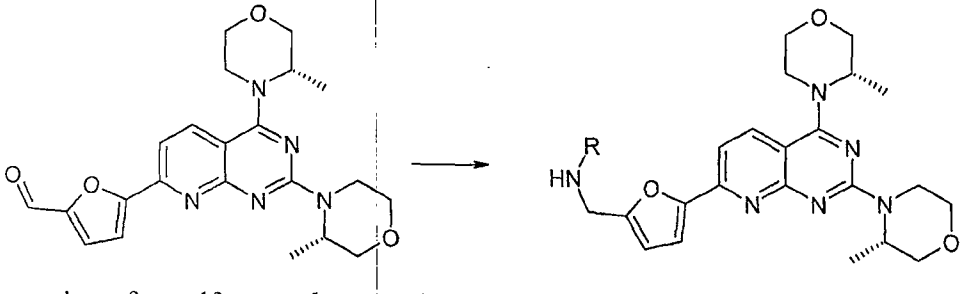
The chloro-substrate was reported in Example 1.

The appropriate chloro-substrate (1 equiv) was dissolved in dioxane (0.16 M). 5-formyl-2-furylboronic acid (1.05 equiv), tripotassium phosphate (1.5 equiv) and bis(tri-t-butylphosphine)palladium (0.05 equiv) were added. The reaction vessel was sealed and exposed to microwave radiation (170 °C, medium absorption setting) for 45 minutes. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 40 to 100 % ethyl acetate in hexane to give the desired product.



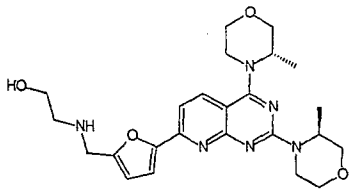
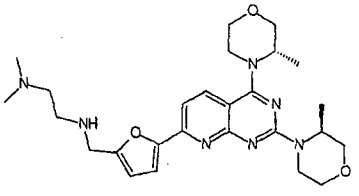
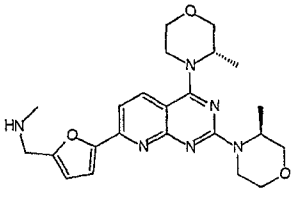
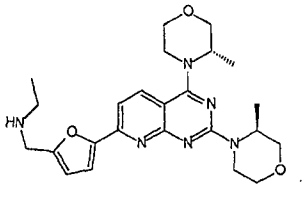
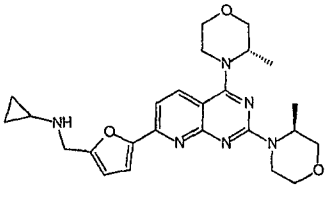
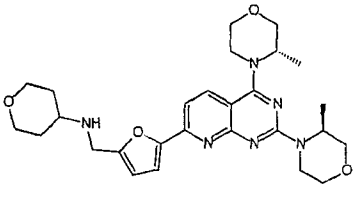
5-[2,4-Bis-(3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-furan-2-carboxaldehyde: (100 % yield, 100 % purity) m/z (LC-MS, ESP): 424 $[M+H]^+$ R/T = 2.75 min

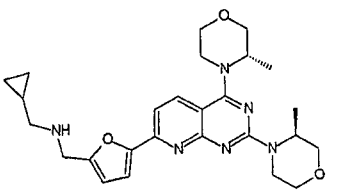
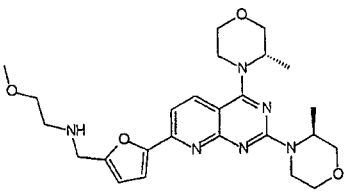
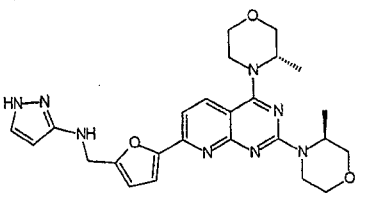
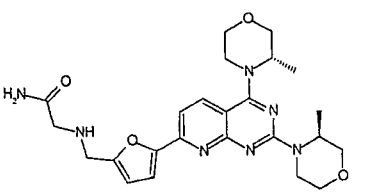
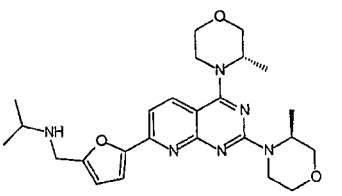
(Compounds 7a to 7k)



The appropriate formylfuran-substrate (1 equiv) was dissolved in a THF/CH_2Cl_2 (1:1) solution (0.036 M). The appropriate amines (2.2 equiv) sodium borohydride (2.4 equiv) and acetic acid (0.03 equiv) were added. The reaction mixture was stirred at room temperature for 24 hours. Upon completion the samples were filtered through a silica cartridge, washed with methanol and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Table 7:

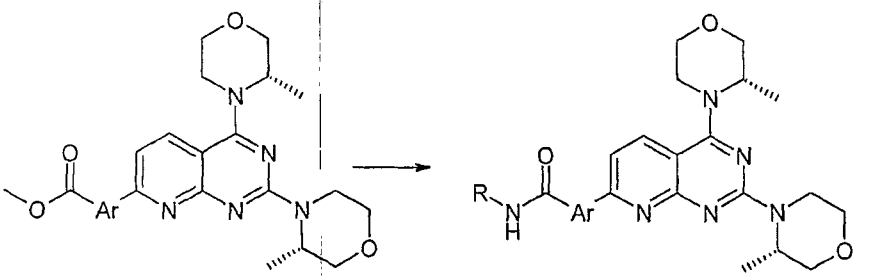
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
7a	97	3.2	496.4	
7b	99	3.32	469.4	
7c	99	3.49	439.4	
7d	99	3.51	453.4	
7e	99	3.58	465.4	
7f	97	3.53	509.4	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
7g	98	3.61	479.4	
7h	99	3.56	483.4	
7i	95	3.86	491.4	
7j	98	3.46	482.4	
7k	99	3.54	467.4	

Tested in Alternative Enzyme Assay: Ex. (7a) 0.59μM; Ex. (7b) 0.13μM; Ex. (7c) 0.091μM; Ex. (7d) 0.097μM; Ex. (7e) 0.15μM; Ex. (7f) 0.12μM; Ex. (7g) 0.17μM; Ex. (7h) 0.33μM; Ex. (7i) 0.079μM; Ex. (7j) 0.12μM; Ex. (7k) 0.14μM.

Example 8

(Compounds 8a to 8b)



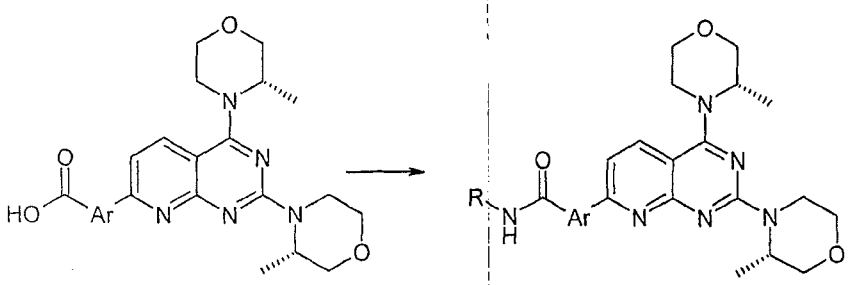
The methylbenzoic ester substrates were reported in Example 1.

Conditions A:

Example 1ba (1 equiv) was dissolved in dioxane (0.16 M). Ethanolamine (51.0 equiv) was added. The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 50 minutes. Upon completion the reaction mixture was concentrated *in vacuo*. The crude residue was then purified by column chromatography on silica gel using a gradient 0 to 5 % MeOH in CH_2Cl_2 to afford the desired product.

Conditions B:

Example 1bg (1 equiv) was dissolved in dioxane (0.05 M). Ethanolamine (2.0 equiv) was added. The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 2 X 20 minutes. Upon completion the reaction mixture was concentrated *in vacuo*. The reaction mixture was partitioned between water and CH_2Cl_2 and extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was then purified by column chromatography on silica gel using a gradient 0 to 5 % MeOH in CH_2Cl_2 to afford the desired product.

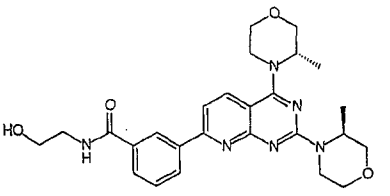
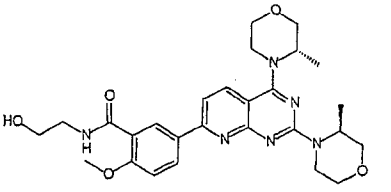
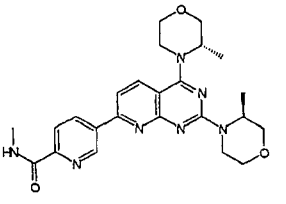
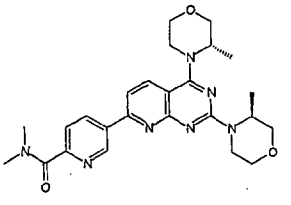


Conditions C:

To a solution of the appropriate carboxylic acid derivative (1 equiv) suspended in CH_2Cl_2 was added HBTU (1.3 equiv) followed by diisopropylethylamine (3 equiv). The mixture was

cooled (-78 °C) and the appropriate amine added (1.1 equiv). The mixture was stirred for 3 hrs before being concentrated to dryness and purified by preparative HPLC to give the desire products.

Table 8:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
8a	100	3.75	493.5	A	
8b	99	3.86	523.5	B	
8c	97	3.79	465.3	C	
8d	98	3.70	507.4	C	

NMR data for Example 8a

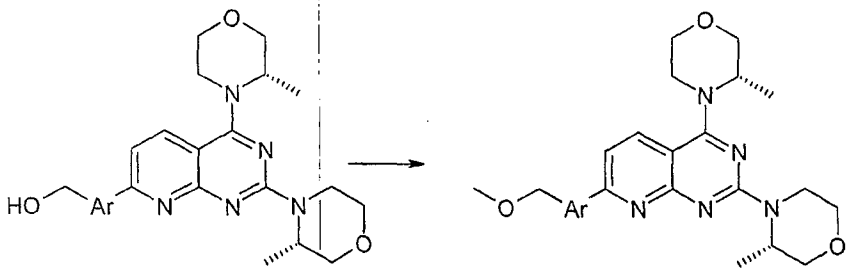
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.55 (ArH, s, 1H), 8.09 (ArH, d, J = 7.85 Hz, 1H), 7.95 (ArH, d, J = 8.42 Hz, 1H), 7.86 (ArH, d, J = 7.86 Hz, 1H), 7.49-7.33 (ArH, m, 2H), 4.89-4.75 (CH, m, 1H), 4.56-4.46 (CH, m, 1H), 4.38-4.26 (CH_2, m, 1H), 3.97-3.87 (CH_2, m, 2H), 3.85-

3.75 (CH_2, m,4H), 3.72-3.55 (CH_2, m, 7H), 3.53-3.44 (CH_2, m, 1H), 3.34-3.24 (CH2, m, 1H), 1.41 (CH_3, d, J = 6.77 Hz, 3H), 1.28 (CH_3, d, J = 6.82 Hz, 3H).

Tested in Alternative Enzyme Assay: Ex. (8a) 0.028μM; Ex. (8b) 0.079μM; Ex. (8c) 0.13μM; Ex. (8d) 2μM.

Example 9

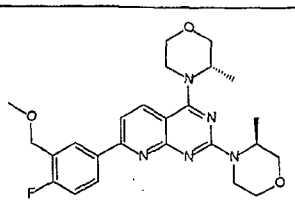
(Compound 9a)



The benzyl alcohol substrate was reported in Example 1.

Example 1bc (1 equiv) was dissolved in THF (0.022 M). Sodium *tert*-butoxide (3.0 equiv) and iodomethane (10.0 equiv) were added. The reaction vessel was stirred at room temperature for 48 hours. Upon completion the sample was filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

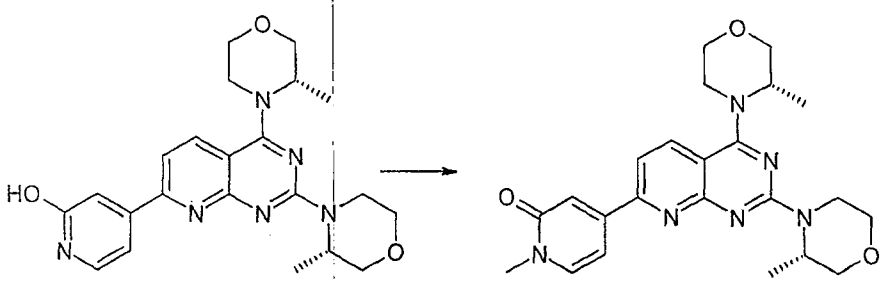
Table 9:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
9a	100	2.87	468.4	

Tested in Alternative Enzyme Assay: Ex. (9a) 0.088μM.

Example 10

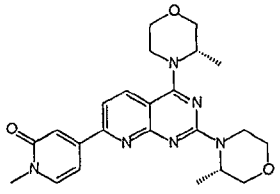
(Compound 10a)



The pyridinone substrate was reported in Example 13.

Example 13c (1 equiv) was dissolved in DMF (0.1 M). Potassium carbonate (1.1 equiv) and iodomethane (1.1 equiv) were added. The reaction vessel was stirred at 100°C for 2 hours. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

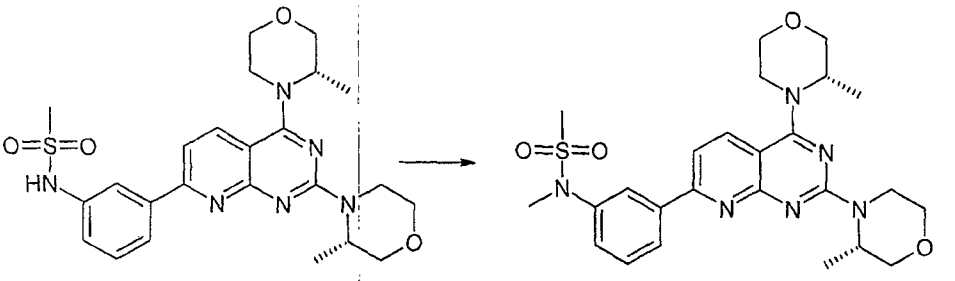
Table 10:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
10a	100	3.67	437.2	

Tested in Alternative Enzyme Assay: Ex. (10a) 0.11μM.

Example 11

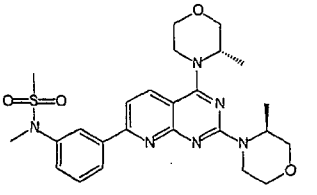
(Compound 11a)



The sulfonamide substrate was reported in Example 1.

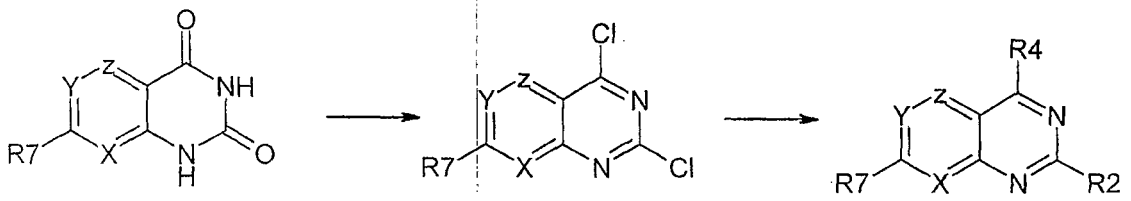
Example 1at (1 equiv) was dissolved in DMF (0.1 M). Potassium carbonate (2.0 equiv) and iodomethane (1.5 equiv) were added. The reaction vessel was heated at 100°C for 2 hours. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Table 11:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
11a	87	4.11	513.3	

Tested in Alternative Enzyme Assay: Ex. (11a) 0.37μM.

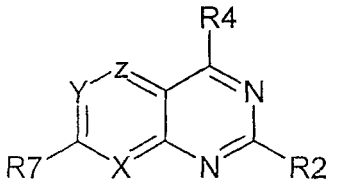
Example 12



To a solution of the appropriate 7-substituted-1H-pteridine-2,4-dione (1 equiv) in anhydrous toluene (sufficient to make a 0.1 M solution) was added Hunig's base (3 equiv). A reflux condenser was attached to the reaction vessel and the mixture heated, under an inert atmosphere) to 70 °C for 30 minutes. After this time, the reaction was cooled to 40 °C whereupon $POCl_3$ (3 equiv) was added. The mixture was then heated, with stirring, to 110 °C for 3 hrs. Upon completion, the reaction was cooled and concentrated *in vacuo* to give a tarry residue which was dissolved in the minimum volume of CH_2Cl_2 and filtered through a thick silica pad. The resulting filtrate was concentrated *in vacuo* to give the desired 2,4-dichloro-7-substituted-pteridine product (typically 65-99 % yield) in suitably pure form to be used without any further purification.

2,4-Dichloro-7-p-tolyl-pteridine;R7=toluyl, R2= Cl, R4=Cl, X=N, Y=C, Z=N: (61 % yield, 99 % purity) m/z (LC-MS, ESP): Did not ionize, R/T = 3.27 min

2,4-Dichloro-7-phenyl-pteridine;R7=phenyl, R2= Cl, R4=Cl, X=N, Y=C, Z=N: (66 % yield, 99 % purity) m/z (LC-MS, ESP): Did not ionize, R/T = 3.10 min



To a cooled (-5 °C) solution of the appropriate amine (1 equiv = R4) in N,N-dimethylacetamide (sufficient to make 0.2 M solutiion) was added the appropriate 2,4-dichloro-7-substituted-pteridine (1 equiv added as a 0.04 M solution in N,N-dimethylacetamide). After approx 10 minutes Hunig's base was added (1 equiv) and the resultant mixture stirred at -5 °C for 30 minutes. After this time, the reaction was allowed to

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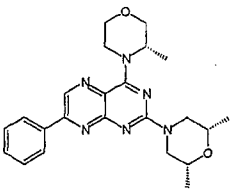
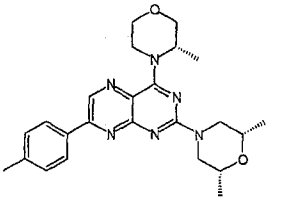
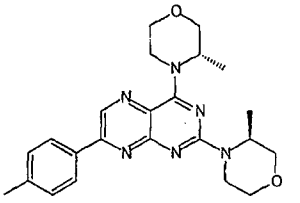
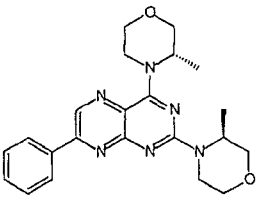
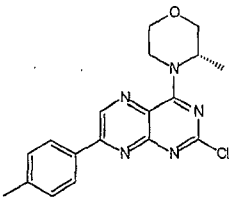
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warm to room temperature, whereupon the appropriate amine (1 equiv = R2) and Hunig's base (1 equiv) were then added. The resultant mixture was heated to 60 °C and maintained at this temperature, with stirring, for 16 hours. Upon completion, the mixture was allowed to cool to room temperature before being purified by preparative HPLC to give the desired product.

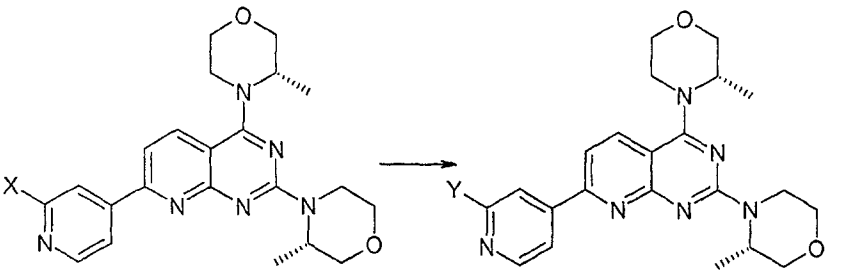
Table 12

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
12a	99	5.33	421.5	
12b	96	5.55	435.4	
12c	95	10.29	421.3	
12d	94	9.48	407.2	
12e	94	9.48	356.2	

Tested in Alternative Enzyme Assay: Ex. (12a) 0.02669μM; Ex. (12b) 0.2147μM; Ex. (12c) 0.04872μM; Ex. (12d) 0.0263μM; Ex. (12e) 0.5414μM.

Example 13

(Compounds 13a to 13f)



The pyridine substrates were reported in Example 1.

Conditions A:

Example 1w (1 equiv) was dissolved in a dry THF/methanol (1:1) solution (0.057 M). Sodium hydride (4.5 equiv) was added. The reaction mixture was stirred at room temperature for 15 minutes under nitrogen. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 40 minutes. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Conditions B:

Example 1w (1 equiv) was dissolved in dry THF (0.057 M). Dimethylethanolamine (10.0 equiv) and sodium hydride (5.0 equiv) were added. The reaction mixture was stirred at room temperature for 15 minutes under nitrogen. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 20 minutes. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Conditions C:

Example 1au (1 equiv) was dissolved in DMSO (0.59 M). 8N aqueous sodium hydroxide solution (50.0 equiv) was added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 20 minutes. Upon completion concentrated aqueous HCl was added carefully. The mixture was neutralized with 2N aqueous sodium hydroxide solution. The suspension was diluted with methanol then filtered through a

sintered funnel. The filtrate was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions D:

Example 1au (1 equiv) was dissolved in NMP (0.1 M). Potassium cyanide (20.0 equiv) was added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 46 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 50 to 100 % ethyl acetate in hexane to give the desired product.

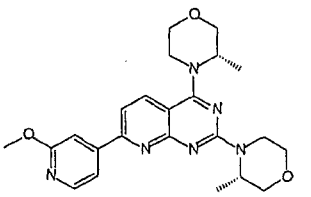
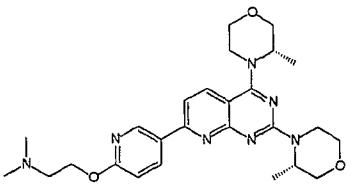
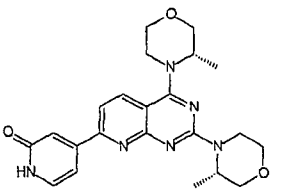
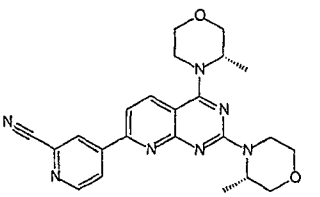
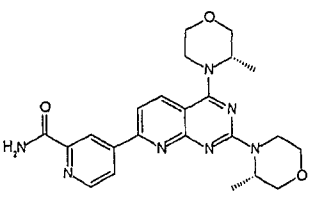
Conditions E:

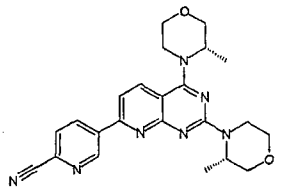
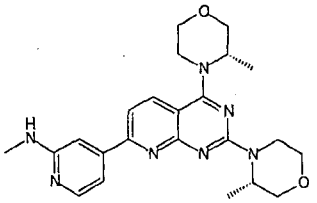
Example 1au (1 equiv) was dissolved in NMP (0.1 M). Potassium cyanide (20.0 equiv) was added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 46 hours. Upon completion the reaction mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 50 to 100 % ethyl acetate in hexane first, then eluting with 10 % methanol in CH_2Cl_2. The crude fractions were then further purified by preparative HPLC to give the desired product.

Conditions F:

Example 1ah (1 equiv) was dissolved in NMP (0.1 M). Potassium cyanide (8.0 equiv) was added. The reaction vessel was sealed and the mixture exposed to microwave radiation (180 °C, medium absorption setting) for 40 minutes. Upon completion the sample was filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Table 13:

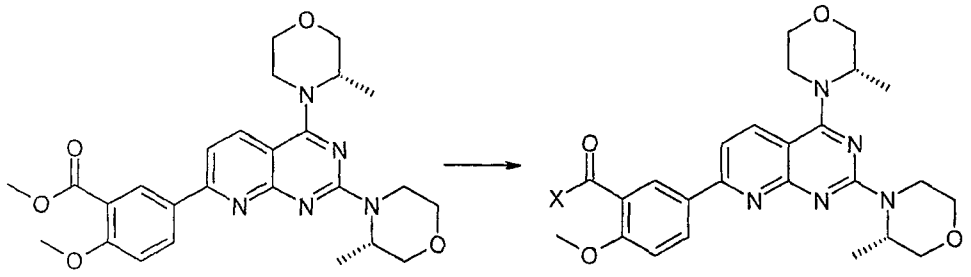
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
13a	99	4	437.3	A	
13b	99	3.42	494.4	B	
13c	97	5.77	423.4	C	
13d	97	3.96	432.4	D	
13e	98	6.62	450.2	E	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
13f	99	3.93	432.3	F	
13g	89	5.03	478.4		

Tested in Alternative Enzyme Assay: Ex. (13a) 0.2μM; Ex. (13b) 0.33μM; Ex. (13c) 0.14μM; Ex. (13d) 0.48μM; Ex. (13e) 0.19μM; Ex. (13f) 0.16μM; Ex. (13g) 0.11μM.

Example 14

(Compounds 14a-14b)



The ester substrate was reported in Example 1.

Ester hydrolysis:

Conditions A

Example 1bg (1 equiv) was dissolved in methanol (0.2 M). 1M Sodium hydroxide aqueous solution (5.0 equiv) was added. The reaction mixture was stirred at room temperature for 3 hours. Upon completion the reaction mixture was neutralised with 1M aqueous HCl and

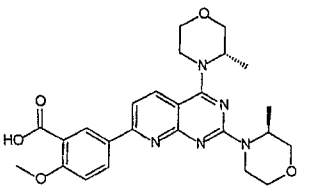
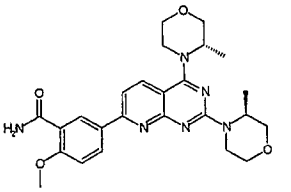
concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 10 % MeOH in CH_2Cl_2 to give the desired product.

Amide formation:

Conditions B

Example 1bg (1 equiv) was suspended in THF (0.05 M). Thionyl chloride (2.5 equiv) was added dropwise at 40°C. The reaction mixture was then heated for an hour at 40°C. Ammonia gas was then slowly bubbled into the reaction mixture. THF was then added for further dilution (0.025 M) and the reaction mixture was heated for an hour at 40°C. Upon completion the reaction mixture was cooled down and concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product.

Table 14:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
14a	98	3.95	480.5	A	
14b	98	7.09	479.4	B	

NMR data for Example 14a

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.82-8.69 (ArH, m, 1H), 8.68-8.56 (ArH, m, 1H), 8.03-7.90 (ArH, m, 1H), 7.52-7.39 (ArH, m, 1H), 7.18-7.05 (ArH, m, 1H), 4.92-4.80 (CH, m, 1H), 4.61-4.47 (CH, m, 1H), 4.37-4.27 (CH_2, m, 1H), 4.07 (OCH_3, s, 3H), 4.00-3.87 (CH_2, m, 2H),

3.85-3.60 (CH_2, m, 6H), 3.57-3.24 (CH_2, m, 3H), 1.41 (CH_3, d, J = 6.65 Hz, 3H), 1.30 (CH_3, d, J = 6.74 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.33, 134.98, 134.96, 132.64, 132.61, 132.58, 119.77, 112.83, 112.11, 100.01, 71.29, 70.90, 67.24, 66.91, 52.80, 46.96, 44.44, 39.34 and 14.74.

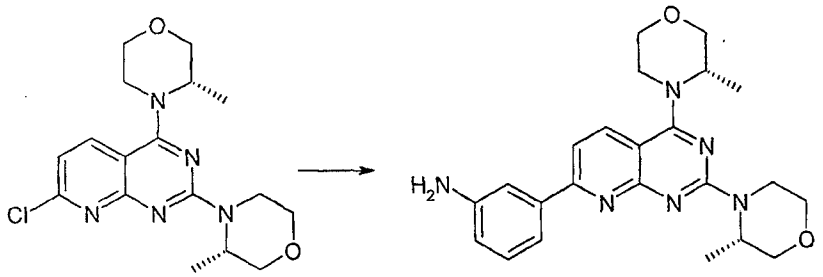
NMR data for Example 14b

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.83 (ArH, d, J = 2.46 Hz, 1H), 8.64 (ArH, dd, J = 8.76, 2.49 Hz, 1H), 8.01 (ArH, d, J = 8.47 Hz, 1H), 7.71 (NH, s, br, 1H), 7.57 (ArH, d, J = 8.50 Hz, 1H), 7.13 (ArH, d, J = 8.83 Hz, 1H), 5.79 (NH, s, br, 1H), 5.00-4.84 (CH, m, 1H), 4.62 (CH, dd, J = 13.82, 0.70 Hz, 1H), 4.37 (CH_2, d, J = 6.77 Hz, 1H), 4.05 (OCH_3, s, 3H), 4.03-3.94 (CH_2, m,2H), 3.91-3.79 (CH_2, m, 3H), 3.79-3.63 (CH_2, m, 4H), 3.64-3.51 (CH_2, m, 1H), 3.44-3.30 (CH_2, m, 1H), 1.47 (CH_3, d, J = 6.78 Hz, 3H), 1.35 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.58, 165.45, 162.87, 159.99, 159.22, 134.71, 133.75, 131.84, 131.65, 120.52, 113.07, 111.87, 104.80, 102.94, 71.33, 70.94, 67.29, 66.94, 56.28, 52.80, 46.93, 44.49, 39.33, 14.72 and 14.34.

Tested in Alternative Enzyme Assay: Ex. (14a) 0.00015μM; Ex. (14b) 0.0032μM.

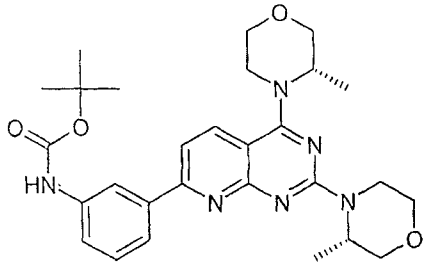
Example 15



The chloro-substrate was reported in Example 1.

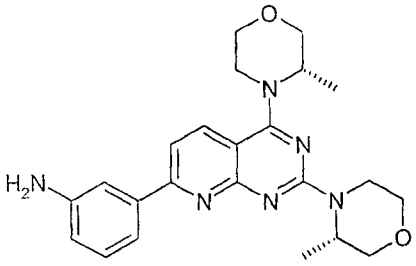
To a mixture of 7-chloro-4-((S)-3-methyl-morpholin-4-yl)-2-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidine (1 equiv), potassium carbonate (1.2 equiv), and 3-BOC-aminophenylboronic acid (1.2 equiv) in acetonitrile/water (1:1) (0.08 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 10 minutes under nitrogen atmosphere. Upon completion the samples were filtered through a

silica cartridge, washed with ethyl acetate and then concentrated *in vacuo*. The crude residue was used as such in the next reaction.



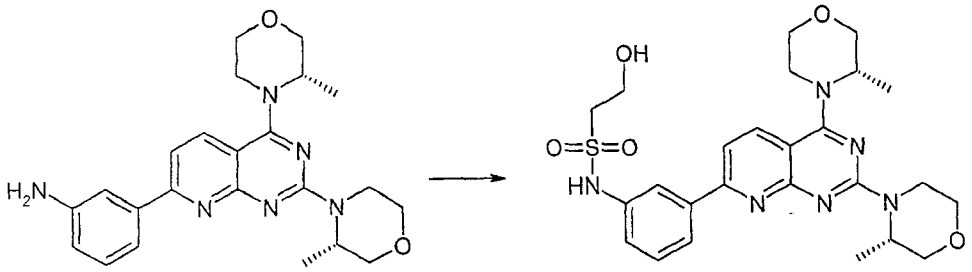
{3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenyl}-carbamic acid tert-butyl ester: (95 % yield, 100 % purity) m/z (LC-MS, ESP): 520.9 $[M+H]^+$ R/T = 3.23 min

The above product (1 equiv) was dissolved in a TFA/ CH_2Cl_2 solution (1:20) (0.018 M). The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was then concentrated *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The aqueous phase was neutralized with 1N aqueous sodium hydroxide. Combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was used as such in the next reaction.

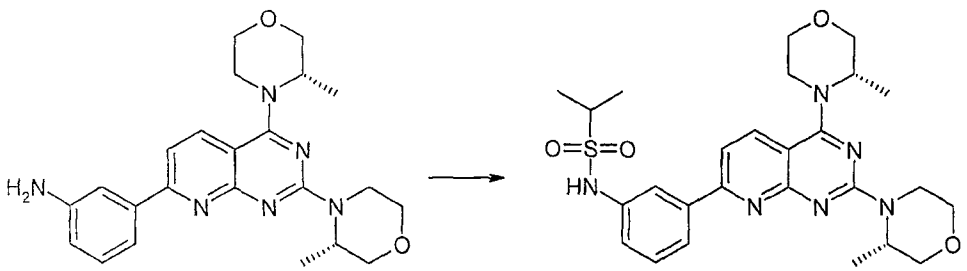


3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenylamine: (100 % yield, 100 % purity) m/z (LC-MS, ESP): 520.9 $[M+H]^+$ R/T = 2.72 min

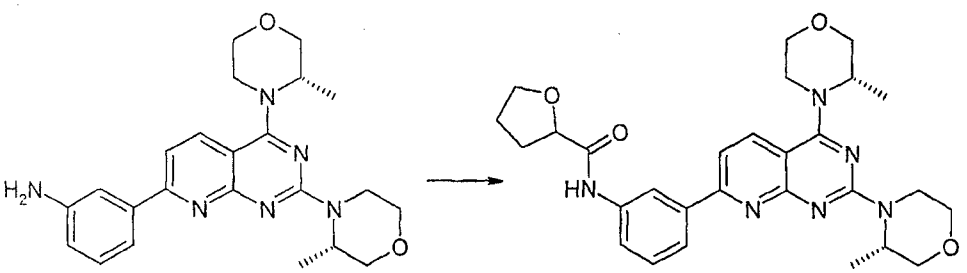
(Compound 15a)



The above product (1 equiv) was dissolved in THF (0.013 M). Chloroethanesulfonyl chloride (3.5 equiv) was gently added to the reaction mixture at 0°C and the reaction mixture was stirred at room temperature for 15 hours. 8N Aqueous sodium hydroxide (50 equiv) was then added and the reaction mixture was heated at 40°C for 12 hours. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 5 % MeOH in CH_2Cl_2 to give the desired product.



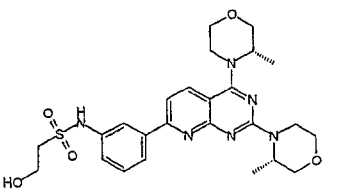
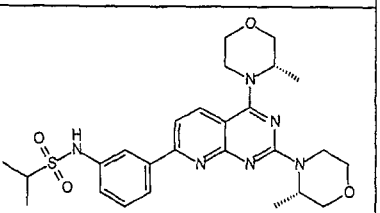
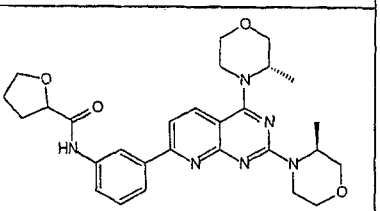
3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenylamine (1 equiv) was dissolved in THF (0.1 M). Pyridine (10 equiv) and isopropylsulfonyl chloride (10 equiv) were added to the reaction mixture at room temperature. The reaction mixture was then stirred at 90°C for 4 hours. The reaction mixture was partitioned between CH_2Cl_2 and water. Organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel eluting with 0 to 60 % EtOAc in hexane to give the desired product.



3-[2,4-Bis-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenylamine (1 equiv) was dissolved in CH_2Cl_2 (0.24 M). Tetrahydro-2-furoic acid (1.1 equiv), HBTU (2.0 equiv) and triethylamine (2 equiv) were added and the reaction mixture was then stirred at room temperature for 3 hours. The reaction mixture was partitioned between CH_2Cl_2 and water. Organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude

residue was purified by column chromatography on silica gel eluting with 0 to 4 % MeOH in TBME to give the desired product.

Table 15:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
15a	98	3.99	529.4	
15b	96	8.28	527.3	
15c	99	4.19	519.3	

NMR data for Example 15b

^{1}H NMR (300 MHz), $CDCl_3$ δ ppm 8.00-7.94 (ArH, m, 2H), 7.81 (ArH, td, J = 7.12, 1.52, 1.52 Hz, 1H), 7.45-7.32 (ArH, m, 3H), 6.84 (NH, s, br, 1H), 4.93-4.80 (CH_2, m, 1H), 4.55 (CH_2, d, J = 12.97 Hz, 1H), 4.38-4.25 (CH_2, m, 1H), 4.01-3.57 (CH_2, m, 9H), 3.57-3.45 (CH_2, m, 1H), 3.36 – 3.32 (CH_2, m, 2H), 1.42 (CH_3, d, J = 6.78 Hz, 3H), 1.37-1.26 (3 X CH_3, m, 9H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.36, 162.85, 161.36, 159.98, 140.27, 137.89, 134.92, 129.80, 124.03, 121.31, 119.64, 113.30, 105.19, 71.28, 70.91, 67.25, 66.91, 52.89, 52.87, 44.42, 39.33, 31.60, 22.66, 16.60, 14.75 and 14.36.

NMR data for Example 15c

^{1}H NMR (300 MHz, CD_3COCD_3, δ ppm 8.52 (ArH, s, 1H), 8.24 (ArH, d, J = 8.48 Hz, 1H), 7.91-7.80 (ArH, m, 2H), 7.62 (ArH, d, J = 8.47 Hz, 1H), 7.46 (ArH, t, J = 7.94, 7.94 Hz, 1H), 6.48 (NH, br, s, 1H), 4.84-4.70 (CH_2, m, 1H), 4.53-4.33 (CH_2, m, 3H), 4.09-3.79 (CH_2, m, 5H), 3.80-3.56 (CH_2, m, 5H), 3.49-3.40 (CH_2, m, 1H), 3.23 – 3.28 (CH_2, m, 1H), 2.20 (CH_2, d, J = 6.66 Hz, 1H), 2.11-1.81 (CH_2, m, 4H), 1.39 (CH_3, d, J = 6.75 Hz, 3H), 1.26 (CH_3, d, J = 6.75 Hz, 3H).

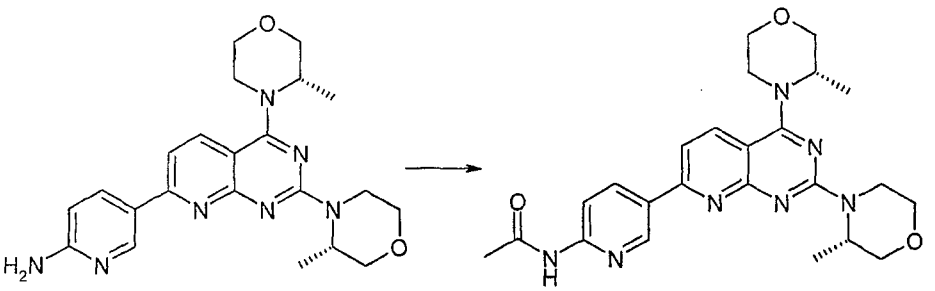
^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm 171.66, 160.37, 147.37, 145.71, 138.93, 138.46, 135.69, 128.98, 126.26, 126.11, 122.52, 121.58, 118.91, 118.37, 104.46, 77.93, 70.31, 70.13, 68.81, 66.28, 66.15, 51.77, 46.41, 43.85, 29.98, 25.06, 14.39 and 13.92.

Tested in Alternative Enzyme Assay: Ex. (15a) 0.0043μM; Ex. (15c) 0.33μM.

Tested in phospho-Ser473 Akt assay: Ex. (15b) 0.5051μM.

Example 16

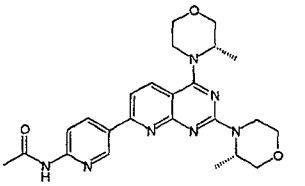
(Compound 16a)



The aminopyridine substrate was reported in Example 1.

Example 1u (1 equiv) was dissolved in pyridine (0.11 M). Acetic anhydride (5.0 equiv) was added and the reaction mixture was heated at 70°C for 6 hours. Upon completion the sample was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Table 16:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
16a	100	3.8	464.4	

NMR data for Example 16a

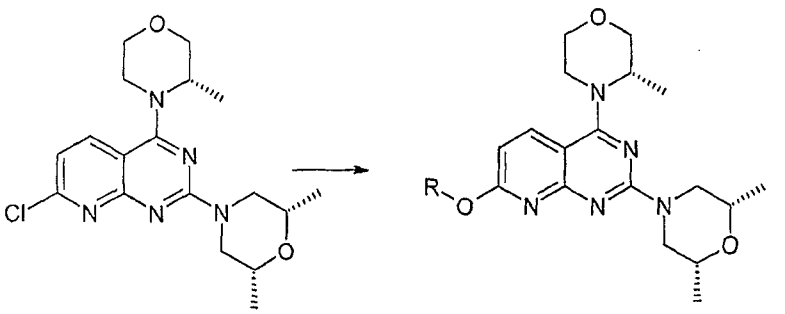
^{1}H NMR (300 MHz,$CDCl_3$) δ ppm 8.18-8.12 (ArH, m, 2H), 8.05 (ArH, d, J = 8.42 Hz, 1H), 7.52-7.40 (ArH, m, 3H), 4.96 (CH, d, br, J = 4.93 Hz, 1H), 4.66 (CH, d, br, J = 12.90 Hz, 1H), 4.40 (d, br, J = 6.71 Hz, 1H), 4.07-3.54 (CH_2, m, 11H), 3.47-3.35 (CH, m, 1H), 1.51 (CH_3, d, J = 6.79 Hz, 3H), 1.39 (CH_3, d, J = 6.82 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.41, 162.93, 161.83, 160.02, 137.14, 136.13, 134.84, 129.19, 128.77, 112.99, 105.03, 71.29, 70.91, 67.26, 66.91, 52.85, 46.95, 44.46, 39.34, 14.73 and 14.37.

Tested in Alternative Enzyme Assay: Ex. (16a) 0.034μM.

Example 17

(Compound 17a)

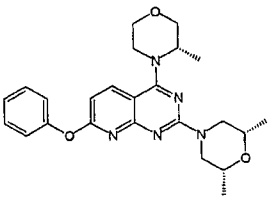


The chloro-substrate was reported in Example 1.

The appropriate chloro-substrate (1 equiv) was dissolved in toluene (0.07 M). Phenol (1.0 equiv), palladium acetate (0.05 equiv), BINAP (0.05 equiv) and tripotassium phosphate (1.0

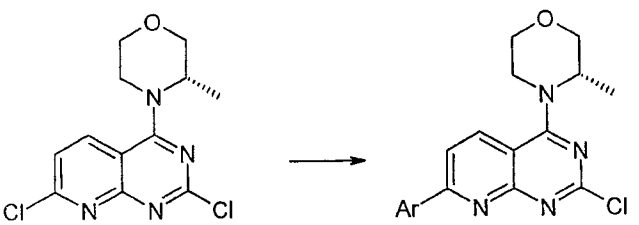
equiv) were added. The reaction vessel was sealed and exposed to microwave radiation (140 °C, medium absorption setting) for 10 minutes. Upon completion the samples was concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired product.

Table 17:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
17a	93	4.70	436.4	

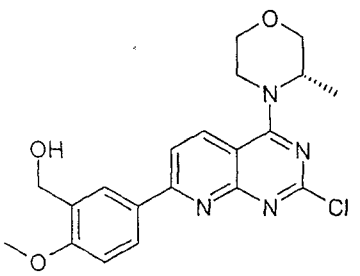
Tested in Alternative Enzyme Assay: Ex. (17a) 0.52μM.

Example 18

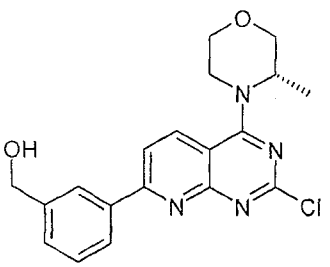


The chloro-substrate was reported in Example 1.

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), and the appropriate boronic acid (1.1 equiv) in acetonitrile/water (1:1) (0.033 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The suspension was sonicated while degassed with nitrogen for 5 minutes then heated to 95 °C for 2 hours. Upon completion the reaction mixture was allowed to cool down to room temperature. The reaction mixture was concentrated *in vacuo* to half original volume. The crude residue was extracted with CH_2Cl_2 and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow solid. The residue was sonicated in diethyl ether, collected by vacuum filtration to give the desired product as a yellow powder.



{5-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-phenyl}-methanol: (78 % yield, 100 % purity) m/z (LC-MS, ESP): 401 $[M+H]^+$ R/T = 3.47 min

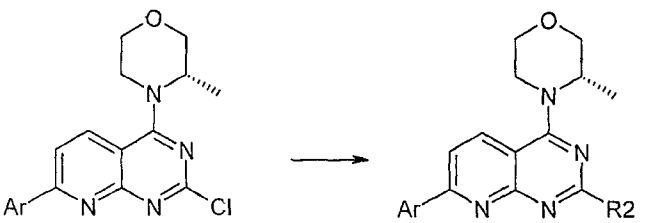


{3-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-phenyl}-methanol: (90 % yield, 90 % purity) m/z (LC-MS, ESP): 371 $[M+H]^+$ R/T = 4.06 min

Alternatively, to a stirred mixture of bis(pinacolato)diboron (1.05 equiv) and potassium acetate (3 equiv) in N-methylpyrrolidine (13.5 equiv), purged with nitrogen, was added the corresponding bromobenzylalcohol (1 equiv) followed by $PdCl_2$(dppf) (0.02 equiv). The mixture was then heated to 60 °C and held for 10min, then heated to 70 °C and held for 15min and finally heated to 80 °C and held for 1h. The appropriate chloro-substrate (1 equiv) was then added followed by $PdCl_2$(dppf) (0.02 equiv) and N-methylpyrrolidine (4.5 equiv). The temperature was then held at 75 °C, then 4.3M aqueous potassium carbonate (3.5 equiv) was added over 13min, then water (12 equiv) was added and the reaction was stirred at 75 °C for 90min. Water (144 equiv) was then added slowly over 70min with stirring while the temperature was reduced to 66 °C. The temperature of the stirred mixture was then kept at 64 °C for 30min, then cooled to 20 °C over 2.5h, and held at 20 °C overnight. The resulting slurry was filtered, and the solid washed first with a 3:1 water:N-methylpyrrolidone mixture (18 equiv of water), then washed with water (24 equiv) and then washed with ethyl actetate (4 x 4.4equiv). The solid was then dried in a vacuum oven at 50 °C to leave the title compound

in suitable clean form to be used without any further purification. For example, {5-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-2-methoxy-phenyl}-methanol: (73 % yield)

(Compounds 18a to 18do)



Conditions A:

The appropriate chloro-substrate (1 equiv) was dissolved in DMA (0.04 M). Tripotassium phosphate (1.5 equiv) and the appropriate nucleophile (secondary amine) (1.5 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (200 °C, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions B:

The appropriate chloro-substrate (1 equiv) was suspended in a propan-2-ol and aqueous ammonia (1:3) solution (0.02 M). The reaction vessel was sealed and the mixture exposed to microwave radiation (140 °C, medium absorption setting) for 20 minutes. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions C:

The appropriate chloro-substrate (1 equiv) was dissolved in dioxane (0.04 M). Diisopropylethylamine (5.0 equiv) and the appropriate nucleophile (secondary amine) (1.5 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 20 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions D:

The appropriate chloro-substrate (1 equiv) was dissolved in dioxane (0.04 M). Tripotassium phosphate (3.0 equiv), xantphos (0.05 equiv), palladium acetate (0.05 equiv) and the

appropriate nucleophile (amine) (1.5 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (150 °C, medium absorption setting) for 20 minutes. Upon completion the samples were filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions E:

The appropriate chloro-substrate (1.0 equiv) was dissolved in dioxane (0.04 M). Diisopropylethylamine (5.0 equiv) and the appropriate nucleophile (secondary amine, with BOC-protected amino side chain) (1.5 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 20 minutes. Upon completion the samples were concentrated *in vacuo*. To the crude residue was then added a 4 M solution of HCl in dioxane (0.15 M). The reaction mixtures were stirred at room temperature for 3 hours. Upon completion the samples were basified with a 2 N sodium hydroxide solution. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions F:

The appropriate nucleophile (substituted imidazole) (10.0 equiv) was dissolved in DMF (0. 4 M). Sodium hydride (5.0 equiv) was then added. The reaction mixture was stirred at room temperature for 10 minutes under nitrogen and a solution of the appropriate chloro-substrate (1.0 equiv) in DMF (0.075 M) was added. The reaction vessel was sealed and the mixture exposed to microwave radiation (150 °C, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, eluted with CH_2Cl_2 and then concentrated *in vacuo*. The crude residue were then purified by preparative HPLC to give the desired products.

Conditions G:

The appropriate chloro-substrate (1 equiv) was dissolved in dioxane (0.04 M). Diisopropylethylamine (5.0 equiv) and the appropriate nucleophile (secondary amine) (4.5 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 40 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions H:

The appropriate chloro-substrate (1 equiv) was dissolved in dioxane (0.04 M). Diisopropylethylamine (5.0 equiv) and the appropriate nucleophile (secondary amine) (10.0 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 60 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions I:

The appropriate chloro-substrate (1 equiv) was dissolved in a solution of 1 % DMA in dioxane (0.04 M). Diisopropylethylamine (5.0 equiv) and the appropriate nucleophile (secondary amine) (10.0 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (180 °C, medium absorption setting) for 60 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions J:

The appropriate chloro-substrate (1 equiv) was dissolved in a solution of 1 % DMA in dioxane (0.04 M). Diisopropylethylamine (7.0 equiv) and the appropriate nucleophile (secondary amine) (3.0 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (150 °C, medium absorption setting) for 60 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions K:

The appropriate chloro-substrate (1 equiv) was dissolved in DMF (0.075 M). Potassium carbonate (5.0 equiv) and the appropriate nucleophile (alcohol) (10.0 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (120 °C, medium absorption setting) for 20 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions L:

The appropriate chloro-substrate (1 equiv) was dissolved in DMF (0.075 M). Potassium carbonate (5.0 equiv) and the appropriate nucleophile (alcohol) (20.0 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (150 °C, medium absorption setting) for 40 minutes. Upon completion the samples were concentrated

in vacuo. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions M:

The appropriate chloro-substrate (1 equiv) was dissolved in DMA (0.13 M). Diisopropylethylamine (2.0 equiv) and the appropriate nucleophile (amine) (2.0 equiv) were then added. The reaction vessel was heated to 100 °C for 3 hours. Upon completion, the reaction mixture was partitioned between dichloromethane and water and the aqueous layer further extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to give a yellow residue which was purified by recrystallisation from diethyl ether.

Conditions N:

5-[2-Chloro-4-((S)-3-methyl-morpholin-4-yl)-pyrido[2,3-d]pyrimidin-7-yl]-pyridin-2-ylamine (1 equiv) was dissolved in DMA (0.21 M). Diisopropylethylamine (1.0 equiv) and the appropriate nucleophile (amine) (1.1 equiv) were then added. The reaction vessel was sealed and the mixture exposed to microwave radiation (130 °C, medium absorption setting) for 10 minutes. Upon completion, the reaction mixture was partitioned between dichloromethane and water and the aqueous layer further extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to give a yellow residue which was purified by column chromatography on silica gel eluting with 0 % to 10 % MeOH in CH_2Cl_2 to give the desired product.

Conditions O:

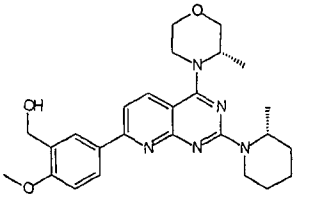
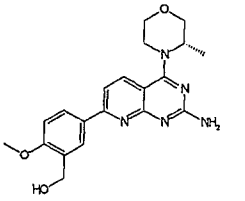
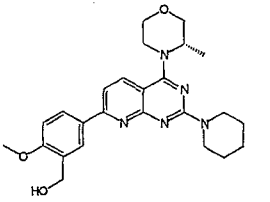
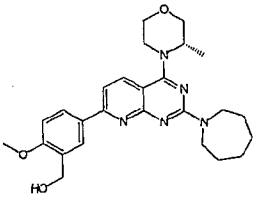
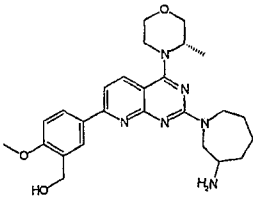
The appropriate chloro-substrate (1 equiv) was dissolved in DMA (0.16 M). Diisopropylethylamine (1.0 equiv) and the appropriate nucleophile (amine) (1.2 equiv) were then added. The reaction vessel was heated to 80 °C for 48 hours. Upon completion, the reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with brine. The combined organic phases were dried ($MgSO_4$), filtered and the filtrate was concentrated *in vacuo* to give a residue which was purified by preparative HPLC to give the desired product.

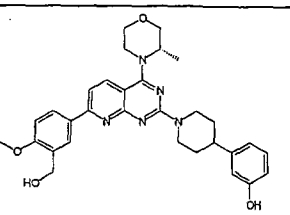
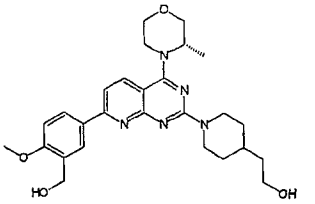
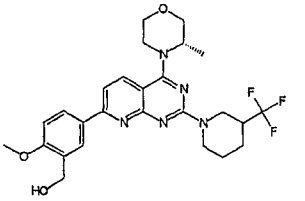
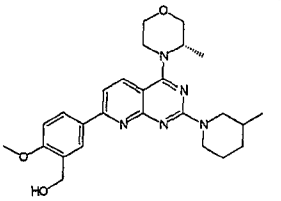
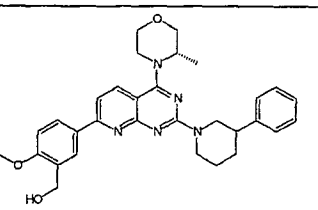
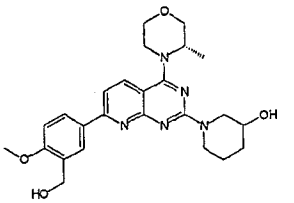
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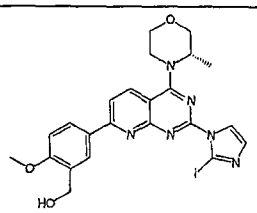
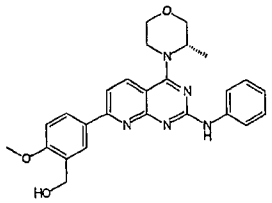
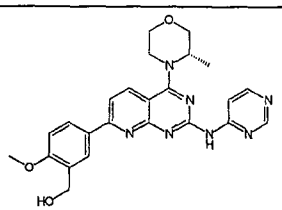
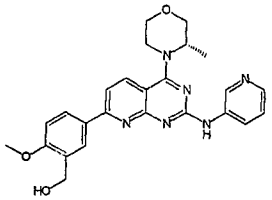
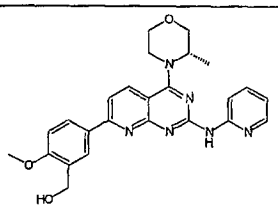
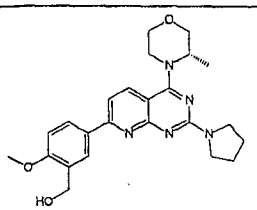
The appropriate chloro-substrate (1 equiv) was dissolved in anisole (0.25 M) (10 vol). Diisopropylethylamine (1.3 equiv) and the appropriate nucleophile (amine) (1.3 equiv) were then added. The reaction vessel was heated to 125 °C and stirred for 11h. Upon completion,

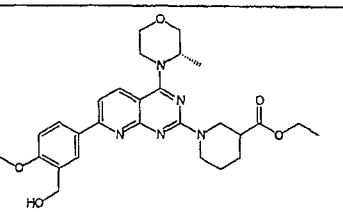
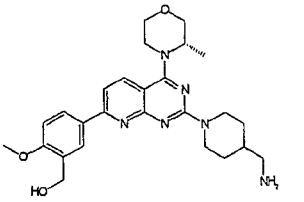
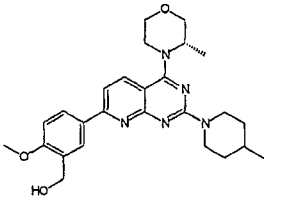
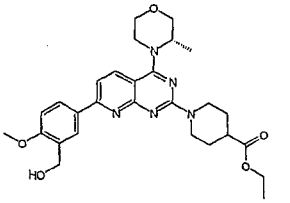
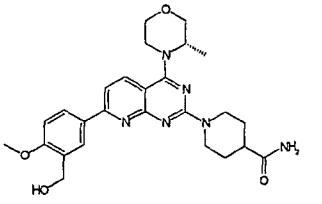
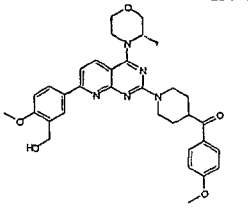
the reaction mixture was allowed to cool to 50 °C. Aqueous 20% citric acid solution (7 vol) was added, stirred for 5min and then allowed to separate partitioned. The aqueous layer was removed and retained. The organic layer was then extracted with a further aliquot of aqueous 20 % citric acid solution (3 vol). The orgainic layer discarded, and the aqueous layers combined. The combined aqueous layers were washed first with anisole (5 vol), then 50% aqueous sodium hydroxide solution (1.23 vol) was added slowly. The resulting aqueous phase was extracted with ethyl acetate (10vol). The aqueous layer was discarded and the organic layer was washed first with 10% aqueous sodium hydroxide solution (5 vol) and then water (5 vol). The organic layer was then slurried with silicycle Si-thiourea scavenger at 50 °C for 2h, then the scavenger was filtered off and washed with ethyl actetate (2 x 1 vol). The organic phase was cooled to 20 °C, seeded to start crystallization and stirred until a slurry obtained. The slurry was heated to 50 °C under vacuum and ethyl acetate (3 vol) was removed by vacuum distillation. 2-Methylpentane (3.4vol) was added and the mixture heated to 60 °C and then slowly cooled to 20 °C over 2h. The resulting slurry was filtered, and the solid washed with 1:1 ethyl actetate:pentane (2 x 0.5vol). The solid was then dried in a vacuum oven at 50 °C to leave the desired product. For example, compound 1a was obtained (50.4% yield). The crude product (1 equiv) was dissolved in DMSO (5 vol based on product weight) at 50 °C. Water (2 vol) was added and the mixture stirred at 50 °C until product crystallizes. The slurry was heated to 60 °C and then water (3vol) was added slowly over 30min so that the temperature was maintained at 60 °C. The mixture was slowly cooled to 20 °C over 2h, and then held at 20 °C for 30min. The resulting slurry was filtered, and the solid washed with 2:1 water:DMSO (0.5:1vol), and then water (3 x 2vol). The solid was then dried in a vacuum oven at 50 °C to leave the desired product.

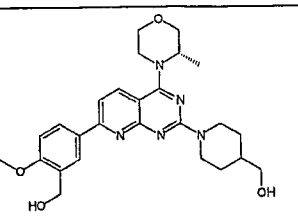
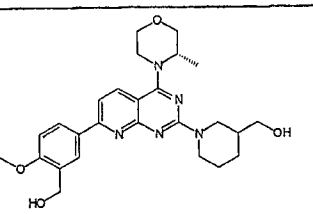
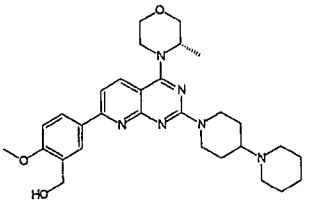
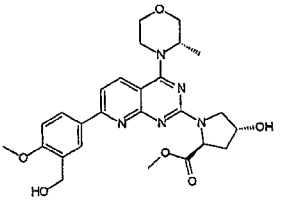
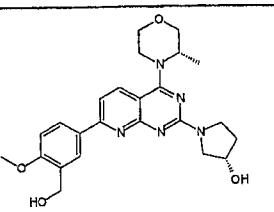
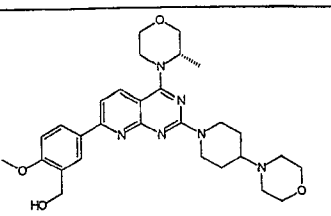
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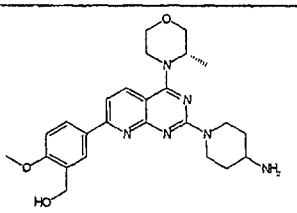
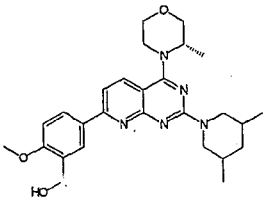
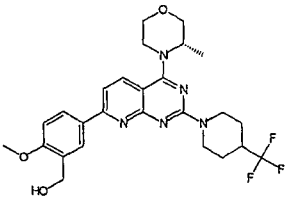
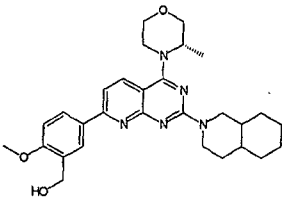
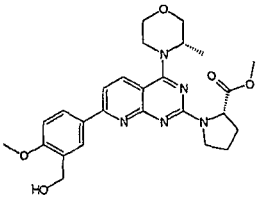
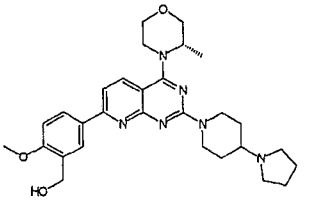
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18a	91	4.43	464.5	A	
18b	98	3.89	382.4	B	
18c	96	4.36	450.4	C	
18d	97	4.48	464.4	C	
18e	93	3.56	479.4	C	

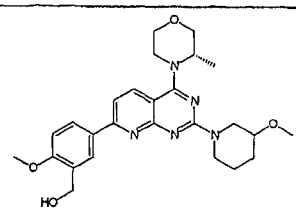
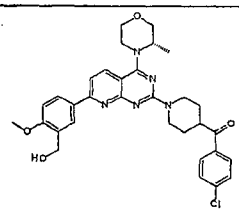
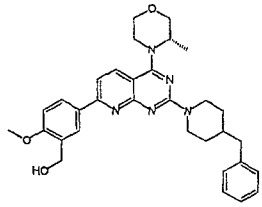
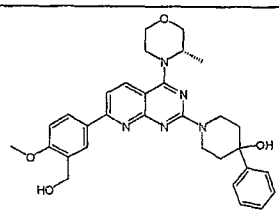
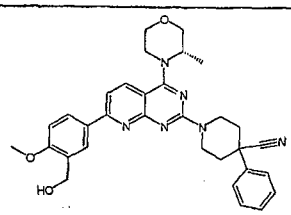
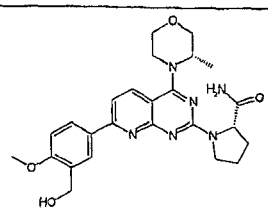
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18f	97	4.45	542.4	C	
18g	97	4.11	494.4	C	
18h	98	4.60	518.4	C	
18i	96	4.54	464.4	C	
18j	98	4.83	526.4	C	
18k	93	3.96	466.4	C	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18l	79	8.73	559.5	D	
18m	94	4.28	458.5	D	
18n	99	3.86	460.5	D	
18o	92	6.48	459.3	D	
18p	91	9.79	459.3	D	
18q	91	8.03	436.3	C	

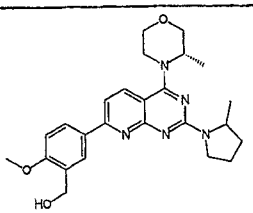
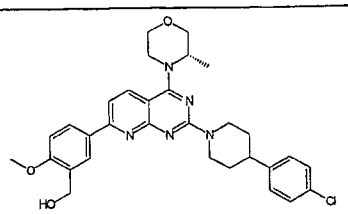
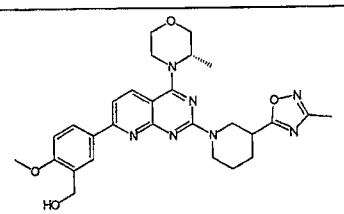
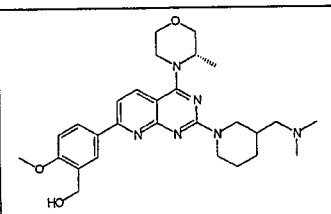
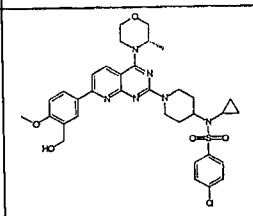
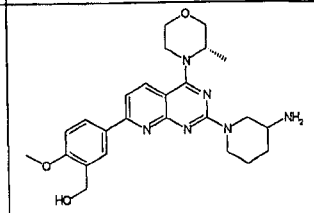
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18r	86	8.77	522.4	C	
18s	81	5.59	479.4	C	
18t	88	9.14	464.4	C	
18u	91	8.76	522.4	C	
18v	92	6.73	493.4	C	
18w	87	9.69	584.5	C	

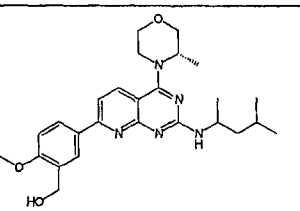
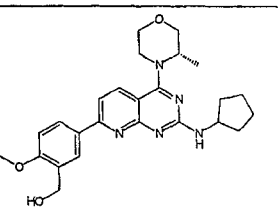
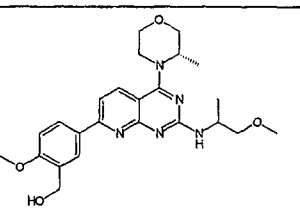
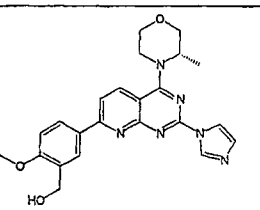
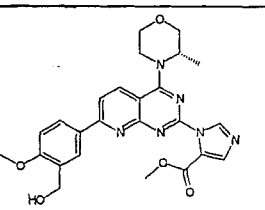
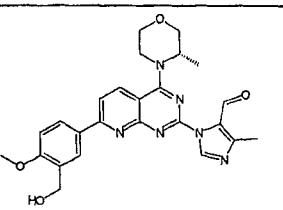
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18x	80	7.26	480.4	C	
18y	85	7.41	480.4	C	
18z	95	5.67	533.4	C	
18aa	88	6.79	510.3	C	
18ab	93	6.81	452.3	C	
18ac	93	5.44	535.4	C	

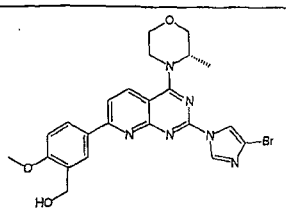
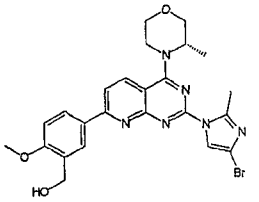
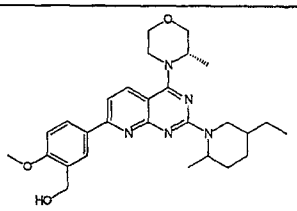
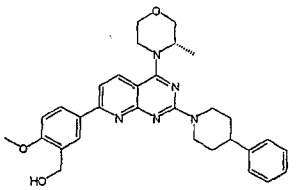
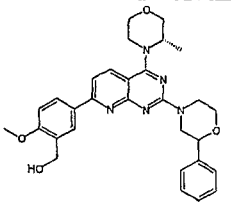
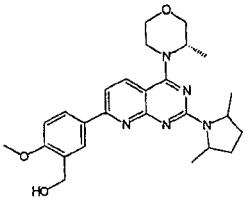
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18ad	99	5.40	465.5	E	
18ae	94	9.86	478.4	C	
18af	94	9.11	518.3	C	
18ag	72,25	10.37,10.81	504.4	C	
18ah	94	7.56	494.3	C	
18ai	96	5.55	519.4	C	

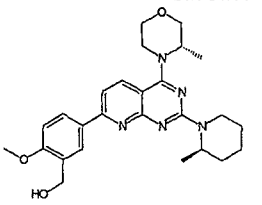
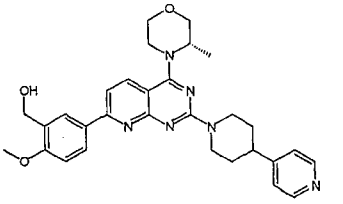
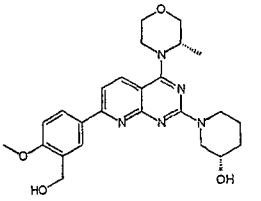
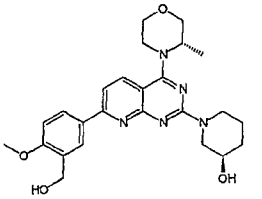
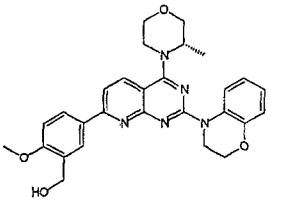
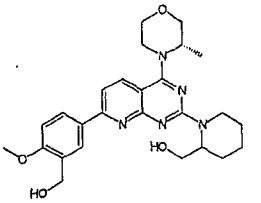
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
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18ak	96	10.49	588.4	C	
18al	96	10.92	540.4	C	
18am	97	8.84	542.4	C	
18an	95	9.74	551.4	C	
18ao	96	6.18	479.3	C	

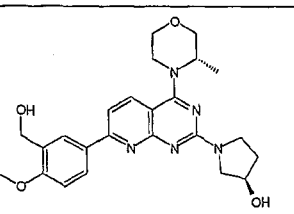
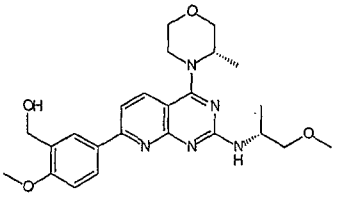
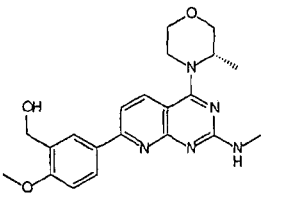
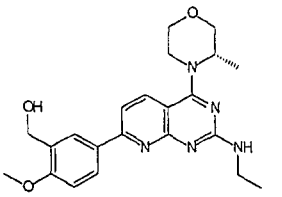
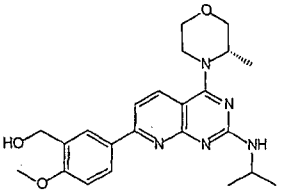
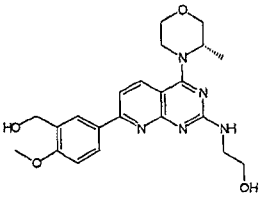
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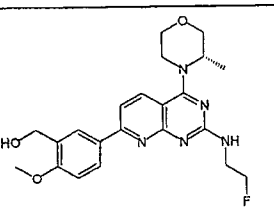
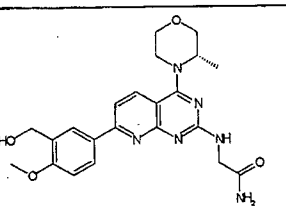
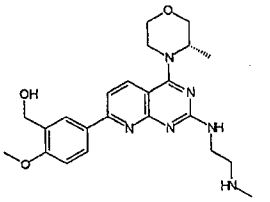
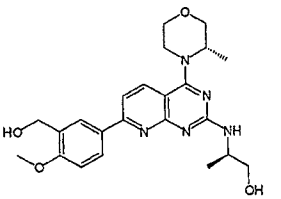
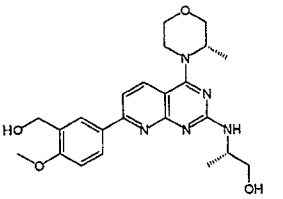
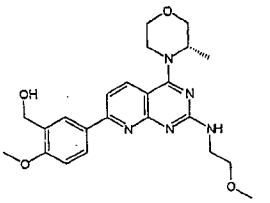
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18ap	92	8.46	450.3	C	
18aq	97	10.99	560.4	C	
18ar	89	8.12	532.4	C	
18as	91	5.71	507.4	C	
18at	99	10.88	679.4	C	
18au	85	5.37	465.4	E	

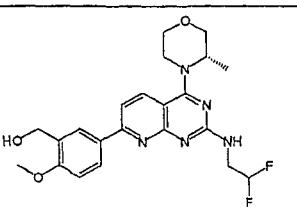
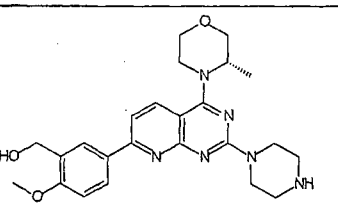
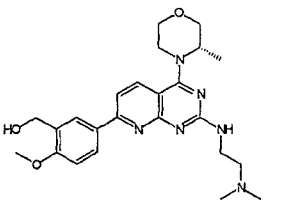
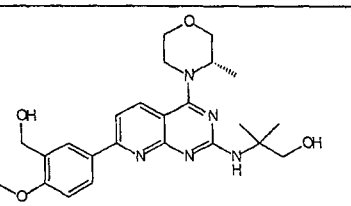
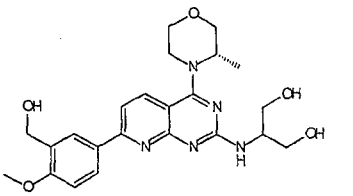
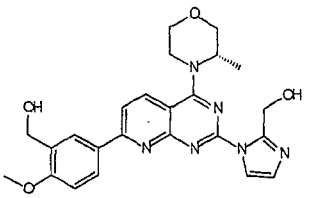
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18av	98	4.54	466.6	C	
18aw	98	4.30	450.5	C	
18ax	99	4.02	454.5	C	
18ay	100	3.83	433.4	F	
18az	92	9.32	491.4	F	
18ba	93	4.54	475.4	F	

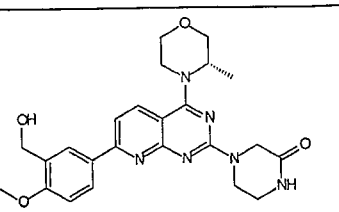
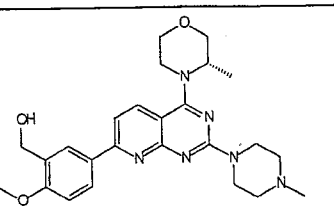
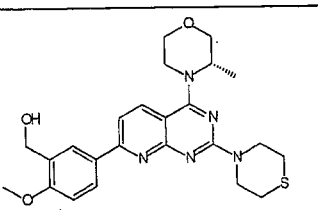
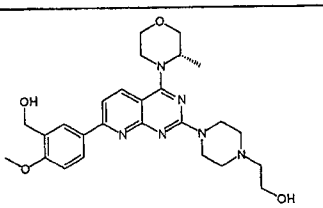
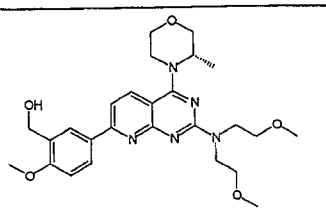
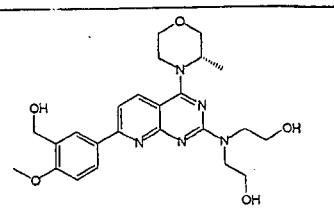
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18bb	100	5.06	511.4	F	
18bc	97	10.48	525.3	F	
18bd	10, 89	4.70, 4.77	492.5, 492.5	C	
18be	99	4.67	526.6	C	
18bf	99	4.48	528.5	C	
18bg	98	4.38	464.5	C	

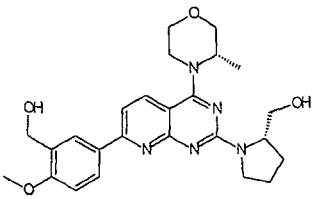
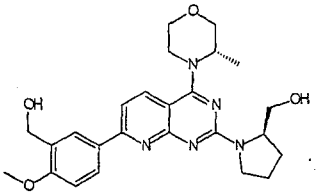
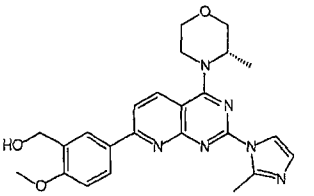
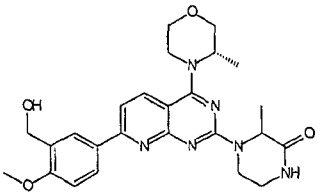
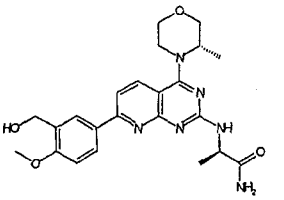
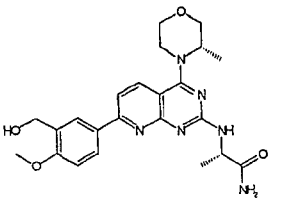
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18bh	98	4.37	464.5	C	
18bi	100	3.56	527.5	C	
18bj	99	3.84	466.4	C	
18bk	99	3.83	466.4	C	
18bl	95	9.06	500.5	C	
18bm	98	7.65	480.5	C	

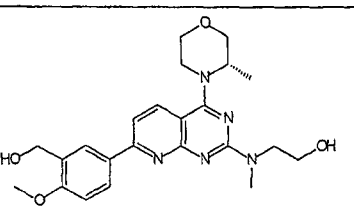
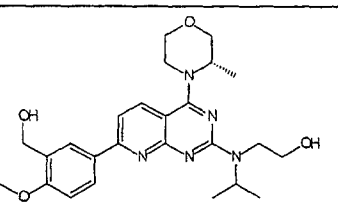
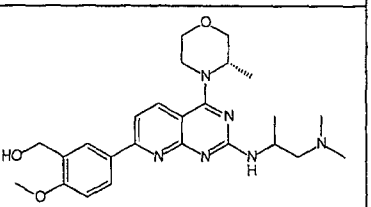
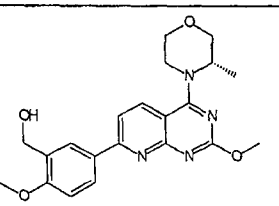
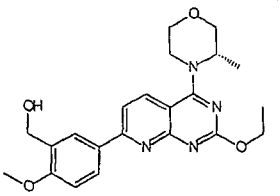
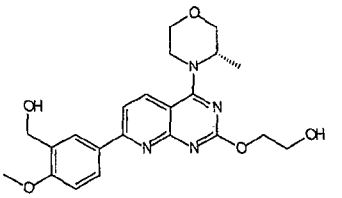
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18bn	97	3.78	452.5	C	
18bo	95	4.03	454.4	C	
18bp	98	4.01	396.4	H	
18bq	99	4.14	410.4	G	
18br	99	4.30	424.4	H	
18bs	93	5.27	426.4	C	

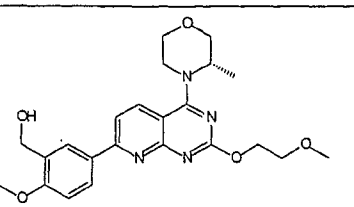
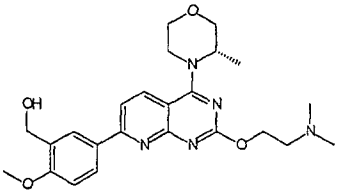
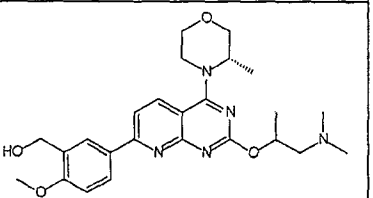
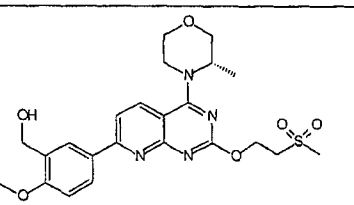
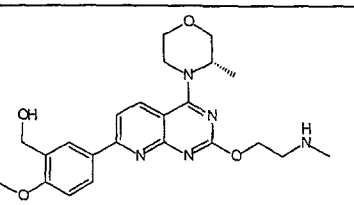
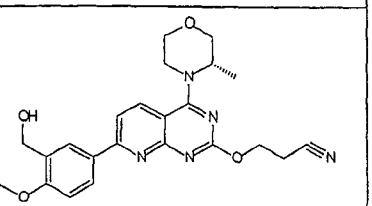
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18bt	94	7.18	428.3	H	
18bu	84	5.95	439.3	I	
18bv	91	4.91	439.4	C	
18bw	94	5.38	440.4	G	
18bx	94	5.40	440.4	G	
18by	92	5.44	440.4	C	

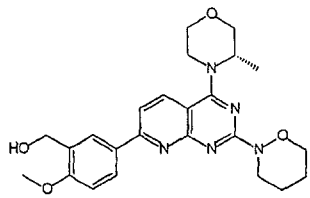
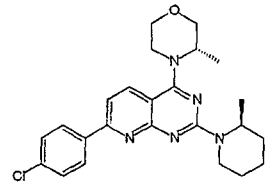
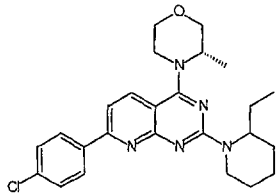
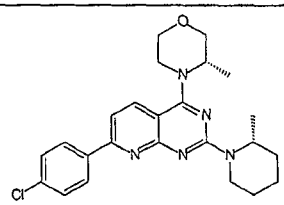
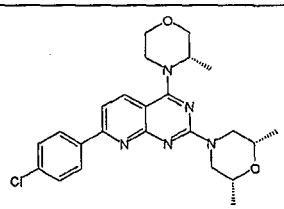
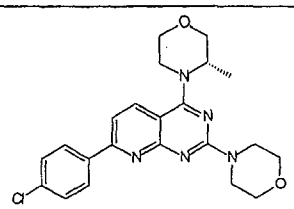
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18bz	97	5.52	446.3	H	
18ca	90	4.92	451.4	C	
18cb	93	4.95	453.4	C	
18cc	96	5.50	454.4	H	
18cd	92	5.18	456.4	H	
18ce	96	5.37	463.4	G	

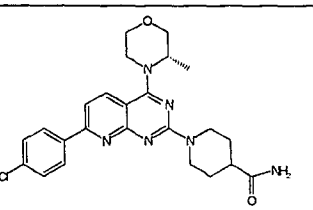
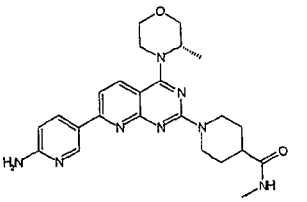
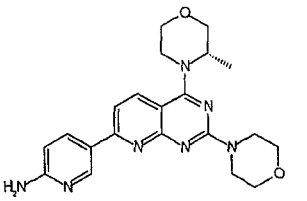
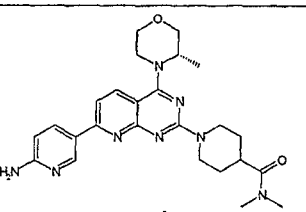
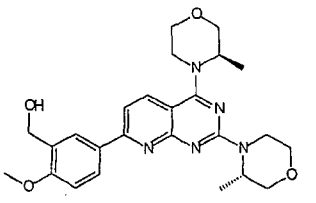
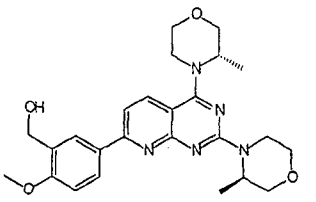
	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18cf	91	5.31	465.4	G	
18cg	92	4.95	465.4	C	
18ch	93	5.73	468.3	C	
18ci	99	4.95	495.4	C	
18cj	97	5.79	498.4	G	
18ck	91	5.28	470.3	G	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18cl	93	5.57	466.3	C	
18cm	92	5.58	466.3	C	
18cn	97	6.87	447.3	F	
18co	93	6.70	479.2	C	
18cp	92	6.18	453.2	J	
18cq	92	6.18	453.1	J	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18cr	92	6.72	440.2	C	
18cs	97	7.84	468.3	I	
18ct	98	5.38	467.3	I	
18cu	98	6.63	397.2	K	
18cv	88	7.17	411.2	L	
18cw	100	6.24	427.2	K	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18cx	83	6.87	441.2	L	
18cy	93	5.45	454.2	K	
18cz	97	5.72	468.3	K	
18da	98	7.96	489.3	K	
18db	98	6.73	440.3	K	
18dc	96	8.26	436.2	K	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18dd	95	4.05	452.4	J	
18de	93	5.36	438.2	A	
18df	93	11.22	452.3	A	
18dg	96	4.86	438.4	A	
18dh	100	4.66	454.4	A	
18di	100	4.37	426.4	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
18dj	98	7.86	467.4	M	
18dk	97	4.77	463.2	N	
18dl	99	4.78	408.1	N	
18dm	97	4.89	477.3	N	
18dn	97	4.03	466.2	O	
18do	99	3.99	466.2	O	

NMR data for Example 18b

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.85 (ArH, d, J = 2.46 Hz, 1H), 8.64 (ArH, dd, J = 8.75, 2.48 Hz, 1H), 8.30 (OH, s, br, 1H), 8.04 (ArH, d, J = 8.47 Hz, 1H), 7.59 (ArH, d, J = 8.54 Hz, 1H), 7.14 (ArH, d, J = 8.83 Hz, 1H), 5.03-4.91 (CH_2, m, 1H), 4.66 (CH_2, dd, J = 13.05, 0.77 Hz, 1H), 4.41 (CH_2, d, J = 6.75 Hz, 1H), 4.07 (OCH_3, s,3H), 4.04-3.98 (CH_2, m, 1H), 3.97-3.68 (CH_2, m, 11H), 3.60 (CH_2, d, J = 2.75 Hz, 1H), 3.41 (CH_2, s, 1H), 1.50 (CH_3, d, J = 6.77 Hz, 3H), 1.39 (CH_3, d, J = 6.81 Hz, 3H)

NMR data for Example 18k

^{1}H NMR (300 MHz, $CHCl_3$) δ ppm 10.59-10.51 (OH, m, 1H), 8.18 (ArH, dd, J = 4.42, 2.17 Hz, 2H), 7.99 (ArH, d, J = 8.45 Hz, 1H), 7.44 (ArH, d, J = 8.48 Hz, 1H), 7.01 (ArH, d, J = 9.22 Hz, 1H), 4.81 (CH_2OH, s, 2H), 4.37-4.11 (CH_2, m, 3H), 4.09-3.65 (OCH_3 + CH_2, m, 13H), 2.02-1.94 (CH_2, m, 1H), 1.73 – 1.38 (CH_2, m, 1H), 1.50 (CH_3, d, J = 6.77 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.05, 161.84, 161.81, 159.16, 150.47, 134.52, 129.29, 128.68, 128.43, 127.47, 117.04, 112.75, 110.28, 104.93, 104.30, 70.96, 67.12, 66.95, 66.77, 61.97, 55.57, 52.75, 50.99, 44.48 and 14.72.

NMR data for Example 18v

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.07 (ArH, dd, J = 7.09, 2.14 Hz, 2H), 7.89 (ArH, d, J = 8.47 Hz, 1H), 7.33 (ArH, d, J = 8.49 Hz, 1H), 6.91 (ArH, d, J = 9.31 Hz, 1H), 6.88 (NH, S, Br, 1H), 5.34 (NH, s, Br, 1H), 4.95 (CH_2, dd, J = 12.22, 0.66 Hz, 2H), 4.70 (CH_2OH, s, 2H), 4.34-4.20 (CH, m, 1H), 3.93-3.53 (OCH_3, + CH_2, m, 10H), 2.91 (CH_2, d, J = 12.29 Hz, 2H), 2.38 (CH_2, s, 2H), 1.89 (CH_2, dd, J = 6.92, 6.38 Hz, 2H), 1.76-1.54 (CH_2, m, 3H), 1.38 (CH_3, d, J = 6.76 Hz, 3H)
^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 176.91, 165.39, 162.98, 161.80, 160.14, 159.13, 134.52, 131.20, 129.28, 128.84, 128.44, 119.99, 112.70, 110.26, 104.34, 70.97, 67.10, 66.94, 61.97, 55.57, 52.76,44.52, 43.73, 43.69, 43.16, 26.88, and 14.70.

NMR data for Example 18ab

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (ArH, d, J = 7.14 Hz, 2H), 8.00 (ArH, d, J = 8.47 Hz, 1H), 7.43 (ArH, d, J = 8.42 Hz, 1H), 7.01 (ArH, d, J = 9.13 Hz, 1H), 4.82 (CH_2OH, s,

2H), 4.71-4.59 (CH_2, m, 1H), 4.47-4.35 (CH_2, m, 1H), 3.97 (OCH_3, s, 3H), 3.85 (CH_2, ddd, J = 17.63, 13.74, 9.24 Hz, 8H), 2.12 (CH_2, s, Br, 5H), 1.50 (CH_3 d, J = 6.75 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.35, 159.10, 134.61, 131.26, 129.22, 128.89, 128.54, 112.41, 110.21, 104.39, 71.06, 66.95, 61.99, 55.56, 52.80, 44.51, 27.01 and 14.78.

NMR data for Example 18ax

^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.27-8.17 (ArH, m, 2H), 8.00 (ArH, d, J = 8.50 Hz, 1H), 7.45 (ArH, d, J = 8.51 Hz, 1H), 7.01 (ArH, d, J = 8.65 Hz, 1H), 5.40 (NH, br, s, 1H), 4.81 (CH_2OH, s, 2H), 4.49-4.35 (CH2, m, 1H), 3.97 (OCH_3, s, 3H), 3.93-3.64 (CH_2, m, 6H), 3.58-3.48 (CH_2, m, 2H), 3.43 (OCH_3, s, 3H), 1.49 (CH_3, d, J = 6.71 Hz, 3H), 1.34 (CH_3, d, J = 6.68 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.67, 161.56, 160.64, 159.19, 134.53, 129.27, 128.83, 128.39, 112.53, 110.30, 76.23, 70.98, 67.00, 62.02, 59.18, 55.57, 52.73, 44.31, 18.23, 18.20 and 14.85.

NMR data for Example 18bn

^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.23-8.15 (ArH, m, 2H), 7.99 (ArH, d, J = 8.45 Hz, 1H), 7.42 (ArH, d, J = 8.46 Hz, 1H), 7.00 (ArH, d, J = 8.35 Hz, 1H), 4.81 (CH_2OH, s, 2H), 4.65 (CH, s, br, 1H), 4.05-3.64 (OCH_3 + CH_2, m, 13H), 3.24 (OH, s, 1H), 1.50 (CH_3, d, J = 6.73 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.18, 162.87, 159.34, 159.06, 134.57, 131.25, 129.26, 128.84, 128.47, 112.36, 110.20, 104.35, 71.00, 70.97, 66.94, 61.91, 55.55, 52.82, 44.43, 27.01 and 14.87.

NMR data for Example 18bo

^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.28-8.17 (ArH, m, 2H), 8.00 (ArH, d, J = 8.49 Hz, 1H), 7.45 (ArH, d, J = 8.50 Hz, 1H), 7.02 (ArH, d, J = 8.60 Hz, 1H), 5.51-5.34 (CH, m, 1H), 4.81 (CH_2OH, s, 2H), 4.47-4.34 (CH, m, 1H), 4.00 (CH_2, d, J = 1.94 Hz, 1H), 3.97 (OCH_3, s, 3H), 3.93-3.89 (CH2, m, 2H), 3.83-3.63 (CH_2, m, 4H), 3.53 (CH_2, d,br, J = 4.02 Hz, 2H), 3.43 (OCH_3, s, 3H), 1.50 (CH_3, d, J = 6.73 Hz, 3H), 1.34 (CH_3, d, J = 6.69 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.69, 161.55, 160.67, 159.19, 134.52, 131.15, 129.26, 128.84, 128.41, 119.72, 112.58, 110.30, 70.98, 67.12, 67.00, 62.05, 59.18, 55.58, 52.73, 44.32, 18.20 and 14.84.

NMR data for Example 18dj

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10-8.03 (ArH, m, 2H), 7.95 (ArH, d, J = 8.41 Hz, 1H), 7.42-7.30 (ArH, m, 3H), 5.52-5.27 (NH_2, m, br,2H), 4.98 (CH_2, dd, J = 12.74, 0.96 Hz, 2H), 4.31-4.29 (CH, m, 1H), 3.97-3.55 (CH_2, m, 8H), 3.07-2.86 (CH_2, m, 2H), 2.45-2.35 (CH_2, m, 1H), 1.99-1.88 (CH_2, m, br, 2H), 1.70 (CH_2, m, 2H), 1.41 (CH_3, d, J = 6.76 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 176.75, 170.03, 165.35, 162.99, 161.12, 160.17, 137.17, 136.10, 134.83, 129.19, 128.76, 112.81, 104.86, 100.00, 70.95, 67.12, 66.91, 52.83, 44.50, 43.72, 43.68, 43.10, 28.88 and 14.73.

NMR data for Example 18dk

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.67 (ArH, d, J = 1.86 Hz, 1H), 8.38 (ArH, dd, J = 8.76, 2.36 Hz, 1H), 8.29 (NH, s, weak signal, 1H), 7.91 (ArH, d, J = 8.45 Hz, 1H), 7.27 (ArH, d, J = 8.46 Hz, 1H), 6.58 (ArH, d, J = 8.75 Hz, 1H), 5.54-5.45 (CH_2, m, 1H), 4.97 (NH_2, br, s, 2H), 4.37-4.24 (CH_2, m, 1H), 3.97-3.54 (CH_2, m, 6H), 3.09-2.87 (CH_2, m, 2H), 2.77 ($NHCH_3$, d, J = 4.82 Hz, 3H), 2.42-2.24 (CH_2, m, 1H), 1.87 (CH_2, d, J = 0.84 Hz, 2H), 1.79-1.59 (CH_2, m, 2H), 1.40 (CH_3, d, J = 6.76 Hz, 3H).

NMR data for Example 18dl

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.68 (ArH, d, J = 1.98 Hz, 1H), 8.49 (ArH, dd, J = 8.87, 2.32 Hz, 1H), 8.38 (NH, s, br,weak signal 1H), 7.99 (ArH, d, J = 8.47 Hz, 1H), 7.34 (ArH, d, J = 8.49 Hz, 1H), 6.67 (ArH, d, J = 8.85 Hz, 1H), 4.38 (CH_2, d, J = 6.77 Hz, 1H), 4.05-3.82 (CH_2, m, 7H), 3.81-3.62 (CH_2, m, 7H), 1.47 (CH_3, d, J = 6.77 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.16, 162.79, 160.31, 159.09, 158.45, 143.98, 139.12, 135.00, 124.48, 111.80, 110.03, 104.70, 70.92, 67.00, 66.90, 52.81, 44.57, 44.40 and 14.78.

NMR data for Example 18dm

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm 8.67 (ArH, d, J = 2.05 Hz, 1H), 8.36 (ArH, dd, J = 8.76, 2.27 Hz, 1H), 7.90 (ArH, dd, J = 8.45, 2.12 Hz, 1H), 7.26 (ArH, dd, J = 8.47, 0.73 Hz, 1H), 6.57 (ArH, d, J = 8.76 Hz, 1H), 5.10-4.87 (NH_2, m, 2H), 4.37-4.22 (CH_2, m, 1H), 3.96-3.51 (CH_2, m, 6H), 3.08 (NCH_3 + CH_2, s, 4H), 2.95-2.91 (NCH_3, s, 3H), 2.80-2.59 (CH_2, m, 1H), 1.76 (CH_2, d, J = 2.61 Hz, 3H), 1.64-1.44 (CH, m, 1H), 1.38 (CH_3, t, J = 6.34, 6.34 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 173.59, 165.46, 165.31, 163.03, 160.17, 158.89, 145.99, 138.35, 134.76, 124.89, 111.71, 109.15, 104.41, 70.96, 66.96, 52.81, 46.85, 44.38, 39.43, 37.26, 35.56, 28.06, 24.95 and 14.71.

NMR data for Example 18dn

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.10 (ArH, d, J = 7.89 Hz, 2H), 7.97 (ArH, d, J = 8.49 Hz, 1H), 7.42 (ArH, d, J = 8.46 Hz, 1H), 6.98 (ArH, d, J = 8.55 Hz, 1H), 4.88 (CH_2, d, J = 5.25 Hz, 1H), 4.77 (CH_2OH, s, 2H), 4.56 (CH_2, d, J = 13.38 Hz, 1H), 4.38 – 4.36 (CH_2, m, 1H), 4.02 – 3.51 (OCH_3 + CH_2, m, 11H), 3.43 – 3.33 (CH_2, m, 1H), 1.47 (CH_3, d, J = 6.77 Hz, 3H), 1.35 (CH_3, d, J = 6.78 Hz, 3H).

^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm 165.11, 162.27, 161.87, 159.54, 159.23, 134.74, 130.76, 129.41, 128.86, 128.39, 113.09, 110.32, 104.45, 71.20, 70.95, 67.17, 66.91, 61.80, 55.57, 52.82, 47.05, 44.44, 39.45, 14.74 and 14.44.

NMR data for Example 18do

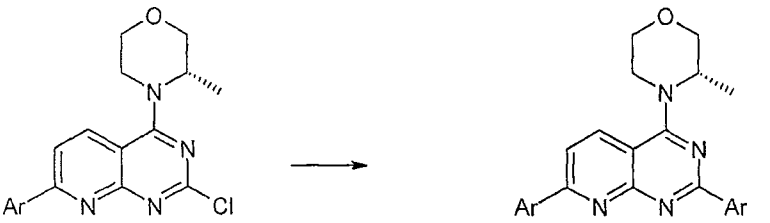
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.10 (ArH, d, J = 8.76 Hz, 2H), 7.98 (ArH, d, J = 8.49 Hz, 1H), 7.42 (ArH, d, J = 8.46 Hz, 1H), 6.97 (ArH, d, J = 8.37 Hz, 1H), 4.88 (CH_2, d, J = 5.46 Hz, 1H), 4.77 (CH_2OH, s, 2H), 4.58 – 4.49 (CH_2, m, 1H), 4.39 – 4.36 (CH_2, d J = 7.41 Hz, 1H), 4.02 – 3.51 (OCH_3 + CH_2, m, 11H), 3.43 – 3.33 (CH_2, m, 1H), 1.48 (CH_3, d, J = 6.78 Hz, 3H), 1.35 (CH_3, d, J = 6.78 Hz, 3H).

^{13}C NMR (75 MHz, CD_3COCD_3) δ ppm 165.05, 161.87, 159.45, 159.24, 134.78, 130.70, 129.44, 128.86, 128.38, 113.14, 110.33, 104.43, 71.19, 70.95, 67.16, 66.90, 61.77, 55.57, 52.82, 47.08, 44.44, 39.47, 14.76 and 14.44.

Tested in Alternative Enzyme Assay: Ex. (18a) 0.03μM; Ex. (18b) 0.1μM; Ex. (18c) 0.066μM; Ex. (18d) 0.15μM; Ex. (18e) 0.039μM; Ex. (18f) 0.038μM; Ex. (18g) 0.031μM; Ex. (18h) 0.23μM; Ex. (18i) 0.03μM; Ex. (18j) 0.088μM; Ex. (18k) 0.019μM; Ex. (18l)

0.097μM; Ex. (18m) 0.042μM; Ex. (18n) 0.31μM; Ex. (18o) 0.51μM; Ex. (18p) 0.25μM; Ex. (18q) 0.11μM; Ex. (18r) 0.18μM; Ex. (18s) 0.037μM; Ex. (18t) 0.054μM; Ex. (18u) 0.073μM; Ex. (18v) 0.014μM; Ex. (18w) 0.25μM; Ex. (18x) 0.014μM; Ex. (18y) 0.023μM; Ex. (18z) 0.088μM; Ex. (18aa) 0.019μM; Ex. (18ab) 0.012μM; Ex. (18ac) 0.014μM; Ex. (18ad) 0.078μM; Ex. (18ae) 0.034μM; Ex. (18af) 0.23μM; Ex. (18ag) 0.25μM; Ex. (18ah) 0.03μM; Ex. (18ai) 0.063μM; Ex. (18aj) 0.022μM; Ex. (18ak) 0.42μM; Ex. (18al) 0.36μM; Ex. (18am) 0.077μM; Ex. (18an) 0.14μM; Ex. (18ao) 0.073μM; Ex. (18ap) 0.013μM; Ex. (18aq) 0.19μM; Ex. (18ar) 0.079μM; Ex. (18as) 0.08μM; Ex. (18at) 0.78μM; Ex. (18au) 0.11μM; Ex. (18av) 0.27μM; Ex. (18aw) 0.058μM; Ex. (18ax) 0.026μM; Ex. (18ay) 0.087μM; Ex. (18az) 0.092μM; Ex. (18ba) 0.16μM; Ex. (18bb) 0.65μM; Ex. (18bc) 0.043μM; Ex. (18bd) 0.19μM; Ex. (18be) 0.79μM; Ex. (18bf) 0.077μM; Ex. (18bg) 0.047μM; Ex. (18bh) 0.04μM; Ex. (18bi) 0.32μM; Ex. (18bj) 0.024μM; Ex. (18bk) 0.022μM; Ex. (18bl) 0.61μM; Ex. (18bm) 0.025μM; Ex. (18bn) 0.01μM; Ex. (18bo) 0.058μM; Ex. (18bp) 0.049μM; Ex. (18bq) 0.072μM; Ex. (18br) 0.03μM; Ex. (18bs) 0.042μM; Ex. (18bt) 0.062μM; Ex. (18bu) 0.047μM; Ex. (18bv) 0.11μM; Ex. (18bw) 0.031μM; Ex. (18bx) 0.035μM; Ex. (18by) 0.039μM; Ex. (18bz) 0.01μM; Ex. (18ca) 0.0026μM; Ex. (18cb) 0.25μM; Ex. (18cc) 0.018μM; Ex. (18cd) 0.025μM; Ex. (18ce) 0.37μM; Ex. (18cf) 0.013μM; Ex. (18cg) 0.067μM; Ex. (18ch) 0.078μM; Ex. (18ci) 0.068μM; Ex. (18cj) 0.055μM; Ex. (18ck) 0.0095μM; Ex. (18cl) 0.023μM; Ex. (18cm) 0.029μM; Ex. (18cn) 0.013μM; Ex. (18co) 0.0052μM; Ex. (18cp) 0.0057μM; Ex. (18cq) 0.027μM; Ex. (18cr) 0.0063μM; Ex. (18cs) 0.0047μM; Ex. (18ct) 0.097μM; Ex. (18cu) 0.08μM; Ex. (18cv) 0.043μM; Ex. (18cw) 0.034μM; Ex. (18cx) 0.024μM; Ex. (18cy) 0.12μM; Ex. (18cz) 0.079μM; Ex. (18da) 0.71μM; Ex. (18db) 0.0031μM; Ex. (18dc) 0.21μM; Ex. (18dd) 0.028μM; Ex. (18de) 0.26μM; Ex. (18df) 0.4μM; Ex. (18dg) 0.3μM; Ex. (18dh) 0.15μM; Ex. (18di) 0.15μM; Ex. (18dj) 0.052μM; Ex. (18dm) 0.061μM; Ex. (18dn) 0.0094μM; Ex. (18do) 0.026μM.Tested in phospho-Ser473 Akt assay: Ex. (18dk) 0.6821μM; Ex. (18dl) 0.2951μM.

Example 19



The chloro-substrates were reported in Example 18.

(Compounds 19a to 19x)

Conditions A:

To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (3.5 equiv), and the appropriate boronic acid (1.0 equiv) in acetonitrile/water (1:1) (0.026 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and heated at 95 °C for 2 hours. Upon completion the samples were filtered through a silica cartridge, washed with CH_2Cl_2 and methanol and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

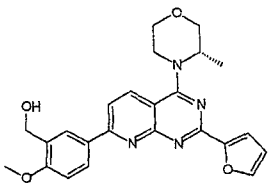
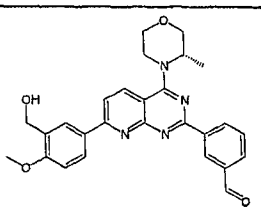
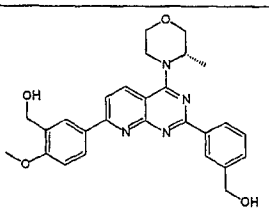
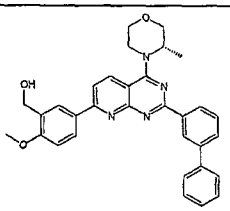
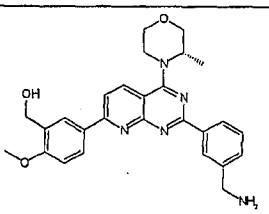
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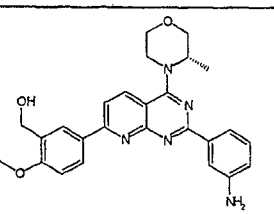
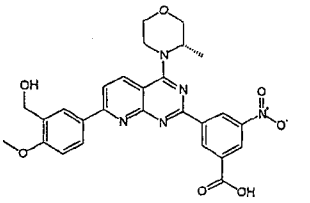
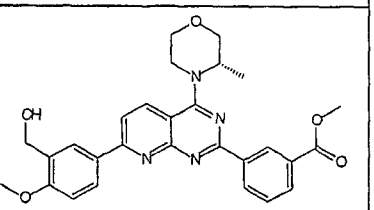
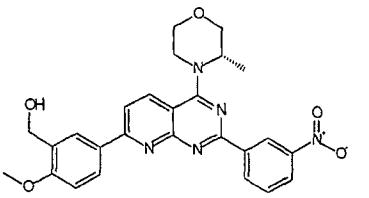
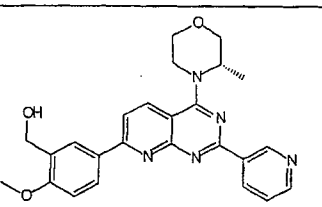
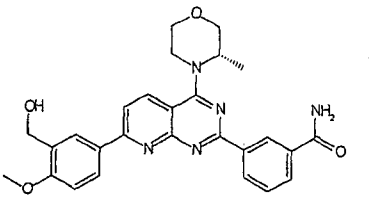
To a mixture of the appropriate chloro-substrate (1 equiv), cesium fluoride (3.5 equiv), and the appropriate boronic acid (1.0 equiv) in acetonitrile (0.026 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and heated at 95 °C for 2 hours. Upon completion the samples were filtered through a silica cartridge, washed with CH_2Cl_2 and methanol and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

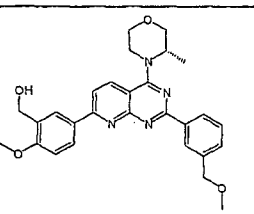
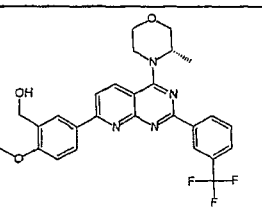
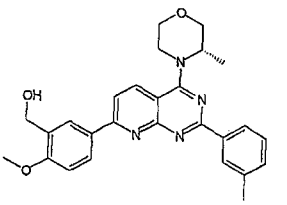
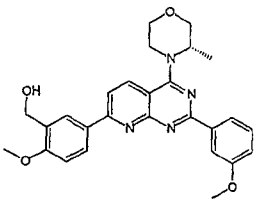
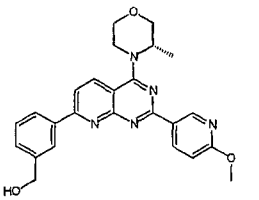
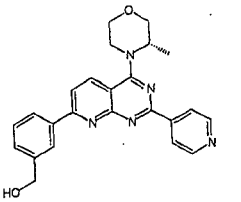
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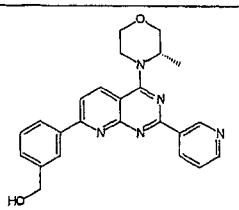
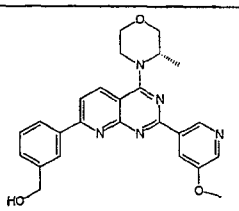
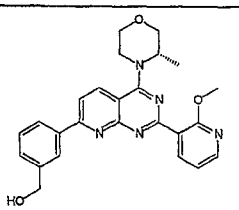
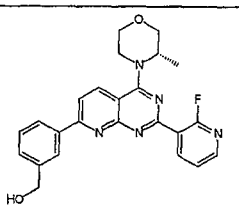
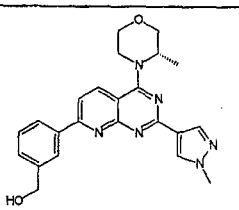
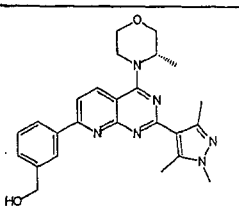
To a mixture of the appropriate chloro-substrate (1 equiv), potassium carbonate (2.5 equiv), and the appropriate pinacolate boron ester or boronic acid (1.1 equiv) in acetonitrile/water (1:1) (0.041 M of chloro-substrate) was added tetrakis(triphenylphosphine) palladium^0 (0.05 equiv). The reaction vessel was sealed and exposed to microwave radiation (150 °C, medium absorption setting) for 30 minutes under nitrogen atmosphere. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

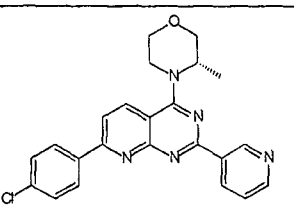
Table 19:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
19a	93	7.66	433.2	A	
19b	88	8.95	471.3	A	
19c	79	7.54	473.3	A	
19d	92	11.14	519.3	A	
19e	99	6.14	472.3	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
19f	90	7.43	458.3	A	
19g	84	10.52	532.3	A	
19h	75	9.58	501.3	B	
19i	94	11.13	488.3	A	
19j	84	7.36	444.3	A	
19k	88	7.33	486.3	A	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
19l	88	8.75	487.3	A	
19m	93	11.64	511.3	A	
19n	87	9.26	457.3	A	
19o	89	9.05	473.3	A	
19p	97	4.31	444.3	C	
19q	95	4.13	414.2	C	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
19r	94	4.14	414.2	C	
19s	97	4.43	444.2	C	
19t	98	4.28	444.2	C	
19u	87	4.41	432.2	C	
19v	98	4.07	417.2	C	
19w	96	4.12	445.3	C	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
19x	99	5.66	418.2	A	

NMR data for Example 19j

^{1}H NMR (300 MHz, DMSO) δ ppm 9.63 (ArH, d, J = 1.49 Hz, 1H), 8.84-8.69 (ArH, m, 2H), 8.49-8.37 (ArH, m, 1H), 8.19 (ArH, dd, J = 8.61, 2.35 Hz, 1H), 8.00 (ArH, d, J = 8.76 Hz, 1H), 7.57 (ArH, ddd, J = 7.99, 4.81, 0.71 Hz, 1H), 7.15 (ArH, d, J = 8.71 Hz, 1H), 5.23 (ArH, dd, J = 2.03, 1.13 Hz, 1H),5.23 (CH, m, 1H), 4.78 (CH, d, J = 6.83 Hz, 1H), 4.61 (CH_2OH, s, 2H), 4.22 (CH_2, d, J = 13.08 Hz, 1H), 4.03-3.92 (CH_2, m, 1H), 3.98 (OCH_3, s, 3H), 3.88-3.61 (CH_2, m, 3H), 2.50 1.49 (CH_3, d, J = 6.79 Hz, 3H)

^{13}C NMR (75 MHz, DMSO) δ ppm 164.91, 161.77, 161.25, 160.36, 158.71, 151.75, 149.97, 136.10, 133.86, 131.45, 129.97, 127.92, 126.79, 124.08, 117.24, 110.92, 108.15, 70.77, 66.83, 66.80, 58.39, 56.04, 52.15, 44.39 and 15.24.

NMR data for Example 19x

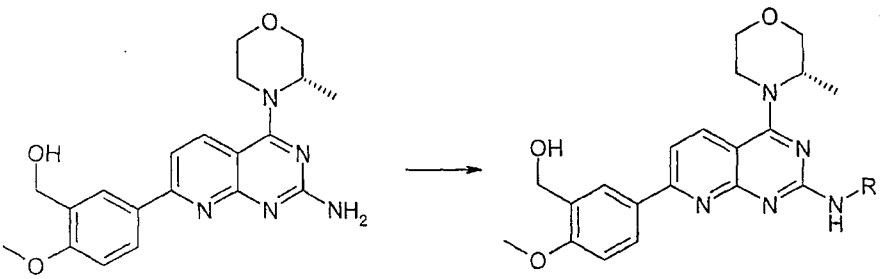
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.86-9.80 (ArH, m, 1H), 9.00-8.91 (ArH, m, 1H), 8.77 (ArH, dd, J = 4.80, 1.71 Hz, 3H), 8.28 (ArH , ddd, J = 9.24, 8.03, 5.57 Hz, 1H), 7.83 (ArH, d, J = 8.64 Hz, 2H), 7.60-7.53 (ArH, m, 2H), 7.53-7.43 (CH, m, 1H), 4.72 (CH_2, d, J = 6.93 Hz, 1H), 4.33-4.23 (CH_2, m, 1H), 4.00-3.80 (CH_2, m, 4H), 1.65 (CH_3, d, J = 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.55, 161.73, 161.53, 151.52, 150.66, 136.99, 136.34, 134.91, 133.42, 129.34, 129.12, 123.19, 119.66, 117.15, 108.64, 106.49, 70.98, 67.02, 52.92, 44.49 and 15.16.

Tested in Alternative Enzyme Assay: Ex. (19a) 0.048μM; Ex. (19b) 0.018μM; Ex. (19c) 0.052μM; Ex. (19d) 0.25μM; Ex. (19e) 0.11μM; Ex. (19f) 0.096μM; Ex. (19g) 0.0087μM; Ex. (19h) 0.77μM; Ex. (19i) 0.28μM; Ex. (19j) 0.057μM; Ex. (19k) 0.077μM; Ex. (19l)

0.12μM; Ex. (19m) 0.41μM; Ex. (19n) 0.22μM; Ex. (19o) 0.19μM; Ex. (19p) 0.24μM; Ex. (19q) 0.14μM; Ex. (19r) 0.012μM; Ex. (19s) 2μM; Ex. (19t) 0.097μM; Ex. (19u) 0.055μM; Ex. (19v) 0.07μM; Ex. (19w) 0.086μM; Ex. (19x) 0.81μM.

Example 20



The amino substrate was reported in Example 18.

(Compounds 20a to 20c)

Conditions A:

The appropriate amino-substrate (1 equiv) was suspended in THF (0.04 M). The appropriate sulfonyl chloride (2.0 equiv) was added. The reaction vessel was sealed and exposed to microwave radiation (140 °C, medium absorption setting) for 10 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions B:

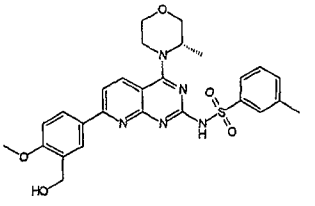
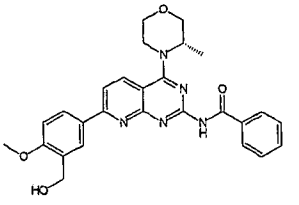
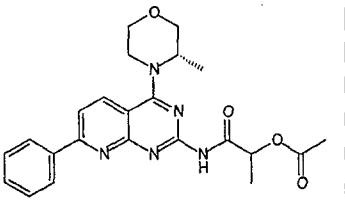
The appropriate amino-substrate (1 equiv) was suspended in DMF (0.04 M). The appropriate acyl chloride (1.2 equiv) and potassium carbonate (2.4 equiv) were added. The reaction vessel was sealed and exposed to microwave radiation (140 °C, medium absorption setting) for 10 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

Conditions C:

The appropriate amino-substrate (1 equiv) was suspended in DMF (0.09 M). The appropriate acyl chloride (3.0 equiv) was added. The reaction vessel was sealed and exposed to microwave radiation (130 °C, medium absorption setting) for 15 minutes. Upon completion the samples were concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired products.

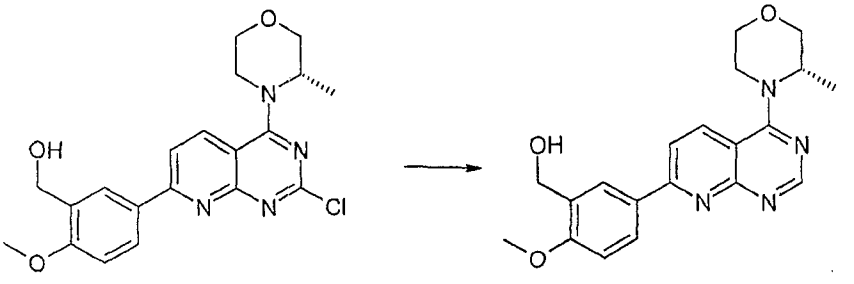
]

Table 20:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Conditions	Example Structure
20a	93	4.67	536.5	A	
20b	97	4.58	486.4	B	
20c	85	4.56	436.3	C	

Tested in Alternative Enzyme Assay: Ex. (20a) 1.4μM; Ex. (20b) 0.67μM; Ex. (20c) 0.024μM.

Example 21

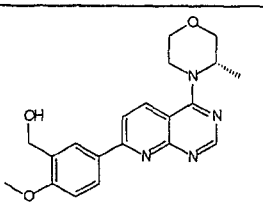


The chloro-substrate was reported in Example 18.

(Compound 21a)

The appropriate chloro-substrate (1 equiv) was dissolved in ethanol (0.025 M). Sodium formate (11.0 equiv) and palladium on carbon (0.5 equiv) were added. The reaction vessel was sealed and heated at 100 °C for 12 hours. Upon completion the sample was filtered through Celite™, and the filtrate was concentrated *in vacuo*. The crude residue was then purified by reverse phase chromatography eluting with a gradient of 5 to 95 % acetonitrile in 0.1 % formic acid/water, to give the desired product.

Table 21:

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Example Structure
21a	97	5.94	367.3	

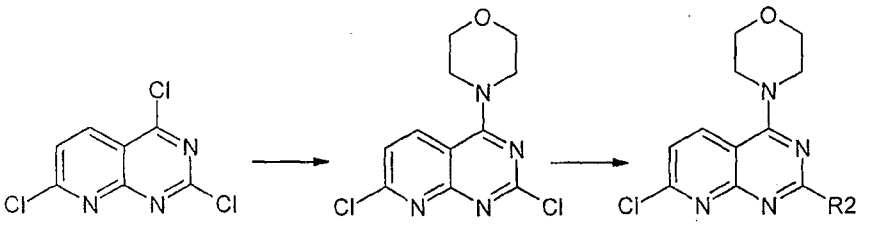
NMR data for Example 21a

^{1}H NMR (300 MHz, DMSO) δ ppm 8.70 (ArH, s, 1H), 8.42 - 8.37 (ArH, m, 2H), 8.16 (ArH, dd, J = 8.59, 2.34 Hz, 1H), 8.01 (ArH, d, J = 8.79 Hz, 1H), 7.14 (ArH, d, J = 8.69 Hz, 1H), 5.20 (CH, t, J = 5.67, 5.67 Hz, 1H), 4.59 (CH_2, d, J = 5.61 Hz, 2H), 4.05 - 3.93 (CH_2, m, 2H), 3.89 (OCH_3, s, 3H), 3.80-3.59 (CH_2, m, 4H), 3.57 (s, 1H), 3.31 (s, 1H), 2.50 (td, J = 3.64, 1.80, 1.80 Hz, 1H), 1.42 (CH_3, d, J = 6.79 Hz, 3H)

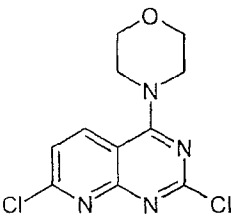
^{13}C NMR (75 MHz, DMSO) δ ppm 164.04, 161.48, 160.52, 158.69, 157.38, 136.11, 131.43, 129.96, 127.87, 126.77, 117.33, 110.93, 109.11, 70.71, 66.83, 58.37, 56.03, 52.14, 44.28 and 15.17.

Tested in Alternative Enzyme Assay: Ex. (21a) 0.2μM.

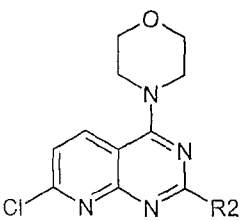
Comparative Example 1



Using the method of Example 1, to a cooled (0-5 °C) stirred solution (0.1 M) of the appropriate trichloro substrate (1 equiv) in CH_2Cl_2 was added diisopropylethylamine (1 equiv) in a dropwise fashion. The appropriate amine (1 equiv) was then added to the reaction mixture portionwise over the period of 1 hour. The solution was maintained at room temperature with stirring for a further 1 hour before the mixture was washed with water (2x1 reaction volume). The aqueous extracts were combined and extracted with CH_2Cl_2 (2x1 reaction volume). The organic extracts were then combined, dried (sodium sulphate), filtered and concentrated *in vacuo* to give an oily residue which solidified upon prolonged drying. The solid was triturated with diethylether and then filtered and the cake washed with cold diethyl ether to leave the title compound in a suitably clean form to be used without any further purification.

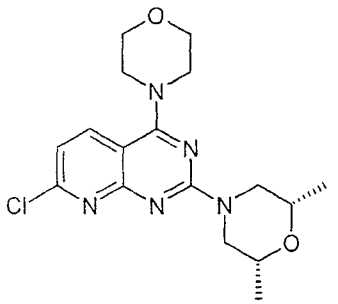


2,7-Dichloro-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine - R1= morpholine: (92% yield, 90% purity) m/z (LC-MS, ESP): 285 $[M+H]^+$ R/T = 3.90 min

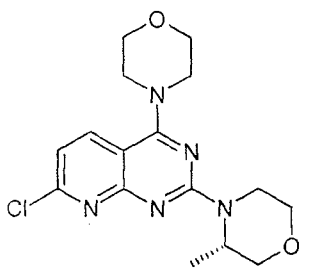


To a solution (0.2 M) of the appropriate dichloro-substrate (1 equiv) in anhydrous dimethyl acetamide under an inert atmosphere was added diisopropylethylamine (1 equiv) followed by the appropriate amine (1 equiv). The resulting mixture was heated for 48 hours at 70 °C before being cooled to ambient temperature. The reaction was diluted with CH_2Cl_2 (1 reaction volume) and then washed with water (3x1 reaction volumes). The organic extract

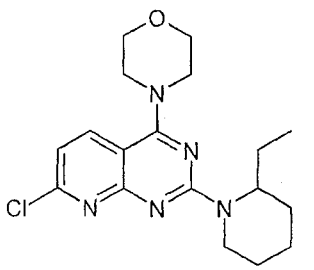
was concentrated *in vacuo* to give a syrup which was dissolved in EtOAC (1 reaction volume) and washed with saturated brine solution before being dried, filtered (sodium sulphate) and concentrated *in vacuo* to give an oil. The crude residue was purified by flash chromatography (SiO_2, eluted with EtOAc:Hex (7:3) going to (1:1)) to give the title compound as a yellow solid that was suitably clean to be used without any further purification.



7-Chloro-2-((2S,6R)-2,6-dimethyl-morpholin-4-yl)-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine - R1= morpholine, R2=cis-dimethylmorpholine: (42% yield, 100% purity) m/z (LC-MS, ESP): 364 $[M+H]^+$ R/T = 2.96 min



7-Chloro-2-((S)-3-methyl-morpholin-4-yl)-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine R1 = morpholine, R2= (S)-3-Methyl-morpholine: (70 % yield, 97 % purity) m/z (LC-MS, ESP): 350 $[M+H]^+$ R/T = 3.44 min



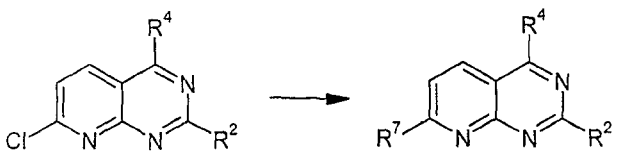
7-Chloro-2-(2-ethyl-piperidin-1-yl)-4-morpholin-4-yl-pyrido[2,3-d]pyrimidine R1 = morpholine, R2= 2-Ethyl-piperidine: (56 % yield, 95 % purity) m/z (LC-MS, ESP): 362 $[M+H]^+$ R/T = 3.78 min

Comparative Examples 1a, 1b, 1c, 1j, and 1k

R^4 = morpholine

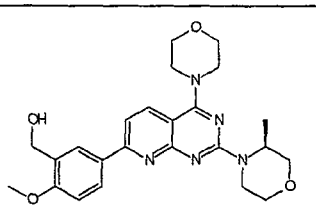
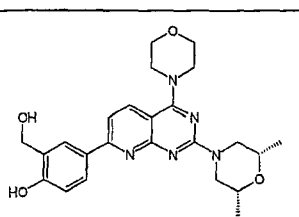
R^2 = (S)-3-methyl-morpholine or cis-dimethylmorpholine or 2-Ethyl-piperidine

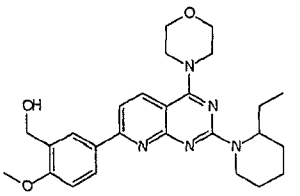
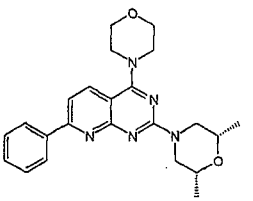
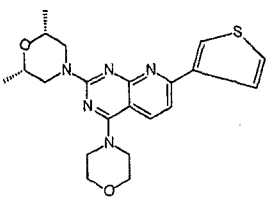
R^7 = aryl or heteroaryl



The appropriate chloro-substrate (1 equiv) was dissolved in a toluene/ethanol (1:1) solution (0.02 M). Sodium carbonate (2 equiv) and the appropriate pinacolate boron ester or boronic acid (1 equiv) were then added followed by tetrakis(triphenylphosphine) palladium^0 (0.1 equiv). The reaction vessel was sealed and the mixture exposed to microwave radiation (140 °C, medium absorption setting) for 30 minutes. Upon completion the samples were filtered through a silica cartridge, washed with EtOAc and then concentrated *in vacuo*. The crude residue was then purified by preparative HPLC to give the desired comparative examples.

The following Comparative Examples were prepared

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Comparative Example Structure
1a	99	4.13	452.3	
1b	95	3.95	452.3	

	Purity (%)	Retention time (min)	m/z $[M+H]^+$	Comparative Example Structure
1c	99	9.01	464.4	
1j	88	8.57	406.5	
1k	93	8.12	412.3	

Example 22

Biological Assay

For mTOR enzyme activity assays, mTOR protein was isolated from HeLa cell cytoplasmic extract by immunoprecipitation, and activity determined essentially as described previously using recombinant PHAS-1 as a substrate (ref. 21).

Examples 1a – 1l, 1ak, 1al, 1ap, 1at, 1az, 3l, 4a, 4c, 4d, 4f, 4i, 4w, 4x, 5q were tested and exhibited IC_{50} values against mTOR of less than 200 nM. For example 5q was measured to have an IC50 of 46nm.

The comparative Examples were also tested and when compared to the corresponding Examples, the exhibited IC_{50} values for the Comparative Examples were higher than those of the corresponding Examples (ie IC50 Comparative Example 1a > IC50 Example 1a). For example Example 1k was measured to have an IC50 of 5nm whereas Comparative Example

1k was measured to have an IC50 of 33nm. Therefore, compounds of the present invention are more active in the mTOR assay.

Example 23

Alternative Enzyme Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5 % CO_2 up to a confluency of 70-90 % in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10 % heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1 % L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulphate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 µl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 10 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) in a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/ml), DTT (1.25 mM) and manganese chloride (10 mM)] were added to the assay plates and incubated with compound for 2 hours at room temperature.

Each reaction was stopped by the addition of 5 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/ml) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue No.

9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200ng/well Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively). Assay plates were left for approx 16 hours at room temperature before measurement. The resultant signals arising from laser light excitation at 680 nm were measured using a Packard Envision instrument.

Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In the presence of an mTOR kinase inhibitor, signal strength is reduced.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 5 % DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding EDTA (83 mM) instead of test compound.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

The compounds tested in this assay exhibited IC_{50} values against mTOR of less than 40μm.

The following compounds exhibited IC_{50} values against mTOR of less than 1μm: 1bp, 1ca, 1cb, 1cd, 12e, 18df, 1m, 1q, 1r, 17, 19h, 19m, 18n, 18o, 18ak, 18al, 18at, 1t, 18bb, 18be, 18bi, 18bl, 1x, 1y, 1ba, 1z, 20b, 1ae, 7a, 7h, 18ce, 5f, 4af, 4ag, 4aj, 5y, 3b, 5j, 5k, 5p, 3w, 3y, 3z, 11a, 18da, 3m, 3o, 3p, 3r, 3s, 1aj, 5r, 5s, 1cn, 2a, 2b, 1cq, 1cr, 2d, 3ad, 2h, 1cw and 1dd, with the following compounds exhibiting IC_{50} values against mTOR of less than 300nM: 1c, 1bq, 1bt, 1ch, 1ci, 4ap, 4at, 4aw, 4ax, 4ay, 4bd, 12b, 18de, 18dh, 18di, 18dg, 21a, 1o, 18b, 18d, 18h, 19d, 19e, 19i, 19l, 19n, 19o, 18p, 18q, 18r, 18w, 18af, 18ag, 18an, 18aq, 18au, 18av, 1v, 18ay, 18ba, 18bd, 1bg, 1w, 1ac, 4p, 9a, 1bb, 1av, 7b, 7e, 7f, 7g, 7k, 7j, 5c, 5d, 5e, 5g, 4v, 4x, 4y, 4z, 4aa, 4ae, 4ah, 4ai, 5u, 5v, 5w, 5x, 3d, 3f, 18bv, 18cb, 3h, 5h, 5i, 5l, 5o, 3i, 3j, 3v, 3x, 3u, 3ab, 1al, 1am, 1an, 1be, 18cy, 18dc, 13a, 19p, 19q, 3k, 3n, 3q, 13f, 13b, 4g, 1au, 5q, 1ay, 18dj, 13c, 13e, 10a, 1cl, 2c, 2e, 1cs, 2i, 8d, 13g and 1cu, with the following compounds exhibiting IC_{50} values against mTOR of less than 100nM: 1b, 1a, 1d, 1bl, 1bm, 1bn, 1f, 1bo, 1i, 1g, 1h, 1br, 1bs, 1bu, 1bv, 1e, 1j, 1bw, 1bx, 1by, 1bz, 1cc, 1ce, 1k, 1cf, 1cg, 1l, 1cj, 4al,

4am, 4an, 4ao, 4aq, 4ar, 4as, 4au, 4av, 4az, 4ba, 4bb, 4bc, 4be, 4bf, 12c, 12d, 12a, 18a, 6a, 1as, 1ax, 1n, 1p, 1s, 1ck, 18c, 18e, 18f, 18g, 18i, 18j, 18k, 1ar, 19a, 19b, 19c, 19f, 19g, 19j, 19k, 18l, 18m, 1bd, 1aq, 18s, 18t, 18u, 18v, 18x, 18y, 18z, 18aa, 18ab, 18ac, 18ad, 18ae, 18ah, 18ai, 18aj, 18am, 18ao, 18ap, 18ar, 18as, 18aw, 18ax, 18az, 18bc, 18bf, 18bg, 18bk, 18bh, 18bj, 15a, 18bm, 8b, 4h, 14a, 8a, 1aa, 1ab, 1ad, 1af, 1ag, 14b, 1bc, 4i, 1ah, 4j, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bh, 16a, 1at, 7c, 7d, 7i, 3a, 3c, 5a, 5b, 4w, 4ac, 4ad, 5t, 3e, 3g, 18bp, 18bq, 18br, 18bs, 18bt, 18bu, 18bw, 18by, 18bz, 18ca, 18cc, 18cd, 18cf, 18cg, 18ch, 18ci, 18cj, 18ck, 18cl, 4ak, 18bx, 18cm, 18cv, 1bi, 1bj, 4a, 1aw, 3t, 3aa, 1ap, 1bf, 18cn, 18co, 18cp, 18cs, 18ct, 18cu, 18cw, 18cx, 18cz, 18cq, 19r, 19t, 3l, 19u, 19v, 19w, 20c, 1u, 4b, 4q, 4t, 4c, 4e, 4f, 18dd, 4d, 1az, 4r, 4s, 2f, 2g, 2j and 1cv. For example, Compound 4aa has an IC_{50} of 151nM.

The Comparative Examples were also tested and when compared to the corresponding Examples, the exhibited IC_{50} values for the Comparative Examples were higher than those of the corresponding Examples. For example Example 1k was measured to have an IC50 of 15nm whereas Comparative Example 1k was measured to have an IC50 of 225nm. Therefore, compounds of the present invention are more active in reducing cell growth.

Example 24

Cell proliferation assay (GI_{50})

Cell growth was assessed using the sulforhodamine B (SRB) assay (A). T47D (ECACC, 85102201) cells were routinely passaged in RPMI (Invitrogen, 42401018) plus 10 % foetal calf serum (FCS), 1 % L-glutamine (Gibco BRL, 25030) to a confluence not greater than 80 %. To undertake the assay, T47D cells were seeded at $2.5x10^3$ cells/ well in 90µl RPMI plus 10 % foetal calf serum, 1 % L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5 % CO_2) in a humidified incubator. Once the cells had fully adhered (typically following 4-5 hours incubation) the plate was removed from the incubator and 10µL of the diluent added to the control wells (A1-12 and B1-12). Compound was prepared in a six point semi-log dilution at 10x the final concentration required e.g. for a 6 point range of 30µM to 100nM in semi-log steps dilution started at 300µM in stock plate. Dosing was completed by addition of 10µL of compound at highest concentration to C1-12 through to the lowest concentration in H1-12. The plates were then incubated for 120 hours prior to SRB analysis.

Upon completion of incubation, media was removed and the cells fixed with 100µl of ice cold 10 % (w/v) trichloroacetic acid. The plates were incubated at 4°C for 20 minutes and then washed four times with water. Each well of cells was then stained with 100µl of 0.4 % (w/v) SRB (Sulforhodamine B, Sigma, Poole, Dorset, UK, Catalogue number S-9012) in 1 % acetic acid for 20 minutes before washing four times with 1 % acetic acid. Plates were then dried for 2 hours at room temperature. The dye from the stained cells was solubilized by the addition of 100µl of 10mM Tris Base into each well. Plates were gently shaken and left at room temperature for 30 minutes before measuring the optical density at 564nM on a Microquant microtiter plate reader. The concentration of inhibitor eliciting a 50 % reduction in growth (GI_{50}) was determined by analysis of staining intensity of the treated cells as a percentage of the vehicle control wells using Excelfit software.

(A) Skehan, P., Storung, R., Scudiero, R., Monks, A., McMahon, J., Vistica, D., Warren, J. T., Bokesch, H., Kenny, S. and Boyd, M. R. (1990) New colorimetric cytotoxicity assay for anticancer-drug screening. J. Natl. Cancer Inst. **82**, 1107-1112.

Examples 1a –11 were tested and exhibited GI_{50} values of less than 300 nM.

The Comparative Examples were also tested and when compared to the corresponding Examples, the exhibited GI_{50} values for the Comparative Examples were higher than those of the corresponding Examples (ie GI_{50} Comparative Example 1a > GI_{50} Example 1a). For example Example 1k was measured to have an GI50 of 32nm whereas Comparative Example 1k was measured to have an GI50 of 268nm. Therefore, compounds of the present invention are more active in reducing cell growth.

Example 25

In Vitro phospho-Ser473 Akt assay

This assay determines the ability of test compounds to inhibit phosphorylation of Serine 473 in Akt as assessed using Acumen Explorer technology (Acumen Bioscience Limited), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning.

A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Teddington, Middlesex, UK, Catalogue No. HTB-132) was routinely maintained at 37°C with 5 % CO_2 up to a confluency of 70–90 % in DMEM containing 10 % heat-inactivated FCS and 1 % L-glutamine.

For the assay, the cells were detached from the culture flask using 'Accutase' (Innovative Cell Technologies Inc., San Diego, CA, USA; Catalogue No. AT104) using standard tissue culture methods and resuspended in media to give $1.7x10^5$ cells per ml. Aliquots (90 µl) were seeded into each of the inner 60 wells of a black Packard 96 well plate (PerkinElmer, Boston, MA, USA; Catalogue No. 6005182) to give a density of ~15000 cells per well. Aliquots (90 µl) of culture media were placed in the outer wells to prevent edge effects. The cells were incubated overnight at 37°C with 5 % CO_2 to allow them to adhere.

On day 2, the cells were treated with test compounds and incubated for 2 hours at 37°C with 5 % CO_2. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with growth media to give a range of concentrations that were 10-fold the required final test concentrations. Aliquots (10 µl) of each compound dilution were placed in a well (in triplicate) to give the final required concentrations. As a minimum reponse control, each plate contained wells having a final concentration of 100 µM LY294002 (Calbiochem, Beeston, UK, Catalogue No. 440202). As a maximum response control, wells contained 1 % DMSO instead of test compound. Following incubation, the contents of the plates were fixed by treatment with a 1.6 % aqueous formaldehyde solution (Sigma, Poole, Dorset, UK, Catalogue No. F1635) at room temperature for 1 hour.

All subsequent aspiration and wash steps were carried out using a Tecan 96 well plate washer (aspiration speed 10 mm/sec). The fixing solution was removed and the contents of the plates were washed with phosphate-buffered saline (PBS; 50 µl; Gibco, Catalogue No. 10010015). The contents of the plates were treated for 10 minutes at room temperature with an aliquot (50 µl) of a cell permeabilisation buffer consisting of a mixture of PBS and 0.5 % Tween-20. The 'permeabilisation' buffer was removed and non-specific binding sites were blocked by treatment for 1 hour at room temperature of an aliquot (50 µl) of a blocking buffer consisting of 5 % dried skimmed milk ['Marvel' (registered trade mark); Premier Beverages, Stafford, GB] in a mixture of PBS and 0.05 % Tween-20. The 'blocking' buffer was removed and the cells were incubated for 1 hour at room temperature with rabbit anti phospho-Akt (Ser473) antibody solution (50 µl per well; Cell Signalling, Hitchin, Herts, U.K., Catalogue No 9277) that had been diluted 1:500 in 'blocking' buffer. Cells were washed three times in a mixture of PBS and 0.05 % Tween-20. Subsequently, cells were incubated for 1 hour at room temperature with Alexafluor488 labelled goat anti-rabbit IgG (50 µl per well; Molecular Probes, Invitrogen Limited, Paisley, UK, Catalogue No. A11008) that had

been diluted 1:500 in 'blocking' buffer. Cells were washed 3 times with a mixture of PBS and 0.05 % Tween-20. An aliquot of PBS (50 µl) was added to each well and the plates were sealed with black plate sealers and the fluorescence signal was detected and analysed.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of Serine 473 in Akt was expressed as an IC_{50} value.

The compounds tested in this assay exhibited IC_{50} values against mTOR of less than 10µm.

The following compounds exhibited IC_{50} values against mTOR of less than 1µm: 1bu, 1ce, 12b, 18de, 18dg, 18j, 1ar, 19e, 19h, 19i, 19l, 19m, 19n, 19o, 18n, 18o, 18z, 18aa, 18ag, 18ai, 18al, 1v, 18az, 1ah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, 1aw, 3u, 1bf, 18ct, 19q, 19s, 19u, 19v, 19w, 1au, 5r, 4t, 18dj, 1cl, 2d, 2e, 1cs, 2h, 2j and 1cw, with the following compounds exhibiting IC_{50} values against mTOR of less than 300nM: 1bo, 1bp, 1j, 1bx, 1by, 1cf, 1ci, 1cj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, 1n, 1p, 1q, 18e, 18h, 19b, 19c, 19f, 19k, 18p, 1bd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, 1ab, 4p, 9a, 1av, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, 1am, 1ao, 18cn, 18cx, 1bk, 13b, 4g, 5s, 4q, 18dd, 1cp, 1cq, 2f, 2g, 13g, 1cv and 1ct, with the following compounds exhibiting IC_{50} values against mTOR of less than 100nM: 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co and 3ad. For example, Compound 18di has an IC_{50} of 151nM

The Comparative Examples were also tested and when compared to the corresponding Examples, the exhibited IC_{50} values for the Comparative Examples were higher than those of the corresponding Examples. For example Example 1k was measured to have an IC50 of 83nm whereas Comparative Example 1k was measured to have an IC50 of 412nm. Therefore, compounds of the present invention are more active in reducing cell growth.

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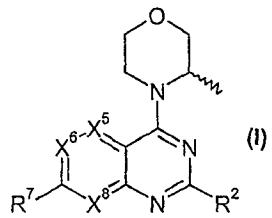
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CLAIMS

1. A compound of formula I:



(I)

, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group,

where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

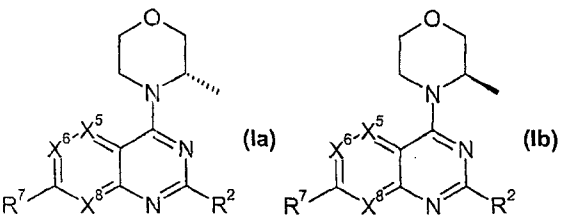
R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally

substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

2. A compound of formula Ia or Ib:



, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group,

where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

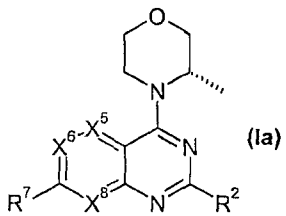
R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7}

alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

3. A compound of formula Ia:



(Ia)

, or a pharmaceutically acceptable salt thereof, wherein:

one or two of X^5, X^6 and X^8 is N, and the others are CH;

R^7 is selected from halo, OR^{O1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$, $NR^{N7b}SO_2R^{S2a}$, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{5-20} aryl group, where R^{O1} and R^{S1} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group; R^{N1} and R^{N2} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N1} and R^{N2} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{C1} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{1-7} alkyl group or $NR^{N8}R^{N9}$, where R^{N8} and R^{N9} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, an optionally substituted C_{5-20} aryl group or R^{N8} and R^{N9} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms;

R^{S2a} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N7a} and R^{N7b} are selected from H and a C_{1-4} alkyl group;

R^2 is selected from H, halo, OR^{O2}, SR^{S2b}, $NR^{N5}R^{N6}$, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group,

wherein R^{O2} and R^{S2b} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted 5- to 20-membered heteroaryl group, or an optionally substituted C_{1-7}

alkyl group; R^{N5} and R^{N6} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted 5- to 20-membered heteroaryl group, and an optionally substituted C_{5-20} aryl group, or R^{N5} and R^{N6} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

4. A compound according to any one of claims 1 to 3, wherein only one of X^5, X^6 and X^8 is N.

5. A compound according to any one of claims 1 to 3, wherein X^6 is CH and X^5 and X^8 are N.

6. A compound according to any one of claims 1 to 4, wherein X^8 is N.

7. A compound according to any one of the preceding claims, wherein R^7 is selected from an optionally substituted C_{5-20} aryl group, OR^{O1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{C1}$ and $NR^{N7b}SO_2R^{S2a}$

8. A compound according to any one of claims 1 to 6, wherein R^7 is an optionally substituted phenyl or pyridyl group.

9. A compound according to any one of claims 1 to 6, wherein R^7 is OR^{O1}, and R^{O1} is a C_{1-7} alkyl group, which may be substituted.

10. A compound according to any one of claims 1 to 6, wherein R^7 is $NR^{N1}R^{N2}$, and R^{N2} is H.

11. A compound according to claim 10, wherein R^{N1} is C_{3-7} cycloalkyl.

12. A compound according to claim 10, wherein R^{N1} is C_{5-6} aryl.

13. A compound according to any one of claims 1 to 6, wherein R^7 is $NR^{N7a}C(O)R^{C1}$, and R^{N7a} is preferably H.

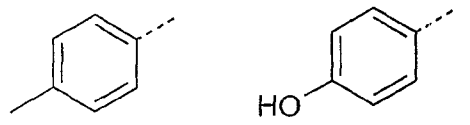
14. A compound according to claim 13, wherein R^{C1} is selected from an optionally substituted C_{5-20} aryl group, C_{3-20} heterocyclyl, C_{1-7} alkyl and $NR^{N8}R^{N9}$, where R^{N8} is hydrogen, and R^{N9} is C_{1-7} alkyl.

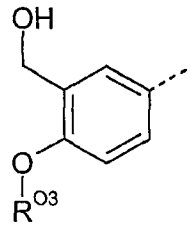
15. A compound according to any one of claims 1 to 6, wherein R^7 is $NR^{N7b}SO_2R^{S2a}$, and R^{N7b} is H.

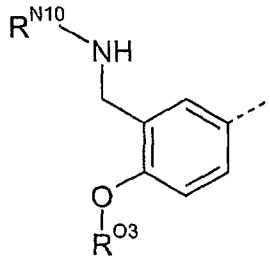
16. A compound according to claim 15, wherein R^{S2a} is C_{1-7} alkyl.

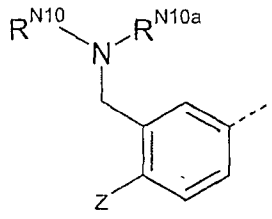
17. A compound according to Claim 8 wherein R^7 is an optionally substituted phenyl group, wherein the optional substituents are preferably selected from halo, hydroxyl, cyano, C_{1-7} alkyl, C_{1-7}alkoxy, sulfonamino (for example $-NHS(=O)_2C_{1-7}$alkyl) amino (for example $-NH_2$, C_{5-6}arylamino, C_{1-7}alkylamino, and di-(C_{1-7}alkyl)amino), and amido (for example $-CONH_2$, $-CONHC_{1-7}$alkyl, $-CON(C_{1-7}$alkyl$)_2$ and -CONHheterocycyl) and wherein the susbtitutent alkyl, alkoxy, or aryl groups may be further optionally substituted by one or more groups selected from halo, hydroxyl, C_{1-7} alkyl, C_{1-7} alkoxy, C_{5-6}aryl, $-NHS(=O)_2C_{1-7}$alkyl, C_{5-6}arylamino, di-(C_{1-7}alkyl)amino and C_{1-7}alkylamino.

18. A compound according to claim 8 wherein R^7 is an optionally substituted phenyl group selected from







and


wherein

Z is H, F or OR^{O3};

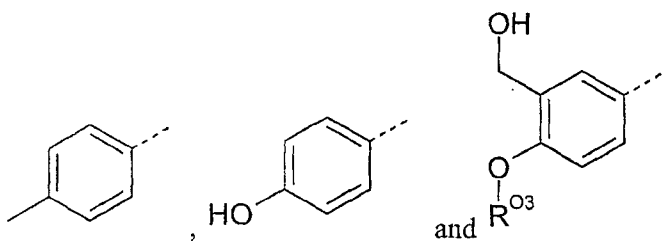
R^{O3} is selected from hydrogen or an optionally substituted C_{1-6} alkyl group;

R^{N10} is selected from hydrogen, $C(O)R^{C2}$, $C(S)R^{C3}$, SO_2R^{S3}, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{5-20} aryl group, or an optionally substituted C_{1-10} alkyl group where R^{C2} and R^{C3} are selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{1-7} alkyl group or $NR^{N11}R^{N12}$, where R^{N11} and R^{N12} are independently selected from H, an optionally substituted C_{1-7} alkyl group, an optionally substituted C_{5-20} heterocyclyl group, an optionally substituted C_{5-20} aryl group or R^{N11} and R^{N12} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms; and R^{S3} is selected from H, an optionally substituted C_{5-20} aryl group, an optionally substituted C_{5-20} heteroaryl group, or an optionally substituted C_{1-7} alkyl group;

R^{N10a} is selected from hydrogen or an optionally substituted C_{1-10} alkyl group; or

R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 3 and 8 ring atoms.

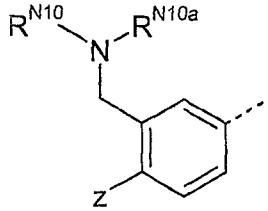
19. A compound according to claim 8, wherein R^7 is an optionally substituted phenyl group selected from



wherein

R^{O3} is selected from hydrogen or an optionally substituted C_{1-6} alkyl group.

20. A compound according to claim 8, wherein R^7 is



wherein

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Z is H, F or OR^{O3};

R^{N10} is selected from hydrogen, $-C(O)CH_3$, $-C(O)CH_2OH$, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CH(CH_3)_2$, $-CH_2CH_2OMe$, $-CH_2C(CH_3)_2$, $-CH_2CH_2C(CH_3)_2$, $-CH(CH_3)CH_2C(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, cycloproyl, cyclopentyl, cyclohexyl, cycloheptyl, $-CH_2$cyclopropyl, methylcyclohexyl, cyanocyclohexyl, pyrazolyl, hydroxypyrrolidinyl, $-CH_2$imidazole;

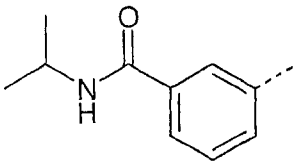
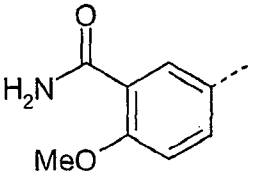
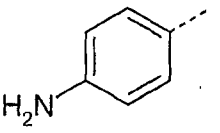
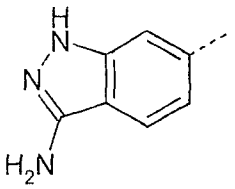
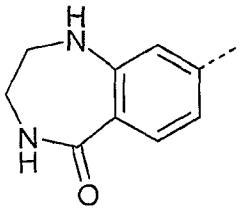
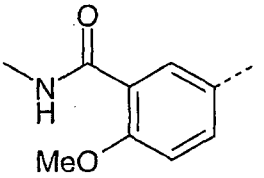
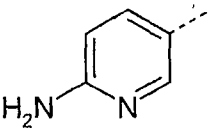
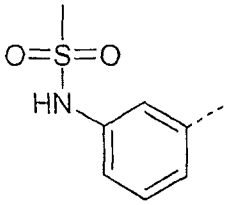
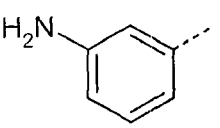
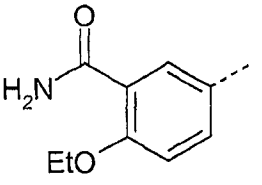
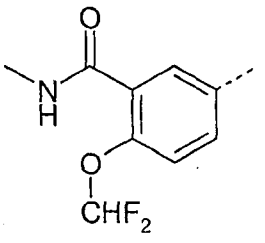
R^{N10a} is hydrogen; or

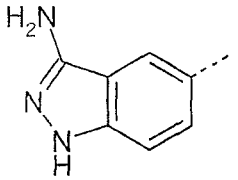
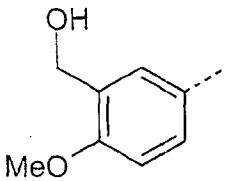
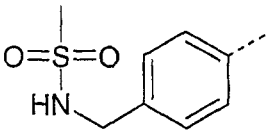
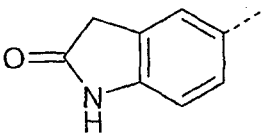
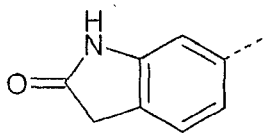
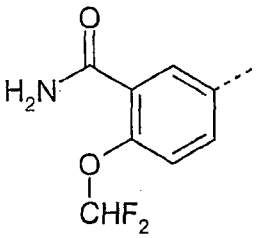
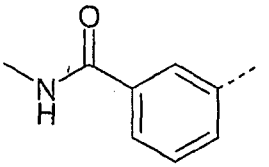
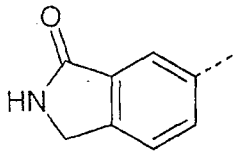
R^{N10} and R^{N10a} together with the nitrogen to which they are bound form an optionally substituted heterocyclic ring containing between 5 or 6 ring atoms;

and where the optional subtsituents are selected from halo, hydroxyl, C_{1-7}alkyloxy.

21. A compound according to claim 8 wherein R^7 is an optionally substituted phenyl group, wherein the optional substituents are selected from fluoro, hydroxyl, cyano, nitro, methyl, methoxy, $-OCH_2CH_3$, $-NH_2$, $-NHSO_2CH_3$, $-CH_2NHSO_2CH_3$, $-OCHF_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, -CONHMe, -CONHEt, $-CONHCH(CH_3)_2$, $-CONHCH_2CH_2F$, $-CONHCH_2CHF_2$, $-CONHCH_2CH_2OH$, -CONMeEt, $-CONMe_2$, N-methylpiperazinylcarbonyl and 4-hydroxypiperidinylcarbonyl

22. A compound according to claim 7 wherein R^7 is selected from

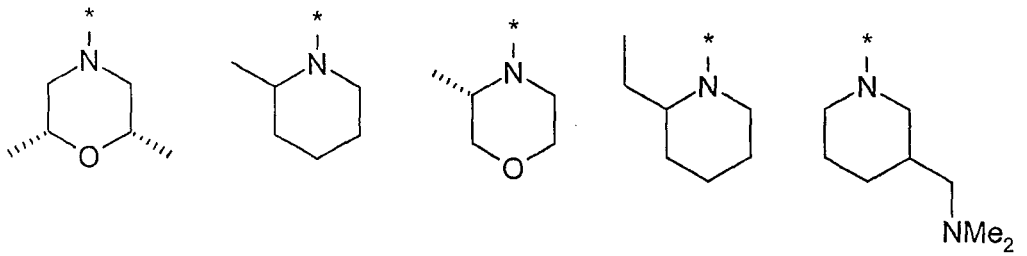
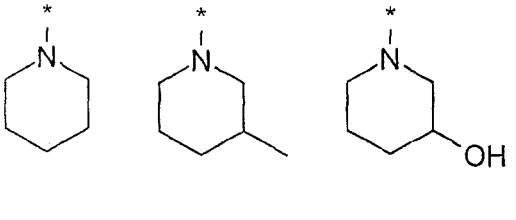

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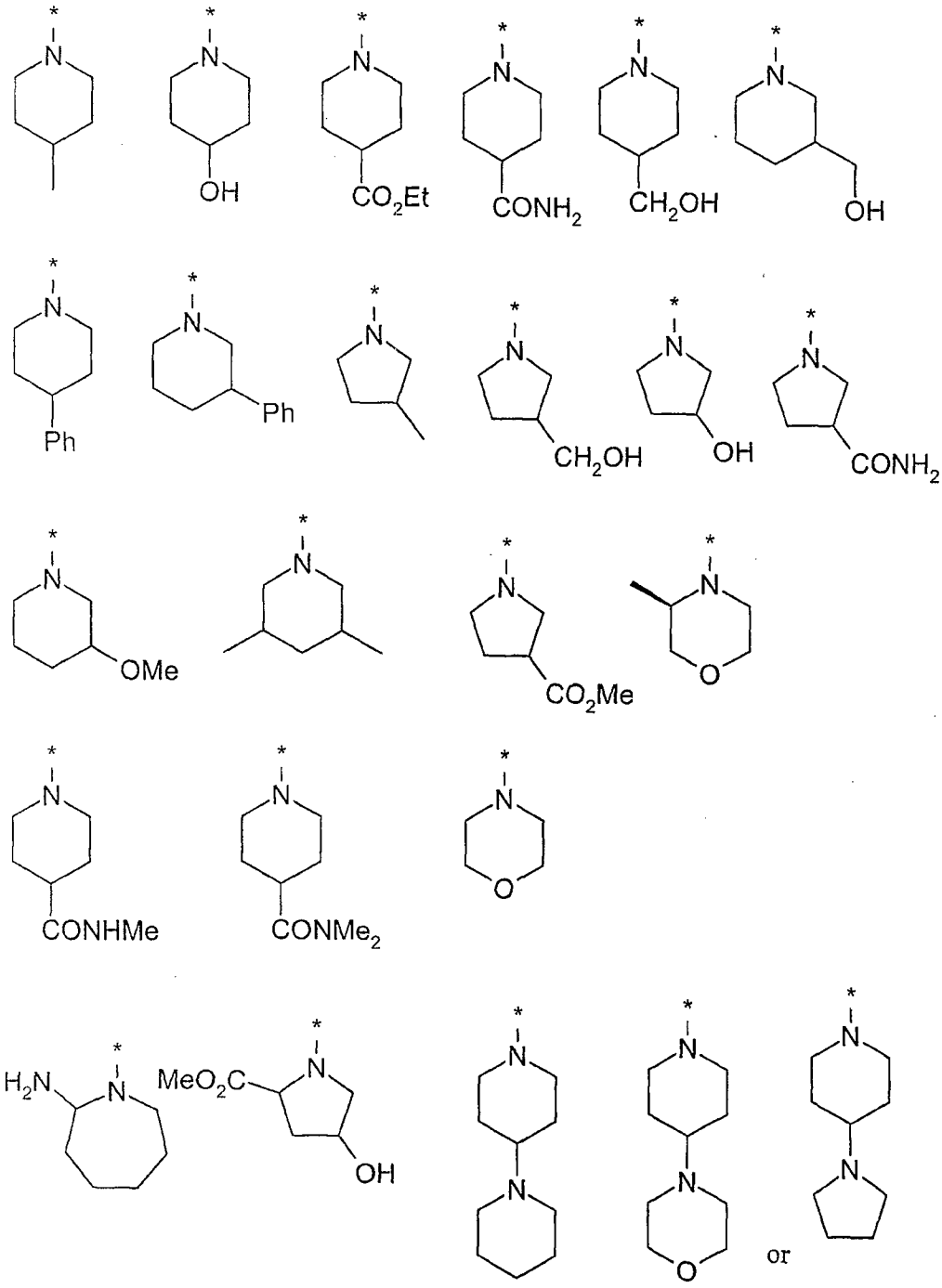







and


23. A compound according to any one of the preceding claims, wherein R^2 is $NR^{N5}R^{N6}$, where R^{N5} and R^{N6} together with the nitrogen to which they are bound form a heterocyclic ring containing between 3 and 8 ring atoms, which may optionally be substituted.

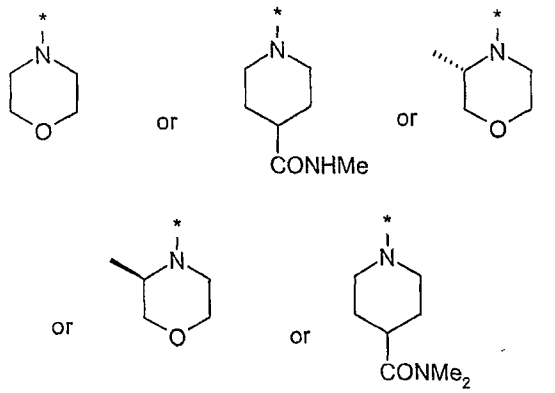
24. A compound according to claim 23, wherein R^2 is selected from morpholino, thiomorpholino, piperadinyl, piperazinyl, homopiperazinyl and pyrrolidinyl.

25. A compound according to Claim 23 wherein R^2 wherein R^2 is

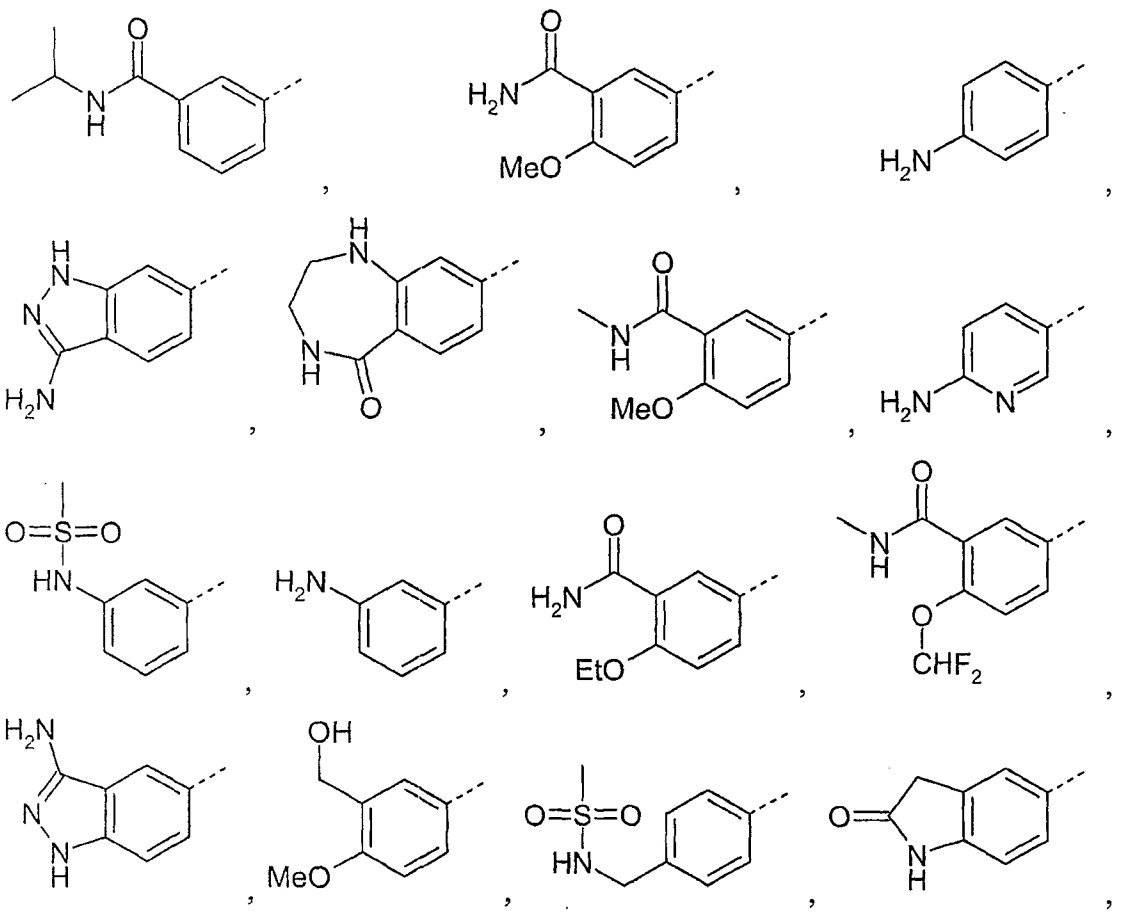



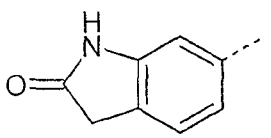
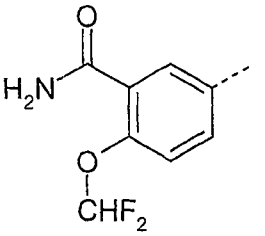
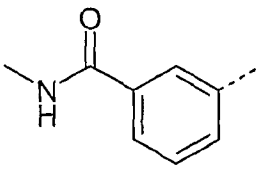
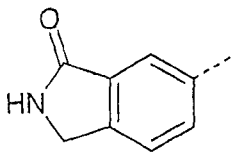


26. A compound according to claim 23, wherein R^2 is

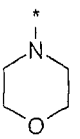
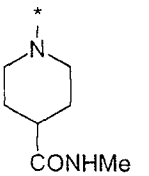
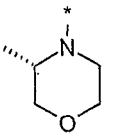
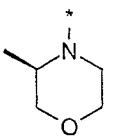
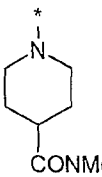


27. A compound according to claim 7 wherein R^7 is selected from




,

,

and


and wherein R^2 is


or

or

or

or


28. A compound according to Claim 1 selected from any one of the Examples.

29. A compound according to Claim 1 selected from any one of Examples 1bu, 1ce, 12b, 18de, 18dg, 18j, 1ar, 19e, 19h, 19i, 19l, 19m, 19n, 19o, 18n, 18o, 18z, 18aa, 18ag, 18ai, 18al, 1v, 18az, 1ah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, 1aw, 3u, 1bf, 18ct, 19q, 19s, 19u, 19v, 19w, 1au, 5r, 4t, 18dj, 1cl, 2d, 2e, 1cs, 2h, 2j, 1cw, 1bo, 1bp, 1j, 1bx, 1by, 1cf, 1ci, 1cj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, 1n, 1p, 1q, 18e, 18h, 19b, 19c, 19f, 19k, 18p, 1bd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, 1ab, 4p, 9a, 1av, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, 1am, 1ao, 18cn, 18cx, 1bk, 13b, 4g, 5s, 4q, 18dd, 1cp, 1cq, 2f, 2g, 13g, 1cv, 1ct, 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v,

18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cr, 1cw, 1cy, 1dv, 15c, 1cl, 1cm, 1cn, 1cq, 1cv, 1cx, 1di, 1dj, 1eb, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

30. A compound according to Claim 1 selected from any one of Examples 1bo, 1bp, 1j, 1bx, 1by, 1cf, 1ci, 1cj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, 1n, 1p, 1q, 18e, 18h, 19b, 19c, 19f, 19k, 18p, 1bd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, 1ab, 4p, 9a, 1av, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, 1am, 1ao, 18cn, 18cx, 1bk, 13b, 4g, 5s, 4q, 18dd, 1cp, 1cq, 2f, 2g, 13g, 1cv, 1ct, 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cl, 1cm, 1cn, 1cq, 1cv, 1cx, 1di, 1dj, 1eb, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

31. A compound according to Claim 1 selected from any one of Examples 1b, 1a, 1c, 1d, 1bl, 1bm, 1f, 1i, 1g, 1h, 1br, 1bs, 1bv, 1e, 1bz, 1cc, 1k, 1cg, 1l, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, 1as, 1s, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, 1bg, 8b, 4h, 1ba, 8a, 1aa, 1ac, 1ae, 1af, 1ag, 14b, 1bc, 4i, 4j, 4k, 4l, 4m, 4n, 4o, 18bn, 18bo, 4u, 1bb, 1at, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc,

18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, 1ak, 1al, 1ap, 1be, 18co, 18cr, 18cs, 18db, 19p, 3l, 1u, 4b, 5q, 4c, 4e, 4f, 4d, 1az, 4r, 4s, 1cn, 1co, 3ad, 1cj, 1ck, 1ct, 1cu, 1cz, 1db, 1dc, 1dd, 1de, 1dg, 1dh, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dt, 1du, 1dw, 1dy, 1dz, 1ea, 1ec, 1ed, 1ee, 18dm, 18dn and 18do.

32. A compound according to Claim 1 selected from any one of Examples 1a, 1u, 1al, 1ap, 1at, 1az, 1co, 1de, 1dg, 1dh, 1dk, 1dl, 1dp, 1dq, 1dr, 1ds, 1dt, 1du, 1dy, 1ec, 1ee, 12d, 14b, 18dn and 18do.

33. A pharmaceutical composition comprising a compound according to any one of claims 1 to 32, and a pharmaceutically acceptable carrier or diluent.

34. A compound according to any one of claims 1 to 32 for use in a method of treatment of the human or animal body.

35. The use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for treating a disease ameliorated by the inhibition of mTOR.

36. A compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, for use as a medicament.

37. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

38. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

39. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian

cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

40. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

41. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the production of an anti-cancer effect in a warm-blooded animal such as man.

42. The use of a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in the treatment of melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

43. A method for producing a mTOR inhibitory effect 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 according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof.

44. A method for producing an anti-cancer effect 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 according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof.

45. A method of treating melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium,

breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, 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 according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a mTOR inhibitory effect in a warm-blooded animal such as man.

47. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

48. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, glioma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, endometrium, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

DERIVADOS DE 2- METILMOFOLINA PIRIDO- , PIRAZO- Y PIRIMIDO-PIRIMIDINA COMO INHIBIDORES DE MTOR

El presente invento se relaciona con compuestos los cuales actúan como inhibidores de mTOR, su uso y sus síntesis.

Fundamento

El factor de crecimiento/activación mitogénica de la ruta de señalización de fosfatidilinositol 3- quinasa (PI3K) /AKT finalmente lleva al regulador clave de ciclo celular y de control del crecimiento mTOR, la diana mamífera de rapamicina (alternativamente conocida como FRAP (FKBP12 y proteína asociada a rapamicina) , RAFT1 (rapamicina y diana de FKBP12) , RAPT1 (diana de la rapamicina 1) - todos derivados de la interacción FKB12, proteína fijdora de de FK- 506, y SEP (proteína efectora de sirolimus)) . mTOR es una serina/treonina quinasa mamífera con un tamaño de aproximadamente 289 kDa y un miembro de las quinasas TOR eucarióticas evolucionariamnte conservadas (ref. 1- 4) . La proteína mTOR es un miembro de la familia proteica de las quinasas similar a la PI3- quinasa (PIKK) debido a su homología C- terminal (dominio catalítico) con quinasa- PI3 y los otros miembros de la familia, ej., AND- PKcs (proteína quinasa ADN dependiente) , ATM (ataxia- telangiectasia mutada) . Además de un dominio catalítico en el extremo C, mTOR contiene un dominio de fijación de complejo FKBP12- rapamicina (FRB) . En el extremo N hasta 20 motivos HEAT (Huntingtina, EF3, subunidad alfa reguladora de PP2A y TOR) mientras que la mayoría del extremo C es un dominio FAT (FRAP- ATM- TRRAP) , y sobre el final del extremo C de la proteína se encuentra un dominio FAT adicional (FAT- C) (ref. 5,6) .

TOR se ha identificado como un regulador central tanto de crecimiento como de proliferación celular, el cual en parte es gobernado por iniciación de traducción. La fosforilación TOR dependiente de S6- quinasa (S6K1) permite traducción de proteínas ribosomales involucradas en progresión de ciclo celular (refs- 7- 9) . La traducción dependiente de cap es regulada por la fosforilación de la proteína 1 (4E- BPI (PHAS- 1)) fijadora del factor iniciador de traducción eucariótica 4E (eIF4E) . Esta modificación previene la fijación de PHAS- 1 con el eOF4E, permitiendo así la formación de un complejo de traducción de eIF4F activo (reseñado en

las ref. 10, 11, 12) . La activación de estos elementos de señalización es dependiente de insulina, otros factores de crecimiento y nutrientes indicando un papel de portero para mTOR en el control de progresión de ciclo celular solamente bajo condiciones ambientales favorables. La cascada de señalización PI3K/AKT yace corriente arriba de mTOR y esto se ha mostrado como desregulado en ciertos cánceres y resulta en activación independiente de factor de crecimiento en, por ejemplo, células deficientes de PTEN. mTOR yace en el eje de control para esta ruta e inhibidores de esta quinasa (ej., sirolimus rapamicina o Rapamune™) y everolimus (RAD001 o Certican™)) están ya aprobados para inmunosupresión y stents eluyentes de fármacos (reseñados en ref. 13, 14) , y ahora recibiendo interés particular como agentes novedosos para tratamiento contra el cáncer.

El crecimiento celular tumoral se origina a partir de la desregulación de mecanismos de control de crecimiento normal tal como la pérdida de funciones supresoras tumorales. Uno de estos supresores tumorales es la fosfatasa y homólogo de tensina removido del cromosoma diez (PTEN) . Se ha mostrado que este gen, también conocido como mutado en múltiples cánceres avanzados (MMAC) , juega un papel significativo en terminación del ciclo celular y es el supresor tumoral más altamente mutado después de p53. Hasta 30% de glioblastoma, cánceres endometriales y de próstata tienen supresiones o mutaciones somáticas de este sitio (ref. 15, 16) .

PI3K convierte fosfatidilinositol 4, 5, bisfosfato (PIP2) en fosfatidilinositol 3,4,5 trifosfato (PIP3) mientras PTEN es responsable de retirar el 3' fosfato de PIP3 que produce PIP2. PI3- K y PTEN actúan para mantener un nivel apropiado de PIP3 el cual recluta y activa así AKT (también conocido como PBK) y la cascada de señalización corriente abajo que luego es iniciada. En ausencia de PTEN, existe regulación inapropiada de esta cascada, AKT se vuelve efectivamente constitutivamente activado y el crecimiento celular es desregulado. Un mecanismo alternativo para la desregulación de este proceso de señalización celular es la identificación reciente de una forma mutante de la isoforma PI3K, p110alfa (ref. 17) . La actividad aumentada aparente de este mutante se considera resulta en producción PIP3 aumentada, presumiblemente en exceso de lo cual la función de PTEN podría contrarrestar. La señalización aumentada desde P13K, resulta por lo tanto en señalización aumentada a mTOR y consecuentemente, sus activadores corriente abajo.

Además de la evidencia que une mTOR con la regulación del ciclo celular (desde G1 a la

fase- S) y que la inhibición de mTOR resulta en inhibición de estos eventos reguladores, se ha mostrado que la desregulación de actividad mTOR resulta en inhibición de crecimiento celular (citada en ref. 7, 18, 19) . El inhibidor conocido de mTOR, rapamicina, inhibe de manera potente la proliferación o crecimiento de células derivadas a partir de un rango de tipos de tejido tal como musculo liso, células T así como también células derivadas de un rango diverso de tipos tumorales incluyendo rabdomiosarcoma, neuroblastoma y meduloblastoma, cáncer pulmonar de células pequeñas, osteosarcoma, carcinoma pancreático y carcinoma de mama y próstata (citado en ref. 20) . La rapamicina ha sido apropiada y está en uso clínico como un inmunosupresor, su prevención de rechazo de órganos es exitosa y tiene pocos efectos secundarios que las terapias anteriores (refs. 20, 21) . La inhibición de mTOR mediante rapamicina y sus análogos (RAD001, CCI- 779) es causada por la interacción anterior del fármaco con la proteína de unión de FK506, FKBP12. Subsecuentemente, el complejo de FKBP12/rapamicina luego se une al dominio FRB de mTOR e inhibe la señalización corriente abajo desde mTOR.

También se ha mostrado que los inhibidores potentes pero no específicos de PI3K, LY294002 y wortmannina inhiben la función de quinasa de mTOR pero actúan por medio de la dianización del dominio catalítico de la proteína (ref. 21) . Además de la inhibición de la función de mTOR mediante pequeñas moléculas dianizando el dominio quinasa, se ha demostrado que la mTOR quinasa muerta no puede transmitir las señales de activación corriente arriba a los efectores corriente debajo de mTOR, PHAS- 1 o quinasa p70S6 (ref. 22) . También se ha mostrado que no todas las funciones de mTOR son sensibles a rapamicina y esto puede estar relacionado con la observación que la rapamicina altera el perfil de sustrato de mTOR más que inhibir su actividad *per se* (ref. 23) . El análisis de las interacciones de mTOR con otros factores celulares ha revelado que además del complejo mTOR- Raptor, también existe un complejo mTOR- Rictor que representa una activada insensible a rapamicina de mTOR (B) (Sarbassov Current Biology, 2004, 14, 1296- 1302) . Esta actividad probablemente explica la discrepancia entre la mTOR quinasa muerta y la alteración de señalización mTOR mediante rapamicina y sus derivados. La discrepancia también identifica la posibilidad de una ventaja terapéutica para inhibir directamente la actividad catalítica de mTOR. Se ha indicado que un inhibidor catalítico de mTOR puede ser un antagonista más efectivo de supervivencia y proliferación de células cancerígenas y que la rapamicina puede ser más útil en combinación con agentes que pueden compensar por no interrumpir completamente la señalización de vía (Choo y Blenis, Cancer Cell,

2006, 9, 77- 79; Hay, Cancer Cell, 2005, 8, 179- 183) . Por lo tanto, se propone que un inhibidor dirigido del dominio quinasa de mTOR puede ser un inhibidor más efectivo de mTOR.

Además de la capacidad de la rapamicina para inducir inhibición de crecimiento (citostasis) por derecho propio, se ha mostrado que la rapamicina y sus derivados potencian la citotoxicidad de un número de quimioterapias incluyendo cisplatina, camptotecina y doxorrubicina (estudiadas en la ref. 20) . La potenciación de la muerte celular inducida por radiación ionizante también se ha observado después de inhibición de mTOR (ref. 24) . La evidencia experimental y clínica ha mostrado que los análogos de rapamicina muestran evidencia de eficacia al tratar cáncer, ya sea solos o en combinación con otras terapias (ver ref. 10, 18, 20) . Estos hallazgos indican que los inhibidores farmacológicos de la mTOR quinasa deben ser de valor terapéuticos para el tratamiento de las diferentes formas de cáncer comprendiendo tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides. En particular, los inhibidores de la mTOR quinasa deben ser de valor terapéutico para el tratamiento de, por ejemplo, cáncer de mama, colorecto, pulmón (incluyendo cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas y cáncer bronquioalveolar) y próstata, y de cáncer del ducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, útero, cerviz y vulva, y de leucemias (incluyendo ALL y CML) , mieloma múltiple y linfomas.

En particular, el carcinoma de células renales se ha identificado como sensible al derivado de rapamicina CCI- 779, que resulta de una perdida de expresión VHL (Thomas, Nature Medicine, 2006, 12, 122- 127) . Los tumores que han perdido el supresor tumoral de leucemia promielocítica (PML) , también han sido mostrados como sensibles a inhibición de mTOR mediante rapamicina como una consecuencia de alteración de la regulación de la ruta de señalización de mTOR (Bernadi, Nature, 2006, 442, 779- 785) y el uso de un inhibidor de la mTOR quinasa en estas enfermedades debe ser de valor terapéutico. Estos últimos ejemplos además de aquellos de deficiencia PTEN o mutación PI3K indican donde un enfoque dirigido al uso de inhibidores mTOR puede ser particularmente efectivo debido al perfil genético, pero no se consideran blancos exclusivos.

Estudios recientes han revelado un papel para mTOR quinasa en otras enfermedades (Easton & Hougton, Expert Opinion on Therapeutic Targets, 2004, 8, 551- 564) . La rapamicina

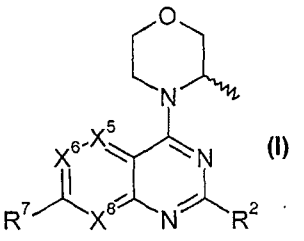
ha demostrado ser un inmunosupresor potente al inhibir proliferación inducida por antígenos de células T. células B y producción de anticuerpos (Sehgal, Procedimientos de Transplantes, 2003, 35, /S- 14S) y por lo tanto los inhibidores de la mTOR quinasa también pueden ser inmunosupresores útiles. La inhibición de la actividad de quinasa de mTOR también puede ser útil en la prevención de restenosis, es decir el control de la proliferación indeseada de células normales en la vasculatura en respuesta a la introducción de stents en el tratamiento de enfermedad de vasculatura (Morice, New England Journal of Medicine, 2002, 346, 1773- 1780) . Además, el análogo de rapamicina, everolimus, puede reducir la severidad e incidencia de vasculopatía de aloinjerto cardiaco (Eisen, New England Journal of Medicine, 2003, 349, 847-858) . La actividad elevada de la mTOR quinasa se ha asociado con hipertrofia cardiaca, la cual es de importancia clínica como un factor de riesgo principal para falla cardiaca y es una consecuencia de tamaño celular aumentado de cardiomiocitos (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29- 37) . Por lo tanto, se espera que los inhibidores de la mTOR quinasa sean de valor en la prevención y tratamiento de una amplia variedad de enfermedades además del cáncer.

La vasta mayoría de farmacología mTOR hasta la fecha se ha enfocado en la inhibición de mTOR a través de la rapamicina o sus análogos. Sin embargo, como se anotó anteriormente, los únicos agentes no rapamicina que se han reportado para inhibir actividad de mTOR a través de un mecanismo dianizador del dominio quinasa son la molécula pequeña LY294002 y el producto natural wortmannina (ref. 21) .

Resumen del Invento

Los presentes inventores han identificado compuestos que son inhibidores ATP-competitivos de mTOR, y por lo tanto son no rapamicina como en su mecanismo de acción.

Por consiguiente, el primer aspecto del presente invento proporciona un compuesto de la fórmula I:



(I)

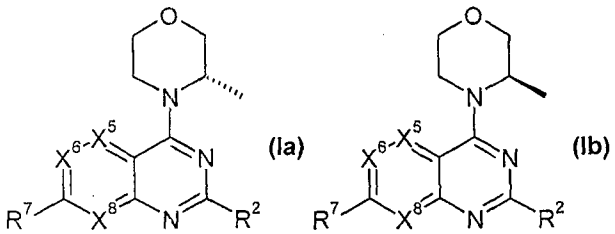
o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos entre X^5, X^6 y X^5 es N, y los otros son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)\ R^{Ci}{}_5\ NR^{N7b}SO_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{O1} y R^{S1} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} son seleccionados de H y un grupo C1- 4 alquilo; R^2 se selecciona a partir de H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{o2} y R^{S2b} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N5} y R^{N6} son

independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, o R^{H5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos.

Según un segundo aspecto del presente invento se proporciona un compuesto de la fórmula Ia o Ib:



, o una sal farmacéuticamente aceptable del mismo, en donde:

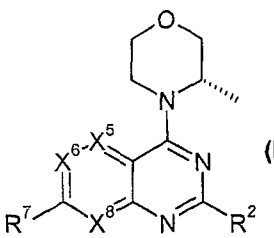
uno o dos de X^5, X^6 y X^8 es N, y los otros son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)\ R^{c1}$, $NR^{N7b}SO_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} y R^{S1} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de

5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} son seleccionados de H y un grupo C1- 4 alquilo;

R^2 se selecciona a partir de H, halo, O^{o2}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{o2} y R^{S2b} son seleccionados de H, C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N5} y R^{N6} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos.

Según un tercer aspecto del presente invento se proporciona un compuesto de la fórmula la:



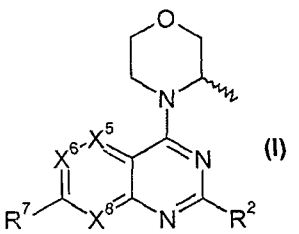
, o una sal farmacéuticamente aceptable del mismo, en donde: uno o dos de X^5, X^6 y X^8 es N, y los otros son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)R^{c1}$, $NR^{N7b}SO_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} y R^{S1} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un

grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos; R^{s2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} son seleccionados de H y un grupo C1- 4 alquilo;

R^2 se selecciona a partir de H, halo, $OR^{02}{}_5$ SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{o2} y R^{S2b} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N5} y R^{N6} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos.

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula I:

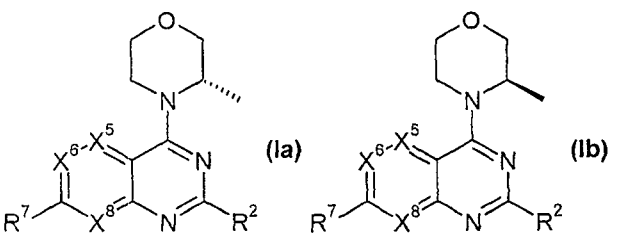


. o una sal farmacéuticamente aceptable del mismo, en donde: uno o dos de X^5, X^6 y X^8 es N, y los otros son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)$ R^{c1}, $NR^{N7b}SO_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{o1} y R^{S1} son seleccionados de H, un grupo C5- 20 arilo opcionalmente

sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico conteniendo entre 3 y 8 átomos cíclicos; R^{c1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido, o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico conteniendo entre 3 y 8 átomos cíclicos; R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} son seleccionados de H y un grupo C1- 4 alquilo; R^2 se selecciona a partir de H, halo, O^{o2}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{o2} y R^{S2b} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N5} y R^{N6} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico conteniendo entre 3 y 8 átomos cíclicos.

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula Ia o Ib:

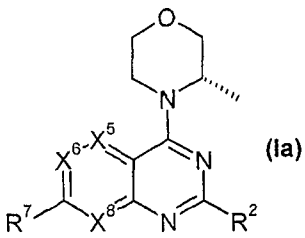


o una sal farmacéuticamente aceptable del mismo, en donde: uno o dos de X^5, X^6 y X^8 es N, y los

otros son CH;

R^7 se selecciona a partir de halo, O^{o1}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(O)\ R^{c1}$, $NR^{N7b}SO_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} y R^{s1} son seleccionados de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico conteniendo entre 3 y 8 átomos cíclicos; R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} son independientemente seleccionados de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} o R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos; R^{s2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} se seleccionan a partir de H o un grupo C1- 4 alquilo; R^2 se selecciona a partir de H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{02} o R^{s2b} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; RN5 y RN6 se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, o RN5 y RN6 junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos.

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula Ia:



(Ia)

, o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos de X^5 , X^6 y X^8 es N, y los demás son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{NI}R^{N2}$, $NR^{N7a}C(0)\ R^{CI}$, $NR^{N7b}S0_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} o R^{S1} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^m o R^{N2} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{NI} o R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos;

R^{CI} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$ donde R^{N8} o R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} o R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos;

R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} o R^{N7b} se seleccionan a partir de H o un grupo C1- 4 alquilo;

R^2 se selecciona a partir de H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{o2} o R^{S2b} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo

opcionalmente sustituido; RN5 y RN6 se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, o RN5 y RN6 junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos.

Según un aspecto adicional del presente invento se proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, o o un vehículo o diluyente farmacéuticamente aceptable.

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, para utilizar en un método de tratamiento del cuerpo humano o animal.

Según un aspecto adicional del presente invento se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para el tratamiento de una enfermedad aliviada mediante la inhibición de mTOR.

Los compuestos de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, tienen actividad como farmacéuticos, en particular como moduladores o inhibidores de actividad mTOR, o se pueden utilizar en el tratamiento de enfermedades/condiciones proliferativas o hiperproliferativas, ejemplos de las cuales incluyen los siguientes cánceres.

(1) carcinoma, incluyendo aquel de vejiga, cerebro, mama, colon, riñón, hígado, pulmón, ovario, páncreas, próstata, estomago, cerviz, colón, endometrio, tiroides o piel;

(2) tumores hematopoyéticos de linaje linfoide, incluyendo leucemia linfocítica aguda, linfoma de células B o Linfoma Burketts;

(3) tumores hematopoyéticos de linaje mieloide, incluyendo leucemias mielogenas agudas o crónicas o leucemia promielocítica;

(4) tumores de origen mesenquimal, incluyendo fibrosarcoma o rabdomiosarcoma; y

(5) otros tumores, incluyendo melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma.

Aspectos adicionales del invento proporcionan el uso de un compuesto de la fórmula (I) , (Ia) o (Ib) , o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para el tratamiento de: cáncer, inmuno- supresión, tolerancia inmune, enfermedad autoinmune, inflamación, pérdida ósea, trastornos intestinales, fibrosis hepática, necrosis hepática, artritis reumatoide, restenosis, vasculopatía de aloinjerto cardiaco, soriasis, beta-talasemia, y condiciones oftálmicas tales como ojo seco. Los inhibidores mTOR también pueden ser efectivos como agentes anti- micóticos.

Otro aspecto adicional del invento se encarga de el uso de un compuesto de la fórmula (I) , (Ia) o (Ib) , o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para utilizar como un adjunto en terapia para el cáncer o para potenciar células tumorales para tratamiento con radiación ionizante o agentes quimioterapéuticos.

Así los compuestos del presente invento proporcionan un método para el tratamiento de cáncer caracterizado por inhibición de mTOR, es decir los compuestos se pueden utilizar para producir un efecto anti- cancerígeno mediado solo o en parte por la inhibición de mTOR.

Se espera que tal compuesto del invento tenga un amplio rango de propiedades anti-cancerígenas puesto que la activación de mutaciones en mTOR se han observado en muchos cánceres humanos, incluyendo pero sin limitar a, melanoma, tumores papilares de tiroides, colangiocarcinomas, cánceres de colon, ovárico o pulmonar. Por lo tanto se espera que un compuesto del invento posea actividad anti- cancerígena contra estos cánceres. Además se espera que un compuesto del presente invento posea actividad contra un rango de leucemias, malignidades linfoides y tumores sólidos tales como carcinomas y sarcomas en tejidos tales como el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas. En particular se espera que tales compuestos del invento retarden de manera ventajosa el crecimiento de tumores sólidos primarios y recurrentes de, por ejemplo, la piel, colon, tiroides, pulmones, endometrio y ovarios. Más particularmente, se espera que tales compuestos del invento, o una sal farmacéuticamente aceptable del mismo, inhiban el crecimiento de aquellos tumores sólidos primarios y recurrentes los cuales están asociados con mTOR, especialmente aquellos tumores que dependen significativamente de mTOR para su crecimiento o diseminación, incluyendo por ejemplo, ciertos tumores de la piel, colon, tiroides, endometrio, pulmones y ovarios. Particularmente los compuestos del presente invento son útiles en el tratamiento de melanomas o gliomas.

Así según este aspecto del invento se proporciona un compuesto de la fórmula I o 1 (A), o una sal farmacéuticamente aceptable del mismo, como se define en la presente para utilizar como un medicamento.

Según un aspecto adicional del invento se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la fabricación de un medicamento para utilizar en la producción de un efecto inhibitorio de mTOR en un animal de sangre caliente tal como el hombre.

Según este aspecto del invento se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la fabricación de un medicamento para utilizar en la producción de un efecto anti- cancerígeno no en un animal de sangre caliente tal como el hombre.

Según una característica adicional del invento, se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la fabricación de un medicamento para utilizar en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según una característica adicional del invento, se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la fabricación de un medicamento para utilizar en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según un aspecto adicional del invento se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la producción de un efecto inhibitorio de mTOR en un animal de sangre caliente tal como el hombre.

Según este aspecto del invento se proporciona el uso de un compuesto de la fórmula (I) ,

(la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en la producción de un efecto anti- cancerígeno en un animal de sangre caliente tal como el hombre.

Según una característica adicional del invento, se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según una característica adicional del invento, se proporciona el uso de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según una característica adicional de este aspecto del invento se proporciona un método para producir un efecto inhibitorio de mTOR en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente.

Según una característica adicional de este aspecto del invento se proporciona un método para producir un efecto anti- cancerígeno en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente.

Según una característica adicional de este aspecto del invento se proporciona un método para tratar melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios, en un animal de sangre caliente, tal como el hombre, en

necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I) , (la) o (lb) o una sal farmacéuticamente aceptable del mismo como se define en la presente.

Según una característica adicional de este aspecto del invento se proporciona un método para tratar melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios, en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de la fórmula (I) , (la) o (lb) o una sal farmacéuticamente aceptable del mismo como se define en la presente.

En un aspecto adicional del invento se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en la producción de un efecto inhibitorio de mTOR en un animal de sangre caliente tal como el hombre.

En un aspecto adicional del invento se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en la producción de un efecto anti- cancerigeno en un animal de sangre caliente tal como el hombre.

En un aspecto adicional del invento se proporciona una composición farmacéutica la cual comprende un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios en un animal de sangre caliente tal como el hombre.

En un aspecto adicional del invento se proporciona una composición farmacéutica la cual

comprende un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, como se define en la presente en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios en un animal de sangre caliente tal como el hombre.

Otros aspectos adicionales del invento se encargan del tratamiento de enfermedad aliviada mediante la inhibición de mTOR, comprendiendo administrar a un sujeto en necesidad de tratamiento una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, preferiblemente en la forma de una composición farmacéutica y el tratamiento de cáncer, comprendiendo administrar a un sujeto en necesidad de tratamiento una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I) , (la) o (lb) , o una sal farmacéuticamente aceptable del mismo, en combinación, preferiblemente en la forma de una composición farmacéutica, de manera simultanea o secuencial con radiación ionizante o agentes quimioterapéuticos.

Definiciones

El término "anillo aromático" se utiliza en la presente en un sentido convencional para referirse a una estructura aromática cíclica, es decir, una estructura con orbitales de π electrones deslocalizados.

El anillo heterocíclico que contiene nitrógeno teniendo entre 3 y 8 átomos cíclicos: El término "El anillo heterocíclico que contiene nitrógeno teniendo entre 3 y 8 átomos cíclicos" como se utiliza en la presente se refiere a un anillo heterocíclico de 3 a 8 miembros que contiene al menos un átomo cíclico de nitrógeno. El término "junto con el nitrógeno al cual están unidos, forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos" como se utiliza en la presente se refiere a un anillo heterocíclico de 3 a 8 miembros que contiene al menos un átomo cíclico de nitrógeno. Ejemplos de estos grupos incluyen, pero no están limitados a:

Ni: aziridina (C_3 es decir 3 miembros) , azetidina (C4 es decir 4 miembros) , pirrolidina (tetrahidropirrola) (C5 es decir 5 miembros) , pirrolina (ej., 3- pirrolina, 2,5-dihidropirrola) (C5 es decir 5 miembros) , 2H- pirrola o 3H- pirrola (isopirrola, isoazol)

(C5 es decir 5 miembros) , piperidina (C6 es decir 6 miembros) , dihidropiridina (C6 es decir 6 miembros) , tetrahidropiridina (C6 es decir 6 miembros) , azepina (C7 es decir 7 miembros) ; N2: imidazolidina (C5 es decir 5 miembros) , pirazolidina (diazolidina) (C5 es decir 5 miembros) , imidazolina (C5 es decir 5 miembros) , pirazolina (dihidropirazol) (C5 es decir 5 miembros) , piperazina (C6 es decir 6 miembros) ;

NiOi: tetrahidrooxazol (C5 es decir 5 miembros) , dihidrooxazol (C5 es decir 5 miembros) , tetrahidroisoxazol (C_5 es decir 5 miembros) , dihidroisoxazol (C_5 es decir 5 miembros) , morfolina (C6 es decir 6 miembros) , tetrahidrooxazina (C6 es decir 6 miembros) , dihidrooxazina (C6 es decir 6 miembros) , oxazina (C6 es decir 6 miembros) ;

N1S1: tiazolina (C5 es decir 5 miembros) , tiazolidina (C5 es decir 5 miembros) , tiomorfolina (C6 es decir 6 miembros) ;

N2O1: oxadiazina (C_6 es decir 6 miembros) ;

N1O1S1: oxatiazina (C6 es decir 6 miembros) .

Alquilo: El término "alquilo" como se utiliza en la presente, se refiere a una fracción monovalente obtenida al retirar un átomo de hidrógeno de un átomo de carbono de un compuesto de hidrocarbonos teniendo entre 1 y 20 átomos de carbono (a menos que se especifique lo contrario) , el cual puede ser alifático o alicíclico, y el cual puede ser saturado o no saturado (ej. parcialmente saturado, completamente saturado) . Así, el término "alquilo" incluye las sub- clases alquilo saturado, alquenilo, alquinilo, cicloalquilo saturado, cicloalquenilo, cicloalquinilo, etc., discutidas a continuación. A menos que se especifique lo contrario, grupos "alquilo" preferibles son grupos alquilo saturado o cicloalquilo saturado, más preferiblemente grupos alquilo saturado.

En el contexto de grupos alquilo, los prefijos (ej. C_{1-4}, C_{1-7}, C_{1-20}, C_{2-7}, C_{3-7}, etc.) denotan el número de átomos de carbono, o rango de numero de átomos de carbono. Por ejemplo, el término "C1- 4 alquilo", como se utiliza en la presente, se refiere a un grupo alquilo con entre 1 y 4 átomos de carbono. Ejemplos de grupos alquilo incluyen C1- 4 alquilo ("alquilo menor") , C1- 7 alquilo, y alquilo C1- 20. Notar que el primer prefijo puede variar según otras limitaciones; por ejemplo, para grupos alquilo no saturados, el primer prefijo debe ser al menos 2; para grupos alquilo cíclicos, el primer prefijo debe ser al menos 3; etc.

El término grupo alquilo saturado incluye alquilo lineal saturado o alquilo ramificado

saturado.

Ejemplos de grupos alquilo saturado (no sustituidos) incluyen, pero no están limitados a, metilo (d) , etilo (C_2) , propilo (C_3) , butilo (C_4) , pentilo (C_5) , hexilo (C_6) , heptilo (C_7) , octilo (C_8) , nonilo (C_9) , decilo (C_{10}) , undecilo (C_{11}) , dodecilo (C_{12}) , tridecilo (C_{13}) , tetradecilo (C_{14}) , pentadecilo (C15) , o eicodecilo (C_{20}) .

Ejemplos de grupos alquilo lineales saturados (no sustituidos) incluyen, pero no están limitados a, metilo (C1) , etilo (C_2) , n- propilo (C_3) , n- butilo (C_4) , n- pentilo (amilo) (C_5) , n- hexilo (C_6) , o n- heptilo (C_7) .

Ejemplos de grupos alquilo ramificados saturados (no sustituidos) incluyen iso- propilo (C3) , iso- butilo (C4) , sec- butilo (C4) , tert- butilo (C4) , iso- pentilo (C5) , y neo- pentilo (C5) .

Alquenilo: El término "alquenilo", como se utiliza en la presente, se refiere a un grupo alquilo con uno o más enlaces dobles carbono- carbono. Ejemplos de grupos de grupos alquenilo incluyen C2- 4 alquenilo, C2- 7 alquenilo, C2- 20 alquenilo.

Ejemplos de grupos alquenilo no saturados (no sustituidos) incluyen, pero no están limitados a, etenilo (vinilo, - $CH=CH_2$) , 1- propenilo (- $CH=CH- CH_3$) , 2- propenilo (alilo, - $CH- CH=CH_2$) , isopropenilo (1- metilvinilo, - C(CH3) =CH2) , butenilo (C4) , pentenilo (C5) , y hexenilo (C6) .

Alquinilo: El término "alquinilo", como se utiliza en la presente, se refiere a un grupo alquilo con uno o más enlaces triples carbono- carbono. Ejemplos de grupos de grupos alquinilo incluyen C2- 4 alquinilo, C2- 7 alquinilo, C2- 20 alquinilo.

Ejemplos de grupos alquinilo no saturados (no sustituidos) alquinilo, pero no están limitados a, etinilo (etinilo, - C=CH) o 2- propinilo (propargilo, - CH_2- C=CH) .

Cicloalquilo: El término "cicloalquilo", como se utiliza en la presente, se refiere a un grupo alquilo el cual también es un grupo aciclilo; es decir, una fracción monovalente obtenida al retirar un átomo de hidrógeno de un átomo alicíclico de un anillo carbocíclico de un compuesto carbocíclico, tal anillo carbocíclico puede ser saturado o no saturado (ej. parcialmente saturado, completamente saturado) , cuya fracción tiene entre 3 y 20 átomos de carbono (a menos que se especifique lo contrario) , incluyendo entre 3 y 20 átomos cíclicos. Así, el término "cicloalquilo" incluye las sub- clases cicloalquilo saturado, cicloalquenilo o cicloalquinilo. Preferiblemente,

cada anillo tiene entre 3 y 7 átomos cíclicos. Ejemplos de grupos de grupos cicloalquilo incluyen C3- 20 cicloalquilo, C3.15 cicloalquilo, C3.10 cicloalquilo, C3- 7 cicloalquilo.

Ejemplos de grupos cicloalquilo incluyen, pero no están limitados a, aquellos derivados de: compuestos de hidrocarbonos monocíclicos saturados: ciclopropano (C3) , ciclobutano (C4) , ciclopentano (C_5) , ciclohexano *(Ce)* , cicloheptano (C7) , metilciclopropano (C4) , dimetilciclopropano (C5) , metilciclobutano (C5) , dimetilciclobutano (Ce) , metilciclopentano (Ce) , dimetilciclopentano (C7) , metilciclohexano (C7) , dimetilciclohexano (C_8) , mentano (C10) ; compuestos de hidrocarbonos monocíclicos no saturados: ciclopropeno (C3) , ciclobuteno (C4) , ciclopenteno (C_5) , ciclohexeno (C6) , metilciclopropeno (C4) , dimetilciclopropeno (C_5) , metilciclobuteno (C_5) , dimetilciclobuteno (C6) , metilciclopenteno (C6) , dimetilciclopenteno (C7) , metilciclohexeno (C7) , dimetilciclohexene (Cg) ; compuestos de hidrocarbonos policíclicos saturados: tuyano (C10) , carano (C10) , pinano (C10) , bornano (C10) , norcarano (C7) , norpinano (C7) , norbornano (C7) , adamantano (C10) , decalina (decahidronaftaleno) (C10) ; compuestos de hidrocarbonos policíclicos no saturados: camfeno (C10) , limoneno (C10) , pineno (C10) ; compuestos de hidrocarbonos policíclicos con un anillo aromático: indeno (C9) , indano (ej., 2,3- dihidro- lH- indeno) (C9) , tetralina (1,2,3,4- tetrahidronaftaleno) (C10) , acenafteno (C12) , fluoreno (C13) , fenaleno (C13) , acefenantreno (Q5) ,aceantreno (Ci6) , colantreno (C20) .

Heterociclilo: El término "heterociclilo", como se utiliza en la presente, se refiere a una fracción monovalente obtenida al retirar un átomo de hidrógeno desde un átomo cíclico de un compuesto heterocíclico, tal fracción tiene entre 3 y 20 átomos cíclicos (a menos que se especifique lo contrario) , de los cuales entre 1 y 10 son heteroátomos cíclicos. Preferiblemente, cada anillo tiene entre 3 y 7 átomos cíclicos, de los cuales entre 1 y 4 son heteroátomos cíclicos. Preferiblemente los heteroátomos cíclicos se seleccionan a partir de O, N o S. El anillo heterocíclico puede, a menos que se especifique lo contrario, tener enlace a carbono o nitrógeno, y en donde un grupo - CH2- se puede opcionalmente reemplazar por un - C(O) - , y un átomo de azufre cíclico se puede opcionalmente oxidar para formar los óxidos- S.

En este contexto, los prefijos (ej. C3- 20, C3- 7, C5- 6, etc.) denotan el número de átomos cíclicos, o rango de numero de átomos cíclicos, bien sea átomos de carbono o heteroátomos. Por ejemplo, el término "C5- 6 heterociclilo" o " heterociclilo de 5 a 6 miembros", como se utiliza en

la presente, se refiere a un grupo heterocíclico con 5 o 6 átomos cíclicos. Ejemplos de grupos de grupos heterociclilo incluyen C3- 20 heterociclilo (es decir heterociclilo de 3 a 20 miembros) , C5- 20 heterociclilo (es decir heterociclilo 5 a 20 miembros) , C3- 15 heterociclilo (es decir heterociclilo de 3 a 15 miembros heterociclilo) , C5- 15 heterociclilo (es decir heterociclilo de 5 a 15 miembros) , C3- 12 heterociclilo (es decir heterociclilo de 3 a 12 miembros) , C5- 12 heterociclilo (es decir heterociclilo de 5 a 12 miembros) , C3- 10 heterociclilo (es decir heterociclilo de 3 a 10 miembros) , C5- 10 heterociclilo (es decir heterociclilo de 5 a 10 miembros) , C3- 7 heterociclilo (es decir heterociclilo de 3 a 7 miembros) , C5- 7 heterociclilo (es decir heterociclilo de 5 a 7 miembros) , y C5- 6 heterociclilo (es decir heterociclilo de 5 a 6 miembros) .

Ejemplos de grupos heterociclilo monocíclicos incluyen, pero no están limitados a, aquellos derivados de:

Ni: aziridina (C3 es decir 3 miembros) , azetidina (C4 es decir 4 miembros) , pirrolidina (tetrahidropirrola) (C5 es decir 5 miembros) , pirrolina (ej., 3- pirrolina, 2,5- dihidropirrola) (C5 es decir 5 miembros) , 2H- pirrola o 3H- pirrola (isopirrola, isoazol) (C5 es decir 5 miembros) , piperidina (C6 es decir 6 miembros) , dihidropiridina (C6 es decir 6 miembros) , tetrahidropiridina (C6 es decir 6 miembros) , azepina (C7 es decir 7 miembros) ; O1: oxirano (C3 es decir 3 miembros) , oxetano (C4 es decir 4 miembros) , oxolano (tetrahidrofuranoo) (C5 es decir 5 miembros) , oxol (dihidrofurano) (C5 es decir 5 miembros) , oxano (tetrahidropirano) (C6 es decir 6 miembros) , dihidropirano (C6 es decir 6 miembros) , pirano (C6 es decir 6 miembros) , oxepin (C7 es decir 7miembros) ;

Si: tiirano (C3 es decir 3 miembros) , tietano (C4 es decir 4 miembros) , tiolano (tetrahidrotiofeno) (C5 es decir 5 miembros) , tiano (tetrahidrotiopirano) (C6 es decir 6 miembros) , tiepano (C7 es decir 7 miembros) ;

O2: dioxolano (C5 es decir 5 miembros) , dioxano (C6 es decir 6 miembros) , o dioxepano (C7 es decir 7 miembros) ;

O3: trioxano (C6 es decir 6 miembros) ;

N2: imidazolidina (C5 es decir 5 miembros) , pirazolidina (diazolidina) (C5 es decir 5 miembros) , imidazolina (C5 es decir 5 miembros) , pirazolina (dihidropirazol) (C5 es decir 5 miembros) , piperazina (C6 es decir 6 miembros) ;

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N_1O_1: tetrahidrooxazol (C5 es decir 5 miembros) , dihidrooxazol (C5 es decir 5 miembros) , tetrahidroisoxazol (C5 es decir 5 miembros) , dihidroisoxazol (C5 es decir 5 miembros) , morfolina (C6 es decir 6 miembros) , tetrahidrooxazina (C6 es decir 6 miembros) , dihidrooxazina (C6 es decir 6 miembros) , oxazina (C6 es decir 6 miembros) :

N1S1: tiazolina (C5 es decir 5 miembros) , tiazolidina (C5 es decir 5 miembros) , tiomorfolina (C6 es decir 6 miembros) ;

N2O1: oxadiazina (C6 es decir 6 miembros) ;

O1S1: oxatiole (C5 es decir 5 miembros) y oxatiane (tioxano) (C6 es decir 6 miembros) ; y,

N1O1S1: oxatiazina (C_6 es decir 6 miembros) .

Ejemplos de grupos heterociclilo monocíclicos sustituidos (no aromáticos) incluyen aquellos derivados de sacaridos, en forma cíclica, por ejemplo, furanosas (C5 es decir 5 miembros) , tales como arabinofuranosa, lixofuranosa, ribofuranosa, o xilofuranosa, y piranosas (C6 es decir miembros) , tales como allopiranosa, altropiranosa, glucopiranosa, manopiranosa, gulopiranosa, idopiranosa, galactopiranosa, y talopiranosa.

Epiro- C3- 7 cicloalquilo o heterociclilo: El término "espiro C3- 7 cicloalquilo o heterociclilo" como se utiliza en la presente, se refiere a un C3- 7 cicloalquilo o anillo C3- 7 heterociclilo (3 a 7 miembros) unido a otro anillo mediante un único átomo común a ambos anillos.

C5- 20 arilo: El término "C5- 20 arilo" como se utiliza en la presente, se refiere a una fracción monovalente obtenida al retirar un átomo de hidrógeno dese un átomo cíclico aromático de un compuesto aromático C5- 20, dicho compuesto teniendo un anillo, o dos o más anillos (ej., fusionados) , y teniendo entre 5 y 20 átomos cíclicos, y en donde al menos dicho anillo es un anillo aromático. Preferiblemente, cada anillo tiene entre 5 y 7 átomos cíclicos.

Los átomos cíclicos pueden ser átomos de carbono, como en "grupos carboarilo" en cuyo caso el grupo puede ser convenientemente conocido como un grupo "C5- 20 carboarilo".

Ejemplos de grupos C5- 20 arilo los cuales no tienen heteroátomos cíclicos (es decir

Grupos C5- 20 carboarilo) incluyen, pero no están limitados a, aquellos derivados de benceno (es decir fenil) (C6), naftaleno (C10), antraceno (Cu), fenantreno (C14), o pireno (C16).

Alternativamente, los átomos cíclicos pueden incluir uno o más heteroátomos, incluyendo pero sin limitar a oxigeno, nitrógeno, y azufre, como en "grupos heteroarilo". En este caso, el grupo puede ser convenientemente conocido como un grupo "C5- 20 heteroarilo", en donde "C5- 20" denotes átomos cíclicos, bien sea átomos de carbono o heteroátomos (o de otra manera conocido como un grupo heteroarilo de 5 a 20 miembros). Preferiblemente, cada anillo tiene entre 5 y 7 átomos cíclicos, de los cuales entre 1 y 4 son heteroátomos cíclicos. Comunmente, heteroátomos se seleccionan a partir de oxigeno, nitrógeno o azufre.

Ejemplos de grupos heteroarilo C5- 20 incluyen, pero no están limitados a, grupos heteroarilo C5 (grupos heteroarilo de 5 miembros) derivados a partir de furano (oxol), tiofeno (tiol), pirrola (azol), imidazol (1,3- diazol), pirazol (1,2- diazol), triazol, oxazol, isoxazol, tiazol, isotiazol, oxadiazol, tetrazol y oxatriazol; y grupos heteroarilo C6 (grupos heteroarilo de 6 miembros) derivados a partir de isoxazina, piridina (azina), piridazina (1,2- diazina), pirimidina (1,3- diazina; ej., citosina, timina, uracil), pirazona (1,4- diazina) o triazina.

El grupo heteroarilo puede estar enlazado por medio de un átomo de un hetero anillo.

Ejemplos de grupos heteroarilo C5- 20 los cuales comprenden anillos fusionados, incluyen, pero no están limitados a, grupos heteroarilo C9 (grupos heteroarilo de 9 miembros) derivados a partir de benzofurano, isobenzofurano, benzotiofeno, indol, isoindol; grupos heteroarilo C10 (grupos heteroarilo de 10 miembros) derivados a partir de quinolina, isoquinolina, benzodiazina, piridopiridina; grupos heteroarilo C14 (grupos heteroarilo de 14 miembros) derivados a partir de acridina o xanteno.

Los anteriores grupos alquilo, heterociclilo y arilo, bien sea solos o como parte de otro sustituyente, pueden por si mismos ser opcionalmente sustituidos con uno o más grupos seleccionados a partir de estos mismos y los sustituyentes adicionales listados a continuación.

Halo: - F, - Cl, - Br, o - I.

Hidroxilo: - OH.

Eter: - O, en donde R es un sustituyente de éter, por ejemplo, un grupo C1- 7 alquilo (también conocido como un grupo C1- 7 alcoxilo), un grupo C3- 20 heterociclilo (también conocido como un grupo C3- 20 heterocicliloxilo), o un grupo C5- 20 arilo (también conocido

como un grupo C5- 20 ariloxilo) , preferiblemente un grupo C1- 7 alquilo.

Nitro: - NO_2.

Ciano (nitrilo, carbonitrilo) : - CN.

Acilo (ceto) : - C(=0) R, en donde R es un sustituyente de acilo, por ejemplo, H, un grupo C1- 7 alquilo (también conocido como C1- 7 alquilacilo o C1- 7 alkanoil) , un grupo C3- 20 heterociclilo (también conocido como C3- 20 heterociclilacilo) , o un grupo C5- 20 arilo (también conocido como C5- 20 ariloacilo) , preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos acilo incluyen, pero no están limitados a, - C(=0) CH_3 (acetilo) , - C(=0) CH_2CH_3 (propionilo) , - C(=0) $C(CH_3)_3$ (butirilo) , o - C(=0) F(benzoilo, fenona)) .

Carboxilo (ácido carboxílico) : - COOH.

Éster (carboxilato, éster del ácido carboxílico, oxicarbonilo) : - C(=0) O, en donde R es un sustituyente de éster, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos de éster incluyen, pero no están limitados a, - C(=0) OCH_3, - C(=0) OCH_2CH_3, - C(=0) $OC(CH_3)_3$, o - C(=0) OPh.

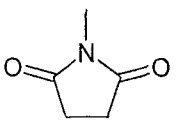
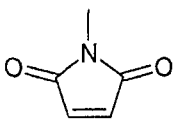
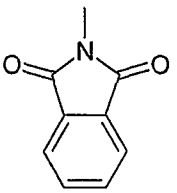
Amido (carbamoilo, carbamilo, aminocarbonilo, carboxamida) : - C(=0) NR^1R^2, en donde R^1 o R^2 son independientemente amino sustituyentes, como se definió para grupos amino. Ejemplos de grupos amido incluyen, pero no están limitados a, - C(=0) NH_2, - C(=0) $NHCH_3$, - C(=0) $N(CH_3)_2$, - C(=0) $NHCH_2CH_3$, y - C(=0) $N(CH_2CH_3)_2$, así como también grupos amido en los cuales R^1 y R^2, junto con el átomo de nitrógeno al cual están unidos, forman una estructura heterocíclica como en, por ejemplo, piperidinocarbonilo, morfolinocarbonilo, tiomorfolinocarbonilo, o piperazinilcarbonilo.

Amino: - NR^1R^2, en donde R^1 y R^2 son independientemente amino sustituyentes, por ejemplo, hidrógeno, un grupo C1- 7 alquilo (también conocido como C1- 7 alquilamino y di- C1- 7 alquilamino) , un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente H o un grupo C1- 7 alquilo, o, en el caso de un grupo amino "cíclico", R^1 y R^2, tomados junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico teniendo entre 4 y 8 átomos cíclicos. Ejemplos de grupos amino incluyen, pero no están limitados a, - NH2, - NHCH3, - $NHCH(CH3)_2$, - $N(CH3)_2$, - $N(CH_2CH3)$ 2, o - NHPh. Ejemplos de grupos amino cíclicos incluyen, pero no están limitados a, aziridinilo, azetidinilo, pirrolidinilo, piperidino,

piperazinilo, perhidrodiazepinilo, morfolino, o tiomorfolino. Los grupos amino cíclicos se pueden sustituir sobre su anillo mediante cualquiera de los sustituyentes definidos aquí, por ejemplo carboxilo, carboxilato y amido.

Aminosulfonilo - S(=0) $2NR^1R^2$, en donde R^1 y R^2 cada uno independientemente es un amino sustituyente, como se definió para grupos amino. Ejemplos de grupos aminosulfonilo incluyen, pero no están limitados a, - $S(=0)_2NH_2$, - $S(=0)_2NHCH_3$, - $S(=0)_2NHCH_2CH_3$ o - $S(=0)_2N(CH_3)_2$.

Acilamido (acilamino) : - NR C(=0) R , en donde R es un sustituyente de amida, por ejemplo, hidrógeno, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente H o un grupo C1- 7 alquilo, más preferiblemente H, y R^2 es un sustituyente de acilo, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos acilamida incluyen, pero no están limitados a, - NHC(=0) CH3 , - NHC(=0) CH_2CH_3, o - NHC(=0) Ph. R^1 y R^2 pueden juntos formar una estructura cíclica, como en, por ejemplo, succinimidilo, maleimidilo, o ftalimidil:

succinimidilo maleimidilo ftalimidilo

Ureido: - $N(R^1)$ $CONR^2R^3$ en donde R2 y R3 son independientemente amino sustituyentes, como se definió para grupos amino, o Rl es un sustituyente de ureido, por ejemplo, hidrógeno, un grupo C1- 7 alquilo, un grupo C_{3-20} heterociclilo, o un grupo C5- 20 arilo, preferiblemente hidrógeno o un grupo C1- 7 alquilo. Ejemplos de grupos ureido incluyen, pero no están limitados a, - $NHCONH_2$, - NHCONHMe, - NHCONHEt, - $NHCONMe_2$, - $NHCONEt_2$, - $NMeCONH_2$, - NMeCONHMe, - NMeCONHEt, - $NMeCONMe_2$, - $NMeCONEt_2$ o - NHC(=0) NHPh.

Aciloxilo (éster inverso) : - OC(=0) R, en donde R es un sustituyente aciloxilo, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos aciloxilo incluyen, pero no están limitados a, - OC(=0) CH3 (acetoxi) , - OC(=0) CH_2CH_3, - OC(=0) $C(CH_3)_3$, - OC(=0) Ph, -

OC(=0) C_6H_4F, o - OC(=0) CH_2Ph.

Tiol: - SH.

Tioéter (sulfuro) : - SR, en donde R es un sustituyente de tioéter, por ejemplo, un grupo C1- 7 alquilo (también conocido como un grupo C1- 7 alquiltio) , un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos C1- 7 alquiltio incluyen, pero no están limitados a, - SCH_3 o - SCH_2CH_3.Sulfoxido (sulfinilo) : - S(=0) R, en dónde R es un sustituyente de sulfoxido, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos sulfoxido incluyen, pero no están limitados a, - S(=0) CH_3 y - S(=0) CH2CH_3.

Sulfonilo (sulfona) : - $S(=0)_2R$, en donde R es un sustituyente de sulfona, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos sulfona incluyen, pero no están limitados a, - $S(=0)_2CH_3$ (metanosulfonilo, mesilo) , - $S(=0)_2CF_3$, - $S(=0)_2CH_2CH_3$, y 4- metilfenilsulfonilo (tosilo)

Tioamido (tiocarbamilo) : - C(=S) NR^1R^2, en donde R^1 y R^2 son independientemente amino sustituyentes, como se definió para grupos amino. Ejemplos de grupos amido incluyen, pero no están limitados a, - C(=S) NH_2, - C(=S) $NHCH_3$, - C(=S) $N(CH_3)_2$, o - C(=S) $NHCH_2CH_3$.

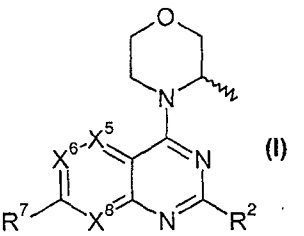
Sulfonamino: - $NR^1S(=0)$ 2R, en donde R^1 es un amino sustituyente, como se definió para grupos amino, y R es un sulfonamino sustituyente, por ejemplo, un grupo C1- 7 alquilo, un grupo C3- 20 heterociclilo, o un grupo C5- 20 arilo, preferiblemente un grupo C1- 7 alquilo. Ejemplos de grupos sulfonamino incluyen, pero no están limitados a, - $NHS(=0)_2CH_3$, - $NHS(=0)_2Fo$ - $N(CH_3)$ $S(=0)_2C_6H_5$.

Además, dos o más sustituyentes adyacentes se pueden enlazar tal que junto con los átomos a los cuales están unidos forman un anillo C3- 7 cicloalquilo, C3- 20 heterociclilo o C5- 20 arilo.

Como se mencionó anteriormente, los grupos que forman los grupos de sustituyentes anteriormente listados, ej. C1- 7 alquilo, C3- 20 heterociclilo o C5- 20 arilo, pueden por sí mismos ser sustituidos. Así, las anteriores definiciones cubren grupos sustituyentes los cuales son

sustituidos.

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula I:



, o una sal farmacéuticamente aceptable del mismo, en donde: uno o dos de X^5, X^6 y X^8 es N, y los demás son CH;

R^7 es halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(-O)R^{c1}$, $NR^{N7b}SO_2R^{S2a}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , donde R^{01} y R^{S1} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o a C 1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroarilo, o C5- 20 arilo es

opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C_{3-20}heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C_{5-20} arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N1} o R^{N2} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o heterocíclilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{C1} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, un grupo C1- 7 alquilo o $NR^{N8}R^{N9}$ donde R^{N8} y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3-

20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{S2a} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroarilo o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

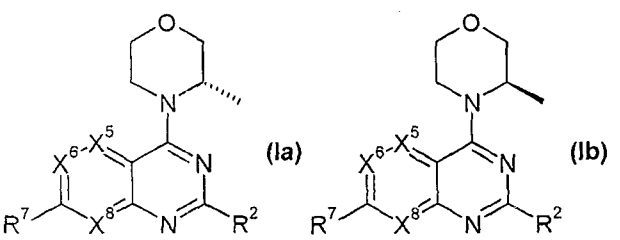
R^{N7a} y R^{N7b} son H o un grupo C1- 4 alquilo;

R^2 es H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino)

, en donde R^{02} o R^{S2b} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20heteroaril o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C_2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{NS} o R^{N6} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 aril o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C_2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) .

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula la o lb:



, o una sal farmacéuticamente aceptable del mismo, en donde: uno o dos de X^5, X^6 o X^8 es N, y

los demás son CH;

R^7 es halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=0)$ R^{cl}, $NR^{N7b}S0_2R^{S2a}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 oarilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , donde R^{01} y R^{S1} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquilo y donde cada C1- 7 alquilo, C5- 20 heteroarilo, o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N1} y R^{N2} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo

heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfóxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ; R^{C1} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, un grupo C1- 7 alquilo o $NR^{N8}R^{N9}$ donde R^{N8} y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{S2a} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroaril o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo,

C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N7a} o R^{N7b} son H o un grupo C1- 4 alquilo;

R^2 es H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino)

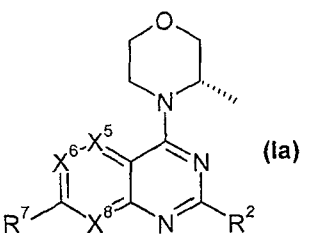
,

en donde R^{o2} o R^{S2b} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroaril o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido,

ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N5} y R^{N6} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) .

Según un aspecto adicional del presente invento se proporciona un compuesto de la fórmula Ia:



(Ia)

. o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos de X^5, X^6 o X^8 es N, y los demás son CH;

R^7 es halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=0)\ R^{c1}$, $NR^{N7b}S0_2R^{S2a}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo,

C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , donde R^{O1} o R^{S1} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroarilo, o C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N1} o R^{N2} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o heterocíclilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20

arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ; R^{cl} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, un grupo C1- 7 alquilo o $NR^{N8}R^{N9}$ donde R^{N8}y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{S2a} es H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroarilo y C5- 20 arilo es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ; R^{N7a} y R^{N7b} son H o un grupo C1- 4 alquilo;

R^2 es H, halo, OR^{02}, $SR^{S2}\backslash NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente

sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) , o un grupo C5- 20 arilo opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino)

en donde R^{o2} o R^{S2b} son H, un grupo C5- 20 arilo, un grupo C5- 20 heteroarilo, o un grupo C1- 7 alquily donde cada C1- 7 alquilo, C5- 20 heteroaril o C5- 20oaril es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) ;

R^{N5} y R^{N6} son independientemente H, un grupo C1- 7 alquilo, un grupo C5- 20 heteroarilo, un grupo C5- 20 arilo, o R^{N5} y R^{N} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos donde cada C1- 7 alquilo, C5- 20 heteroarilo, C5- 20 arilo o anillo heterocíclico es opcionalmente sustituido por uno o más grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, y tiol, o C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino (cada uno opcionalmente sustituido por uno o más

grupos seleccionados a partir de halo, hidroxilo, nitro, ciano, carboxilo, tiol, C1- 7 alquilo, C2- 7 alquenilo, C2- 7 alquinilo, C3- 7 cicloalquilo, C3- 7 cicloalquenilo, C3- 20 heterociclilo, C5- 20 arilo, C5- 20 heteroarilo, éter, acilo, éster, amido, amino, acilamido, ureido, aciloxilo, tioéter, sulfoxido, sulfonilo, tioamido y sulfonamino) .

Preferencias Adicionales

Las siguientes preferencias pueden aplicar a cada aspecto del presente invento, donde sen aplicable. Las preferencias para cada grupose pueden combinar con aquellas para cualquiera o todos los demás grupos, según sea apropiado.

X^5, X^6, o X^8

Cuando dos de X^5, X^6 o X^8 son N, preferiblemente X^5 y X^8 son N.

Se prefiere que solamente uno entre X^5, X^6 y X^8 sea N. Más preferiblemente uno de X^5 o X^8 es N, o más preferiblemente X^8 es N.

R^7

R^7 es preferiblemente seleccionado de un grupo C5- 20 arilo opcionalmente sustituido, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{cl}$ y $NR^{N7b}S0_2R^{S2a}$, donde R^{01}, R^{SI}, R^{N1}, R^{N2}, R^{N7a}, R^{N7b}, R^{cl} y R^{S2a} son como se definieron anteriormente. Adicionalmente se prefiere que R^7 se seleccione de un grupo C5- 20 arilo opcionalmente sustituido, OR^{01}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{cl}$ y $NR^{N7b}S0_2R^{s2a}$.

Si R^7 es OR^{01}, entonces preferiblemente R^{01} es un grupo C1- 7 alquilo, el cual se puede sustituir.

Si R^7 es $NR^{N1}R^{N2}$, entonces preferiblemente R^{N2} se selecciona a partir de H y C1- 4 alquilo (ej. metilo) o más preferiblemente es H. Si R^{N1} es C1- 7 alquilo, éste preferiblemente se selecciona de C3- 7 cicloalquilo. Si $_RN1$ es C5- 20 arilo, éste preferiblemente se selecciona de C5- 10 arilo (ej. fenilo, pirrolilo, piridilo, pirazolilo, furanilo, tiofenilo, pirazinilo, pirimidinilo, tetrazolilo, tiazolilo, indazolilo, imidazolilo, triazolilo, oxadiazolilo) o más preferiblemente C5- 6 arilo (ej. fenilo, pirrolilo, piridilo, pirazolilo, furanilo, tiofenilo, pirazinilo, pirimidinilo, tetrazolilo, tiazolilo, imidazolilo, triazolilo, oxadiazolilo) . Grupos particularmente preferidos incluyen furilo, fenilo, piridilo, pirrolilo, pirazolilo o tiofenilo. Los grupos anteriormente

mencionados son opcionalmente sustituidos, y en algunas realizacones son preferiblemente sustituidos. Grupos sustituyentes pueden incluir, pero no están limitados a, C1- 7 alquilo, C3- 20 heterociclilo. C5- 20 arilo. carboxilo, éster, éter, (eg C1- 7 alcoxilo) , hidroxilo, ariloxilo, ciano, halo. nitro, amido, sulfonilo, sulfoniloamino, amino sulfonilo o amino.

Si R^7 es $NR^{N7a}C(0)\ R^{cl}$, entonces R^{N7a} es preferiblemente H. R^{cl} puede ser un grupo C5- 20 arilo opcionalmente sustituido (ej. fenilo, imadazolilo, quinoxalinilo) , C3- 20 heterociclilo, C1- 7 alquilo (ej. propenilo, metilo (sustituido con tiofenilo)) o $NR^{N8}R^{N9}$. R^{N8} es preferiblemente hidrógeno, y R^{N9} es preferiblemente C1- 7 alquilo (ej. etilo) .

Si R^7 es $NR^{N7b}S0_2R^{S2a}$, entonces R^{N7b} es preferiblemente H. R^{S2a} es preferiblemente C1- 7 alquilo (ej. metilo) .

Si R^7 es un grupo C5- 20 arilo, éste preferiblemente es un grupo C5- 10 arilo opionalmente sustituido y más preferiblemente un grupo C5- 6 arilo opcionalmente sustituido. Más preferiblemente éste es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilamino y C1- 7 alquilamino y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino y C1- 7 alquilamino.

Si R^7 es un grupo heteroarilo de 5 a 20 miembros, éste preferiblemente es un grupo heteroarilo de 5 a 10 miembros opcionalmente sustituido o más preferiblemente un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido.

En una realización, R^7 es un grupo C5- 20 arilo opcionalmente sustituido o un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, sulfonamino (por ejemplo - NHS(=0) 2C1- 7alquil) amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $CONH_2$, - CONH C1- 7 alquilo. - $CON(C1\text{- }7alquilo)_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo. alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, - NHS(=0) 2

C1- 7 alquilo, C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7 alquilamino.

En una realización, R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, sulfonamino (por ejemplo - $NHS(=0)_2C1$- 7alquil) amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $CONH_2$, - CONH C1- 7alquilo, - CON (C1- 7alquilo) $_2$ o –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, - $NHS(=0)_2$ C1- 7 alquilo, C5- 6 arilamino, di- (C1- 7alquil) amino y C1- 7 alquilamino.

En una realización, R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo- NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , o amido (por ejemplo - $CONH_2$, - CONH C1- 7 alquilo, - $CON(C1- 7alquilo)_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7 alquil) amino y C1- 7 alquilamino.

En una realización, R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - OCH2CH3, - NH_2, - $NHS0_2CH_3$, - $CH_2NHS0_2CH_3$, - $OCHF_2$, - CH_2OH, - $C0_2H$- $CONH_2$, - CONHMe, - CONHEt, - $CONHCH(CH_3)_2$, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo.

En una realización, R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - CH_2OH, - $C0_2H$- $CONH_2$, - CONHMe, - CONHEt, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo.

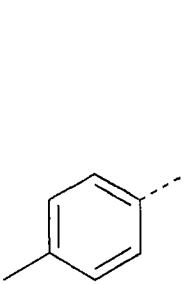
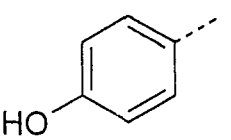
En una realización, R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de metoxilo, - OCH_2CH_3, - NH_2, - $NHS0_2CH_3$, - $CH_2NHS0_2CH_3$, - $OCHF_2$, - CH_2OH, - $CONH_2$, - CONHMe o - $CONHCH(CH_3)_2$.

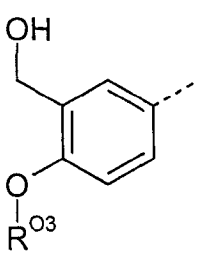
En una realización R^7 es un grupo heteroarilo que contiene nitrógeno de 5 o 5 miembros opcionalmente sustituido tal como un grupo de piridina, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH_2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $C0_2NH_2$, - $C0_2NHC1$- 7 alquilo, - $C0_2N(C1$- 7alquilo)$_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino y C1- 7 alquilamino.

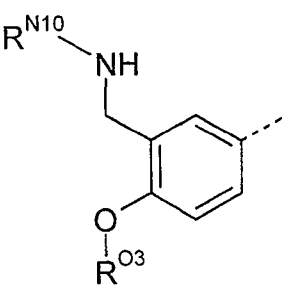
En una realización, R es un grupo piridinilo opcionalmente sustituido, halo, hidroxilo, ciano. C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - CO2NH2, - $C0_2NH$ C1- 7 alquilo, - $C0_2N(C1$- 7alquil) 2 o –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo pueden ser adicionalmente opcionalmente sustituidos por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino y C1- 7 alquilamino.

En una realización, R^7 es un grupo piridinilo opcionalmente sustituido con NH_2.

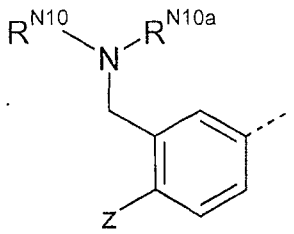
En una realización, R^7 es un grupo fenilo opcionalmente sustituido seleccionado de


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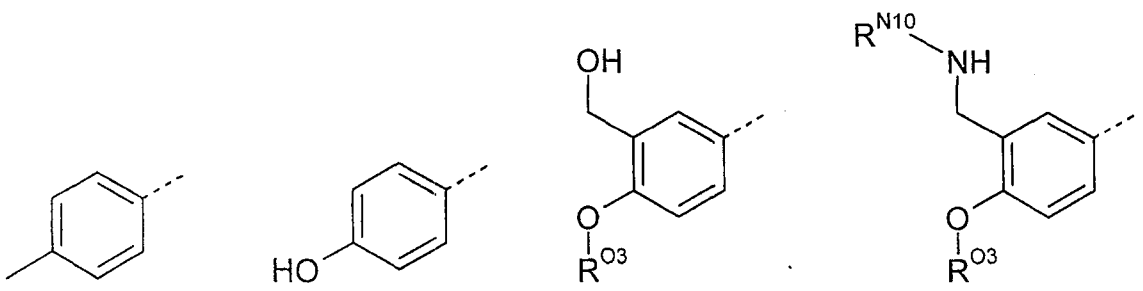
en donde

Z es H, F o OR^{O3};

R^{O3} se selecciona a partir de hidrógeno o un grupo C1- 6 alquilo opcionalmente sustituido;

R^{N1o} se selecciona a partir de hidrógeno, C(0) R^{C2}, C(S) R^{C3}, $S0_2R^{S3}$, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente ^{sustituido} donde R^{C2} y R^{C3} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{N11} y R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos; y R^{S3} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heteroarilo opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o R^{N10} o R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos.

En una realización, R^7 es un grupo fenilo opcionalmente sustituido seleccionado de

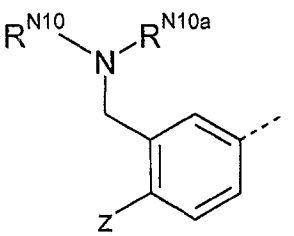


en donde

R^{03} se selecciona a partir de hidrógeno o un grupo C1- 6 alquilo opcionalmente sustituido; y R^{N10}

se selecciona a partir de C(0) R^{C2}, C(S) R^{C3}, $S0_2R^{S3}$, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente ^{sustituido} donde R^{C2} o R^{C3} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{N11} y R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos; y R^{S3} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heteroarilo opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido.

En una realización, R^7 es



en donde

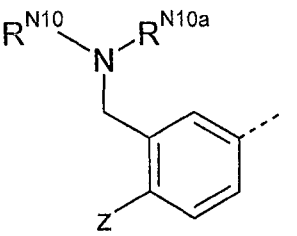
Z es H, F o OR^{03};

R^{N10} se selecciona a partir de hidrógeno, C(0) R^{C2}, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente ^{sustituido} donde R^{C2} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{N11} y R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos.

En una realización, R^7 es



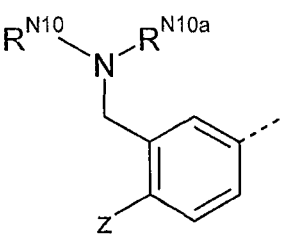
en donde

Z es H, F o OR^{03};

R^{N10} se selecciona a partir de hidrógeno, C(0) R^{C2}, un grupo C5- 6 heteroarilo opcionalmente sustituido, un grupo C6 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente sustituido donde R^{C2} se selecciona a partir de CH_3 o CH_2OH;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

y donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino. En una realización, R^7 es



en donde

Z es H, F o OR^{03};

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH_3, - C(0) CH_2OH, - CH_3, - CH_2CH_3, - CH_2CH_2OH, - $CH(CH_3)_2$, - CH_2CH_2OMe, - $CH_2C(CH_3)_2$, - $CH_2CH_2C(CH_3)_2$, - $CH(CH_3)$ $CH_2C(CH_3)_2$, - CH2CH2CH_2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH_2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, -

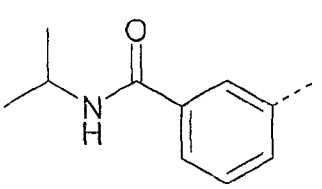
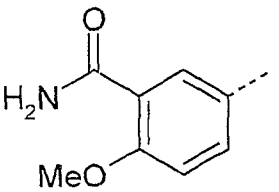
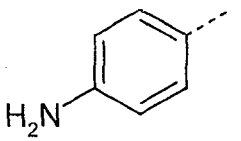
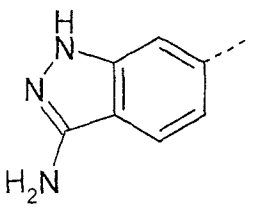
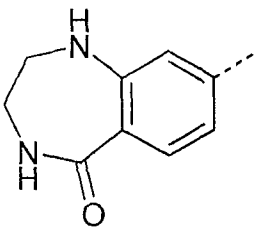
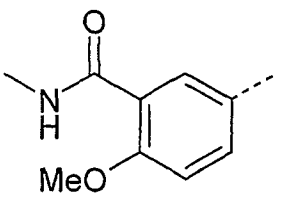
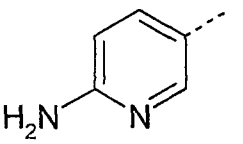
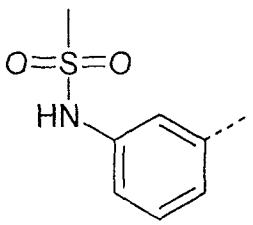
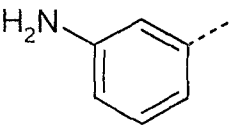
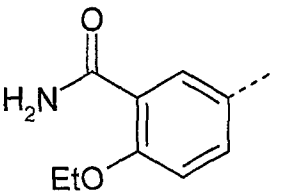
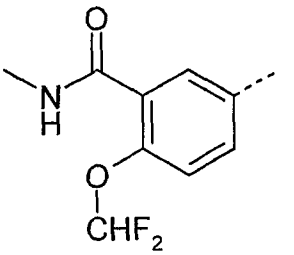
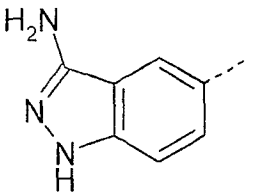
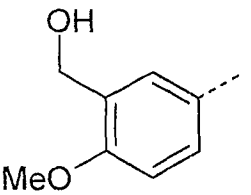
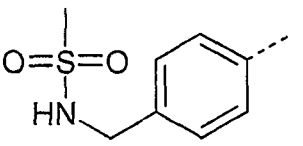
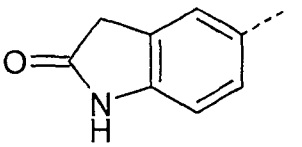
CH_2imidazol ;

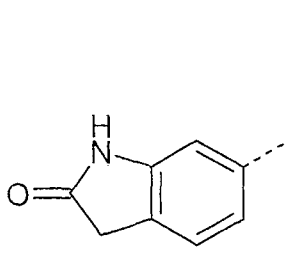
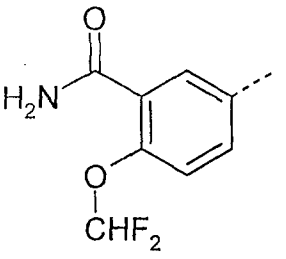
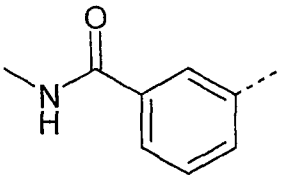
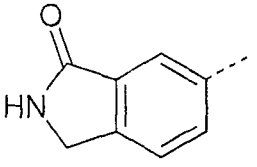
R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos;

y donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo.

En una realización adicional del invento R^7 se selecciona a partir de


,

,

y


En una realización R^2 es OR^{O2} donde R^{O2} es un grupo C1- 7 alquilo opcionalmente sustituido.

En una realización R^2 es OR^{02} donde R^{O2} es - CH_3, - CH_2CH_3, - CH_2CH_2OH, - $CH_2CH_2OCH_3$, o - $CH(CH_3)$ $CH_2N(CH_3)_2$.

Preferiblemente R^2 es $NR^{N5}R^{N6}$, donde R^{N5} y R^{N6} son como se definieron anteriormente, o más preferiblemente R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, el cual puede opcionalmente ser sustituido. El anillo preferiblemente tiene entre 5 y 7 átomos cíclicos. Grupos preferidos opcionalmente sustituidos incluyen, pero no están limitados a imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituido) o pirrolidinilo.

N- sustituyentes preferidos para los grupos piperazinilo u homopiperazinilo incluyen ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - $C(=0)$ OCH_3, - $C(=0)$ OCH_2CH_3 o - $C(=0)$ $OC(CH_3)_3$.

N- sustituyentes preferidos para los grupos piperazinilo u homopiperazinilo incluyen Grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - $C(=0)$ OCH_3, - $C(=0)$ OCH_2CH_3 o - $C(=0)$ $OC(CH_3)_3$.

C- sustituyentes preferidos para los grupos incluyen C1- 4 alquilo, preferiblemente metilo. Los grupos pueden tener uno o más sustituyentes, por ejemplo uno o dos sustituyentes;

C- sustituyentes preferidos para los grupos incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo,. Los grupos pueden tener uno o más sustituyentes, por ejemplo uno o dos sustituyentes.

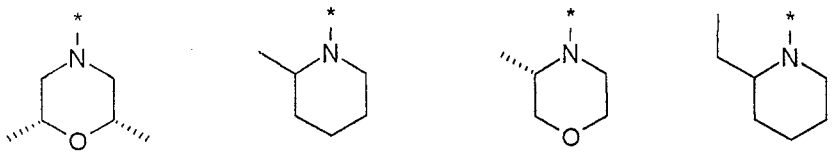
En una realización R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de amino, ciano, halo, hidroxilo, éster, un anillo C3- 7 cicloalquilo, un anillo C6 carboarilo, un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde el anillo heterocíclico, el anillo cicloalquilo, el anillo carboarilo, los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo)

En una realización R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo)

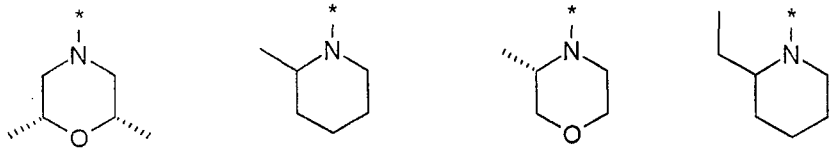
En una realización R^2 es $NR^{N5}R^{N6}$, donde R^{N5} es un grupo C1- 7 alquilo opcionalmente sustituido o un grupo fenilo opcionalmente sustituido, y R^{N6} es hidrógeno.

En una realización R^2 es $NR^{N5}R^{N6}$, donde R^{N5} es - $CH(CH_3)$ CH_2OCH_3, ciclopentilo o un grupo fenilo, y R^{N6} es hidrógeno.

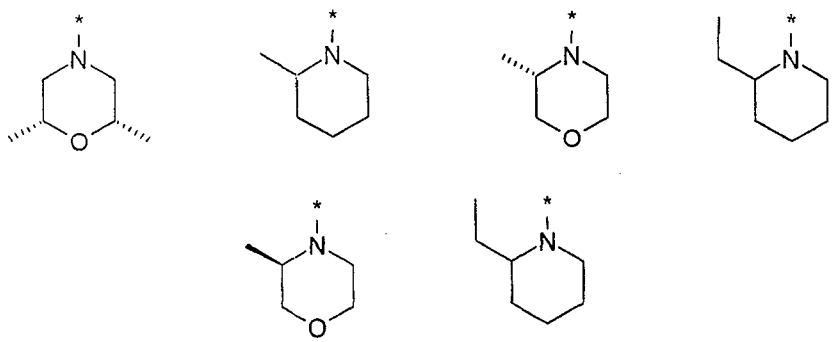
Grupos R^2 preferidos son pirrolidinilo, morfolino, piperadinilo y homopiperadinilo. Grupos más preferidos son morfolino o piperadinilo. Estos preferiblemente son sustituidos con uno o más alquilo sustituyentes, por ejemplo metilo o etilo sustituyentes. Más preferiblemente estos son sustituidos con uno o dos metilo sustituyentes. Si estos grupos llevan dos metilo sustituyentes, estos preferiblemente están sobre átomos separados de carbono. Los alquilo sustituyentes también pueden ser opcionalmente sustituidos. Ejemplos de sustituyentes opcionales de los alquilo sustituyentes incluyen halo, hidroxilo, éter o amino. Grupos particularmente preferidos incluyen grupos metilmorfolino, grupos dimetilmorfolino y grupos metilpiperidinilo, por ejemplo:



Grupos más preferidos son morfolino o piperadinilo. Estos son preferiblemente sustituidos con uno o más alquilo sustituyentes, por ejemplo metilo o etilo sustituyentes. Más preferiblemente estos son sustituidos con uno o dos metilo sustituyentes. Si estos grupos llevan dos metilo sustituyentes, estos preferiblemente están sobre átomos separados de carbono. Grupos particularmente preferidos incluyen grupos metilmorfolino, grupos dimetilmorfolino o grupos metilpiperidinilo, por ejemplo:



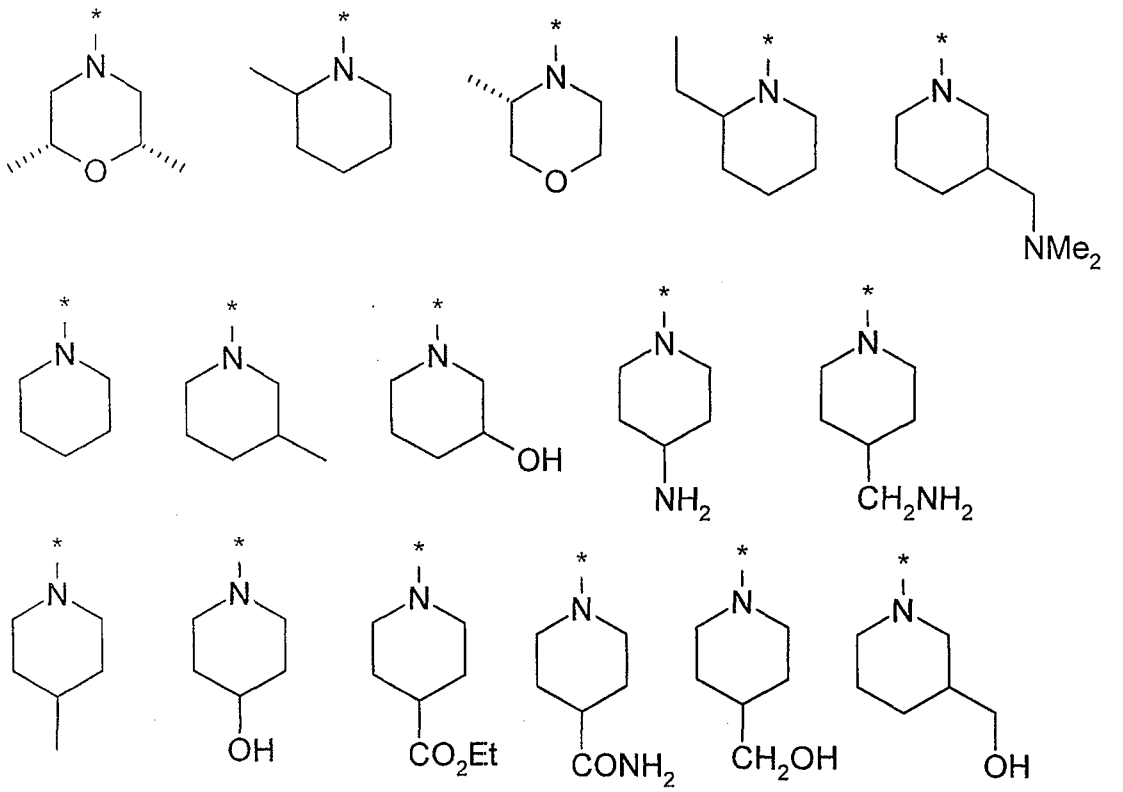
Grupos R2 preferidos son pirrolidinilo, morfolino, piperadinilo o homopiperadinilo. Grupos más preferidos son morfolino o piperadinilo. Estos preferiblemente son sustituidos con uno o más alquilo sustituyentes, por ejemplo metilo o etilo sustituyentes. Más preferiblemente estos son sustituidos con uno o dos metilo sustituyentes. Si estos grupos llevan dos metilo sustituyentes, estos preferiblemente están sobre átomos separados de carbono. Los alquilo sustituyentes también pueden ser opcionalmente sustituidos. Ejemplos de sustituyentes opcionales de los alquilo sustituyentes incluyen halo, hidroxilo, éter o amino. Grupos particularmente preferidos incluyen grupos metilmorfolino, grupos dimetilmorfolino o grupos metilpiperidinilo, por ejemplo:

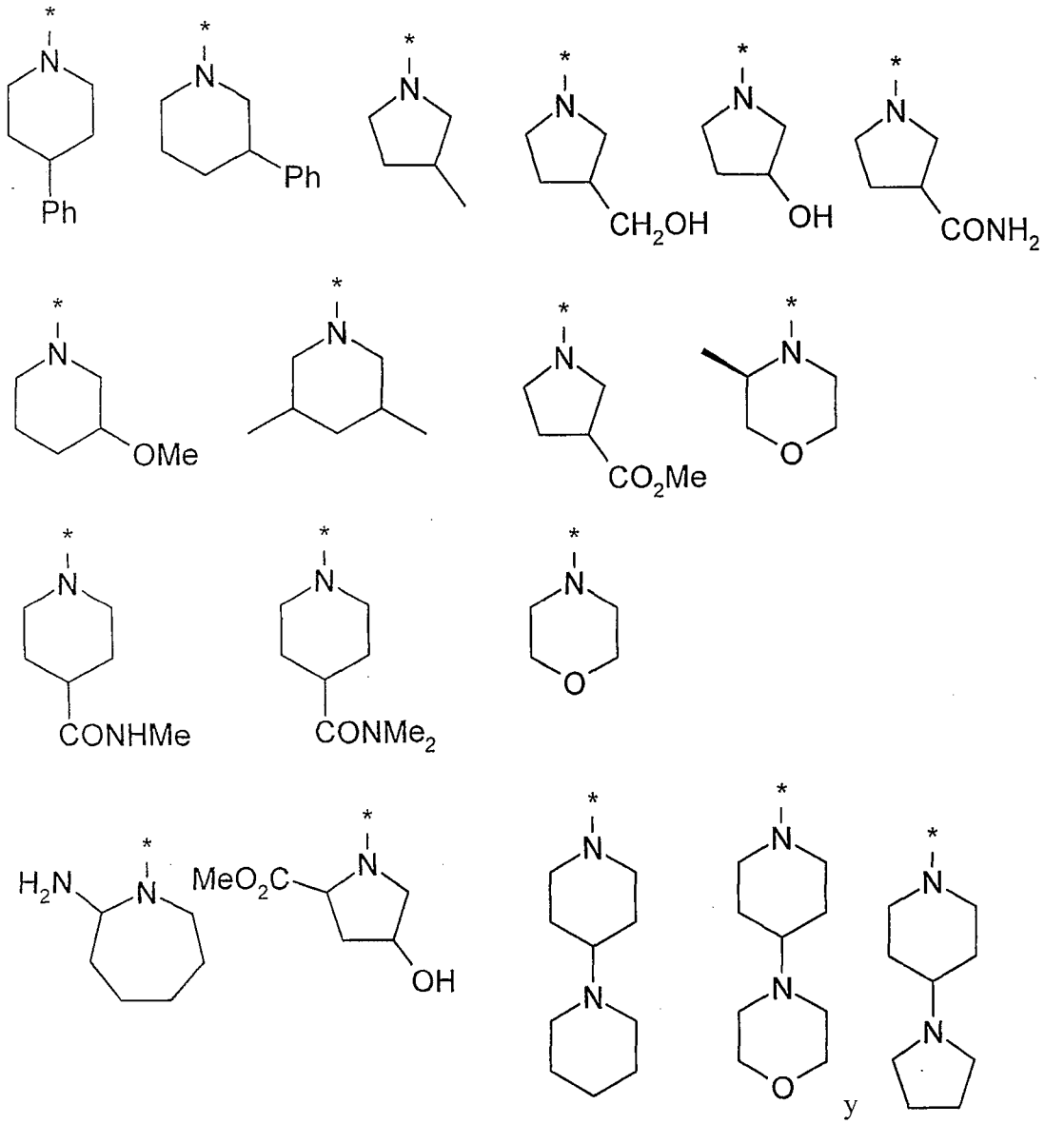


Grupos R^2 adicionalmente preferidos son pirrolidinilo, morfolino, piperadinilo y

homopiperadinilo opcionalmente sustutidos en donde los sustituyentes opcionales se seleccionan a partir de hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo $-NH_2$, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , amido (por ejemplo - $CONH_2$, - CONHC1- 7 alquilo, - CON(C1- 7alquil) $_2$) , éster (por ejemplo - C02C1- 7alquilo) , C6 arilo y el grupo heterociclilo de 3 a 7 miembros y en donde los grupos sustituyentes alquilo, alcoxilo, arilo o heterocililo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, - NH2, di- (C1- 7alquil) amino y C1- 7 alquilamino. Grupos más preferidos son morfolino, piperadinilo y homopiperadinilo los cuales se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de
hidroxilo, metilo, etilo, - $C0_2Me$, - $C0_2Et$, - CH_2OH, - CH_2Ome, - CH_2NMe_2, - $CONH_2$, - CONHMe, - $CONMe_2$, fenilo, pirrolidinilo, morfolino y piperadinilo.

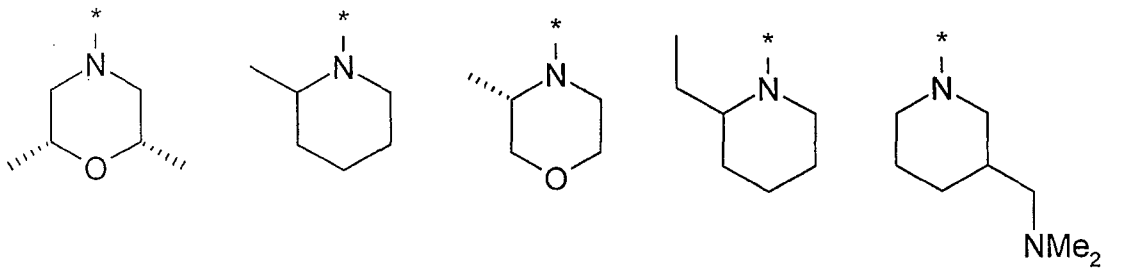
En una realización adicional del invento R^2 se selecciona a partir de

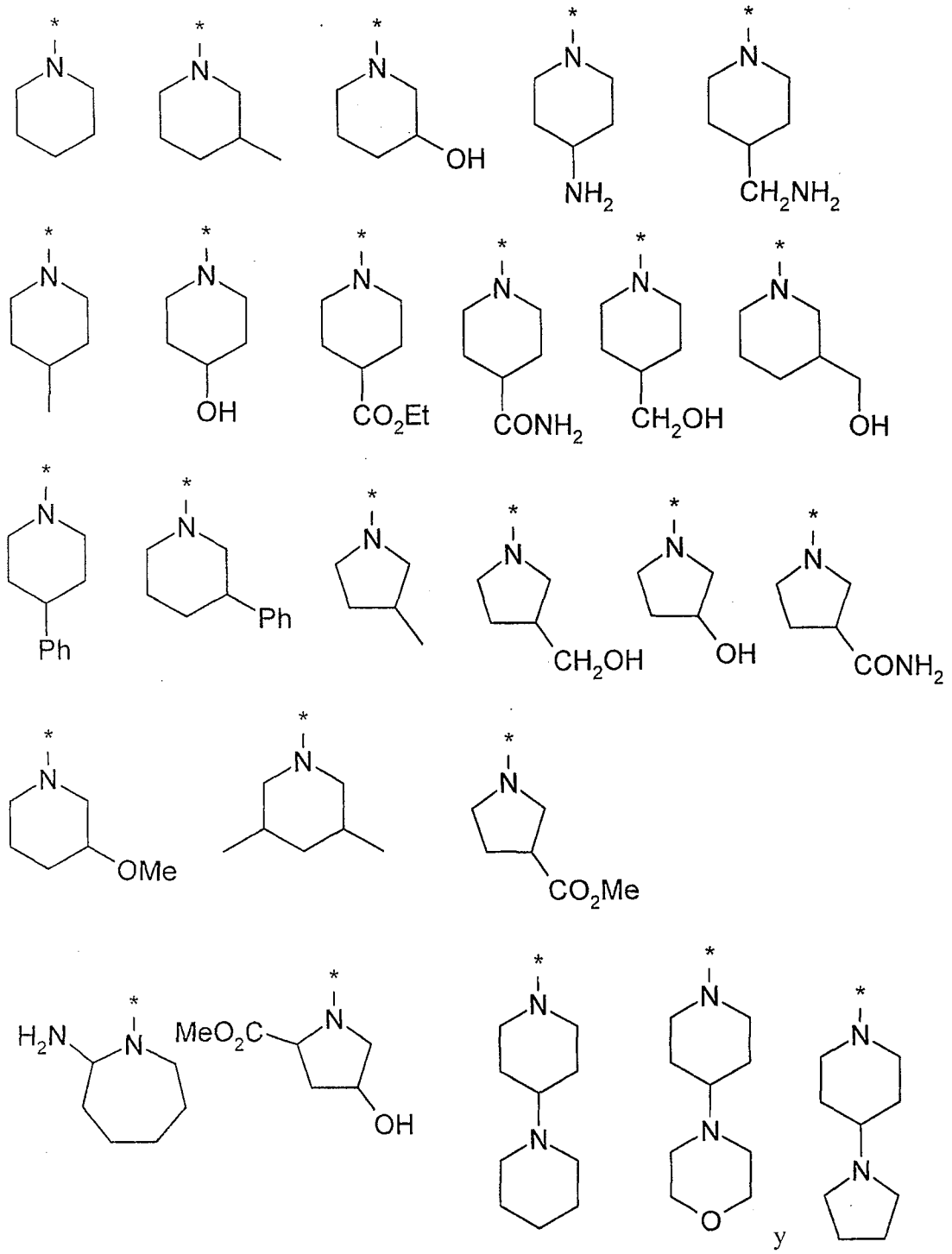




y

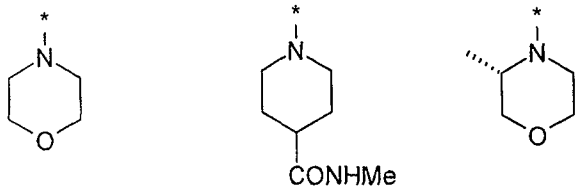
En una realización adicional del invento R^2 se selecciona a partir de



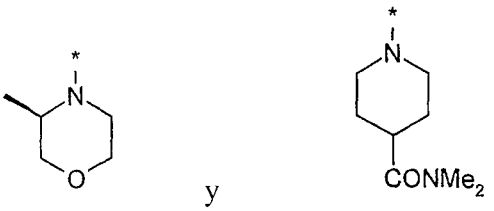


y

En una realización adicional del invento R^2 se selecciona a partir de



y



En una realización del invento, se proporciona un subgrupo de compuestos de la fórmula (I) o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N

R^7 se selecciona a partir de un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, OR^{01}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=0)$ R^{cl} y $NR^{N7b}S0_2R^{S2a}$; y

R^2 se selecciona a partir de OR^{02}, $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (I) o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 o X^8 es N;

R7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido de 5 o 6 miembros, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , o amido (por ejemplo - CONH2, - CONHC1- 7alquilo, - CON(C1- 7alquil) $_2$ Y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino y C1- 7 alquilamino; y

R2 se selecciona a partir de OR^{02}, $NR^{N5}R^{N6}$, un grupo C5- 6 heteroarilo opcionalmente

sustituido, y un grupo C6 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (I) o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N;

R^7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $CONH_2$, - CONH C1- 7 alquilo, - CON(C1- 7alquilo) $_2$ y - CONHheterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7alquilamino; y R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X5, X6 y X8 es N;

R^7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - CONH2, - CONH C1- 7 alquilo, - CON(C1- 7 alquilo) $_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7 alquilamino; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituidos) o pirrolidinilo opcionalmente sustituidos, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH3, - C(=0) OCH2CH3 y - C(=0) OC(CH3) 3, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización del invento, se proporciona un subgrupo de compuestos de fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N;

R7 se selecciona a partir de un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, OR^{01}, $NR^{N1}R^{N2}$, $NR^{N7a}C(=0)\ R^{cl}$ y $NR^{N7b}S02R^{S2a}$; y

R^2 se selecciona a partir de OR^{02}, $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X5, X6 o X8 es N;

R^7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH_2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $CONH_2$, - CONH C1- 7 alquilo, - CON(C1- 7alquilo) $_2$ o –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7 alquilamino; y R^2 se selecciona a partir de OR^{02},

$NR^{N5}R^{N6}$, un grupo C5- 6 heteroarilo opcionalmente sustituido, y un grupo C6 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 Y X^8 es N;

R^7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo $-NH_2$, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - $CONH_2$, - CONHC1- 7 alquilo, - CON(C1- 7alquilo) $_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7 alquilamino; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N;

R^7 es un grupo C5- 6 arilo opcionalmente sustituido o un grupo heteroarilo de 5 o 6 miembros opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - CONH2, - CONHC1- 7 alquilo, - CON(C1- 7alquil) $_2$ y –CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6arilo,

C5- 6 arilamino, di- (C1- 7alquil) amino o C1- 7alquilamino; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo opcionalmente sustituido imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituido) o pirrolidinilo, en donde N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH_3, - C(=0) OCH_2CH_3 o - C(=0) $OC(CH_3)_3$, o C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - OCH_2CH_3, - NH_2, - $NHSO_2CH_3$, - $CH_2NHSO_2CH_3$, - $OCHF_2$, - CH_2OH, - CO_2H, - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH(CH_3)_2$, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, ~$CONHCH_2CH_2OH$, - CONMeEt, - CONMe2, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de amino, ciano, halo, hidroxilo, éster, un anillo C3- 7 cicloalquilo, un anillo C6 carboarilo, un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde el anillo heterocíclico, el anillo cicloalquilo, el anillo carboarilo, los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino o C5- 6 aril) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales :

X^5 y X^6 son cada uno CH; X8 es N;

R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - OCH_2CH_3, - NH_2, - $NHS0_2CH_3$, - $CH_2NHS0_2CH_3$, - $OCHF_2$, - CH_2OH, - CO_2H, - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH(CH_3)_2$, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y

R2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo opcionalmente sustituido imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituido) o pirrolidinilo, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH_3, - C(=0) OCH_2CH_3 y - C(=0) $OC(CH_3)_3$, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de - NH2, fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - CH_2OH, - $C0_2H$ - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH_2CH_2F$, $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - CONMe2, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y

R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos forman grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituidos) o

pirrolidinilo, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH3, - C(=0) OCH_2CH_3 y - C(=0) $OC(CH3)_3$, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X6 son cada uno CH;

X8 es N;

R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de - NH_2, fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - CH_2OH, - $C0_2H$ - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - CONMe2, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo opcionalmente sustituido imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituidos) o pirrolidinilo, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH_3, - C(=0) OCH_2CH_3 y - C(=:0) $OC(CH_3)_3$, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

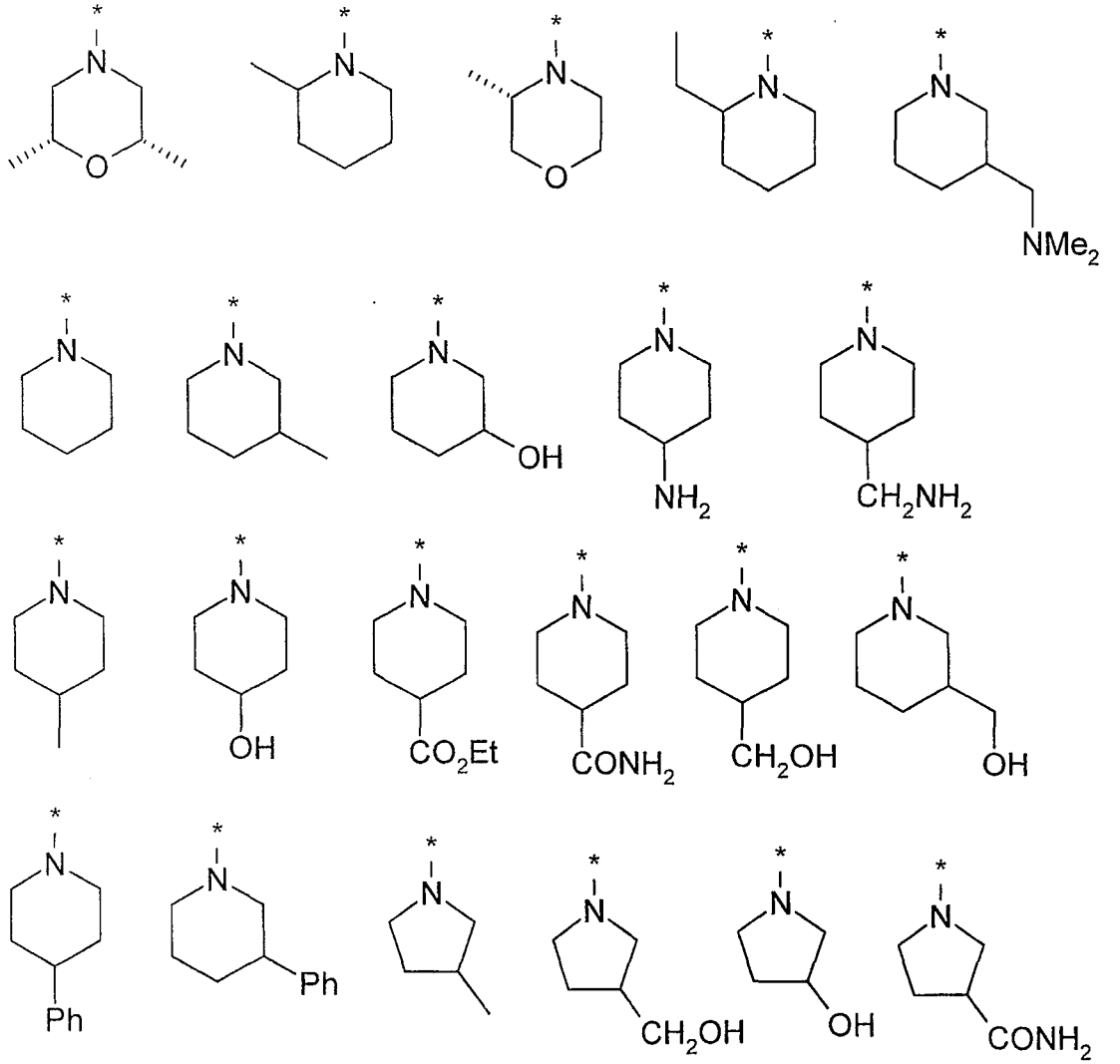
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

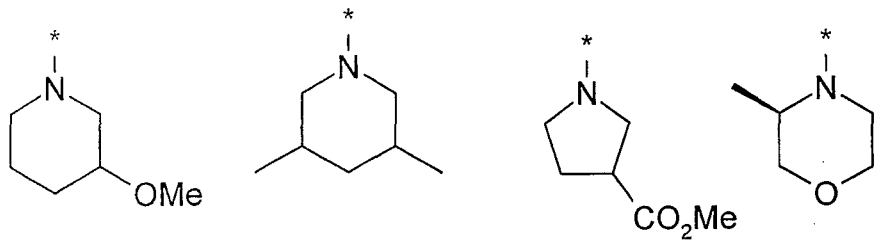
X^5 y X^6 son cada uno CH;

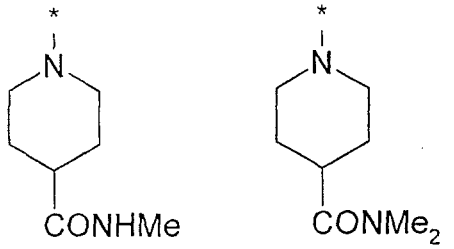
X^8 es N;

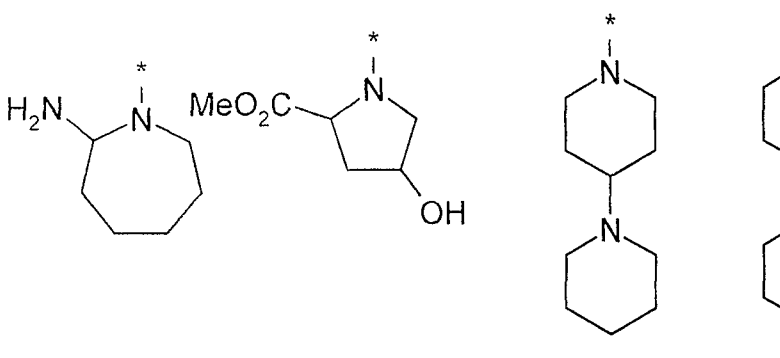
R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - OCH_2CH_3, - NH_2, - $NHS0_2CH_3$, - $CH_2NHS0_2CH_3$, - $OCHF_2$, - CH_2OH, - CO_2H, - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH(CH_3)_2$, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - CONMe2, N- metilpiperazinilcarbonilo y 4-hidroxipiperidinilcarbonilo; y

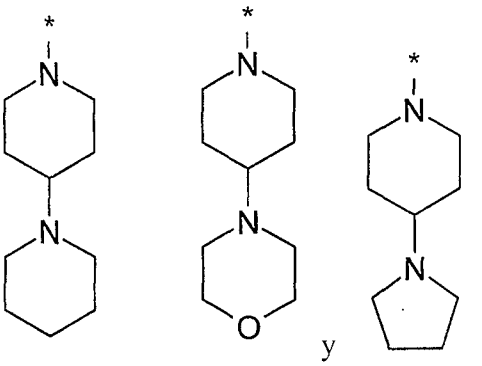
R^2 es un grupo seleccionado de











y

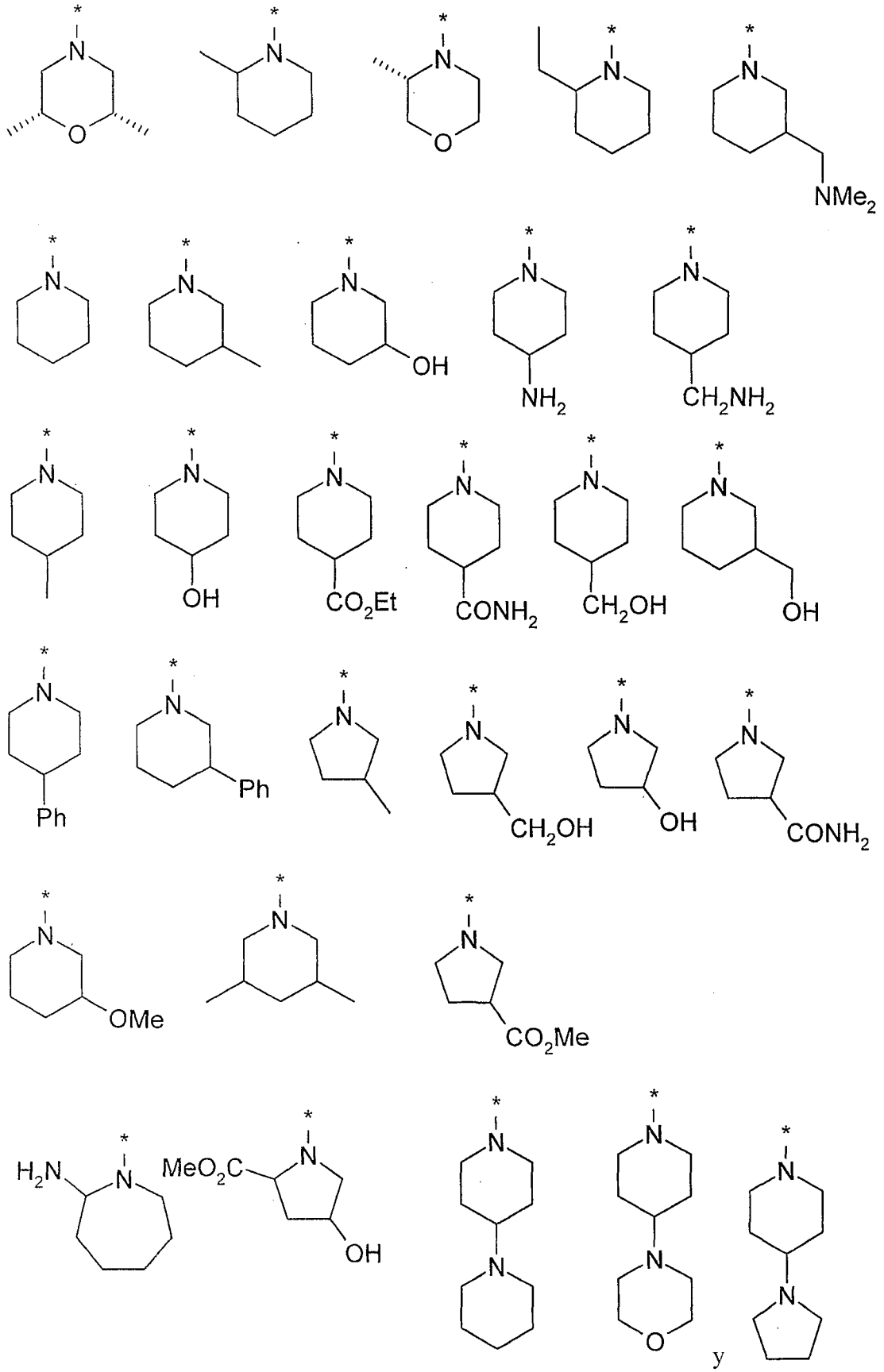
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) o (Ia) . y sales farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de - NH2, fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - CH_2OH, - $C0_2H$ - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y

R^2 es un grupo seleccionado de


NMe2
OH
NH2
CH2NH2
OH
CO2Et
CONH2
CH2OH
OH
Ph
Ph
CH2OH
OH
CONH2
OMe
CO2Me
H2N
MeO2C
OH

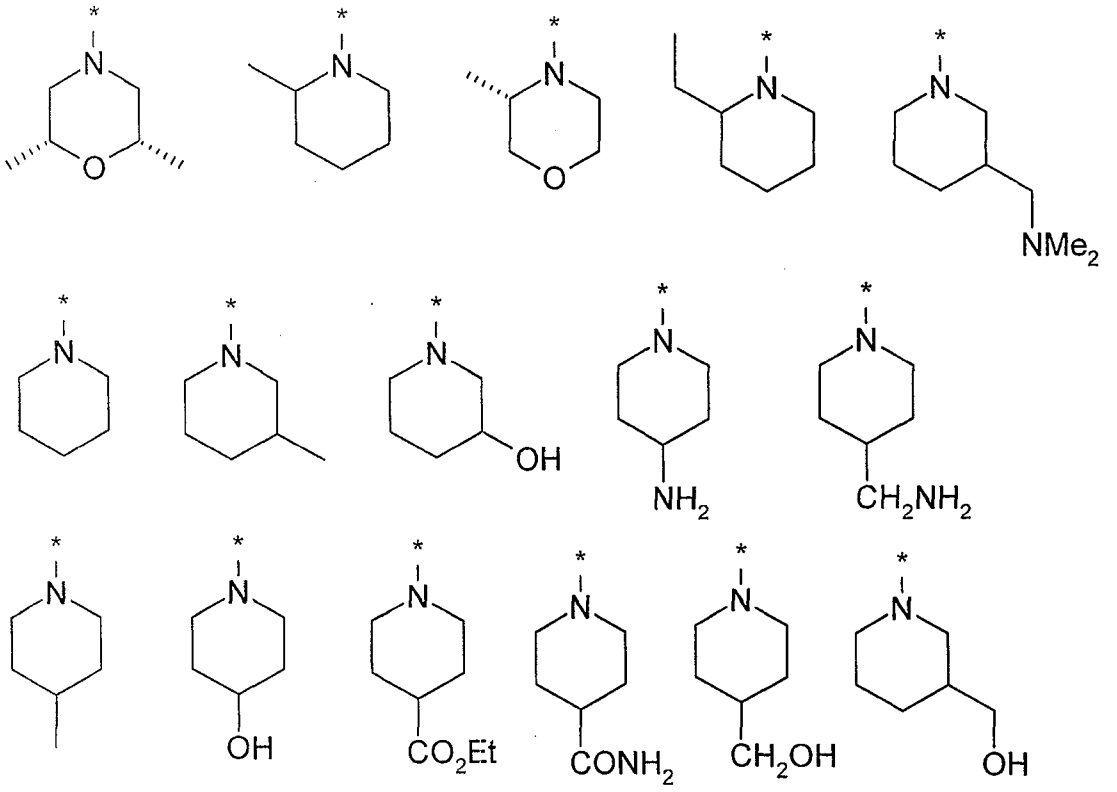
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) . (la) o (lb) . y una sal farmacéuticamente aceptable de los mismos, en los cuales:

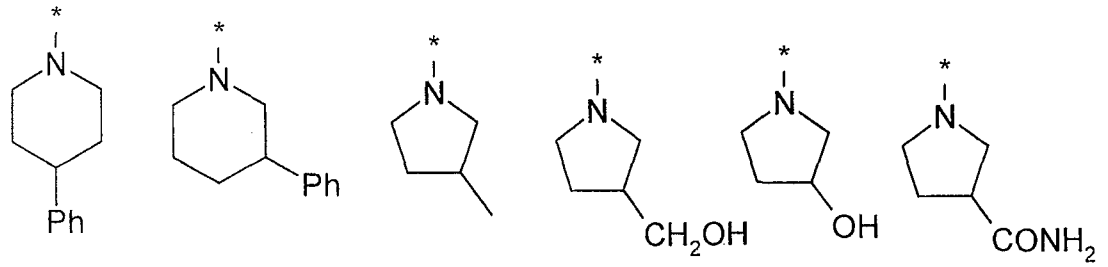
X^5 y X^6 son cada uno CH;

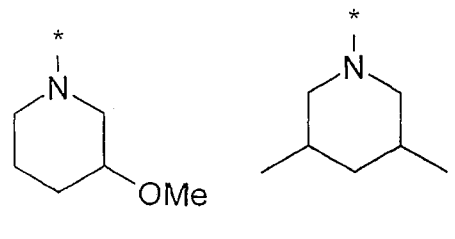
X^8 esN;

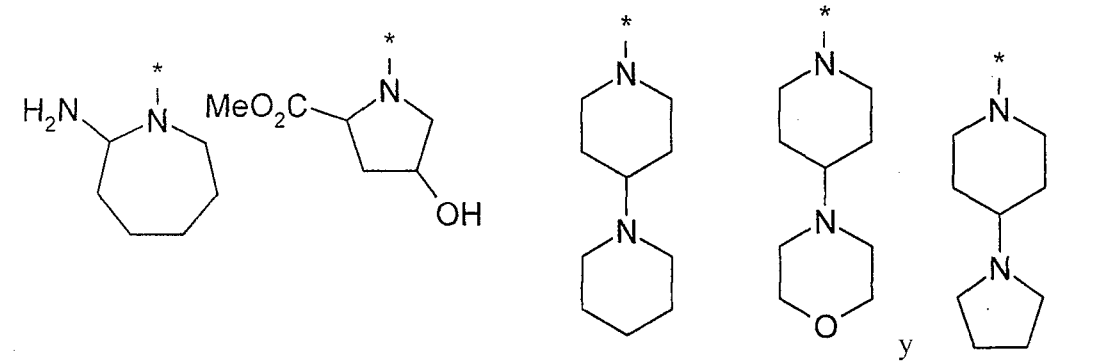
R^7 es un grupo fenilo o piridinilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de - NH_2, fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - CH_2OH, - $C0_2H$ - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo; y

R^2 es un grupo seleccionado de









y

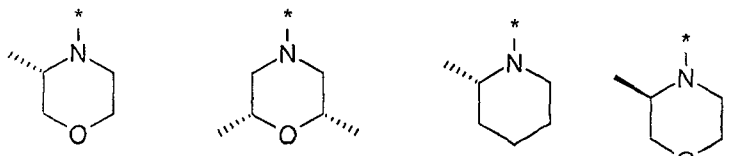
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I), (Ia) o (Ib), y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es grupo 4- clorofenilo, 4- metilfenilo, 4- metoxifenilo, 3- hidroximetil- 4- metoxifenilo. 3,5- dimetoxi- 4- hidroxifenilo, 4- hidroxifenilo, 3- hidroxifenilo o un grupo 3-hidroximetilfenilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos



forman un grupo o o o .

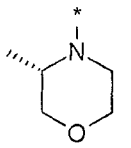
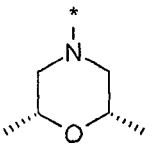
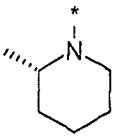
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I)

o (la) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH; X^8 es N;

R^7 es un grupo 4- clorofenilo, 4- metilfenilo, 4- metoxifenilo, 3- hidroximetil- 4- metoxi-fenilo, 3,5- dimetoxi- 4- hidroxifenilo, 4- hidroxifenilo, 3- hidroxifenilo o un grupo 3-hidroximetilfenilo; y

R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos

Forman un grupo  o  o 

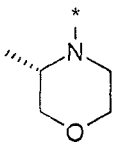
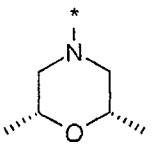
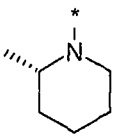
En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es un grupo 4- clorofenilo, 4- metilfenilo, 4- metoxifenilo, 3- hidroximetil- 4- metoxi-fenilo, 3,5- dimetoxi- 4- hidroxifenilo, 4- hidroxifenilo, 3- hidroxifenilo o un grupo 3-hidroximefhilfenilo; y

R2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos

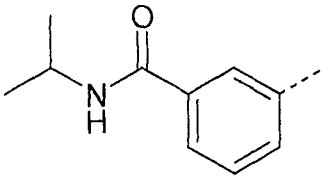
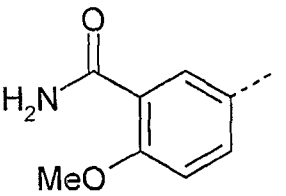
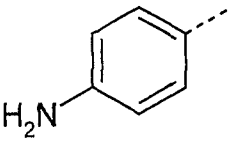
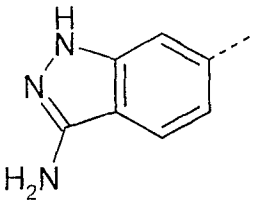
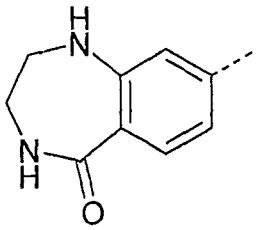
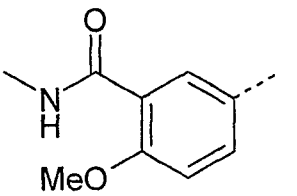
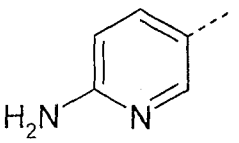
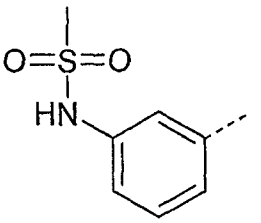
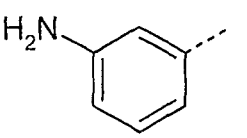
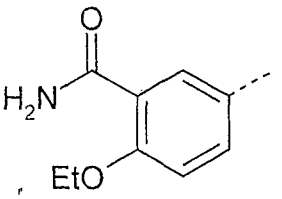
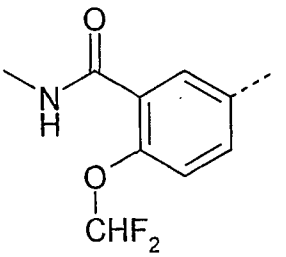
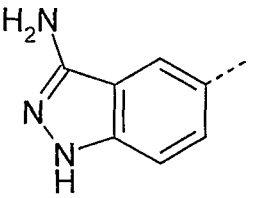
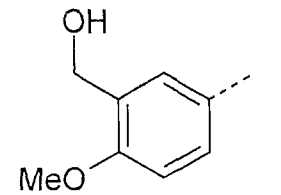
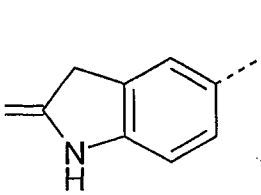
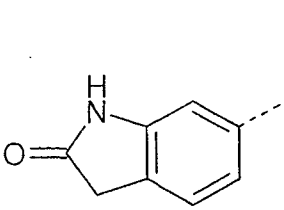
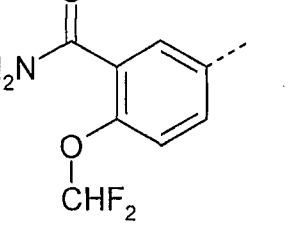
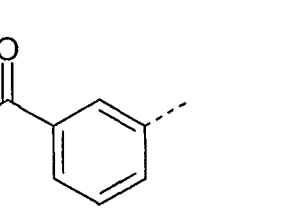
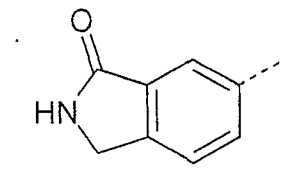
forman un grupo  o  o 

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (I) , (la) o (lb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

R^7 es un grupo

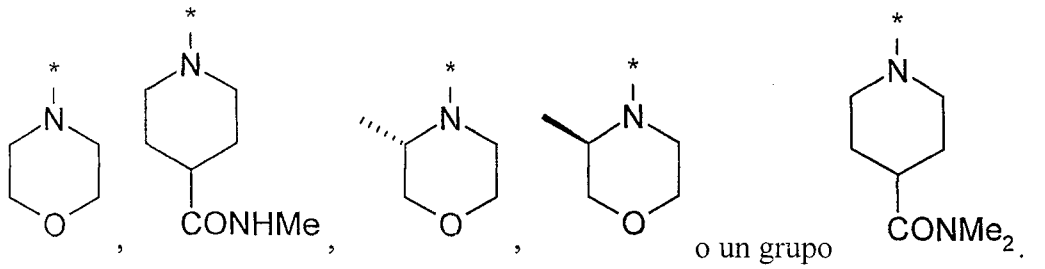

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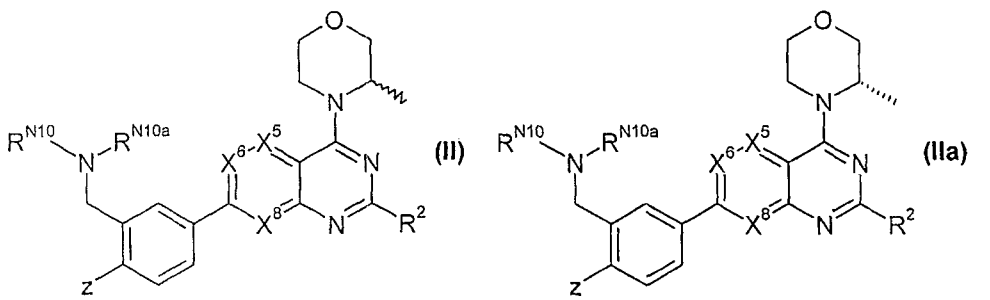
o

; y

R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos forman un grupo



En una realización del invento, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y una sal farmacéuticamente aceptable de los mismos,



en donde:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{03};

RN^{10} se selecciona a partir de hidrógeno, C(0) R^{C2}, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente sustituido y donde R^{C2} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{N11} y R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o R^{N10} y RN^{10a} junto con el nitrógeno al cual están unidos forman un anillo

heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{03} es un grupo C1- 6 alquilo opcionalmente sustituido; y

R^2 se selecciona a partir de $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido.

En otra realización. se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{O3}

R^{N10} es seleccionado de hidrógeno, C(0) R^{C2}, un grupo C5- 6 heteroarilo opcionalmente sustituido. un grupo C6 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente sustituido donde R^{C2} se seleccionan a partir de CH_3 o CH_2OH donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino; o

R^{N10} o R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino;

R^{O3} es un un grupo C1- 3 alquilo no sustituido; y

R^2 se selecciona a partir de $NR^{N5}R^{N6}$, un grupo C5- 6 heteroarilo opcionalmente sustituido, o un grupo C6 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ;

RN^{10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH; Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ; R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo; R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un

grupo imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituidos) o pirrolidinilo, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH_3, - C(=0) OCH_2CH_3 y - C(=0) OC(CH3) 3, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, cicloproilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol;

R^{N10a} es hidrógeno; o

R^{N10} y RN10a junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo; R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo morfolino, tiomorfolino, piperidinilo, homopiperidinilo, piperazinilo (preferiblemente N- sustituidos) , homopiperazinilo (preferiblemente N- sustituido) o pirrolidinilo, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, o C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) . En una realización adicional, se proporciona un subgrupo de

compuestos de la fórmula (II) o (IIa) , y una sal farmacéuticamente aceptable de los mismos, en los cuales: X^5 y X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

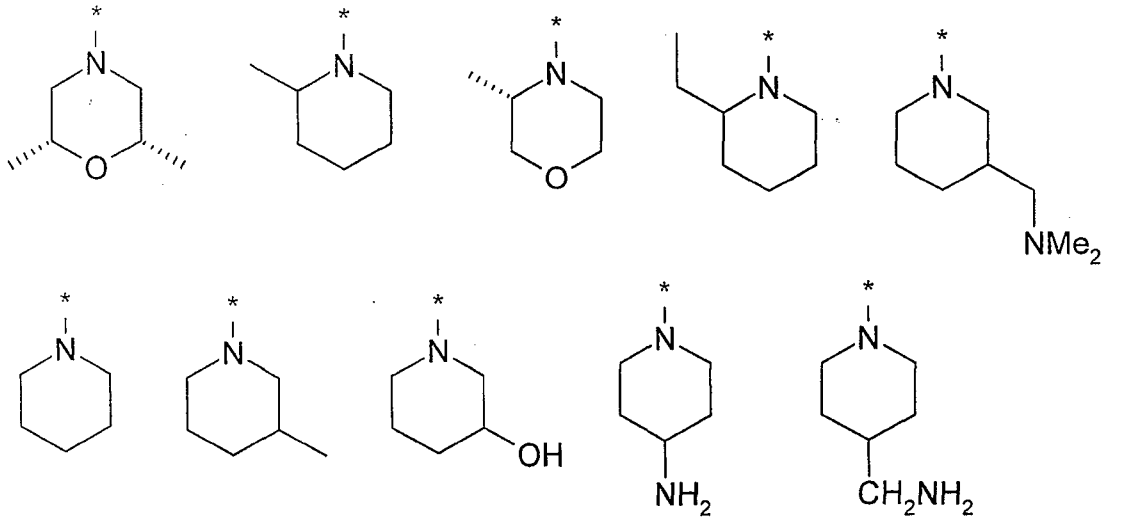
R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol;

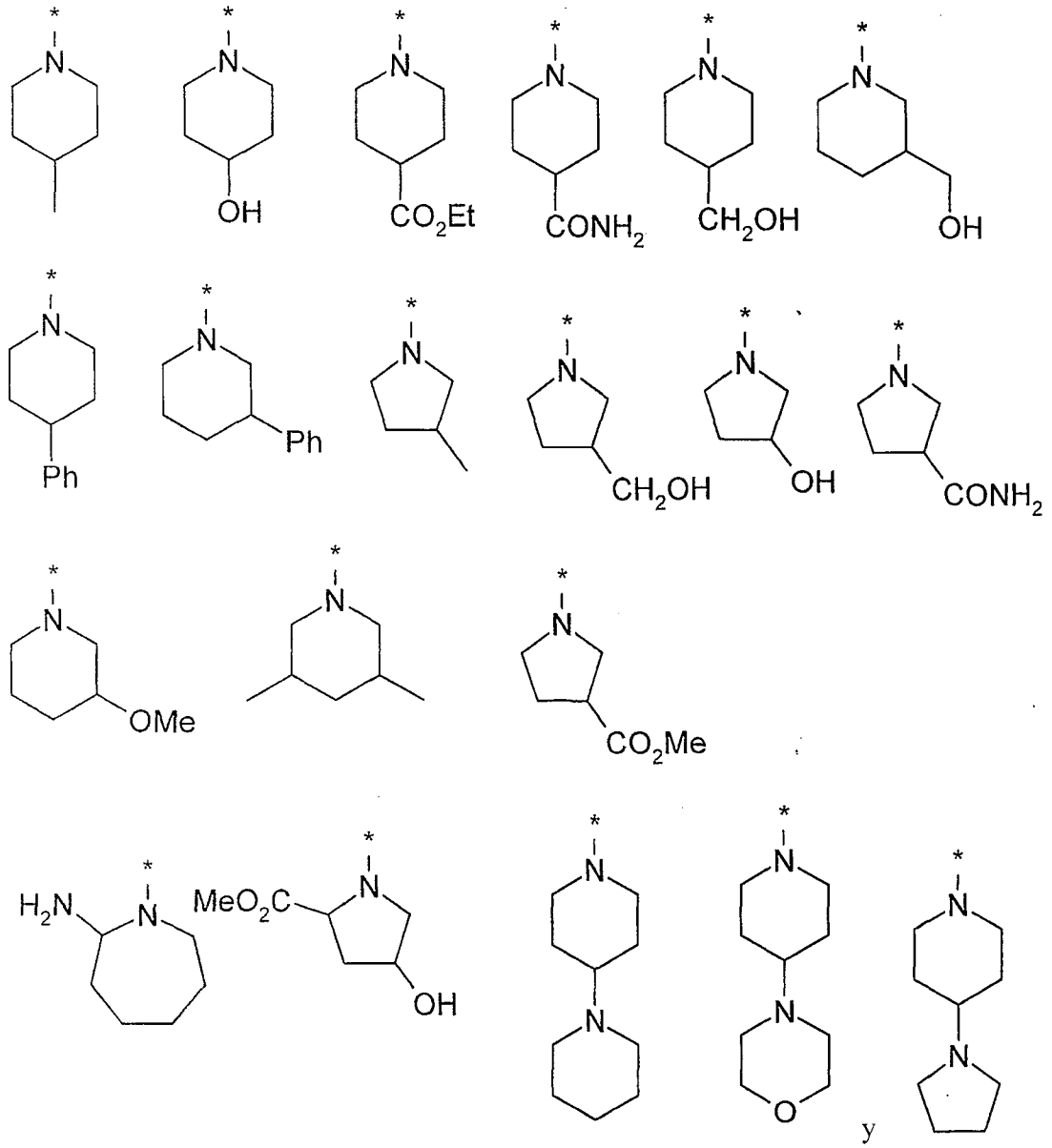
R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es un grupo seleccionado de





y

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 o X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

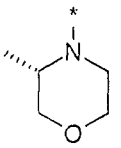
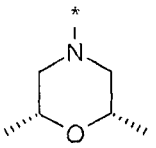
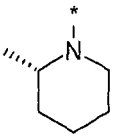
R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, -

CH2imidazol ; RN10a es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman anillo heterocíclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; o

R^2 es $NR^{N5}R^{N6}$ donde RN5 y RN6 junto con el nitrógeno al cual están unidos forman un


grupo

o

o .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) o (IIa) . y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

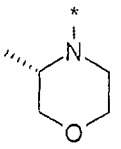
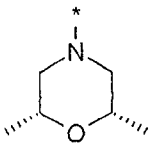
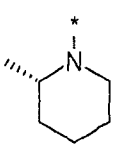
X^8 es N; Z es H, F o OR^{O3}

R^{N10} es seleccionado de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3,- CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe5 - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol; R^{N10a} es hidrógeno; o

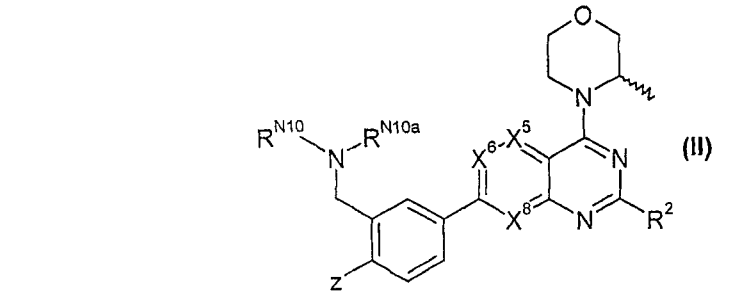
R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

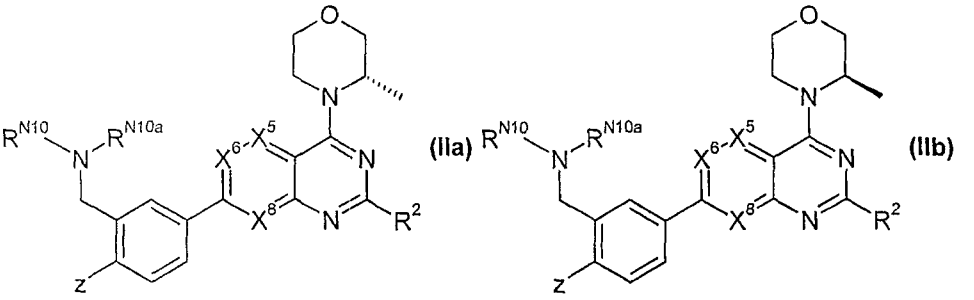
R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un


grupo

o

o .

En una realización del invento, se proporciona un subgrupo de compuestos de la fórmula (I) , (Ia) o (Ib) en donde el compuesto es un compuesto de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptable de los mismos,





en donde:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{O3};

R^{N10} se selecciona a partir de hidrógeno, C(0) R^{C2}, un grupo C5- 20 heteroarilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente sustituido donde R^{C2} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{N11} y R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o R^{N10} y RN10a junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{O3} es un grupo C1- 6 alquilo opcionalmente sustituido; y

R^2 se selecciona a partir de $NR^{N5}R^{N6}$, un grupo C5- 20 heteroarilo opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{O3}

RN10 se selecciona de hidrógeno, C(0) R^{C2}, un grupo C5- 6 heteroarilo opcionalmente sustituido, un grupo C6 arilo opcionalmente sustituido, o un grupo C1- 10 alquilo opcionalmente sustituido donde RC2 se seleccionan a partir de CH_3 o CH_2OH donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7alquilamino o di- C 1- 7alquilamino;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, C1- 7 alquiloxilo, C1- 7 alquilamino y di- C1- 7 alquilamino;

R^{O3} es un un grupo C1- 3 alquilo no sustituido; y

R^2 se selecciona a partir de $NR^{N5}R^{N6}$, un grupo C5- 6 heteroarilo opcionalmente sustituido, y un grupo C6 arilo opcionalmente sustituido.

En otra realización, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH_3, - C(0) CH2OH, - CH3, - CH2CH3, -

CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ;

R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 5 y 7 átomos cíclicos los cuales pueden opcionalmente ser sustituidos, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, y C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

solamente uno entre X^5, X^6 y X^8 es N, y los demás son CH;

Z es H, F o ORO^3

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol;

R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo opcionalmente sustituido imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo (preferiblemente N- sustituido) , homopiperazinilo (preferiblemente N- sustituido) o pirrolidinilo, en donde los N- sustituyentes opcionales sobre los grupos piperazinilo y homopiperazinilo incluyen grupos C1- 7 alquilo o ésteres, en particular, ésteres que llevan un grupo C1- 7 alquilo como un sustituyente de éster, ej. - C(=0) OCH3, - C(=0) OCH2CH3 o - C(=0) OC(CH3) 3, y C- sustituyentes opcionales para los grupos imidazolilo, morfolino, tiomorfolino, piperadinilo, homopiperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo incluyen fenilo, éster, amida y C1- 4 alquilo, preferiblemente metilo, aminometilo, hidroximetilo o hidroxietilo.

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y una sal farmacéuticamente aceptable de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH. - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopenril, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol;

RN^{10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un grupo opcionalmente sustituido morfolino, tiomorfolino, piperidinilo, homopiperidinilo, piperazinilo (preferiblemente N- sustituido) , homopiperazinilo (preferiblemente N- sustituido) o

grupo pirrolidinilo, en donde los sustituyentes opcionales se seleccionan a partir de ciano, halo, hidroxilo, o C1- 7 alquilo saturado y C1- 7 alcoxilo saturado (en donde los grupos alquilo y alcoxilo saturados se pueden opcionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alcoxilo, amino y C5- 6 arilo) .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

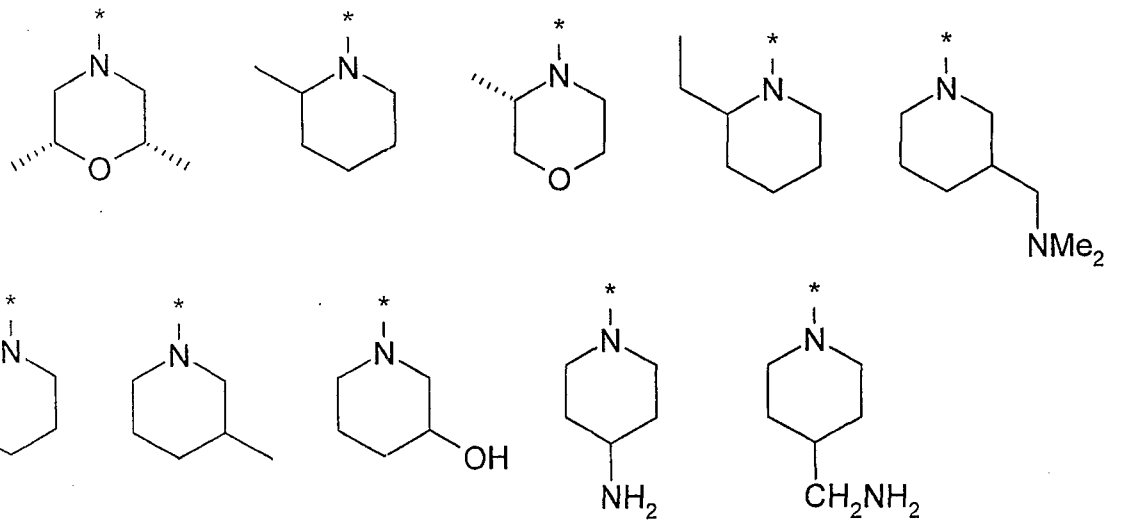
Z es H, F o OR^{O3}

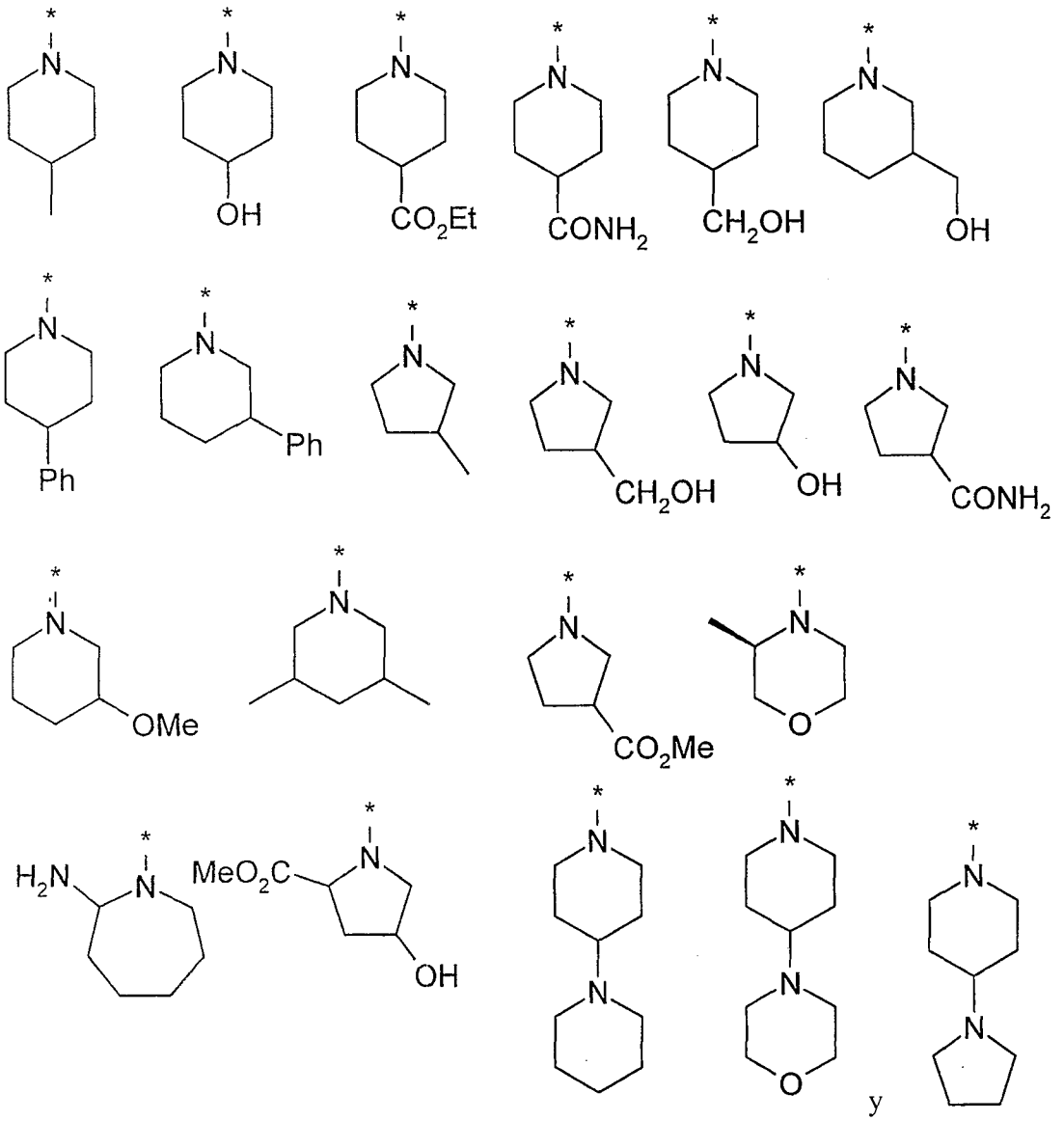
R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ; RN10a es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es un grupo seleccionado de





y

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

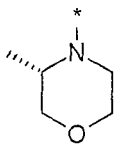
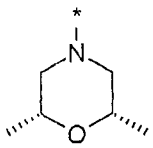
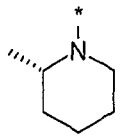
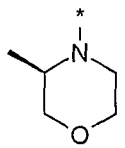
R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH^ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH_2imidazol;

R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; o

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos

forman un grupo  o  o  o  .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

X^8 es N;

Z es H, F o OR^{O3}

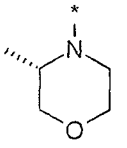
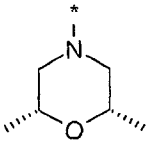
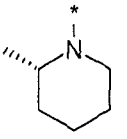
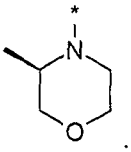
R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ;

R^{N10a} es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos

forman un grupo  o  o  o  .

En una realización adicional, se proporciona un subgrupo de compuestos de la fórmula (II) , (IIa) o (IIb) , y sales farmacéuticamente aceptables de los mismos, en los cuales:

X^5 y X^6 son cada uno CH;

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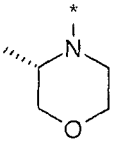
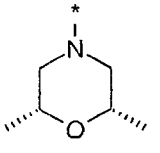
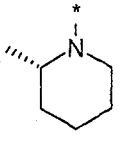
Z es H, F o OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH3, - C(0) CH2OH, - CH3, - CH2CH3, - CH2CH2OH, - CH(CH3) 2, - CH2CH2OMe, - CH2C(CH3) 2, - CH2CH2C(CH3) 2, - CH(CH3) CH2C(CH3) 2, - CH2CH2CH2N(CH3) 2, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH2ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH2imidazol ; RN10a es hidrógeno; o

R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heteroríclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos, donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7 alquiloxilo;

R^{O3} es un grupo metilo; y

R^2 es $NR^{N5}R^{N6}$ donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos

forman un grupo  o  o  .

En otro aspecto del invento, se proporciona un compuesto, o una sal farmacéutica del mismo, seleccionado de cualquiera de los Ejemplos.

En un aspecto adicional del invento, se proporciona un compuesto, o una sal farmacéutica del mismo, seleccionado de Ejemplos Ibu, Ice, 12b, 18de, 18dg, 18j, lar, 19e, 19h, 19i, 191, 19m, 19n, 19o, 18n, 18°, 18z, 18aa, 18ag, 18ai, 18al, lv, 18az, lah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, law, 3u, lbf, 18ct, 19q, 19s, 19u, 19v, 19w, lau, 5r, 4t, 18dj, lcl, 2d, 2e, lcs, 2h, 2j, lew, lbo, lbp, lj, lbx, lby, lef, lei, lcj, 4an, 4ap, 4av,

12d, 18dh, 18di, 6a, En, lp, lq, 18e, 18h, 19b, 19c, 19f, 19k, 18p, lbd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, lab, 4p, 9a, lav, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, lam, lao, 18cn, 18cx, lbk, 13b, 4g, 5s, 4q, 18dd, lep, lcq, 2f, 2g, 13g, lev, let, lb, la, lc, Id, lbl, lbm, Si, li, lg, lh, lbr, lbs, lbv, le, lbz, lec, lk, leg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12ª, 18ª, las, Es, 18c, 18d, 18f, 18g,18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, lba, 8a, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41, 4m, 4n, 4o, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4ª, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, lco, 3ad, lcr, lew, ley, ldv, 15c, lcl, 1cm, len, lcq, lev, lex, ldi, ldj, leb, lcj, lck, let, leu, lcz, ldb, ldc, ldd, lde, ldg, ldh, ldk, ldl, 1dm, ldn, ldo, ldp, ldq, ldt, ldu, ldw, ldy, ldz, lea, lee, led, lee, 18dm, 18dn y 18do.

En un aspecto adicional del invento, se proporciona un compuesto, o una sal farmacéutica del mismo, seleccionado de los Ejemplos lbo, lbp, lj, lbx, lby, lef, lei, lcj, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, En, lp, lq, 18e, 18h, 19b, 19c, 19f, 19k, 18p, lbd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, lab, 4p, 9ª, lav, 3ª, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, lam, lao, 18cn, 18cx, lbk, 13b, 4g, 5s, 4q, 18dd, lep, lcq, 2f, 2g, 13g, lev, let, lb, la, lc, Id, lbl, lbm, Si, li, lg, lh, lbr, lbs, lbv, le, lbz, Ice, Ik, leg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12ª, 18ª, las, Es, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, lba, 8ª, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41, 4m, 4n, 4º, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5ª, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4ª, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, lco, 3ad, lcl, 1cm, lcn, lcq, lev, lex, ldi, ldj, leb, lcj, lck, let, leu, lcz, ldb, ldc, ldd, lde, ldg, ldh, ldk, ldl, 1dm, ldn, ldo, ldp, ldq, ldt, ldu, ldw, ldy, ldz, lea, lee, led, lee, 18dm, 18dn y 18do.

En un aspecto adicional del invento, se proporciona un compuesto, o una sal farmacéutica del mismo, seleccionado de los Ejemplos lb, la, lc, Id, lbl, lbm, Si, li, lg, lh, lbr, lbs, lbv, le, lbz, lec, lk, leg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf,

12c, 12ª, 18ª, las, Es, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, lba, 8ª, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41, 4m, 4n, 4°, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5ª, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4ª, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, lco, 3ad, lcj, lck, let, leu, lcz, ldb, ldc, ldd, lde, ldg, ldh, ldk, ldl, 1dm, ldn, ldo, ldp, ldq, ldt, ldu, ldw, ldy, ldz, lea, lee, led, lee, 18dm, 18dn y 18do.

En un aspecto adicional del invento, se proporciona un compuesto, o una sal farmacéutica del mismo, seleccionado de los Ejemplos la, lu, lal, lap, lat, laz, lco, lde, ldg, ldh, ldk, ldl, ldp, ldq, ldr, lds, ldt, ldu, ldy, lee, lee, 12d, 14b, 18dn o 18do.

Incluye Otras formas

Incluidas en las anteriores están las conocidas formas iónicas, de sal, solvatadas, o protegidas de estos sustituyentes. Por ejemplo, una referencia a ácido carboxílico (- COOH) también incluye la forma aniónica (carboxilato) (- COO^-) ,una sal o solvato del mismo, así como también formas protegidas convencionales. De manera similar, una referencia a un grupo amino incluye la forma protonada (- $N^+HR^1R^2$) , una sal o solvato del grupo amino, por ejemplo, una sal de hidrocloruro, así como también formas protegidas convencionales de un grupo amino. De manera similar, una referencia a un grupo hidroxilo también incluye la forma aniónica (- O^-) ,una sal o solvato del mismo, así como también formas protegidas convencionales de un grupo hidroxilo.

Isómeros, Sales, Solvatos, Formas Protegidas, y Profármacos

Ciertos compuestos pueden existir en una o más formas geométrica, óptica, enantiomérica, diastereomérica, epimérica, estereoisomérica, tautomérica, conformacional, o anomérica particulares, incluyendo pero sin limitar a, formas cis- o trans- ; formas E- y Z- ; formas *c-* , *t-* , *y r-* ; formas *endo-* y *exo-* ; formas R- , S- , y *meso-* ; formas *D-* y *L-* ; formas *d-* y *l*; formas (+) y (-) ; formas ceto- , enol- , o enolato; formas syn- y anti; formas sinclinales- y anticlinales; formas α- y β- ; formas axiales y equatoriales; formas en bote, silla, *twist*, sobre, y silla media; o combinaciones de las mismas, de aquí en adelante colectivamente conocidas como

"isómeros" (o "formas isoméricas") .

Si el compuesto está en forma cristalina, éste puede existir en una número de formas polimórficas diferentes. Por ejemplo, la se aisló como Forma A: 2- Teta° 6.9 (46%) , 8.53 (100%) , 10.1 (21%) , 10.86 (24%) , 11.65 (11%) , 13.31 (14%) , 13.75 (7%) , 14.37 (54%) , 15.21 (5%) , 16.19 (13%) , 16.81 (39%) , 17.19 (40%) , 17.97 (21%) , 18.41 (65%) , 18.78 (80%) , 20.66 (8%) , 21.07 (89%) , 22.05 (19%) , 22.36 (42%) , 24 (7%) , 24.36 (33%) , 25.25 (31%) , 25.54 (16%) , 26.92 (18%) , 27.26 (8%) , 28.03 (8%) , 28.39 (21%) , 29 (8%) , 29.91 (13%) , 30.62 (23%) , 31.48 (9%) , 32.72 (5%) , 33.27 (11%) , 34.88 (4%) , 35.48 (5%) , 36.16 (4%) , 36.88 (4%) , 37.37 (4%) , 37.91 (6%) , 38.65 (4%) y 39.83 (4%) . Una forma menos estable, Forma B, también se ha aislado a partir de agua / THF: 2- Teta° 3.67 (7%) , 7.28 (7%) , 8.52 (7%) , 9.22 (30%) , 11.42 (78%) , 12.69 (24%) , 13 (15%) , 13.41 (44%) , 13.6 (26%) , 14.51 (19%) , 15.56 (13%) , 16.25 (9%) , 17.11 (13%) , 17.55 (18%) , 18.24(64%) , 18.59(56%) , 19.51 (33%) , 19.85 (26%) , 20.32 (13%) , 21.49 (17%) , 21.79 (13%) , 22.23 (18%) , 22.84 (26%) , 23.72 (23%) , 25.46 (74%) , 26.1 (100%) , 26.72 (43%) , 27.94 (16%) , 28.35 (8%) , 34.74 (10%) , 35.34 (6%) , 36.72 (9%) o 38.55 (4%) .

Notar que, excepto como se discute más adelante para formas tautoméricas, especificamente excluidas del término "isómeros", como se utiliza en la presente, son isómeros estructurales (o constitucionales) (es decir isómeros que difieren en las conexiones entre átomos más que unicamente por la posición de los átomos en el espacio) . Por ejemplo, una referencia a un grupo metoxilo, - OCH_3, no se debe entender como una referencia a su isómero estructural, un grupo hidroximetilo, - CH_2OH. De manera similar, una referencia a orto- clorofenilo no se debe entender como una referencia a su isómero estructural, meta- clorofenilo. Sin embargo, una referencia a una clase de estructuras puede bien incluir formas estructuralmente isoméricas que caen dentro de esa clase (ej., C1- 7 alquilo incluye n- propilo y iso- propilo; butilo incluye n- , iso- , sec- , y tert- butilo; metoxifenilo incluye orto- , meta- , y para- metoxifenilo) .

La anterior exclusión no se refiere a formas tautoméricas, por ejemplo, formas ceto- , enol- , o enolato- , como en, por ejemplo, los siguientes pares tautoméricos: ceto/enol, imina/enamina, amida/imino alcohol, amidina/amidina, nitrosy/oxima, tiocetona/enetiol, N- nitroso/hiroxiazo, y nitro/aci- nitro.

Notar que especificamente incluidos en el término "isómero" están los compuestos con

una o más sustituciones isotópicas. Por ejemplo, H puede estar en cualquier forma isotópica, incluyendo ^{1}H, ^{2}H (D) , y ^{3}H (T) ; C puede estar en cualquier forma isotópica, incluyendo ^{12}C, ^{13}C, y ^{14}C; O puede estar en cualquier forma isotópica, incluyendo ^{16}o y ^{18}o; y similares.

A menos que se especifique lo contrario, una referencia a un compuesto particular incluye todas estas formas isoméricas, incluyendo mezclas (completa o parcialmente) racémicas u otras mezclas de las mismas. Métodos para la preparación (ej. síntesis asimétrica) o separación (ej. cristalización fraccional y medios cromatográficos) de tales formas isoméricas son bien sea conocidos en en el estado de la técnica o son facilmente obtenidos al adaptar los métodos enseñados en la presente, o métodos conocidos, en una forma conocida.

A menos que se especifique lo contrario, una referencia a un compuesto particular también incluye formas iónicas, de sal, solvatos, y protegidas del mismo, por ejemplo, como se discute a continuación, así como también sus formas polimórficas diferentes.

Puede ser conveniente o deseable preparar, purificar, y/o manipular una sal correspondiente del compuesto activo, por ejemplo, una sal farmacéuticamente aceptable. Ejemplos de sales farmacéuticamente aceptables se discuten en ref. 25.

Por ejemplo, si el compuesto es aniónico, o tiene un grupo funcional el cual puede ser aniónico (ej., - COOH puede ser - COO^{-}) , entonces una sal se puede formar con un catión apropiado. Ejemplos de cationes inórganicos apropiados incluyen, pero no están limitados a, iones de métales alcalinos tales como Na^{+} y K^{+}, cationes alcalinoterreos tales como $C^{a2}+$ y Mg^{2+}, y otros cationes tales como Al^{3+}. Ejemplos de cationes orgánicos apropiados incluyen, pero no están limitados a, ión de amonio (es decir, NH_4^{+}) y iones de amonio sustituidos (ej., NH_3R^{+}, NH_2R^{2} , NHR_3^{+}, NR_4^{+}) . Ejemplos de algunos iones de amonio sustituidos apropiados son aquellos derivados de: etilamina, dietilamina, diciclohexilamina, trietilamina, butilamina, etilendiamina, etanolamina, dietanolamina, piperazina, bencilamina, fenilbencilamina, colina, meglumina, trometamina, así como también aminoácidos, tales como lisina y arginina. Un ejemplo de un ión cuaternario común de amonio es $N(CH_3)_4^{+}$.

Si el compuesto es catiónico, o tiene un grupo funcional el cual puede ser catiónico (ej., - NH_2 puede ser - NH_3^{+}) , entonces una sal se puede formar con un anión apropiado. Ejemplos de aniones inórganicos apropiados incluyen, pero no están limitados a, aquellos derivados de los siguientes ácidos inorgánicos: clorhídrico, hidrobrómico, hidroyódico, sulfúrico, sulfuroso,

nítrico, nitroso, fosfórico, y fosfóroso. Ejemplos de aniones orgánicos apropiados incluyen, pero no están limitados a, aquellos derivados de los siguientes ácidos orgánicos: acético, propiónico, succínico, glicólico, esteárico, palmítico, láctico, málico, pamóico, tartárico, cítrico, glucónico, ascórbico, maléico, hidroximaleico, fenilacético, glutámico, aspártico, benzóico, cinámico, pirúvico, salicílico, sulfanílico, 2- acetioxibenzóico, fumárico, toluensulfónico, metanosulfónico, etanosulfónico, etanodisulfónico, oxálico, isetiónico, valérico, y glucónico. Ejemplos de aniones poliméricos apropiados incluyen, pero no están limitados a, aquellos derivados de los siguientes ácidos poliméricos:ácido tánico, carboximetilcelulosa.

Puede ser conveniente o deseable preparar, purificar, y/o manipular un solvato correspondiente del compuesto activo. El término "solvato" se utiliza en la presente en un sentido convencional para referirse a un complejo de soluto (ej. compuesto activo, salt de compuesto activo) o solvente.

Si el solvente es agua, el solvato puede ser convenientemente conocido como un hidrato, por ejemplo, un mono- hidrato, un di- hidrato, un tri- hidrato, etc.

Puede ser conveniente o deseable preparar, purificar, y/o manipular el compuesto activo en una forma quimicamente protegida. El término "forma quimicamente protegida," como se utiliza en la presente, se refiere a un compuesto en el cual uno o más grupos funcionales reactivos están protegidos contra reacciones químicas indeseadas, es decir, están en la forma de un grupo protegido o protector (también conocido como un grupo enmascarado o enmascarador o un grupo bloqueado o bloqueador) . Al proteger un grupo funcional reactivo, las reacciones que involucran otros grupos funcionales reactivos no protegidos pueden ser realizadas, sin afectar el grupo protegido; el grupo protector puede ser retirado, usualmente en un paso subsiguiente, sin afectar sustancialmente el resto de la molécula. Ver, por ejemplo, ref. 26.

Por ejemplo, un grupo hidroxilo puede ser protegido como un éter (- O) o un éster (- OC(=0) R) , por ejemplo, como: un éter t- butílico; un bencilo, benzhidrilo (difenilmetilo) , o éter tritílico (trifenilmetilo) ; un trimetilsililo o t- butildimetilsililo éter; o un éster acetílico (- OC(=0) CH_3, - OAc) .

Por ejemplo, un grupo aldehido o cetona puede ser protegido como un acetal o cetal, respectivamente, en los cuales el grupo carbonilo (>C=0) es convertido en un diéter (>C(OR) $_2$) , mediante la reacción con, por ejemplo, un alcohol primario. El grupo aldehido o cetona es

facílmente regenerado mediante hidrólisis utilizando un gran exceso de agua en presencia de ácido.

Por ejemplo, un grupo amina puede ser protegido, por ejemplo, como una amida o un uretano. por ejemplo, como: una amida de metilo (- NHCO- CH_3) ; una amida de benziloxilo (- NHCO- $OCH_2C_6H_5$, - NH- Cbz) ; como una amida de t- butoxilo (- NHCO- $OC(CH_3)_3$, - NH- Boc) : una amida 2- bifenil- 2- propoxilo (- NHCO- $OC(CH_3)_2C_6H_4C_6H_5$, - NH- Bpoc) , como una amida de 9- fluorenilmetoxilo (- NH- Fmoc) , como una amida de 6- nitroveratriloxilo (- NH- Nvoc) , como una una amida de 2- trimetilsililetiloxilo (- NH- Teoc) , como una amida de 2.2,2- tricloroetiloxilo (- NH- Troc) , como una amida de alliloxilo (- NH- Alloc) , como una amida de 2(- fenilsulfonil) etiloxilo (- NH- Psec) ; o, en casos apropiados, como un N- oxido.

Por ejemplo, un grupo de ácido carboxílico puede ser protegido como un éster por ejemplo, como: un éster C1- 7 alquílico (ej. éster metílico; un éster t- butílico) ; un éster C1- 7 haloalquílico (ej.un éster C1- 7 trihaloalquílico) ; un éster triC1- 7 alquilsilil- C1- 7 alquílico; o un éster C5- 20 arilo- C1- 7 alquílico (ej. un éster bencílico; un éster nitrobencílico) ; o como una amida, por ejemplo, como una amida de metilo.

Por ejemplo, un grupo tiol puede ser protegido como un tioéter (- SR) , por ejemplo, como: tioéter bencílico; éter acetamidometílico (- S- CH2NHC(=0) CH_3) .

Puede ser conveniente o deseable preparar, purificar, y/o manipular el compuesto activo en la forma de un profármaco. El término "profármaco", como se utiliza en la presente, se refiere a un compuesto el cual, cuando se metaboliza (ej. *en vivo*) , proporciona el compuesto activo deseado. Típicamente, el profármaco es inactivo, o menos activo que el compuesto activo, pero puede proporcionar propiedades ventajosas metabólicas, de manipulación o administración.

Por ejemplo, algunos profármacos son ésteres del compuesto activo (ej. un éster metabolicamente lábil fisiológicamente aceptable) . Durante el metabolismo, el grupo éster (- C(=0) O) es escindido para rendir el fármaco activo. Tales ésteres se pueden formar mediante esterificación, por ejemplo, de cualquiera de los grupos ácido carboxílicos (- C(=0) OH) en el compuesto precursor, con, donde sea apropiado, protección anterior de cualquiera de los grupos reactivos presentes en el compuesto precursor, seguido por desprotección si se requiere. Ejemplos de tales ésteres metabolicamente lábiles incluyen aquellos en donde R es C1- 20 alquilo (ej. - Me, - Et) ; C1- 7 aminoalquilo (ej. aminoetilo; 2- (N,N- dietilamino) etilo; 2- (4 morfolino) etilo) ; y

aciloxi- C1- 7 alquilo (ej. aciloximetilo; aciloxietilo; ej. pivaloiloximetilo; acetoximetilo; 1- acetoxietilo; l- (l- metoxi- l- metil) etil- carbonxiloxi- etilo; 1 - (benzoiloxi) etilo; isopropoxi- carboniloximetilo; 1 - isopropoxi- carboniloxietilo; ciclohexil- carboniloximetilo;1 - ciclohexil- carboniloxietilo; ciclohexiloxi- carboniloximetilo; 1- ciclohexiloxi- carboniloxietilo; (4- tetrahidropiranoiloxi) carboniloximetilo; l- (4- tetrahidropiranoiloxi) carboniloxietilo; (4 tetrahidropiranoil) carboniloxirnetilo; y 1 - (4- tetrahidropiranoil) carboniloxietilo) .

Formas profármaco adicionalmente apropiadas incluyen sales de fosfonato y glicolato. En particular, los grupos hidroxilo (- OH) , se pueden preparar en profármacos de fosfonato mediante la reacción con clorodibenzilfosfito, seguido por hidrogenación, para formar un grupo de fosfonato - O- P(=0) (OH) 2. Tal grupo puede ser depurado mediante enzimas de fosfotasa durante el metabolismo para proporcionar el fármaco activo con el grupo hidroxilo.

También, algunos profármacos son activados de manera enzimática para proporcionar el compuesto activo, o un compuesto que, ante reacción química adicional, proporciona el compuesto activo. Por ejemplo, el profármaco puede ser un derivado de azúcar u otro conjugado de glicosido, o puede ser un derivado de éster aminoácido.

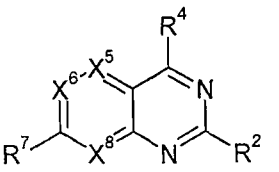
Acrónimos

Por conveniencia, muchas fracciones químicas se representan utilizando abreviaturas conocidas, incluyendo pero sin limitar a, metilo (Me) , etilo (Et) , n- propilo (nPr) , iso- propilo (iPr) , n- butilo (nBu) , tert- butilo (tBu) , n- hexilo (nHex) , ciclohexilo (cHex) , fenilo (Ph) , bifenilo (biPh) , bencilo (Bn) , naftilo (naph) , metoxilo (MeO) , etoxilo (EtO) , benzoilo (Bz) , y acetilo (Ac) .

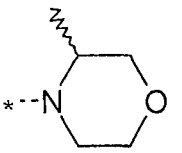
Por conveniencia, muchos compuestos químicos se representan utilizando abreviaturas conocidas, incluyendo pero sin limitar a, metanol (MeOH) , etanol (EtOH) , iso- propanol (i-PrOH) , metil etil cetona (MEK) , éter o éter dietílico (Et20) , ácido acético (AcOH) , diclorometano (cloruro de metileno, DCM) , ácido trifluoroacético (TFA) , dimetilformamida (DMF) , tetrahidrofurano (THF) , y dimetilsulfoxido (DMSO) .

Síntesis General

Los compuestos de la fórmula I se pueden representar mediante la Fórmula 1

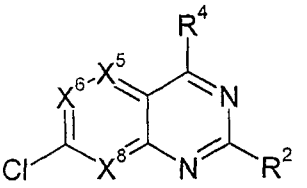


Formula 1



en donde R^4 representa

Los compuestos de la Fórmula 1 se pueden sintetizar a partir de los compuestos de la

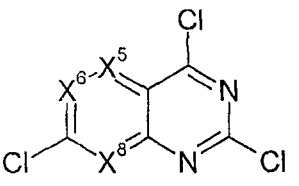


Formula 2

Fórmula 2:

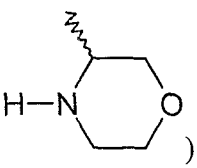
Cuando R7 es $NR^{N1}R^{N2}$, esto es mediante la reacción con R^7H. Cuando R7 es un grupo amida, urea o sulfonamida, esto es mediante la reacción con amoniaco seguido por reacción de la amida primaria resultante con el cloruro ácido apropiado, isocianato o sulfonil cloruro. Cuando R^7 es OR^{O1} o SR^{S1}, esto es mediante la reacción con carbonato de potasio en el alcohol o solvente tiol apropiado. Cuando R7 es un grupo C3- 20 hetericiclilo opcionalmente sustituido o grupo C5- 20 arilo, esto es mediante la reacción con $R^7B(OAlk)_2$, donde cada Alk es independientemente C1- 7 alquilo o junto con el oxigeno al cual están unidos forman un grupo c5- 7 heterociclilo.

Los compuestos de la Fórmula 2 se pueden sintetizar a partir de los compuestos de la



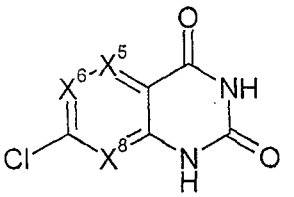
Formula 3

Fórmula 3:



mediante reacción con HR^4 (ej.,) seguido por la reacción con HR^2.

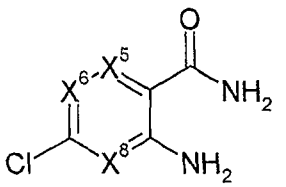
Los compuestos de la Fórmula 3 se pueden sintetizar a partir de compuestos de la Fórmula 4:



Formula 4

mediante tratamiento con $POCl_3$ o N,N- diisopropilamina, por ejemplo.

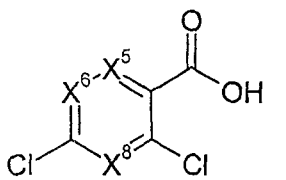
Compuestos de la Fórmula 4 se pueden sintetizar a partir de los compuestos de la Fórmula 5:



Formula 5

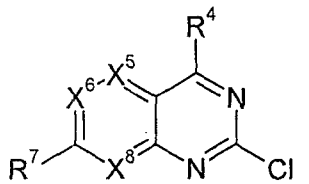
mediante tratamiento con cloruro de oxalilo, por ejemplo.

Los compuestos de la Fórmula 5 se pueden sintetizar a partir de los compuestos de la Fórmula 6, por ejemplo mediante la reacción con amoniaco líquido seguido por la reacción con cloruro de tionilo y gas de amoniaco:



Formula 6

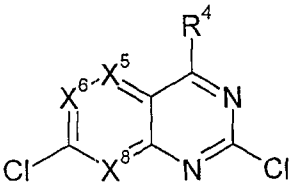
Alternativamente los compuestos de la Fórmula 1 se pueden sintetizar a partir de los compuestos de la Fórmula 7:



Formula 7

mediante la reacción con HR^2.

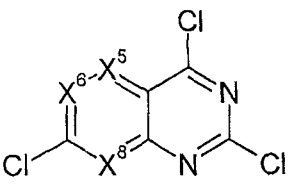
Los compuestos de la Fórmula 7 se pueden sintetizar a partir de los compuestos de la Fórmula 8:



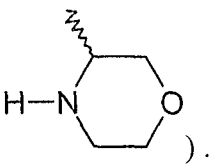
Formula 8

Cuando R^7 es $NR^{N1}R^{N2}$, esto es mediante la reacción con R^7H. Cuando R^7 es un grupo amida, urea o sulfonamida, esto es mediante la reacción con amoniaco seguido por reacción de la amida primaria resultante con el cloruro ácido apropiado, isocianato o sulfonil cloruro. Cuando R^7 es OR^{O1} o SR^{S1}, esto es mediante la reacción con carbonato de potasio en el alcohol o solvente tiol apropiado. Cuando R^7 es un grupo C3- 20 hetericiclilo opcionalmente sustituido o grupo C5- 20 arilo, esto es mediante la reacción con $R^7B(OAlk)_2$, donde cada Alk es independientemente C1- 7 alquilo o junto con el oxigeno al cual están unidos forman un grupo C5- 7 heterociclilo.

Compuestos de la Fórmula 8 se pueden sintetizar a partir de los compuestos de la Fórmula 3:

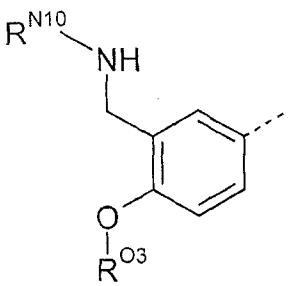


Formula 3

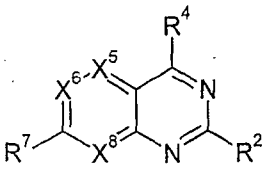


mediante reacción con HR4 (ej.).

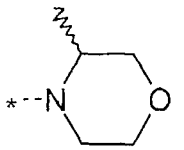
Cuando R7 es



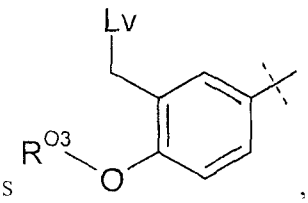
el compuesto de la Fórmula 1 se puede preparar mediante reacción con un compuesto de la fórmula la:



Formula 1a

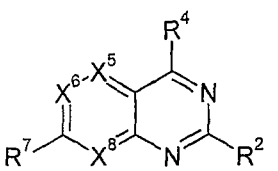


en donde R4 representa , y

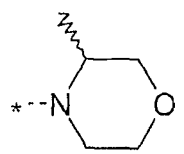


R^7 es , en donde Lv es un grupo saliente, tal como un halógeno, por ejemplo cloro, o un grupo OSO_2, donde R es alquilo o arilo, tal como metilo, mediante la reacción con $R^{N10}NH_2$.

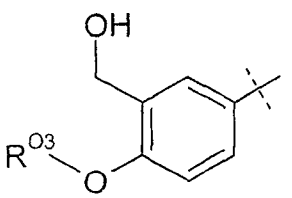
Compuestos de la Fórmula la se pueden sintetizar mediante reacción de un compuesto de la fórmula lb



Formula 1b



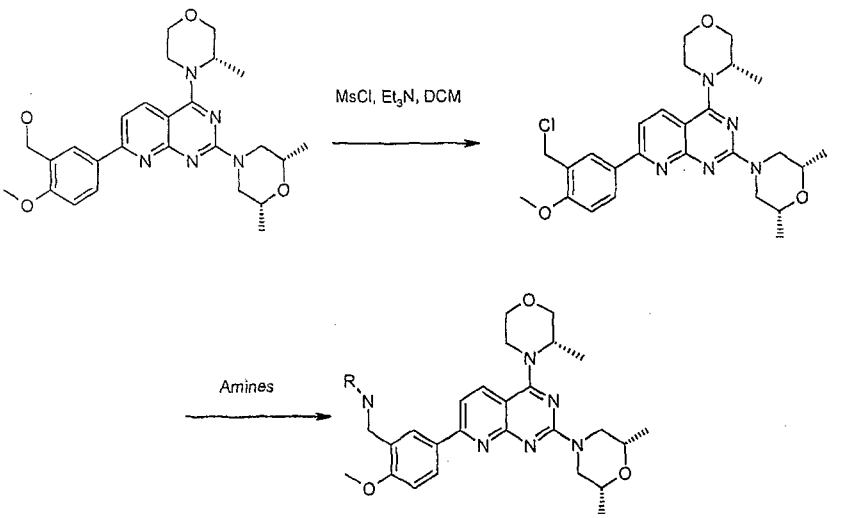
en donde R^4 representa , y



R^7 es ,

con un alquilo o aril sulfonil cloruro en presencia de una base.

Por ejemplo:



Compuestos de la Fórmula Ib se pueden preparar mediante la reacción con $R^7B(OAlk)_2$, donde cada Alk es independientemente C1- 7 alquilo o junto con el oxigeno al cual están unidos forman un grupo C5- 7 heterociclilo.

Uso

El presente invento proporciona compuesto activos, especificamente activos para inhibir la actividad de mTOR.

El término "activo" como se utiliza en la presente, se refiere a compuestos que son capaces de inhibir actividad mTOR, y especificamente incluye ambos compuestos con actividad intrinseca (fármacos) así como también profármacos de tales compuestos, tales profármacos pueden por sí mismos exhibir poca o nada de actividad intrínseca.

Un ensayo que se puede convenientemente utilizar para evaluar la inhibición de mTOR ofrecida por un compuesto particular se describe en los ejemplos a continuación.

El presente invento adicionalmente proporciona una método para inhibir la actividad de mTOR en una célula comprendiendo colocar en contacto dicha célula con una cantidad efectiva de un compuesto activo, preferiblemente en la forma de una composición farmacéuticamente aceptable. Tal método puede ser practicado *en vitro* o *en vivo*.

Por ejemplo, se puede cultivar una muestra de células *en vitro* o un compuesto activo se puede poner en contacto con dichas células, y observar el efecto del compuesto sobre las células. Como ejemplos de "efecto", se puede determinar la inhibición de crecimiento celular durante

cierto tiempo o la acumulación de las células en la fase G1 del ciclo celular durante cierto tiempo. Donde se encuentra que el compuesto activo ejerce una influencia sobre las células, esto se puede utilizar como un marcador pronóstico o diagnóstico de la eficacia del compuesto en métodos para tratar un paciente que lleva células del mismo tipo celular.

El término "tratamiento", como se utiliza en la presente en el contexto de tratar una condición, generalmente se refiere a tratamiento o terapia, bien sea de un humano o un animal (ej. aplicaciones veterinarias) , en los cuales se logran algunos efectos terapéuticos deseados, por ejemplo, la inhibición del progreso de la condición, e incluye una reducción en la tasa de progreso, una terminación en la tasa de progreso, alivio de la condición, y cura de la condición. Tratamiento como una medida profiláctica (es decir profilaxis) también se incluye.

El término "adjunto" como se utiliza en la presente se relaciona con el uso de compuestos activos en conjuncción con medios terapéuticos conocidos. Tales medios incluyen regímenes citotóxicos de fármacos y/o radiación ionizante como se utiliza en el tratamiento de diferentes tipos de cáncer. Ejemplos de agentes anti- cancerígenos adjuntos que se podrían combinar con compuestos del invento incluyen, pero no están limitados a, lo siguiente: agentes alquilantes: mostazas de nitrógeno, mecloretamina, ciclofosfamida, ifosfamida, melfalán, clorambucil: Nitrosoureas: carmustina (BCNU) , lomustina (CCNU) , semustina (metilo- CCNU) , etilenimina/metilmelamina, trietilenmelamina (TEM) , tiofosforamida de trietileno (tiotepa) , hexametilmelamina (HMM, altretamina) : Alquilo sulfonatos; busulfan; Triazinas, dacarbazina (DTIC) : Antimetabolitos; análogos de ácido fólico, metotrexato, trimetrexato, análogos de pirimidina, 5- fluorouracilo, fluorodeoxiuridina, gemcitabina, arabinósido de citosina (AraC, citarabina) , 5- azacitidina, 2,2'- difluorodeoxicitidina: Análogos de purina; 6- mercaptopurina, 6- tioguanina, azatioprina, 2'- deoxicoformicina (pentostatina, eritrohidroxinoniladenina (EHNA) , fosfato de fludarabina, 2- Clorodeoxiadenosina (cladribina, 2- CdA) : Inhibidores de la topoisomerasa I; camptotecina, topotecan, irinotecan, rubitecan: Productos naturales; fármacos antimitóticos, paclitaxel, alcaloides vinca, vinblastina (VLB) , vincristina, vinorelbina, Taxotere™ (docetaxel) , estramustina, fosfato de estramustina; epipodofilotoxinas, etopósido, tenipósido: Antibióticos; actimomicina D, daunomicina (rubidomicina) , doxorubicina (adriamicina) , mitoxantrona, idarubicina, bleomicinas, plicamicina (mitramicina) , mitomicina C, dactinomicina: Enzimas; L- asparaginasa, RNAsa A: Modificadores de respuesta biológica;

interferona- alfa, IL- 2, G- CSF, GM- CSF: Agentes de diferenciación; derivados de ácido retinóico: Radiosensibilizadores;, metronidazol, misonidazol, desmetilmisonidazol, pimonidazol, etanidazol, nimorazol, RSU 1069, E09, RB 6145, SR4233, nicotinamida, 5- bromodeoziuridina, 5- iododeoxiuridina, bromodeoxicitidina: Complejos de coordinación de platino; cisplatino, carboplatino: Antracenediona; mitoxantrona, urea AQ4N Substituida, hidroxiurea; derivados de Metilhidrazina, N- metilhidrazina (MIH) , procarbazina; Supresor adrenocortical, mitotano *(o.p* '- DDD) , aminoglutetimida: Citoquinas; interferona (α,β,γ) , interleucina; Hórmonas y antagonistas; adrenocorticosteroides/antagonistas, prednisona y equivalentes, dexametasona, aminoglutetimida; Progestinas, caproato de hidroxiprogesterona, acetato de medroxiprogesterone, acetato de megestrol; Estrógenos, dietilestilbestrol, estradiol de etinilo /equivalentes; Antiestrogeno, tamoxifeno; Andrógenos, propionato de testosterona, fluoximesterona/equivalentes; Antiandrógenos, flutamida, análogos de hórmonas liberadores de gonadotropina, leuprolida; Antiandrógenos no esteroidales, flutamida; inhibidores EGFR, VEGF inhibidores; inhibidores de proteasoma.

También se pueden utilizar compuestos activos como aditivos de cultivos celulares para inhibir mTOR, por ejemplo, sensitizar células a agentes quimioterapeuticos conocidos o tratamientos de radiación ionizante *en vitro.*

También se pueden utilizar compuestos activos como parte de un *ensayo en vitro*, por ejemplo, para determinar si un huesped candidato tiene probabilidad de beneficiarse del tratamiento con el compuesto en cuetión.

Cáncer

El presente invento proporciona compuestos activos que son agentes anti- cancerígenos o adjuntos para tratar cáncer. Alguien con experiencia común en el estado de la técnica facilmente puede determinar si un compuesto candidato trata una condición cancerosa para cualquier tipo celular particular, ya sea solo o en combinación.

Ejemplos de canceres incluyen, pero no están limitados a, cáncer pulmonar, cáncer pulmonar de células pequeñas, cáncer gastrointestinal, cáncer intestinal, cáncer de colon, carcinoma de mama, carcinoma ovárico, cáncer prostático, cáncer testicular, cáncer hepático, cáncer renal, cáncer de vejiga, cáncer pancreático, cáncer cerebral, sarcoma, osteosarcoma, Sarcoma de Kaposi, melanoma o leucemias.

Cualquier tipo de célula puede ser tratada, incluyendo pero sin limitar a, pulmón gastrointestinal (incluyendo, ej., intestinos, colon) , mama (mammaria) , ovario, próstata, hígado (hepatico) , riñón (renal) , vejiga, páncreas, cerebro, y piel.

El tratamiento anti- cancerígeno definido aquí anteriormente se puede aplicar como una única terapia o puede involucrar, además del compuesto del invento, cirugía convencional o radioterapia o quimioterapia. Tal quimioterapia puede incluir una o más de las siguientes categorías de agentes anti- tumorales:-

(i) otros fármacos antoproliferativos/antineoplásicos o combinaciones de las mismos, como se utilizan en oncología médica, tales como agentes alquilantes (por ejemplo cis platin, oxaliplatin, carboplatin, ciclofosfamida, mostaza de nitrógeno, melfalán, clorambucil, busulfan, temozolamida o nitrosoureas) ; antimetabolitos (por ejemplo gemcitabina o antifolatos tales como fluoropirimidinas como 5 fluorouracil y tegafur, raltitrexed, metotrexato, arabinósido de citosina, e hidroxiurea) ; antibióticos antitumorales (por ejemplo antraciclinas como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina- C, dactinomicina y mitramicina) ; agentes antimitóticos (por ejemplo alcaloides vinca como vincristina, vinblastina, vindesina o vinorelbina y taxoids como taxol y taxotero e inhibidores de la poloquinasa) ; e inhibidores de la topoisomerasa (por ejemplo epipodofillotoxinas como etoposida y teniposida, amsacrina, topotecan o camptotecina) ;

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifen, fulvestrant, toremifeno, raloxifeno, droloxifeno y yodoxifeno) , antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida o acetato de ciproterona) , antagonistas LHRH o agonistas LHRH (por ejemplo goserelina, leuprorelina y buserelina) , progestógenos (por ejemplo acetato de megestrol) , inhibidores de aromatasa (por ejemplo como anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5*- reductasa tales como finasterida;

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

plasminógeno de uroquinasa o anticuerpos contra Heparanasa) ;

(iv) inhibidores de función de factor de crecimiento: por ejemplo tales inhibidores incluyen anticuerpos de factor de crecimiento y anticuerpos de receptores de factor de crecimiento (por ejemplo el anticuerpo anti erbB2 trastuzumab [Herceptin™], el anticuerpo anti-EGFR panitumumab, el anticuerpo anti erbBl cetuximab [Erbitux, C225] y cualquier anticuerpo de factor de crecimiento o de receptores de factor de crecimiento divulgados por Stern et al. Reseñas Criticas en oncología/hematología, 2005, Vol. 54, ppl 1- 29) ; tales inhibidores también incluyen inhibidores de la tirosina quinasa, por ejemplo inhibidores de la familia de factores de crecimiendo epidermal (por ejemplo inhibidores de la tirosina quinasa de la familia EGFR tales como N- (3- cloro- 4- fluorofenil) - 7- metoxi- 6- (3- morfolinopropoxi) quinazolin- 4- amina (gefitinib, ZD1839) , N- (3- etinilfenil) - 6,7- bis(2- metoxietoxi) quinazolin- 4- amina (erlotinib, OSI774) y 6- acrilamido- N- (3- cloro- 4- fluorofenil) - 7- (3- morfolinopropoxi) - quinazolin- 4- amina (CI 1033) , inhibidores de la erbB2 tirosina quinasa tales como lapatinib, inhibidores de la familia de factores de crecimientode hepatocitos, inhibidores de la familia de factores de crecimiento derviados de plaquetas tales como imatinib, inhibidores de serina/treonina quinases (por ejemplo inhibidores de señalización Ras/Raf tales como inhibidores de la farnesil transferasa, por ejemplo sorafenib (BAY 43- 9006)) , inhibidores de señalización celular a través de quinasas MEK y/o AKT, inhibidores de la familia de factores de crecimiento de hepatocitos, inhibidores de c- kit, inhibidores de abl quinasa, inhibidores de quinasa de receptores IGF (factor de crecimiento tipo insulina) ; inhibidores de la aurora quinasa (por ejemplo AZD1152, PH739358, VX- 680, MLN8054, R763, MP235, MP529, VX- 528 O AX39459) o inhibidores de quinasa dependientes de ciclina tales como inhibidores CDK2 y/o CDK4;

(v) agentes antiangiogénicos tales como aquellos que inhiben los efectos de factor de crecimiento endotelial vascular, [por ejemplo el anticuerpo de factor de crecimiento celular endotelial anti- vaxular bevacizumab (Avastin™) e inhibidores del receptor de tirosina quinasa de VEGF tales como 4- (4- bromo- 2- fluoroanilino) - 6- metoxi- 7- (l- metilpiperidin- 4- ilmetoxi) quinazolina (ZD6474; Ejemplo 2 dentro de WO 01/32651) , 4- (4- fluoro- 2- metilindol- 5- iloxi) - 6- metoxi- 7- (3- pirrolidin- l- ilpropoxi) quinazolina (AZD2171; Ejemplo 240 dentro de WO 00/47212) , vatalanib (PTK787; WO 98/35985) y SU11248 (sunitinib; WO 01/60814) , compuestos tales como aquellos divulgados en las Solicitudes de Patentes Internacionales W097/22596, WO 97/30035, WO 97/32856 y WO 98/13354 o compuestos que

funcionan mediante otros mecanismos (por ejemplo linomida, inhibidores de la función de integrina avb3 o angiostatina)];

(vi) agentes de daño vascular tales como Combretastatina A4 y los compuestos divulgados en Solicitudes de Patentes Internacionales WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 o WO 02/08213;

(vii) terapias antisentido, por ejemplo aquellas que están dirigidas a las dianas listadas anteriormente, tal como ISIS 2503, un antisentido anti- ras;

(viii) enfoques de terapia genética, incluyendo por ejemplo enfoques para reemplazar genes aberrantes tales como enfoques de p53 aberrante o BRCA1 o BRCA2, GDEPT aberrantes (terapia de profármacos enzimáticos dirigida por genes) tales como aquellos que utilizan citosina deaminasa, timidina quinasa o una enzima de nitroreductasa bacterial y enfoques para aumentar la tolerancia del paciente a quimioterapia o radioterapia tales como terapia genética de resistencia a múltiples fármacos; y

(ix) enfoques de inmonoterapia, incluyendo por ejemplo enfoques *ex vivo* y *en vivo* para aumentar la inmunogenicidad de células tumorales del paciente, tal como transfección con citoquinas tales como interleucina 2, interleucina 4 o factor estimulador de colonias de macrofagas granulociticas, enfoques para disminuir energía de células T, enfoques que utilizan células inmunes transfectadas tales como células dendriticas transfectadas con genes de citoquina, enfoques que utilizan líneas celulares tumorales transfectadas con genes citoquina y enfoques que utilizan anticuerpos anti- idiotípicos.

Administración

El compuesto activo o composición farmaceutica que comprende el compuesto activo se puede administrar a un sujeto mediante cualquier ruta de administración conveniente, bien sea sistematicamente/ perifericamente o en el sitio de acción deseada, incluyendo pero sin limitar a, oral (ej. mediante ingestión) ; topical (incluyendo ej. transdermal, intranasal, ocular, bucal, o sublingual) ; pulmonar (ej. mediante terapia de inhalación o insuflación, ej. un aerosol, ej. a través de boca o nariz) ; rectal; vaginal; parenteral, por ejemplo, mediante inyección, incluyendo subcutanea, intradermal, intramuscular, intravenosa, intraarterial, intracardiaca, intratecal, intraespinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratraqueal, subcuticular,

intraarticular, subaracnoide, y intraesternal; mediante implante de un depósito, por ejemplo, subcutaneamente o intramuscularmente.

El sujeto puede ser un eucarionte, un animal, un animal vertebrado, un mamífero, un roedor (ej. un conejillo de indias, un hamster, una rata, un ratón) , murino (ej. un ratón) , canino (ej. un perro) , felino (ej. un gato) , equino (ej. un caballo) , un primate, simio (ej. un mono) , un mono (ej. tití, babuino) , un simio (ej. gorilla, chimpance, orangutan, gibón) , o un humano.

Formulaciones

Mientras es posible que el compuesto activo sea administrado solo, es preferible presentarlo como una composición farmacéutica (ej., fórmulación) comprendiendo al menos un compuesto activo, como se definió anteriomente, junto con uno o más vehículos, adyuvantes, excipientes, diluyentes, rellenos, amortiguadores, estabilizantes, preservativos, lubricantes, u otros materiales farmacéuticamente aceptables bien conocidos por aquellos en experiencia en el estado de la técnica y opcionalmente otros agentes terapéuticos o profilácticos.

Así, el presente invento además proporciona composiciones farmacéuticas, como se definió anteriomente, o métodos para fabricar una composición farmacéutica comprendiendo mezclar al menos un compuesto activo, como se definió anteriomente, junto con uno o más vehículos, excipientes, amortiguadores, adyuvantes estabilizantes, o otros materiales farmacéuticamente aceptables, como se describe en la presente.

El término "farmacéuticamente aceptable" como se utiliza en la presente se refiere a compuestos, materiales, composiciones, y/o formas de dosificación que están, dentro del alcance de un juicio médico acertado, apropiados para utilizar en contacto con los tejidos de un sujeto (ej. humano) sin toxicidad excesiva, irritación, respuesta alérgica, u otro problema o complicación, de medida igual a una tasa beneficio/riesgo razonable. Cada vehículo, excipiente, etc. también debe ser "aceptable" en el sentido de ser compatible con los demás ingredientes de la fórmulación.

Vehículos, diluyentes, excipientes apropiados, etc. se pueden encontrar en textos farmacéuticos estándares. Ver, por ejemplo, refs. 27 a 29.

Las formulaciónes se pueden presentar convenientemente en forma de dosificación unitaria o se pueden preparar mediante cualquier método bien conocido en el estado de la técnica

de farmacia. Tales métodos incluyen el paso de llevar a asociación el compuesto activo con el vehículo el cual constituye uno o más ingredientes accesorios. En general, las formulaciónes se preparar al llevar uniformemente o intimamente el compuesto activo en asociación con vehículos líquidos o o vehículos sólidos finamente divididos o ambos, y luego si es necesario formar el producto.

Las formulaciónes pueden estar en la forma de líquidos, soluciones, suspensiones, emulsiones, elixires, jarabes, tabletas, pastillas, granulos, polvos, cápsulas, grageas, píldoras,, ampollas. supositorios. pesarios, geles, pastas, cremas, esprays, atomizaciones, espumas, lociones. aceites. bolos, electuarios, o aerosoles.

Formulaciónes apropiadas para administración oral (ej., mediante ingestión) se pueden presentar como unidades discretas tales como cápsulas, grageas o tabletas, cada una conteniendo una cantidad predeterminada del compuesto activo; como un polvo o granulos; como una solución o suspensión en un líquido acuoso o no acuoso; o como una emulsión líquida de aceite en agua o una emulsión líquida de agua en aceite; como un bolo; como un electuario; o como una pasta.

Una tableta se puede fabricar mediante medios convencionales, ej. compresión o moldeado, opcionalmente con uno o más ingredientes accesorios. Las tabletas comprimidas se pueden preparar al comprimir en una maquina apropiada el compuesto activo de una manera fluida libre tal como un polvo o granulos, opcionalmente mezclado con uno o más aglomerantes (ej. povidona, gelatina, acacia, sorbitol, tragacanto, hidroxipropilmetilcellulosa) ; rellenos o diluyentes (ej. lactosa, celulosa microcristalina, fosfato de hidrógeno y cálcio) ; lubricantes (ej. estearato de magnesio, talco, sílice) ; desintegrantes (ej. glicolato de almidón de sodio, povidona entrecruzada, celulosa carboximetilo sódica entrecruzada) ; agentes tensoactivos o dispersantes o humectantes (ej., laurilsulfato sódico) ; y preservativos (ej., p- hidroxibenzoato de metilo, p-hidroxibenzoato de propilo, ácido sórbico) . Las tabletas moldeadas se pueden fabricar al moldear en una maquina apropiada una mezcla del compuesto en polvo humedecida con un diluyente líquido inerte. Las tabletas opcionalmente se pueden recubrir o ranurar y se pueden fórmular para proporcionar liberación lenta o controlada del compuesto activo utilizando, por ejemplo, hidroxipropilmetilcellulosa en proporcones variables para proporcionar el perfil de liberación deseado. A las tabletas opcionalmente se puede proporcionar un recubrimiento entérico, para

proporcionar liberación en partes del intestino diferentes del estomago.

Formulaciónes apropiadas para administración tópica (ej. transdermal, intranasal, ocular, bucal, o sublingual) se pueden fórmular como un unguento, crema, suspensión, loción, polvo, solución, pasta, gel, espray, aerosol, o aceite. Alternativamente, una fórmulación puede comprender un parche o un vendaje tal como un vendaje o emplasto adhesivo impregnado con compuesto activos y opcionalmente uno o más excipientes o diluyentes.

Formulaciónes apropiadas para administración tópica en la boca incluyen pastillas comprendiendo el compuesto activo en una base saborizada, usualmente sacarosa y acacia o tragacanto; pastillas comprendiendo el compuesto activo en una base inerte tal como gelationa y glicerina, o sacarosa y acacia; y enjuages bucales comprendiendo el compuesto activo en un vehículo líquido apropiado.

Formulaciónes apropiadas para administración tópica en ojos también incluyen gotas oftálmicas en donde el compuesto activo se disuelve o suspende en un vehículo apropiado, especialmente un solvente acuoso para el compuesto activo.

Formulaciónes apropiadas para administración nasal, en donde el vehículo es un sólido, incluyen un polvo grueso con un tamaño de particula, por ejemplo, en el rango entre 20 y 500 micras aproximadamente el cual se administra en la manera en la cual es aspirado es tomado, es decir mediante inhalación rápida a través del pasaje nasal desde un recipiente del polvo mantenido cerca de la nariz. Formulaciónes apropiadas en donde el vehículo es un líquido para administración como, por ejemplo, espray nasal, gotas nasales, o mediante administración en aerosol mediante nebulizador incluyen soluciones acuosas o aceitosas del compuesto activo.

Formulaciónes apropiadas para administración mediante inhalación incluyen aquellas presentadas como un espray en aerosol desde un paquete presurizado, con el uso de un propulsor adecuado, tales como diclorodifluorometano, triclorofluorometano, dichoro- tetrafluoroetano, dioxido de carbono, u gases apropiados.

Formulaciónes apropiadas para administración tópica a través de la piel incluyen unguentos, cremas, y emulsiones. Cuando se fórmula en un unguento, el compuesto activo opcionalmente se puede emplear ya sea con un parafínico o una base de unguento miscible en agua. Alternativamente, el compuesto activo se puede fórmular en una crema con con una base de crema de aceite en agua. Si se desea, la fase acuosa de la base de crema puede incluir, por

ejemplo, al menos 30% por peso aproximadamente de un alcohol polihídrico, es decir, un alcohol que tiene dos o más grupos hidroxilo tales como glicol de propileno, butano- 1,3- diol, manitol, sorbitol, glicerol y glicol de polietileno y mezclas de los mismos. Las formulaciónes tópicas deseablemente pueden incluir un compuesto que aumenta la absorción o penetración del compuesto activo a través de la piel u otras áreas afectadas. Ejemplos de tales mejoradores de penetración dérmica incluyen dimetilsulfoxido y análogos relacionados.

Cuando se fórmula como una emulsión tópica, la fase aceitosa opcionalmente puede comprender solamente un emulsificador (de otra manera conocido como un emulgente) , o puede comprender una mezcla de al menos un emulsificador con una grasa o un aceite o con ambos una grasa y un aceite. Preferiblemente, se incluye un emulsificador hidrofílico junto con un emulsificador lipofílico el cual actúa como un estabilizador. También se prefiere incluir ambos un aceite y una grasa. Juntos, los emulsificadores con o sin estabilizadores componen la conocida cera emulsificante, y la cera junto con el aceite y/o base componen la conocida base de unguento emulsificante la cual forma la fase dispersada aceitosa de las formulaciónes en crema.

Emulgentes o estabilizantes de emulsión apropiados incluyen Tween 60, Span 80, alcohol cetoestearílico, alcohol miristílico, monoestearato de gliceriloyo laurilsulfato sódico. La elección de aceites o grasas apropiados para la fórmulación se base en lograr la propiedades cosméticas deseadas, puesto que la solubilidad del compuesto activo en la mayoría de aceites comunmente a ser utilizados en formulaciónes de emulsiones farmacéuticas puede ser muy baja. Por lo tanto la crema debe ser preferiblemente un producto no graso, que no mancha y lavable con consistencia apropiada para evitar filtración desde tubos u otros recipientes. Ésteres alquilicos mono o dibásicos, de cadena lineal o ramificada tales como di- isoadipato, estearato de isocetilo, diéster de glicol de propileno de ácidos grasos de coco, miristato de isopropilo, oleato de decilo, palmitato de isopropilo, estearato de butilo, palmitato de 2- etilhexilo o se puede utilizar una mezcla de ésteres de cadena ramificada conocida como Crodamol CAP, los últimos tres ésteres siendo preferidos. Estos se pueden utilizar solos o en combinación dependiendo de las propiedades requeridas. Alternativamente, se pueden utilizar lípidos con punto de fusión alto tales como parafina suave blanca y/o parafina líquida u otros aceites minerales.

Formulaciónes apropiadas para administración rectal se pueden presentar como un supositorio con una base apropiada comprendiendo, por ejemplo, manteca de cacao o un

salicilato.

Formulaciónes apropiadas para administración vaginal se pueden presentar como pesarios, tampones, cremas, geles, pastas, espumas o formulaciónes en espray conteniendo además del compuesto activo, tales vehículos como se conocen en el estado de la técnica como apropiados.

Formulaciónes apropiadas para administración parenteral (ej., mediante inyección, incluyendo cútanea, subcutanea, intramuscular, intravenosa e intradermal) , incluyen soluciones de inyección esteril, libre de pirógenos, isotónicas, acuosas o no acuosas las cuales pueden contener anti- oxidantes, amortiguadores, preservativos, estabilizantes, bacteriostáticos, y solutos los cuales hacen isotónica la fórmulación con la sangre del recipiente objetivo; y suspensiones esteriles acuosas y no acuosas las cuales pueden incluir agentes de suspensión y agentes espesantes, y liposomas u otros sistemas microparticulados los cuales están diseñados para dianizar el compuesto hacia componentes sanguíneos o uno o más organos. Ejemplos de vehículos isotónicos para utilizar en tales formulaciónes incluyen Inyección de Cloruro de Sodio, Solución de Ringer, o Inyección de Ringer - Lactato. Típicamente, la concentración del compuesto activo en la solución está entre 1 ng/ml y 10 µg/ml aproximadamente, por ejemplo entre 10 ng/ml y 1 µg/ml. Las formulaciónes se pueden presentar en recipientes sellados de dosis unitaria o múltiples dosis, por ejemplo, ampolletas o tubitos, y se pueden almacenar en una condición liofilizada requiriendo solamente la adición del vehículo líquido estéril, por ejemplo agua para inyecciones, inmediatamente antes de utilizar. Se pueden preparar soluciones o suspensiones de inyección extemporaneas a partir de polvos estériles, gránulos, y tabletas. Formulaciónes pueden estar en la forma de liposomas o otros sistemas microparticulados los cuales están diseñados para dirigir el compuesto activo hacia componentes hemáticos o uno o más organos.

Dosificación

Se apreciará que dosificaciones apropiadas de los compuestos activos, y composiciones que comprenden los compuestos activos, pueden variar de paciente a paciente. Determinar la dosificación óptima generalmente involucrará el balance del nivel de beneficio terapéutico contra cualquier riesgo o efectos secundarios perjudiciales de los tratamientos del presente invento. El nivel de dosificación seleccionado dependerá de una variedd de factores incluyendo, pero sin

limitar a la actividad del compuesto particular, la ruta de administración, el tiempo de administración, la tasa de excreción del compuesto, la duración del tratamiento, otros fármacos, compuestos, y/o materiales utilizados en combinación, y la edad, sexo, peso, condición, salud general, e historia médica anterior del paciente. La cantidad de compuesto y ruta de administración finalmente será decisión del médico, aunque generalmente la dosificación será para lograr concentraciones locales en el sitio de acción lo cual logra el efecto deseado sin producir daño sustancial o efectos secundarios perjudiciales.

La administración *en vivo* se puede realizar en una dosis, continua o intermitentemente (ej., en dosis divididas a intervalos apropiados) durante todo el curso de tratamiento. Métodos para determinar los medios más efectivos y dosificación de administración son bien conocidos por aquellos con experiencia en el estado de la técnica y variarán con la fórmulación utilizada para terapia, el propósito de la terapia, la célula objetivo tratada, y el sujeto tratado. Administraciones únicas o múltiples se pueden realizar con el nivel y patrón de dosis seleccionados por el médico a cargo.

En general, una dosis apropiada del compuesto activo está en el rango entre 100 µg y 250 mg aproximadamente por kilogramo de peso corporal del sujeto por día. Donde el compuesto activo es una sal, un éster, profármaco, y similares, la cantidad administrada se calcula sobre la base del compuesto precursor y así el peso actual a ser utilizado es aumentado proporcionalmente.

Además de su uso en medicina terapéutica, los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables también son útiles como herramientas farmacológicas en el desarrollo o estandarización de sistemas de prueba en vitro o *en vivo* para la evaluación de los efectos de inhibidores de mTor en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapéuticos.

En la anterior composición farmacéutica, proceso, método, uso y características de fabricación de medicamentos, también se aplican las realizaciones alternativas y preferidas de los compuestos del invento descritos en la presente.

Ejemplos

Métodos Eperimentales Generales

Se realizó cromatografía de capa delgada utilizando placas con soporte vítreo Merck Kieselgel 60 F254. Las placas se visualizaron mediante el uso de una lámpara UV (254 nm) . Se empleó gel de sílice 60 (tamaños de 40- 63 um) suministrado por E.M.Merck para cromatografía rápida. Los espectros ^{1}H NMR se registraron a 300 MHz sobre un instrumento Bruker DPX- 300. Los cambios químicos se referenciaron con relación a tetrametilsilano.

Purificación de muestras

Las muestras se purificaron sobre unidades Gilson LC. Fase movil A - TFA acuoso al 0.1%, fase movil B - Acetonitrilo; tasa de flujo 6 ml/min; Gradiente - típicamente comenzando a 90 % A/10 % B durante 1 minuto, llegando a 97 % después de 15 minutos, manteniendose durante 2 minutos, luego regresando a las condiciones iniciales. Columna: Cromatografía Jones Genesis 4µm, Columna C18, 10 mm X 250 mm. Adquisión máxima basada en detección UV a 254 nm.

Identificación de muestras

Método de Control de Calidad (QC) QC2- AQ

Los espectros de masa se registraron sobre un instrumento Waters ZQ en modo de ionización con electrospray. Fase movil A - ácido fórmico acuoso al 0.1%. Fase movil B - ácido fórmico al 0.1% en acetonitrilo; Tasa de flujo 2 ml/min; Gradiente - comenzando a 100 % A/0 % B durante 1 minuto, llegando a 95 % B después de 7 minutos y manteniendose durante 2 minutos antes de regresar a las condiciones iniciales. Columna: Varia, actualmente Genesis AQ 120ª 4u 50mm X 4.6mm, Hichrom Ltd. Detección PDA Waters 996, rango de exploración 210- 400 nm.

Método de Control de Calidad (QC) QC2- Long

Los espectros de masa se registraron sobre un instrumento Waters ZQ en modo de ionización de Electroatomización. Fase movil A - ácido fórmico acuoso al 0.1%. Fase movil B - ácido fórmico al 0.1% en acetonitrilo; Tasa de flujo 2 ml/min; Gradiente - comenzando a 95 % A/5 % B. llegando a 95 % B después de 20 minutos y manteniendose durante 3 minutos antes de regresar a las condiciones iniciales. Columna: Varia, pero siempre C18 50 mm X 4.6 mm

(actualmente Genesis C18 4u 50mm X 4.6mm, Hichrom Ltd) . Detección PDA Waters 996, rango de exploración 210- 400 nm.

Método de Control de Calidad (QC) QC2- QC

Los espectros de masa se registraron sobre un instrumento Waters ZQ en modo de ionización de Electroatomización. Fase movil A - ácido fórmico acuoso al 0.1%. Fase movil B - ácido fórmico al 0.1% en acetonitrilo; Tasa de flujo 2 ml/min; Gradiente - comenzando a 95 % A/5 % B, llegando a 95 % B después de 5 minutos y manteniendose durante 5 minutos antes de regresar a las condiciones iniciales. Columna: Varia, pero siempre C18 50 mm X 4.6 mm (actualmente Genesis C18 4 urn 50 X 4.6 mm, Hichrom Ltd) . Detección PDA Waters 996, rango de exploración 210- 400 nm.

Método de Control de Calidad (QC) QC3- AQ- Long

Los espectros de masa se registraron sobre un instrumento Waters ZQ en modo de ionización de Electroatomización. Fase movil A - ácido fórmico acuoso al 0.1%. Fase movil B - ácido fórmico al 0.1% en acetonitrilo; Tasa de flujo 2 ml/min; Gradient - comenzando a 100 % A/0 % B durante 1 minuto, llegando a 95 % B después de 20 minutos o manteniendose durante 5 minutos antes de regresar a las condiciones iniciales. Columna: Varia, actualmente Genesis AQ 4um 50mm X 4.6mm, Hichrom Ltd. Detección PDA Waters 996, rango de exploración 210- 400 nm.

Los ejemplos lu, 9a, 18bs, 18bv, 18bw, 18bx, 18by, 18bz, 18ca, 18cb, 18cc, 18cd, 18ce, 18cf, 18cg, 18ch, 18ci, 18cj, 18ck, 18cL 18cm, 18dk, 18dland 18dm se analizaron utilizando el Método de Control de Calidad (QC) QC2- AQ.

Los ejemplos 12c, 12d, 13c, 13e, 13g, 14b, 15b, 18aa, 18ab, 18ac, 18ad, 18ae, 18af, 18ag, 18ah, 18ai, 18aj, 18ak, 18al, 18am, 18an, 18ao, 18ap, 18aq, 18ar, 18as, 18at, 18au, 18az, 18bc, 18bl, 18bm, 18bt, 18bu, 18cn, 18co, 18cp, 18cq, 18cr, 18cs, 18ct, 18cu, 18cv, 18cw, 18cx, 18ci, 18cz, 18da, 18db, 18dc, 18df, 18dj, 181, 18o, 18q, 18r, 18s, 18t, 18u, 18v, 18w, 18x, 18y, 18z, 19a, 19b, 19c, 19d, 19e, 19f, 19g, 19h, 19i, 19j, 19k, 191, 19m, 19n, 19o, la, laa, lab, lac, lad, lae, laf, lag, lah, lai, lak, las, lau, laz, lbb, lcq, let, ldg, lee, lg, li, lm, lw, lx, ly, lz, 21a, 3a, 3ac, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3v, 3w, 3x, 3y, 3z, 4j, 4k, 41, 4m, 4n, 4o, 4p, 6a, comparativos del Ejemplo lc, comparativos de Ejemplo lj y comparativos del Ejemplo Ik se analizaron utilizando el Método de Control de Calidad (QC) QC2- Long.

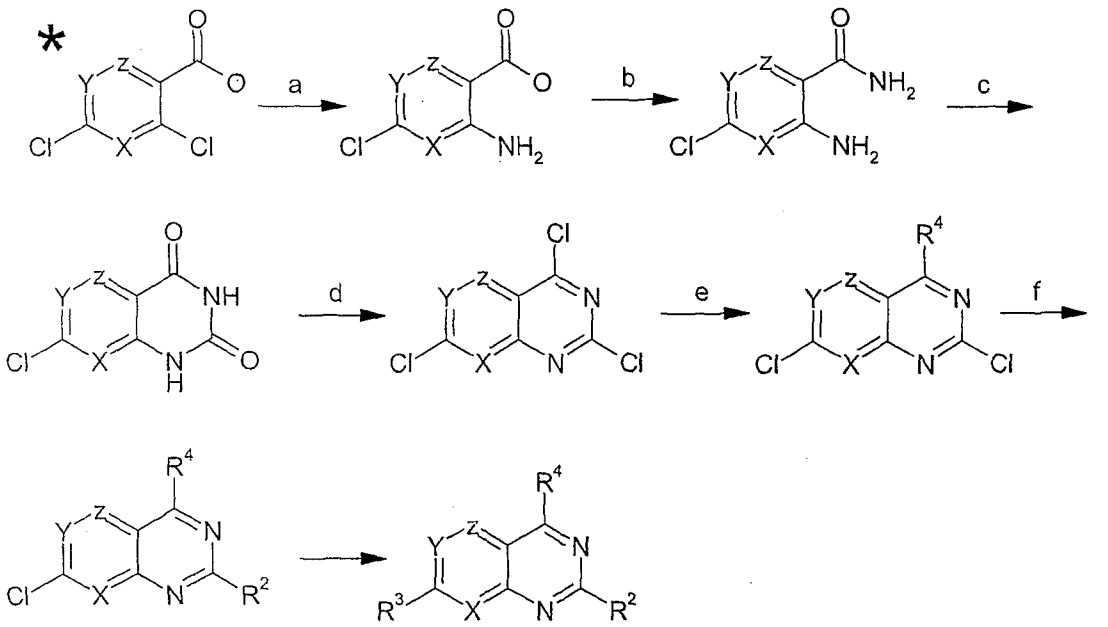
Los ejemplos 10a, 11a, 12a, 12b, 12e, 13a, 13b, 13d, 13f, 14a, 15a, 15c, 16a, 17a, 18a, 18av, 18aw, 18ax, 18ay, 18b, 18ba, 18bb, 18bd, 18be, 18bf, 18bg, 18bh, 18bi, 18bj, 18bk, 18bn, 18bo, 18bp, 18bq, 18br, 18c, 18d, 18dd, 18de, 18dg, 18dh, 18di, 18dn, 18do, 18e, 18f, 18g, 18h, 18i, 18j, 18k, 18m, 18n, 19p, 19q, 19r, 19s, 19t, 19u, 19v, 19w, 19x, laj, lal, lam, Ian, lao, lap, laq, lar, lat, lav, law, lax, lay, lb, lba, lbc, lbe, lbf, lbg, lbh, lbi, lbj, lbk, lbl, lbm, lbn, lbo, lbp, lbq, lbr, lbs, lbt, lbu, lbv, lbw, lbx, lby, lbz, lc, lea, leb, lec, led, Ice, lef, leg, lch, lei, lcj, lck, lcl, 1cm, len, lco, lep, lcr, les, leu, lev, lew, lex, Ici, lcz, Id, Ida, ldb, ldc, ldd, lde, ldf, ldh, ldi, ldj, Idk, ldl, 1dm, ldn, ldo, ldp, ldq, ldr, Ids, ldt, ldu, ldv, ldw, ldx, ldy, ldz, le, lea, leb, led, lee, Si, lh, lj, Ik, 11, En, lo, lp, lq, lr, Es, It, lv, 20a, 20b, 20c, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 3aa, 3ab, 3ad, 3k, 31, 3m, 3n, 3o, 3p, 3q, 3r, 3s, 3t, 3u, 4a, 4aa, 4ab, 4ac, 4ad, 4ae, 4af, 4ag, 4ah, 4ai, 4aj, 4ak, 4al, 4am, 4an, 4ao, 4ap, 4aq, 4ar, 4as, 4at, 4au, 4av, 4aw, 4ax, 4ay, 4az, 4b, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4q, 4r, 4s, 4t, 4u, 4v, 4w, 4x, 4y, 4z, 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 51, 5m, 5n, 5o, 5p, 5q, 5r, 5s, 5t, 5u, 5v, 5w, 5x, 5y, 5z, 7a, 7b, 7c, 7d, 7e, 7f, 7g, 7h, 7i, 7j, 7k, 8a, 8b, 8c, 8d, comparativos del Ejemplo la y comparativos del Ejemplo lb, se analizaron utilizando el Método de Control de Calidad (QC) QC2- QC.

Los ejemplos 18p y lbd se analizaron utilizando el Método de Control de Calidad (QC) QC3-AQ~Largo.

Síntesis de microondas

Las reacciones se realizaron utilizando una unidad de síntesis acelerada con microondas Personal Chemistry™ Emrys Optimizer con brazo robótico. Rango de potencia entre 0- 300 W a 2.45 GHz. Rango de presión entre 0- 20 barios; aumento de temperatura entre 2- 5°C/seg; rango de temperatura 60- 250°C.

Procedimiento general para la sítesis de derivados de piridopirimidina 2,4,7- substituida:

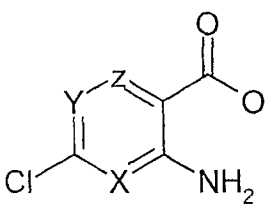


ácido *2- amino- 6- cloronicotínico - X=N, Y=C, Z=C

ácido *3- amino- cloroisonicotínico - X=C, Y=N, Z=C

ácido *3- Amino- cloropiridina- 2- carboxílico - X=C, Y=C, Z=N

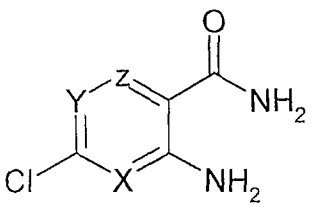
a) NH3,14 barios ; b) (i) SOCl2, THF, r.t, (ii) NH_3 c) Cloruro de oxalilo, Tolueno, Δ; d) DIPEA, $POCl_3$, Tolueno o Anisol, Δ;e) Amina apropiada, diisopropiletilamina, CH_2Cl_2 o Anisol; f) Amina apropiada, amina de diisopropiletilo, DMA, 70 °C;



Al ácido amino apropiado (1 equiv) se agregó amoniaco líquido (suficiente para preparar una solución 0.6M de sustrato en amoniaco) . La suspensión se selló en un recipiente a presión el cual luego se calentó lentamente a 130 °C. Se notó que a esta tempeatura, se observó una presión de 18 barios. Esta temperatura y presión se mantuvieron durante 16 horas más después de lo cual la mezcla se enfrió a temperatura ambiente. El recpiente a presión se abrió y la reacción se vertió

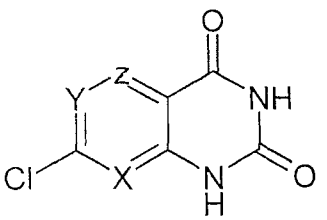
en agua helada (1 volumen de reacción) . La solución resultante se acidificó a ph 1- 2 utilizando HCl concentrado el cual produjo la formación de un precipitado. La mezcla ácida se dejo calentar a temperatura ambiente y se agitó durante 30 minutos más Luego la suspensión se extrajo con éter dietílico (3 X 400 ml) . Luego los extractos orgánicos combinados se filtraron y el filtrado se concentró al vacío para proporcionar un sólido blancoel cual se secó adicionalmente sobre P_2O_5 para proporcionar el compuesto del título (típicamente rendimiento de 80- 90% o 90 %+ puro) en forma apropiadamente pura para utilizar sin purificación adicional.

ácido 2- amino- 6- cloronicotínico - X=N, Y=C, Z=C: (90 % rendimiento, *96* % pureza) m/z (LC- MS. ESP) : 173 $[M+H]^+$ R/T = 3.63 min



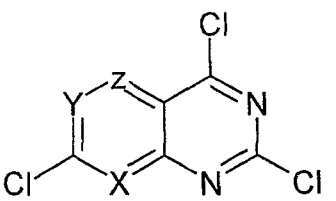
A una solución 0.3 M de aminoácido(1 equiv) en THF anhidro, bajo una atmósfera inerte, se agregó cloruro de tionilo (3.3 equiv) por goteo. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Después de este tiempo la reacción se concentró al vacío para proporcionar un residuo sólido crudo amarillo. El sólido crudo se disolvió en THF (igual a volumen de reacción inicial) y se concentró al vacío nuevamente para proporcionar un residuo sólido amarillo. El residuo se disolvió una vez más en THF y se concentró como antes para proporcionar un residuo sólido el cual luego se disolvió en THF (para proporcionar una solución de 0.3M) y gas de amoniaco burbujeado a través de la solución durante 1 hora. El precipitado resultante se retiro mediante filtración y el filtrado se concentró al vacío para proporcionar un precipitado amarillo el cual se trituró con agua a 50 °C luego se seco para proporcionar el compuesto del titulo (típicamente 90- 95 % rendimiento) y apropiadamente suficientemente limpio para utilizar sin purificación adicional.

2- Amino- 6- cloronicotinamida - X=N, Y=C, Z=C: (92 % rendimiento, 93 % pureza) m/z (LC-MS. ESP) : 172 $[M+H]^+$ R/T = 3.19 min



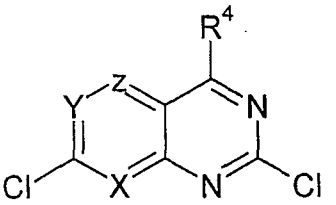
A una solución agitada (0.06 M) de sustrato (1 equiv) en tolueno anhidro bajo una atmósfera inerte se agregó cloruro de oxalilo (1.2 equiv) por goteo. Luego la mezcla resultante se calentó hasta reflujo (115 °C) durante 4 horas después de lo cual se enfrió y agitó durante 16 horas más. Luego la mezcla de reacción cruda se concentró a la mitad de su volumen *al vacío* y filtró para proporcionar el producto deseado en forma apropiadamente pura para utilizar sin purificación adicional.

7- Cloro- lH- pirido[2,3- d]pirimidina- 2,4- diona- X=N, Y=C, Z=C: (95 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 196 [M- H]" R/T = 3.22 min



A una suspensión 0.5 M agitada de la diona apropiada (1 equiv) en tolueno anhidro bajo una atmósfera inerte se agregó lentamente diisopropiletilamina (3 equiv) . Luego la mezcla de reacción se calentó a 70 °C durante 30 minutos y luego se enfrió a temperatura ambiente antes de la adición de $POCl_3$ (3 equiv) . Luego la reacción se calentó a 100 °C durante 2.5 horas antes de enfriar y concentrar *al vacío* para proporcionar una pasta aguada cruda la cual luego se suspendio en EtOAc y filtró a través de una almohadilla delgada de Celite™. El filtrado se concentró *al vacío* para proporcionar un aceite marrón el cual se disolvió en CH_2Cl_2 y se agitó sobre gel de sílice durante 30 minutos. Después de este tiempo el sílice se retiró mediante filtración, el filtrado se concentró y el residuo crudo se purificó mediante cromatografia rápida (SiO_2) para proporcionar el compuesto del titulo en forma analiticamente pura.

2.4.7- Tricloro- pirido[2,3- d]pirimidina- X=N, Y=C, Z=C: (48 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 234 $[M+H]^+$ R/T = 4.21 min



A una solución agitada fria (0- 5°C) (0.1 M) del tricloro- sustrato apropiado (1 equiv) en CH_2Cl_2 se agregó diisopropiletilamina (1 equiv) por goteo. Luego la amina apropiada (1 equiv) se agregó a la mezcla de reacción por porciones durante el periodo de 1 hora. La solución se mantuvo a temperatura ambiente con agitación durante 1 hora más antes de lavar la mezcla con agua (2x1 volumen de reacción) . Los extractos acuosos se combinaron y extrajeron con CH_2Cl_2 (2x1 volumen de reacción) . Luego los extractos orgánicos se combinaron, secaron (sulfato de sodio) . filtraron y concentraron *al vacío* para proporcionar un residuo aceitoso el cual se solidificó ante secado prolongado. El sólido se trituró con éter dietílico y luego se filtró y la torta se lavó con éter dietílico frio para dejar el compuesto del título en una forma limpia apropiada para utilizar sin purificación adicional.

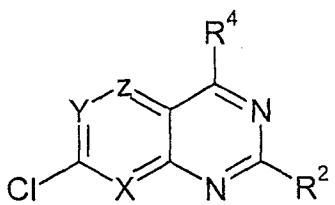
2.7- Dicloro- 4- morfolin- 4- il- pirido[2,3- d]pirimidina - Rl= morfolina, X=N, Y=C, Z=C: (92 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 285 $[M+H]^+$ R/T = 3.90 min

2,7- Dicloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina - Rl= (S) - 3- Metil- morfolina, X=N, Y=C, Z=C: (87 % rendimiento, 92 % pureza) m/z (LC- MS, ESP) : 301 $[M+H]^+$ R/T = 4.13 min

2,7- Dicloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina - Rl= ®- 3- Metil- morfolina: (99 % rendimiento, 94 % pureza) m/z (LC- MS, ESP) : 301 $[M+H]^+$ R/T = 3.49 min

Alternativamente, a una suspensión 0.47 M agitada de la diona apropiada (1 equiv) en anisol anhidro bajo una atmósfera inerte se agregó $POCl_3$ (2.6 equiv) . La mezcla se calentó a 55 °C y luego se agregó diisopropiletilamina (2.6 equiv) lentamente. Luego la mezcla de reacción se calentó a 85- 90 °C durante 30 minutos. Se agregó agua en porciones (0.15 equiv) , y la mezcla de reacción se mantuvo a 85- 90 °C durante 30 minutos adicionales. La reacción se enfrió a 50 °C, y luego 15% del solvente anisol se retiró mediante destilación al vacío. Luego la mezcla se enfrió a - 5 °C y se agregó diisopropiletilamina (1.1 equiv) . Luego se agregó una solución 4.9M

de la amina apropiada (1.05 equiv) en Anisol a la mezcla de reacción continuamente durante un periodo de 1 hora. Luego la solución se calentó a 30 °C y la reacción se monitoreo mediante HPLC hasta terminar la reacción. Luego se agregó un tercio de la mezcla resultante de la reacción anterior durante 10 minutos a una mezcla agitada de 1.95M hidróxido de potasio acuoso (3.9 equiv) y i- butanol (6.9 equiv) a 60 °C. La agitación se detuvo, las fases se dejaron separar, y la fase acuosa se retiró. Se reasumió la agitación, y se agregó 1.95M hidroxido de potasio acuoso (3.9 equiv) a la fase orgánica retenida. Luego se agrego el segundo tercio de la mezcla de reacción resultante de la reacción anterior durante 10 minutos a 60 °C. Nuevamente, la agitación fue detenida, las fases se dejaron separar, y la fase acuosa se retiró. Se reasumió la agitación, y y se agregó 1.95M hidroxido de potasio acuoso (3.9 equiv) a la fase orgánica retenida. El tercio restante de la mezcla de reacción resultante de la reacción anterior luego se agregó durante 10 minutos a 60 °C. Nuevamente, la agitación fue detenida, las fases se dejaron separar, y la fase acuosa se retiró. Luego se agregó agua a la fase orgánica con agitación, y la mezcla agitada se calentó a 75 °C. La agitación fue detenida, las fases se dejaron separar, y la fase acuosa se retiró. La fase orgánica resultante fue agitada y dejada enfriar a 30 °C, y luego a medida que la mezcla se calentó a 60 °C, se agregó heptano (11.5 equiv) durante 20 minutos cuando la mezcla estuvo a 40 °C aproximadamente. Después de ser calentada a 60 °C, la mezcla se enfrió durante 2.5h a 10 °C. Después de 30min, la pasta aguada resultante se filtró, lavó con una mezcla 10:1 heptano:anisol (2 x 1.4equiv) y luego se lavó con heptano (2 x 1.4equiv) . Luego el sólido se secó en un horno de vacío a 50 °C para dejar el compuesto del título en una forma limpia apropiada para utilizar sin purificación adicional.



A una solución (0.2 M) del dicloro- sustrato apropiado (1 equiv) en acetamida de dimetilo anhidro bajo una atmósfera inerte se agregó diisopropiletilamina (1 equiv) seguido por la amina apropiada (1 equiv) . La mezcla resultante se calentó durante 48 horas a 70 °C antes de ser enfriada a temperatura ambiente. La reacción se diluyó con CH_2Cl_2 (1 volumen de reacción)

y luego se lavó con agua (3x1 volumenes de reacción) . El extracto orgánico se concentró *al vacío* para proporcionar un jarabe el cual se disolvió en EtOAc (1 volumen de reacción) y se lavó con solución de salmuera saturada antes de secar (sulfato de sodio) y concentrar *al vacío* para proporcionar un aceite. El residuo crudo se purificó mediante cromatografia rápida (SiO_2, eluida con EtOAc:Hex (7:3) llegando a (1:1)) para proporcionar el compuesto del titulo como un sólido amarillo que fue apropiadamente limpio para utilizar sin purificación adicional.

7- Cloro- 2- ((2S,6R) - 2,6- dimetil- morfolin- 4- il) - 4- morfolin- 4- il- pirido[2,3- d]pirimidina - Rl= morfolina, R2=cis- dimetilmorfolina, X=N, Y=C, Z=C: (45 % rendimiento, 85 % pureza) m/z (LC- MS, ESP) : 348 $[M+H]^+$ R/T = 4.16 min

7- Cloro- 4- ((S) ~3 - metil- morfolin- 4- il) - 2- ((S) - 3 - metil- morfolin- 4- il) - pirido[2,3 - d]pirimidina - Rl= (S) - 3- Metil- morfolina, R2=(S) - 3- Metil- morfolina, X=N, Y=C, Z=C: (71 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 364 $[M+H]^+$ R/T = 3.52 min

7- Cloro- 2- (2- etilo- piperidin- l- il) - 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina - Rl = (S) - 3- Metil- morfolina, R2 = 2- Etilo- piperidina, X=N, Y=C, Z=C: (51 % rendimiento, 98 % pureza) m/z (LC- MS, ESP) : 376 $[M+H]^+$ R/T = 3.88 min

7- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- morfolin- 4- il- pirido[2,3- d]pirimidina, - Rl = (S) - 3- Metil- morfolina, R2 = morfolina, X=N, Y=C, Z=C: (72 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 350 $[M+H]^+$ R/T = 3.45 min

7- Cloro- 2- ((2S,6R) - 2,6- dimetil- morfolin- 4- il) - 4- ((S) - 3- metil- morfolin- 4- il- pirido[2,3- d]pirimidina - Rl= (S) - 3- Metil- morfolina, R2=cis- dimetilmorfolina: (33 % rendimiento) m/z (LC- MS, ESP) : 378 $[M+H]^+$ R/T - 3.68 min

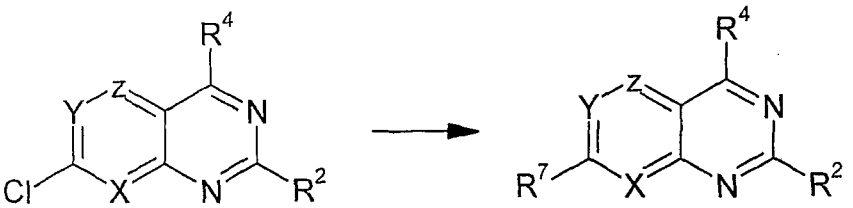
7- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- (®- 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina, - Rl = R2 = (R) - 3- Metil- morfolina: (48 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 364 $[M+H]^+$ R/T = 2.80 min

A una solución 0.33 M de 2,7- dicloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina (1 equiv) en N,N- dimetilacetamida se agregó base de Hunig (1 equiv) seguido por la amina apropiada (1.1 equiv) . La mezcla de reacción se calentó a 40 °C durante 1 hora. Después de este tiempo la reacción se dejo enfriar, se diluyó con EtOAc (1 volumen de reacción) y luego se lavó con agua (1 volumen de reacción) . La fracción acuosa se retiró y extrajo

adicionalmente con EtOAc (2X1 volumen de reacción) . Los extractos orgánicos combinados se secaron ($MgSO_4$) , filtraron y concentraron *al vacío* para proporcionar un residuo aceitoso crudo el cual se purificó mediante cromatografía rápida (SiO_2) utilizando EtOAc/Hexanos como eluyente el cual proporció los productos deseados en una forma apropiadamente limpia.

7- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- tiomoifolin- 4- il- pirido[2,3- d]pirimidina: (30 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 366.4$[M+H]^+$ R/T = 3.00 min

7- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- (4- metil- piperazin- l- il) - pirido[2,3- d]pirimidina:(32 % rendimiento, 95 % pureza) m/z (LC- MS, ESP) : 363.4$[M+H]^+$ R/T = 2.37 min

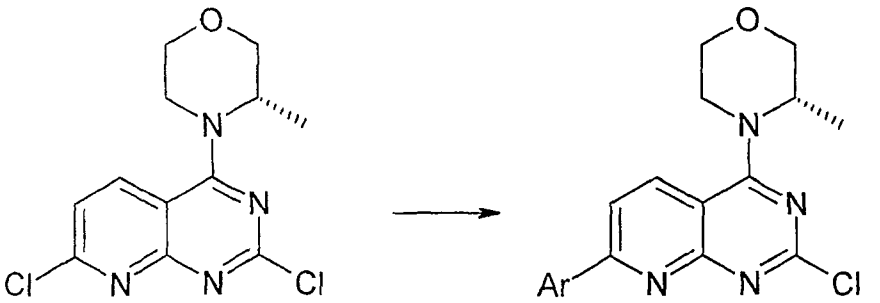


El cloro- sustrato apropiado (1 equiv) se disolvió en una solución tolueno/etanol (1:1) (0.02 M) . Luego se agregó carbonato de sodio (2 equiv) y el pinacolato de éster borónico apropiado o ácido borónico (1 equiv) , seguido por tetrakis(trifenilfosfina) paladio (0.1 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron *al vacío.* Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

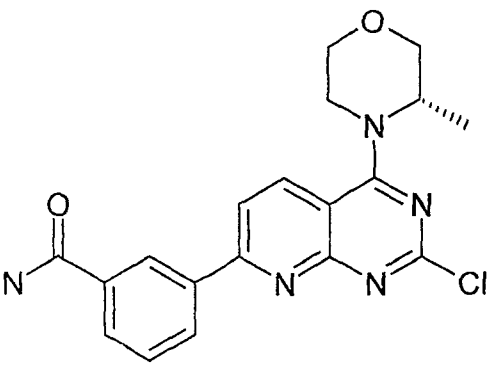
Ejemplo 1:

Preparación de Intermedios de piridopirimidina 2,4,7- substituida:

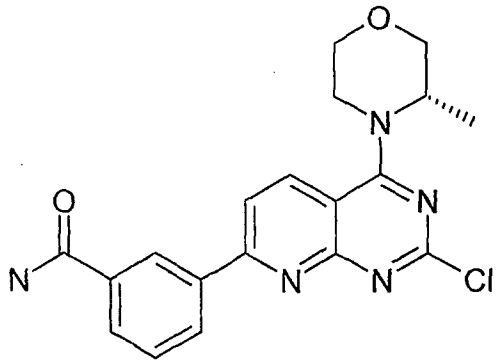
Procedimientos para la síntesis de derivados de 2- cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 7- aryl- pirido[2,3- d]pirimidina



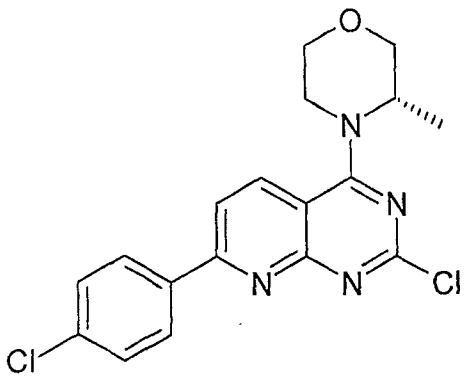
A una solución (0.1 M) de 2,7- dicloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3-d]pirimidina (1 equiv) en MeCN/H_2O (1:1 mezcla) se agregó el pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y carbonato de potasio (3 equiv) . La mezcla se degasificó con nitrógeno durante 20 minutos antes de la adición de tetrakis(trifenilfosfina) paladio° (0.05 equiv) . La reacción se degasificó durante 5 minutos más antes de ser calentada a reflujo bajo una atmósfera inerte durante 3 horas. Después de lo cual, se concentró al vacío y el residuo crudo se particionó entre CH_2Cl_2/H_2O. La fracción orgánica se secó (MgS04) , filtró y concentró al vacío para proporcionar un aceite el cual se purificó adicionalmente mediante cromatografia rápida (SiO_2) utilizando 5 % MeOH en CH_2Cl_2 como eluyente.



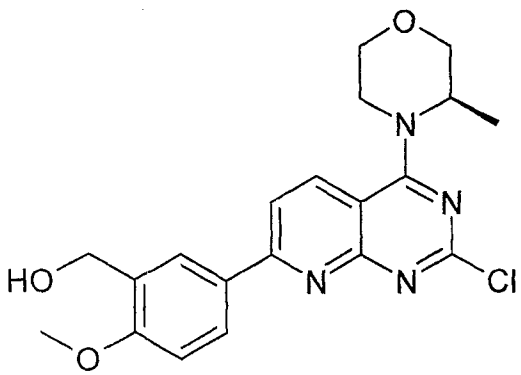
3- [2- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- benzamida: (27% rendimiento, 99 % pureza) m/z (LC- MS,ESP) :384.3 [M+H]+, R/T = 3.13 min)



5- [2- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- ilamina: (93 % rendimiento, 89 % pureza) m/z (LC- MS,ESP) :357 [M+H]+, R/T = 2.53 min)

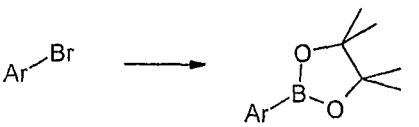


2- Cloro- 7- (4- cloro- fenil) - 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina: (80 % rendimiento, 85 % pureza) m/z (LC- MS,ESP) :357.5 $[M+H]^+$, R/T = 4.26 min)

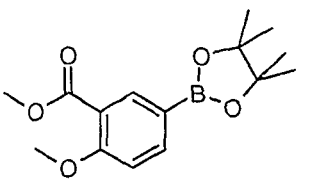


{ 5- [2- Cloro- 4- (®- 3 - metil- morfolin- 4- il) - pirido[2,3 - d]pirimidin- 7- il]- 2- metoxi- fenil}- metanol: (97 % rendimiento, 93 % pureza) m/z (LC- MS,ESP) :401 $[M+H]^+$, R/T = 3.42 min)

Procedimientos para la síntesis de éster borónico:

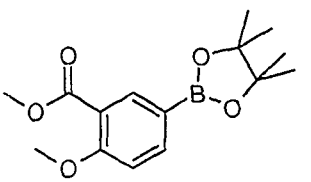


Se disolvió éster metílico del ácido 5- bromo- 2~metoxibenzóico (1 equiv) en dioxano (0.1 M) . Se agregó Bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) o dppf (0.05 equiv) y la mezcla se degasificó con nitrógeno durante 20 minutos. Se agregó (1,1'-Bis(difenilfosfino) ferroceno- dicloropaladio (0.05 equiv) y la mezcla se degasificó durante 5 minutos más. La mezcla de reacción se calentó a 120 °C durante 2 horas bajo nitrógeno. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con CH_2Cl_2 y se filtró a través de Celite™. El filtrado se concentró al vacío para proporcionar un aceite oscuro. El residuo se particionó entre EtOAc y bicarbonato de sodio acuoso saturado y la capa acuosa se extrajo adicionalmente con EtOAc. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y el filtrado se concentró al vacío para proporcionar un residuo oscuro el cual se purificó mediante cromatografia en columna rápida sobre gel de sílice eluyendo con entre 0 y 30 % de etilacetato en hexano.



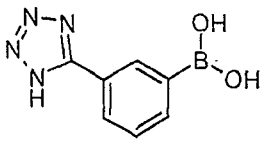
Éster metílico del ácido 2- Metoxi- 5- (4,4,5,5- tetrametil- [1,3,2]dioxaborolan- 2- il) - benzóico: (77 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 293.5 [M+H]+ R/T = 4.24 min

Procedimientos para la síntesis de ácidos tetrazolil- borónicos:



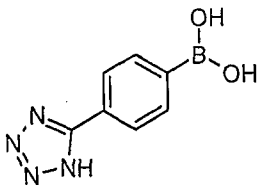
El éster de boro de cianofenilpinacolato apropiado o ácido borónico (1 equiv) se disolvió en DMF (0.67 M) . se agregó Azida de sodio (6 equiv) y cloruro de amonio (6 equiv) . La mezcla de reacción se calentó a 120°C durante 2.5 horas. Después de enfriar, la mezcla de

reacción se vertió en una mezcla de agua helada y EtOAc. Se agregó nitrato de sodio y la fase acuosa se acidificó mediante HCl 6N hasta pH 2. La mezcla se dejo agitar a temperatura ambiente durante 30 minutos y luego se extrajo con EtOAc y n- butanol. Las fracciones orgánicas se recolectaron, secaron sobre sulfato de sodio, filtraron y concentraron al vacío, para proporcionar un residuo crudo el cual se purificó adicionalmente consecuentemente:



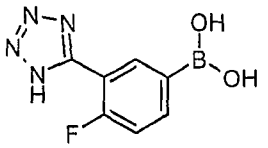
El residuo crudo se recristalizó a partir de CH_2Cl_2/hexano, obteniendo el producto deseado como un sólido blanco.

[3- (lH- tetrazol- 5- il) fenil]ácido borónico: (15 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 191 [M+H]+ R/T = 2.49 min



El residuo crudo se recristalizó a partir de CH_2Cl_2/hexano, para proporcionar el producto deseado como un sólido blanco.

Ácido [4- (lH- tetrazol- 5- il) fenil]borónico: (64 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 191 [M+H]+ R/T - 2.49 min



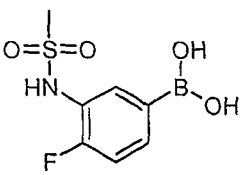
El residuo se purificó mediante columna de fase inversa utilizando un gradiente a partir de acetotrilo de 5 % a 20 % en solución de 0.1 % ácido fórmico/agua, proporcionando el producto deseado.

Ácido [4- fluoro- 3- (lH- tetrazol- 5- il) fenil]borónico: (18 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 207 [M- H]- R/T = 2.51 min

Procedimiento para la síntesis de ácido metanosulfoniloamido- borónico:

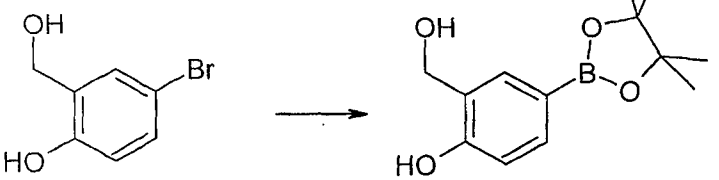


Se disolvió ácido 3- Amino- 4- fluorofenilborónico (1 equiv) en THF (0.1 M) . Se agregó cloruro de metano- sulfonilo (10 equiv) y piridina (1 equiv) . La mezcla de reacción se calentó a 70°C durante 30 minutos. Después de enfriar, la mezcla de reacción se concentró al vacío, para proporcionar un residuo crudo el cual se utilizo sin purificación adicional.



Ácido 3- (Metanosulfoniloamino) - 4- fluoro- fenilborónico: (51 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 232 [M- H]- R/T = 2.50 min

Procedimiento para la síntesis de 3- hidroximetil- 5- (4,4,5,5- tetrametil- [1,3,2] dioxaborolan- 2- il) - pyridin- 2- ol

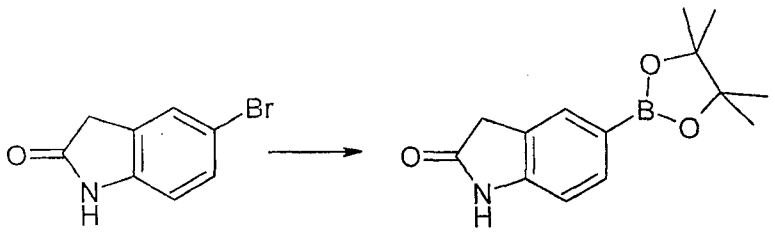


A una solución 0.18 M de alcohol 5- bromo- 2- hidroxibencílico (1 equiv) en dioxano se agregó bis(pinacolato) diboro (1.2 equiv) y acetato potásico (3.5 equiv) seguido por 1,1'- bis(difenilfosfino) ferroceno (0.05 equiv) . La mezcla se degasificó con nitrógeno durante 20 minutos. Se agregó $PdCl_2$ (dppf) (0.05 equiv) y la mezcla se degasificó durante 5 minutos más.

Luego la reacción se calentó a reflujo bajo una atmósfera inerte durante 2 horas. Al terminar, la reacción se enfrió, filtró y concentró al vacío para proporcionar un residuo crudo el cual se purificó mediante cromatografía rápida (SiO_2) utilizando EtOAc/Hexanos —1:1 como eluyente para proporcionar el producto deseado.

3- Hidroximetil- 5- (4,4,5,5- tetrametil- [1,3,2] dioxaborolan- 2- il) - piridin- 2- ol- 6- Bromo- 3 H- pirido[2,3- d]pirimidin- 4- ona: (67 % rendimiento, 94 % pureza) m/z (LC- MS,ESP) :251 $[M- H]^-$ R/T = 3.32 minutos)

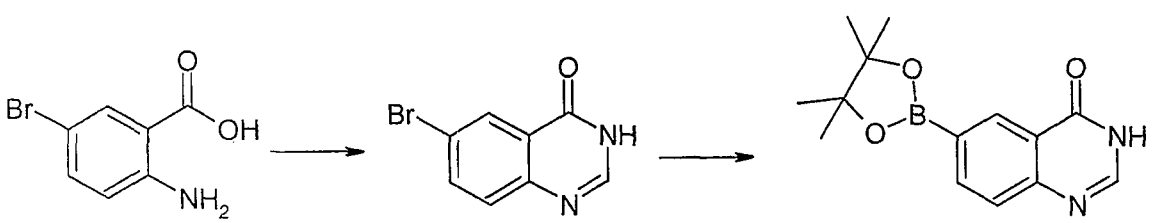
Procedimiento para la síntesis de 5- (4,4,5,5- Tetrametil- [l,3,2]dioxaborolan- 2- il) - l,3- dihidro- pirrolo[2,3- b] piridin- 2- ona



A una solución 0.05 M de 5- bromo- l,3- dihidro- pirrolo[2,3- b]piridin- 2- ona (1 equiv) en dioxano se agregó bis(pinacolato) diboro (1.2 eqiv) y acetato potásico (1.5 equiv) seguido por l.l`- bis(difenilfosfino) ferroceno (0.05 equiv) . La mezcla se degasificó con nitrógeno durante 20 minutos. Se agregó $PdCl_2$(dppf) (0.05 equiv) y la mezcla se degasificó durante 5 minutos más. Luego la reacción se calentó a 120 °C bajo una atmósfera inerte durante 8 horas. Al terminar, la reacción se enfrió, filtró y concentró al vacío para proporcionar un residuo crudo el cual se purificó mediante cromatografia rápida (SiOa) utilizando EtOAc/Hexanos - 4:1 como eluyente para proporcionar el producto deseado.

5- (4.4.5.5- Tetrametil- [l,3,2]dioxaborolan- 2- il) - l,3- dihidro- pirrolo[2,3- b]piridin- 2- ona: (68 % rendimiento, 92 % pureza) m/z (LC- MS,ESP) :260 $[M- H]^-$ R/T = 3.52 minutos)

Procedimiento para la síntesis de éster borónico de 6- (4,4,5,5- Tetrametil- [l,3,2]dioxaborolan- 2- il) - 3H- pirido[2,3- d]pirimidin- 4- ona



A una solución 1.2 M de ácido 5- bromoantranílico (1 equiv) en N,N- dimetilformamida se agregó acetato de formamidina (1 equiv) . La mezcla se calentó a reflujo y se agitó a esta temperatura durante 16 horas. Después de este tiempo, la reacción fue enfriada y se agregó

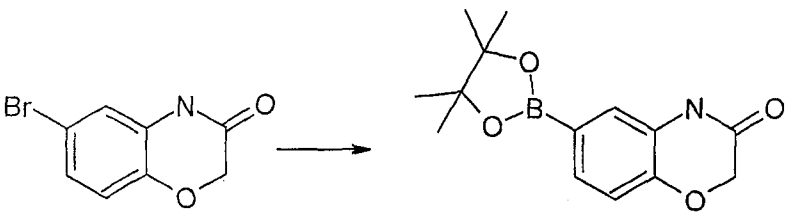
cuidadosamente solución $NaHCO_3$ (5 % en H_2O) (3 volumes) y la mezcla se agitó vigorosamente. El precipitado resultante se recolectó mediante filtración y luego se lavó con agua (2X1 volume) y luego éter t- butilmetílico (2X1 volumen) antes de ser secado en un horno de vacío para proporcionar el producto deseado el cual no requirio purificación adicional.

6- Bromo- 3H- pirido[2,3~d]pirimidin- 4- ona: (91 % rendimiento, inserto) m/z (LC- MS,ESP) :225 $[M- H]^-$ R/T = 2.31 minutos)

A una solución (0.35M) de 6- bromo- 3H- pirido[2,3- d]pirimidin- 4- ona (1 equiv) en dioxano se agregó bis(pinacolato) diboron (1.2 eqiv) y acetato potásico (1.5 equiv) seguido por 1,1`- bis(difenilfosfino) ferroceno (0.05 equiv) . La mezcla se degasificó con nitrógeno durante 20 minutos. Se agregó $PdCl_2$(dppf) (0.05 equiv) y la mezcla se degasificó durante 5 minutos más. Luego la reacción se calentó a reflujo bajo una atmósfera inerte durante 16 horas. Después de este tiempo, la mezcla fue enfriada, filtrada a través de Celite ™ y luego particionada entre CH_2Cl_2/$NaHCO_3$(aq) . La fracción orgánica fue retirada, secada ($MgSO_4$) , filtrada y concentrada al vacío. El residuo crudo se purificó mediante cromatografia rápida (SiO_2) 1:1- Hexanos:EtOAc llegando un EtOAc puro. Luego el material puro se disolvió en el volumen mínimo de CH_2Cl_2 y se agregó hexano para precipitar el producto deseado como un sólido cristalino blanco

6- (4.4.5.5- Tetrametil- [l,3,2]dioxaborolan- 2- il) - 3H- pirido[2,3- d]pirimidin- 4- ona (15 % rendimiento, 96 % pureza) m/z (LC- MS,ESP) : Ión de masa no observable, R/T = 3.30 min)

Procedimiento para la síntesis de 7- (4,4,5,5- Tetrametil- [1,3,2] dioxaborolan- 2- il) - lH- pirido [2,3- b] [1,4] oxazin- 2- ona



A una solución 0.3 M de 7- bromo- lH- pirido[2,3- b][l,4]oxazin- 2- ona (1 equiv) se agregó bis(pinacolato) diboro (1.10 equiv) , acetato potásico (3.5 equiv) y 1,1' bis(difenilfosfino) ferroceno (0.05 equiv) . La mezcla se degasificó con nitrógeno durante 20 minutos antes de la adición de $PdCl_2$(dppf) (0.05 equiv) y degasificar durante 5 minutos más

minutos. Se fijo un condensador al recipiente de reacción y la mezcla se calentó a reflujo bajo

una atmósfera inerte durante 16 horas. Después de este tiempo, la reacción fue enfriada, filtrada a través de Celite ™. La torta fue lavada CH_2Cl_2 y el filtrado se concentró al vacío antes de ser disuelto nuevamente en EtOAc y lavado con H_2O y luego salmuera saturada. La fracción orgánica fue separada, secada (MgSO4) y concentrada al vacío para proporcionar un residuo crudo el cual se purificó adicionalmente mediante cromatografía rápida (SiO_2) utilizando 1:1-EtOAc :Hexanos llegando un EtOAc puro como eluyente para proporcionar el producto deseado.

7- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - lH- pirido[2,3- b][1,4]oxazin- 2- ona: (97% rendimiento, 90 % pureza) m/z (LC- MS,ESP) :317 [M+H+MeCN]+, R/T = 3.72 min)

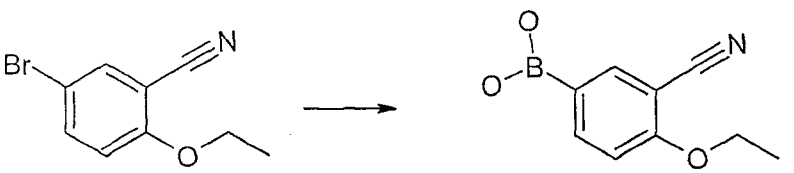
Procedimiento para la síntesis de ácido 2- Metoxinicotinonitrilo- 5- borónico



A una solución fria (- 78 °C) (0.25 M) de 5- bromo- 2- metoxibenzonitrilo en THF se agregó por goteo n- BuLi (1.10 equiv de una solución 2.5 M en hexanos) . La mezcla se mantuvo a esta temperatura con agitación durante 45 minutos antes de la adición de triisopropilborato (1.25 equiv) . Luego la reacción se calentó a - 20 °C antes de la adición de 1N HCl (0.5 volumenes de reacción) . La mezcla se dejo calentar a temperatura ambiente y se agitó durante 20 minutos adicionales. Después de este tiempo la mezcla se diluyó con H_2O y luego se extrajo con Et_2O (3X4 volumenes de reacción) . Luego las fracciones orgánicas combinadas se secaron ($MgSO_4$) . filtraron y concentraron al vacío para proporcionar un sólido blancuzco el cual corresponde al compuesto del título.

Ácido 2- Metoxinicotinonitrilo- 5- borónico: (44 % rendimiento, 90 % pureza) m/z (LC-MS,ESP) : 177.0 [M+H]+, R/T = 2.87 min)

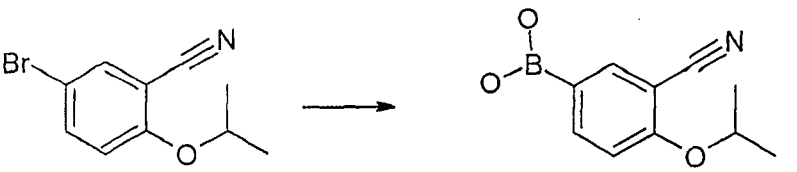
Procedimiento para la síntesis de ácido 2- Etoxinicotinonitrilo- 5- borónico



A una solución fria (- 78 °C) (0.25 M) de 5- bromo- 2- etoxibenzonitrilo en THF se agregó por goteo n- BuLi (1.10 equiv de una solución 2.5 M en hexanos) . La mezcla se mantuvo a esta temperatura con agitación durante 45 minutos antes de la adición de triisopropilborato (1.25 equiv) . Luego la reacción se calentó a - 20 °C antes de la adición de 1N HCl (0.5 volumenes de reacción) . La mezcla se dejo calentar a temperatura ambiente y se agitó durante 20 minutos adicionales. Después de este tiempo la mezcla se diluyó con H_2O y luego se extrajo con Et20 (3x4 volumenes de reacción) . Luego las fracciones orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío para proporcionar un sólido blancuzco el cual corresponde al compuesto del título.

Ácido 2- Etoxinicotinonitrilo- 5- ácido: (23 % rendimiento, 97 % pureza) m/z (LC- MS.ESP) : 191.0 [M+H]+,R/T = 3.09min)

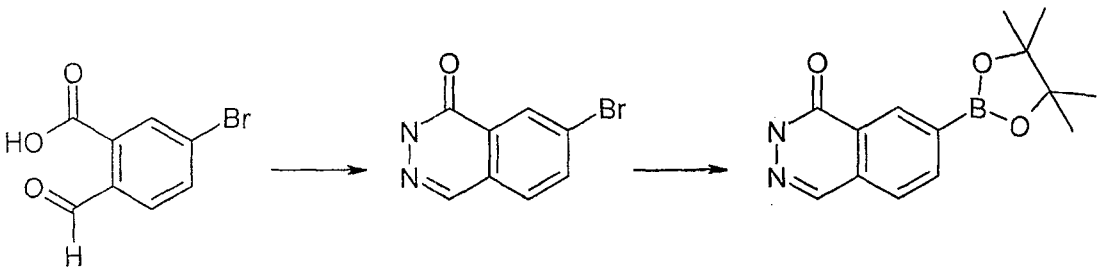
Procedimiento para la síntesis de ácido 2- Isopropoxinicotinonitrilo- 5- borónico



A una solución fria (- 78 °C) (0.25 M) de 5- bromo- 2- isopropoxi- nicotinonitrilo en THF se agregó n- BuLi (1.10 equiv de una solución 2.5 M en hexanos) por goteo. La mezcla se mantuvo a esta temperatura con agitación durante 45 minutos antes de la adición de triisopropilborato (1.25 equiv) . Luego la reacción se calentó a - 20 °C antes de la adición de 1N HCl (0.5 volumenes de reacción) . La mezcla se dejo calentar a temperatura ambiente y se agitó durante 20 minutos adicionales. Después de este tiempo la mezcla se diluyó con H_2O y luego se extrajo con Et_2O (3x4 volumenes de reacción) . Luego las fracciones orgánicas combinadas fueron secadas ($MgSO_4$) , filtradas y concentradas al vacío para proporcionar un sólido blancuzco el cual se trituró con CH_2Cl_2 para proporcionar el compuesto deseado.

Ácido 2- Isopropoxi- nicotinonitrilo- 5- borónico: (100 % rendimiento, 97 % pureza) m/z (LC-MS,ESP) :204.2 [M+H]\ R/T = 3.25 min)

Procedimiento para la síntesis de 7- (4,4,5,5- Tetrametil- [l,352]dioxaborolan- 2- il) - 2H- ftalazin- 1- ona



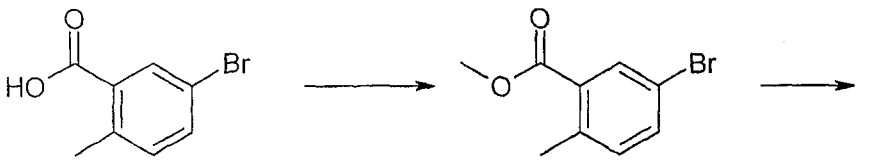
A una solución 3M de ácido 5- bromo- 2- formil- benzoico (1 equiv) en agua se agregó hidrato de hidrazina (5 equivs) . La reacción se calentó a 95 °C durante 4 horas después de lo cual se formó un precipitado blanco en la mezcla. La reacción fue enfriada, y filtrada. El material sólido blanco se lavó con metanol frio y se secó para proporcionar el producto deseado.

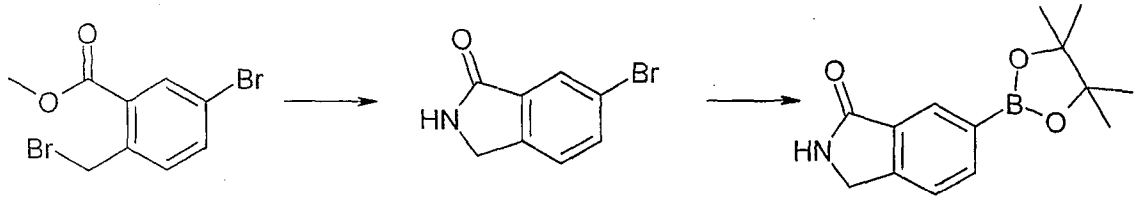
7- Bromo- 2H- ftalazin- 1- ona: (73 % rendimiento, 95 % pureza) m/z (LC- MS,ESP) :225.2 $[M+H]^+$, R/T = 2.99 min)

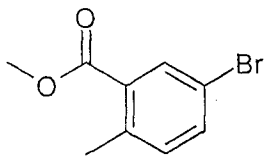
Se disolvió Bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) y 1,1'-bis(difenilfosfino) ferroceno (0.05 equiv) en dioxano. La mezcla se degasificó con nitrógeno durante 20 minutos antes de la adición de $PdCl_2$(dppf) (0.05 equiv) . La mezcla se degasificó durante 5 minutos más. La mezcla se calentó a reflujo durante 16 horas y luego se dejo enfriar a temperatura ambiente. Se agregó agua a la mezcla antes de ser extraída con con EtOAc (2X2 volumenes de reacción) . Las fracciones orgánicas combinadas se secaron ($MgS0_4$) , filtraron y concentraron al vacío antes de ser purificadas mediante cromatografía rápida (SiO_2) hexanos puros llegando a 1:1 - Hexanos:EtOAc luego EtOAc puro para proporcionar el producto deseado como un sólido cristalino blanco.

7- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 2H- ftalazin- 1- ona: (86 % rendimiento, 92 % pureza) m/z (LC- MS,ESP) : 191.3 [M+H]+, R/T = 2.29 min)

Procedimiento para la síntesis de 6- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 2,3- dihidro- isoindol- 1- ona:

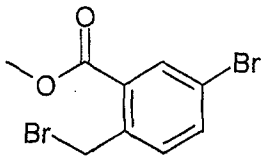






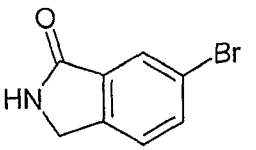
Se disolvió ácido 5- Bromo- 2- metilbenzoico (1 equiv) en una mezcla 1:9 MeOH/tolueno (0.1 M) . La mezcla de reacción fue enfriada a 0°C y se agregó lentamente una solución de trimetilsililodiazometano (1.05 equiv) en éter dietílico (2M) hasta que se observó un matiz amarillo persistente. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró al vacío. El residuo resultante fue sonicado con hexano, recolectado mediante filtración al vacío sobre un embudo sinterizado, secado y utilizado sin purificación adicional.

Éster metílico del ácido 5- Bromo- 2- metil- benzóico: (99 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : no ionisation R/T = 4.43 min



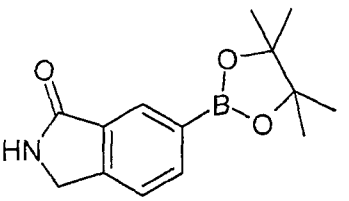
A una solución de éster metílico del ácido 5- Bromo- 2- metilo- benzóico (1 equiv) en cloroformo (0.1 M) se agregó N- bromosuccinimida (1.2 equiv) y peróxido de benzoilo (0.05 equiv) . La mezcla de reacción se agitó a reflujo durante 16 horas. Luego se diluyó con cloroformo y un precipitado se recolectó mediante filtración al vacío sobre en embudo sinterizado. El filtrado se concentró al vacío. El residuo subsiguiente se purificó mediante cromatografía en columna rápida sobre gel de sílice eluyendo con DCM en hexano (0 a 20 %) para proporcionar el producto deseado como un aceite incoloro claro.

Éster metílico del ácido 5- Bromo- 2- bromometil- benzoico: 80 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : no ionisation R/T = 4.40 min



Una solución de éster metílico del ácido 5- bromo- 2- bromometil- benzóico (1 equiv) en una mezcla 1:1 THF/MeOH se trató mediante burbujeado suave de gas de amoniaco durante 40 minutos a temperatura ambiente. La mezcla de reacción se concentró al vacío. El residuo fue sonicado en CH_2Cl_2 durante 15 minutos luego filtrado para proporcionar el producto deseado como un sólido blanco.

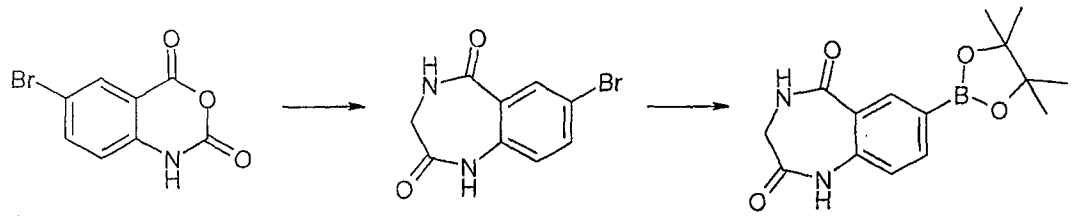
6- Bromo- 2,3- dihidro- isoindol- 1- ona: (98 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 212.3/214.3 $[M+H]^+$ R/T = 2.98 min

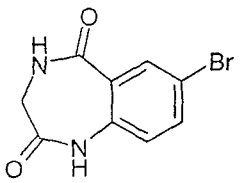


A una solución de 6- bromo- 2,3- dihidro- isoindol- 1- ona (1 equiv) en dioxano seco (0.1 M) se agregó bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) y dppf (0.05 equiv) . La mezcla de reacción se degasificó con nitrógeno durante 20 minutos. Se agregó $PdCl_2$(dppf) (0.05 equiv) a la mezcla de reacción, la cual se degasificó durante 5 minutos más. La mezcla de reacción se calentó a 70°C durante 2 horas bajo nitrógeno luego se calentó a 120°C durante 16 horas. La mezcla de reacción se particionó entre EtOAc y agua. La fase acuosa se extrajo adicionalmente con EtOAc y las fases orgánicas combinadas se secaron ($MgS0_4$) , filtraron y concentraron al vacío. El residuo fue sonicado en EtOAc, la suspensión se filtró sobre un embudo sinterizado y el sólido gris recolectado fue secado y utilizado sin purificación adicional.

6- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 2,3- dihidro- isoindol- 1- ona: (82 % rendimiento, 29 % pureza, la impureza principal es el ácido borónico 43 %) m/z (LC- MS, ESP) : 519.5 [2M+H]+ R/T = 3.38 min

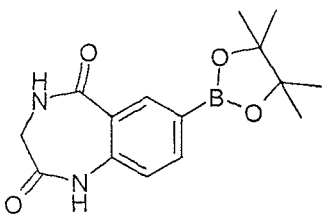
Procedimiento para la síntesis de 7- (4,4,5,5- Tetrametil- [1,3?2]dioxaborolan- 2- il) - 3,4- dihidro- 1H- benzo[e][1,4]diazepina- 2,5- diona:





A una solución de anhidrido 5- bromoisatóico (1 equiv) en agua (1 M) se agregó glicina (1.4 equiv) y trietilamina (1 equiv) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 4 horas para proporcionar una solución turbia. La mezcla de reacción se concentró al vacío. Se agregó ácido acético y la mezcla de reacción se agitó a 140°C durante 4.5 horas. La mezcla de reacción fue enfriada lentamente a temperatura ambiente. Se formó un precipitado. La mezcla de reacción se diluyó con éter dietílico, luego se filtró a través de un embudo sinterizado para proporcionar el producto deseado.

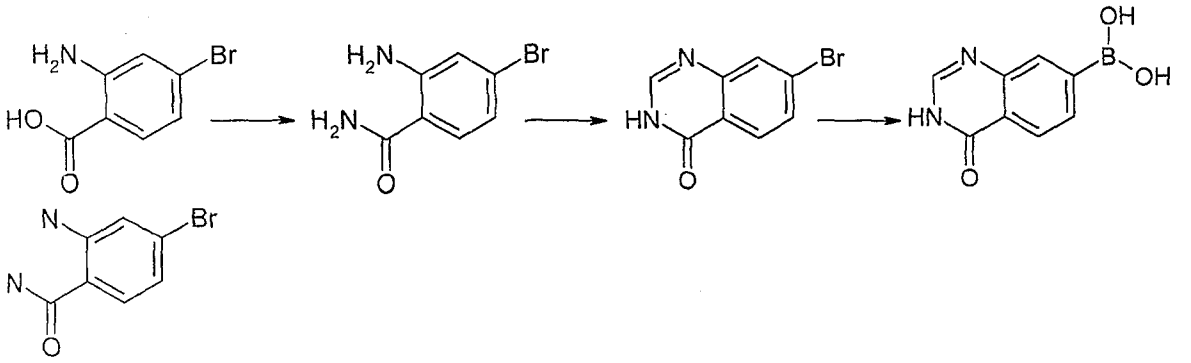
7- Bromo- 3,4- dihidro- lH- benzo[e][l,4]diazepina- 2,5- diona: (75 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 255.2/257.2 [M+H]+ R/T = 2.67 min



A una solución de 7- bromo- 3,4- dihidro- lH- benzo[e][l,4]diazepina- 2,5- diona (1 equiv) en dioxano seco (0.1 M) se agregó bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) y dppf (0.05 equiv) . La mezcla de reacción se degasificó con nitrógeno durante 20 minutos. Se agregó PdCl2(dppf) (0.05 equiv) a la mezcla de reacción, la cual se degasificó durante 5 minutos más. La reacción se calentó a 120 °C durante 16 horas bajo nitrógeno. La mezcla de reacción se particionó entre CH_2Cl_2/MeOH y agua. La fase acuosa se extrajo adicionalmente con CH_2Cl_2/MeOH. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo fue sonicado con hexano/ CH_2Cl_2, filtrado, sonicado

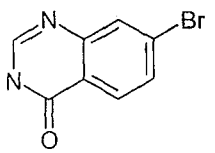
en CH_2Cl_2 y filtrado para proporcionar el producto deseado.

7- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 3,4- dihidro- 1H- benzo[e][1,4]diazepina- 2,5- diona: (63 % rendimiento, 85 % pureza; la impureza principal es el ácido borónico 15 %) m/z (LC- MS, ESP) : 303.4 [M+H]+ R/T = 3.08 min



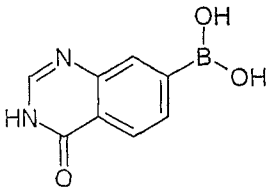
A una solución de ácido 2- amino- 4- bromobenzoico (1 equiv) en DMA (0.23 M) , se agregó cloruro de amonio (7 equiv) , HBTU (1 equiv) y diisopropiletilamina (2 equiv) . La mezcla de reacción se agitó durante 24 horas a temperatura ambiente. Se evaporó DMA y el residuo se purificó mediante cromatografía en columna rápida sobre gel de sílice eluyendo con un gradiente de TBME/hexano para proporcionar el producto deseado como un sólido blanco.

2- Amino- 4- bromo- benzamida: 40 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 215 [M+H]+ R/T = 3.00 min



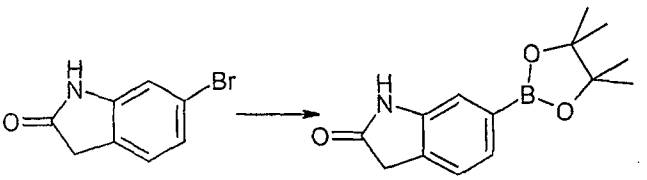
A una solución de 2- amino- 4- bromo- benzamida (1 equiv) en DMA (0.14 M) se agregó ortoformato de trietilo (10 equiv) y ácido trifluoroacético (1 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (160 °C, ambiente de absorción de medios) durante 30 minutos. La mezcla de reacción se concentró al vacío y el residuo se filtró a través de una almohadilla de sílice con 10 % metanol en etilacetato proporcionando el producto requerido como un sólido amarillo palido.

7- Bromo- 3H- quinazolin- 4- ona: (71 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 268 [M+H]+ R/T = 2.94 min



A una solución de 7- bromo- 3H- quinazolin- 4- ona (1 equiv) en dioxano (0.04 M) se agregó bispinacolato diboro (2.2 equiv) , acetato potásico (1.5 equiv) , dppf (0.1 equiv) y $PdCl_2$(dppf) (0.1 equiv) . La mezcla de reacción se degasificó con nitrógeno durante 5 minutos, sonicó y agitó a 120°C durante 3 horas. La mezcla de reacción se concentró al vacío. El residuo se filtró a través de una almohadilla de Celite™ junto con sílice con etilacetato. El agua madre se concentró al vacío proporcionando un sólido marrón el cual se purificó adicionalmente mediante cromatografía en columna rápida sobre gel de sílice eluyendo con un gradiente de metanol/éter dietílico (0 a 5 %) para proporcionar el producto deseado como un sólido blanco.

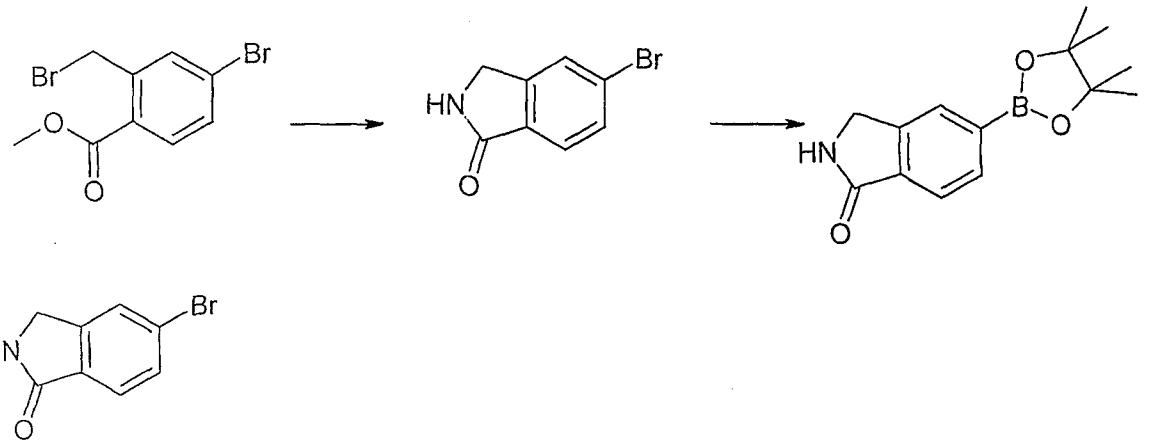
7- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 3H- quinazolin- 4- ona: (53 % rendimiento, 61 % pureza; la impureza principal es ácido borónico 39 %) m/z (LC- MS, ESP) : $[M+H]^+$ R/T = min



A una solución de 6- bromo- 2- oxindol (1 equiv) en NMP (0.05 M) se agregó bispinacolato diboro (2.4 equiv) , acetato potásico (1.5 equiv) , dppf (0.05 equiv) y $PdCl_2$(dppf) (0.05 equiv) . La mezcla de reacción se agitó a 130°C durante 3 horas y luego se concentró al vacío. El residuo se particionó entre agua y etilacetato. La fase orgánica se secó sobre sulfato de sodio anhidro, filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna rápida sobre gel de sílice eluyendo con EtOAc/hexano (9/1) , proporcionando el producto deseado como un sólido rojo.

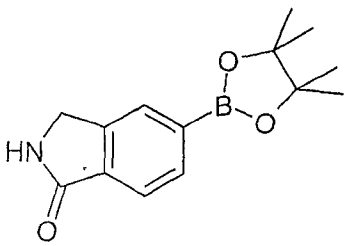
6- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 1,3- dihidro- indol- 2- ona: (22 % rendimiento, 51 % pureza; la impureza principal es ácido borónico 28 %) m/z (LC- MS, ESP) : 260 [M+H]+ R/T = 3.51 min

Procedimiento para la síntesis de 5- (4,4,5,5- Tetrametil- [l,3»2]dioxaborolan- 2- il) - 2,3- dihidro- isoindol- l- ona:



Se preparó éster metílico del ácido 4- Bromo- 2- bromometil- benzóico según la literatura. Una solución de éster metílico del ácido 4- Bromo- 2- bromometil- benzóico (1 equiv) en una mezcla 1:1 THF/MeOH se trató mediante burbujeado suave de gas de amoniaco durante 4 horas a temperatura ambiente. La mezcla de reacción se concentró al vacío. El residuo fue sonicado en agua, filtrado, luego sonicado en éter dietílico y filtrado para proporcionar el producto deseado como un sólido blanco.

5- Bromo- 2,3- dihidro- isoindol- l- ona: (81 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 212.3/214.3 [M+H]+ R/T = 3.06 min

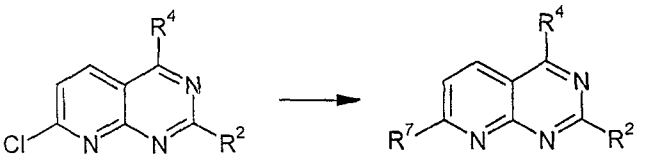


A una solución de 5- bromo- 2,3- dihidro- isoindol- l- ona (1 equiv) en dioxano seco (0.1 M) se agregó bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) y dppf (0.05 equiv) . La mezcla de reacción se degasificó con nitrógeno durante 20 minutos. Se agregó PdCl2(dppf) (0.05 equiv) a la mezcla de reacción, la cual se degasificó durante 5 minutos más. La mezcla de reacción se calentó a 70°C durante 2 horas bajo nitrógeno, luego se calentó a 120°C durante 16 horas. La mezcla de reacción se particionó entre EtOAc y agua. La fase acuosa se extrajo adicionalmente con EtOAc y las fases orgánicas combinadas se secaron (MgS04) ,

filtraron y concentraron al vacío. El residuo se disolvió en CH_2Cl_2 y se agregó hexano. La suspensión resultante fue filtrada y el polvo marrón recolectado fue secado y utilizado sin purificación adicional.

5- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 2,3- dihidro- isoindol- 1- ona: (94 % rendimiento, 76 % pureza, la impureza principal es el ácido borónico 13 %) m/z (LC- MS, ESP) : 260.4 $[2M+H]^+$ R/T = 3.51 min

Procedimientos para la preparación de Ejemplos 1a a 1du



R^4 = (S) - 3- metil- morfolina

R^2 = (S) - 3- metil- morfolina o cis- dimetilmorfolina o 2- Etil- piperidina o morfolina o tiomorfolina o 4- metilpiperazina

R^7 = arilo o heteroarilo

Procedimientos para acoplamiento de Suzuki:

La síntesis del cloro- sustrato apropiado se ha descrito en el presente documento como intermedios. El pinacolato de éster borónico apropiado o ácidos borónicos se prepararon según la síntesis descrita en el presente documento (como intermedios) o comercialmente disponibles, típicamente de los siguientes proveedores:

Sigma- Aldrich, Lancaster, Frontier Scientific, Boron Molecular, Interchim, Asymchem, Combi-blocks, Apollo Scientific, Fluorochem, ABCR, Digital Speciality Chemicals.

Condiciones A:

El cloro- sustrato apropiado (1 equiv) se disolvió en una solución tolueno/etanol (1:1) (0.02 M) . Luego se agregó carbonato de sodio (2 equiv) y el pinacolato de éster borónico apropiado o ácido borónico (1 equiv) seguido por tetrakis(trifenilfosfina) paladio (0.1 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron al vacío. Luego el producto

crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones B:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.4 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en n- butanol (0.03 M de cloro- substrato) se agitó a 120 °C durante 2 horas. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con CH_2Cl_2 y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones C:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.4 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) en acetonitrilo/agua (1:1) (0.041 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y se expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 30 minutos bajo atmósfera de nitrógeno. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con CH_2Cl_2 y metanol y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones D:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (1.2 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.2 equiv) en acetonitrilo/agua (1:1) (0.083 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 25 minutos bajo atmósfera de nitrógeno. Al terminar la muestra se purificó mediante cromatografía en columna sobre gel de sílice utilizando un gradiente MeOH/ CH_2Cl_2 para proporcionar el producto deseado el cual se recristalizó a partir de éter dietílico.

Condiciones E:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.4 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.3 equiv) en acetonitrilo/agua (1:1)

(0.041 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y calentó a 95 °C durante 16 horas. Al terminar, la mezcla de reacción se particionó entre HCl acuoso y CH_2Cl_2 y se lavó con HCl acuoso. Las fases acuosas combinadas se extrajeron con CH_2Cl_2 (2x) , se neutralizaron con NaOH acuoso (2N) para proporcionar una solución turbia que fue extraída con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con salmuera, secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 4 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones F:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.0 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.5 equiv) en acetonitrilo/agua (1:1) (0.028 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y calentó a 120 °C durante 2 horas bajo atmósfera de nitrógeno. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 4 % MeOH en CH_2Cl_2 para proporcionar el producto deseado el cual se recristalizó a partir de hexano/éter dietílico.

Condiciones G:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.05 equiv) en acetonitrilo/agua (1:1) (0.068 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y calentó a 100 °C durante 5 horas bajo atmósfera de nitrógeno. Al terminar, la mezcla de reacción se particionó entre salmuera y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 4 % MeOH en CH_2Cl_2 para proporcionar los productos deseados los cuales se recristalizaron a partir de hexano/ CH_2Cl_2.

Condiciones H:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 100 °C durante 8 horas. Al terminar la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones I:

Las condiciones I fueron similares a las condiciones H excepto del método de calentamiento: 100 °C durante 2 horas.

Condiciones J:

A mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (1.2 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.2 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.03 M de cloro- substrato) se agitó a 100 °C durante 2 horas. Al terminar la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones K:

Las condiciones K fueron similares a las condiciones G excepto del método de calentamiento: 100 °C durante 16 horas.

Condiciones L:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (1.10 equiv) en acetonitrilo/agua (1:1) (0.041 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (100 °C, ambiente de absorción de medios) durante 90 minutos. Al terminar, la mezcla de reacción fue parcialmente concentrada. El residuo se particionó entre agua y etilacetato y se extrajo con etilacetato y n- butanol. Las fases

orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 30 a 10 % hexano en etilacetato para proporcionar el producto deseado el cual se recristalizó a partir de hexano/ CH_2Cl_2.

Condiciones M:

Una mezcla del cloro- sustrato apropiado (1 equiv) , fluoruro de cesio (3.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.09 M de cloro- substrato) se agitó a 115 °C durante 48 horas. Al terminar, la muestra se concentró al vacío a volumen original medio. El residuo se particionó entre agua y CH_2Cl_2. La fase orgánica se secó ($MgSO_4$) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 100 % etilacetato en hexano para proporcionar el producto deseado.

Condiciones N:

Una mezcla del cloro- sustrato apropiado (1 equiv) , fosfato de tripotasio (1.5 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.05 equiv) y bis(tri- t- butilfosfine) paladio (0.05 equiv) se suspendió en dioxano (0.16 M de cloro- substrato) . El recipiente de reacción se selló y expuso a radiación microondas (170 °C, ambiente de absorción de medios) durante 45 minutos. Al terminar, la muestra se concentró al vacío. El residuo se particionó entre agua y CH_2Cl_2. La fase orgánica se secó ($MgSO_4$) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 40 a 100 % etilacetato en hexano para proporcionar el producto deseado.

Condiciones O:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en n- butanol (0.068 M de cloro- substrato) se agitó a 95 °C durante 15 minutos. Al terminar, el residuo se particionó entre etilacetato y salmuera. La fase orgánica se secó (MgSO4) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografia

en columna sobre gel de sílice eluyendo con 30 a 100 % etilacetato en hexano para proporcionar el producto deseado el cual se recristalizó a partir de etilacetato/hexano.

Condiciones P:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.0 equiv) , y pinacolato de éster borónico apropiado o ácido borónico (2.0 equiv) en acetonitrilo/agua (1:1) (0.041 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (120 °C, ambiente de absorción de medios) durante 10 minutos bajo atmósfera de nitrógeno. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con CH_2Cl_2 y concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones Q:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) se disolvió en n- butanol (0.056 M de cloro- substrato) . El recipiente de reacción se selló y expuso a radiación microondas (150°C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con CH_2Cl_2 y metanol y luego se concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con etilacetato y luego 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones R:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.2 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.05 M de cloro- substrato) se agitó a 115 °C durante 1.5 horas. Al terminar, la reacción cruda se filtró y el filtrado se concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 5 a 20 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones S:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (10.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.2 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 100 °C durante 2 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado el cual se recristalizó a partir de hexano/ CH_2Cl_2.

Condiciones T:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (2.0 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) se disolvió en acetonitrilo/agua (0.02 M de cloro- substrato) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, la muestra se concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones U:

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1.0 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 110 °C durante 8 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con salmuera, secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 2 % MeOH en CH_2Cl2 para proporcionar el producto deseado el cual se recristalizó a partir de hexano/ CH_2Cl_2.

Condiciones V:

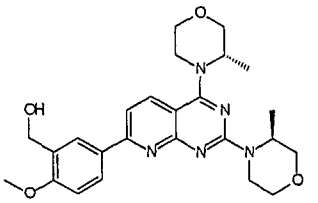
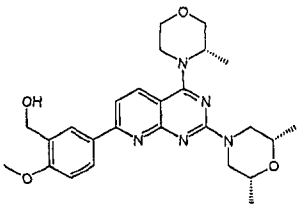
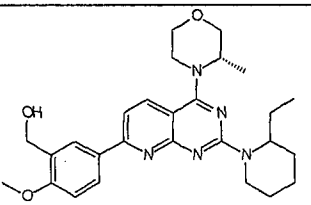
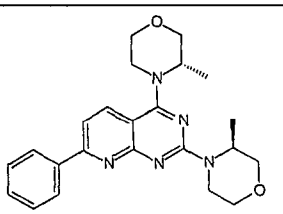
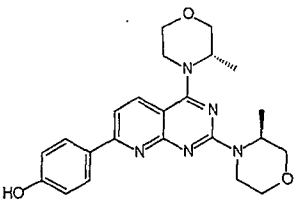
Una mezcla del cloro- sustrato apropiado (1 equiv) , fluoruro de cesio (3.0 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 100 °C durante 16 horas. La mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. La fase orgánica se secó ($MgSO_4$) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado el cual se recristalizó a partir de hexano/CH_2Cl_2.

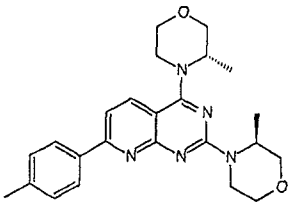
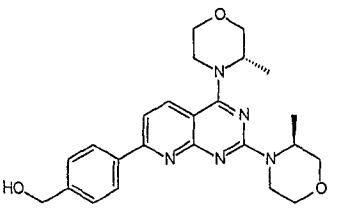
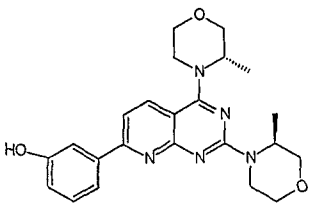
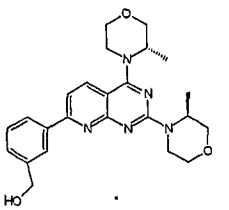
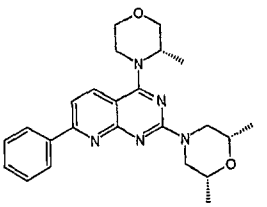
Condiciones W:

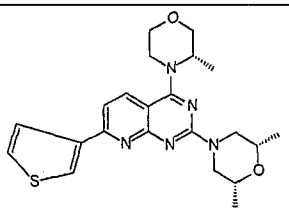
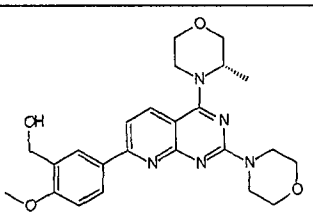
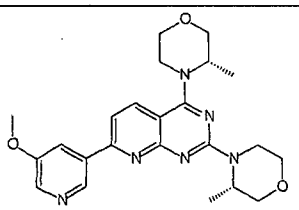
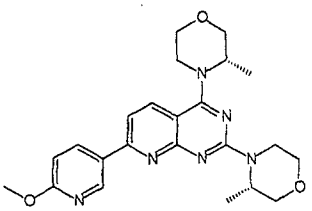
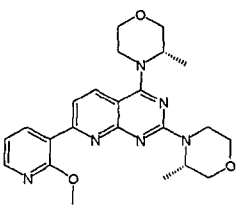
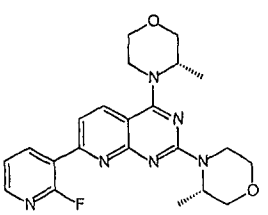
Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , pinacolato de éster borónico apropiado o ácido borónico (1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) se disolvió en acetonitrilo/agua (0.04 M de cloro- substrato) . El recipiente de reacción se selló y expuso a radiación microondas (110 °C, ambiente de absorción de medios) durante 10 minutos. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 2 % MeOH en TBME para proporcionar el producto deseado.

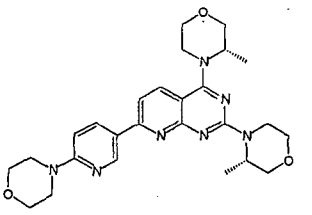
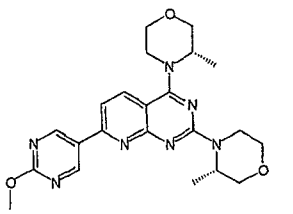
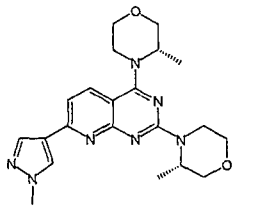
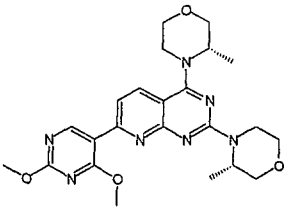
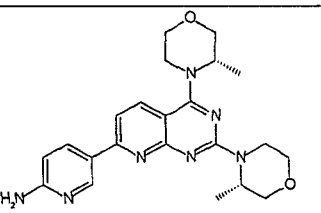
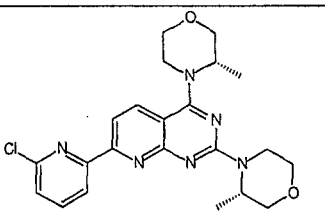
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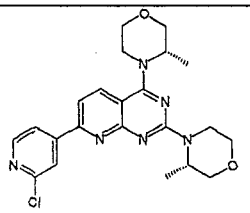
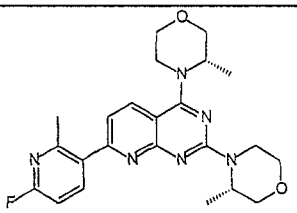
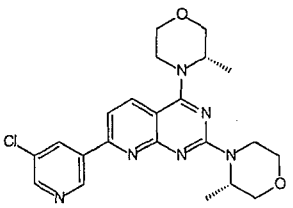
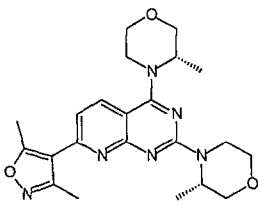
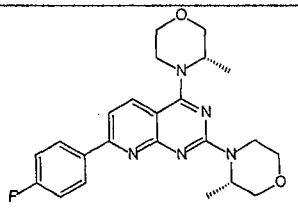
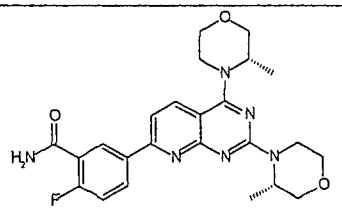
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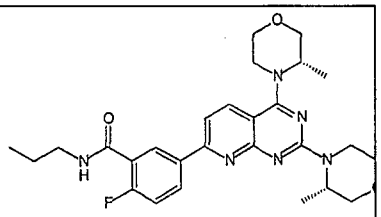
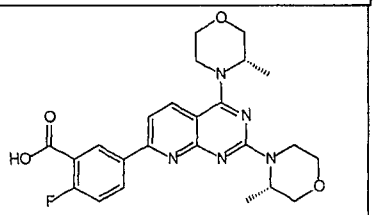
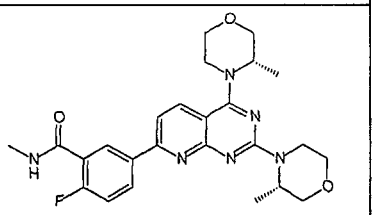
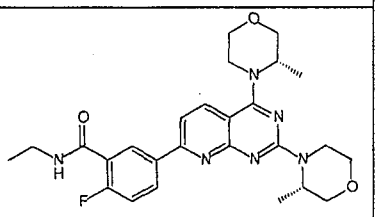
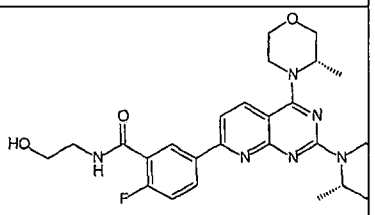
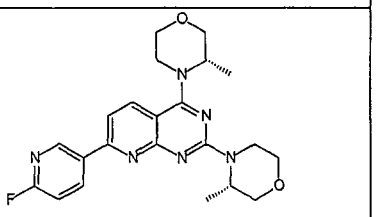
Ia	96	7.66	466.6	A	
Ib	99	4.31	480.4	A	
Ic	98	4.67	478.4	A	
Id	99	4.13	406.2	A	
Ie	99	3.94	422.3	A	

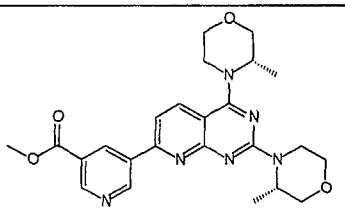
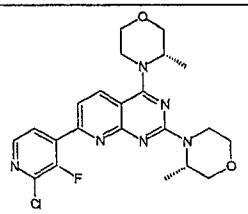
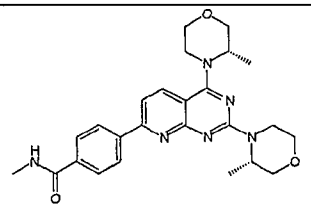
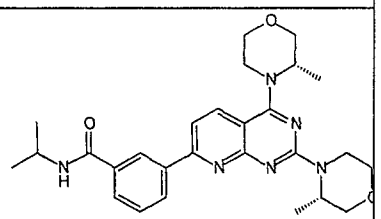
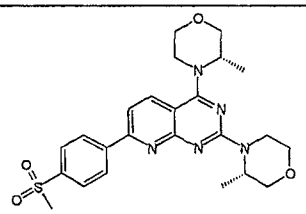
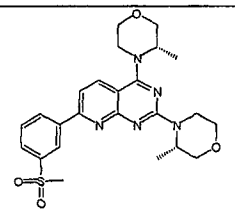
If	99	4.32	420.3	A	
Ig	99	3.83	436.3	A	
Ih	89	3.99	422.2	A	
Ii	*96*	3.85	436.3	A	
Ij	99	4.5	420.3	A	

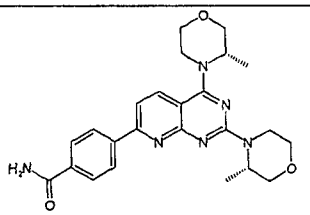
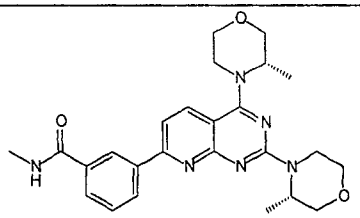
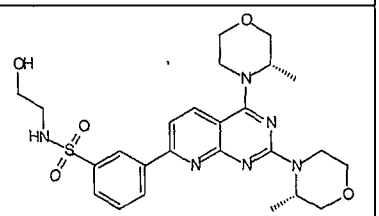
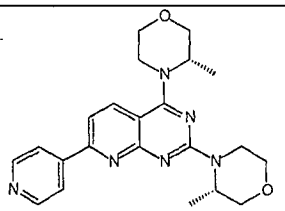
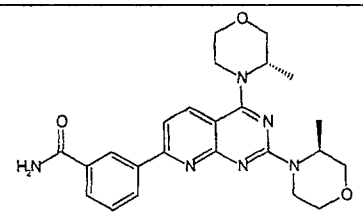
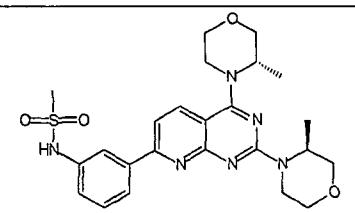
Ik	98	4.49	426.3	A	
11	100	3.91	452.3	A	
Im	99	3.99	437.4	B	
In	99	4.2	437.4	B	
Io	99	4.23	437.4	B	
IP	99	4.16	425.4	B	

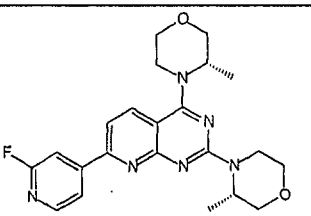
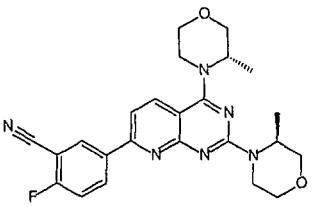
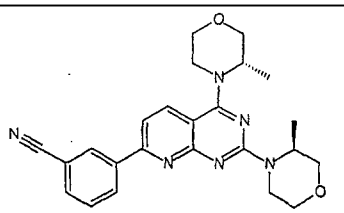
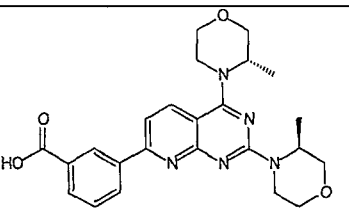
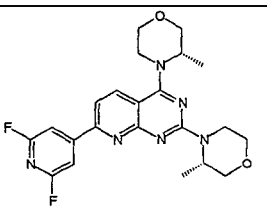
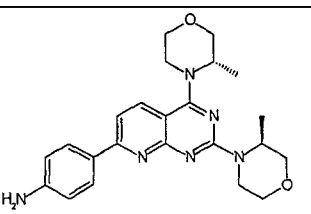
Iq	98	4.1	492.5	B	
II-	98	1.09	438.4	B	
Is	99	3.98	410.4	B	
It	100	4.04	468.5	B	
Iu	100	4.95	422.3	B	
Iv	98	4.32	441.4	B	

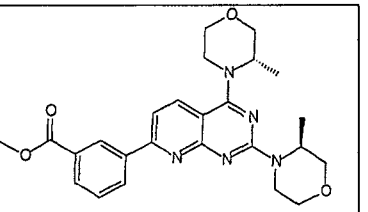
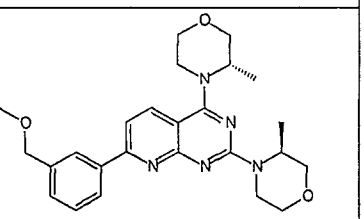
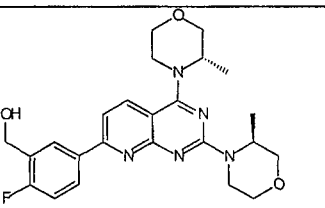
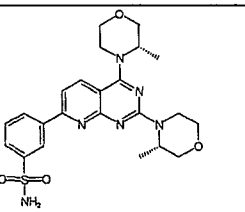
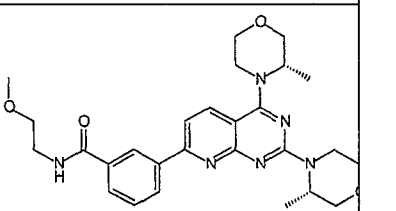
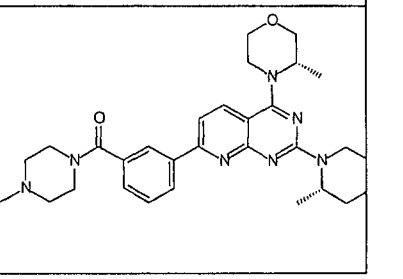
lw	91	6.46	441.3	B	
lx	98	7.16	439.3	B	
ly	97	6.54	441.4	B	
lz	95	5.92	425.5	B	
laa	100	8.28	424.4	B	
lab	99	6.67	467.4	B	

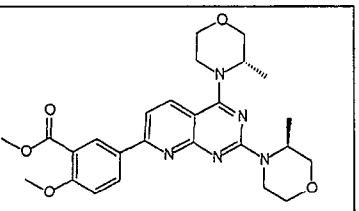
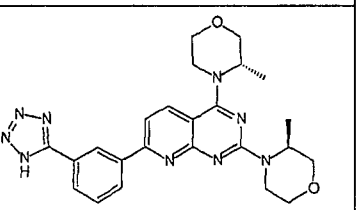
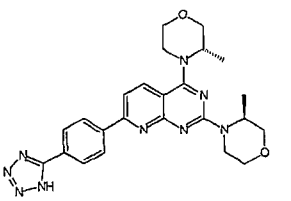
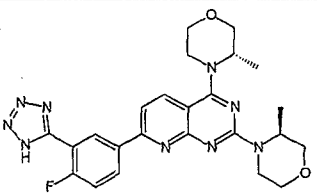
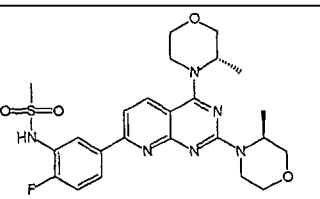
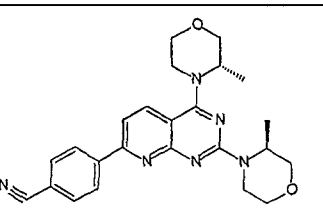
lac	100	8.01	509.5	B	
lad	100	7.23	468.4	B	
lae	100	6.99	481.4	B	
laf	99	7.55	495.4	B	
lag	100	6.51	511.4	B	
lah	99	6.95	425.2	B	

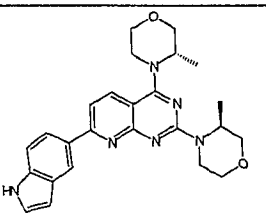
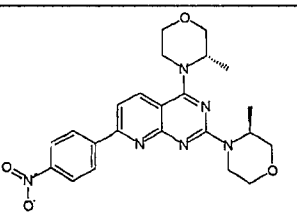
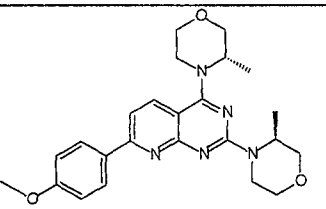
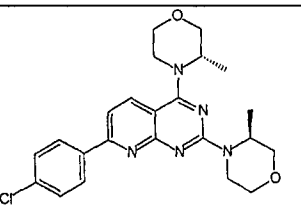
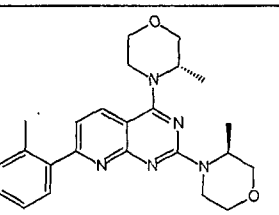
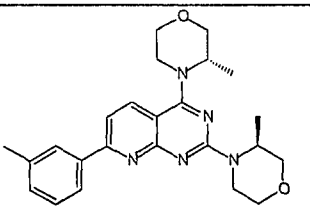
lai	89	7.52	465.2	B	
laj	80	4.5	459.3	B	
lak	97	6.79	463.2	C	
lal	99	4.07	491.4	C	
lam	99	3.94	484.3	C	
lan	99	3.95	484.3	**c**	

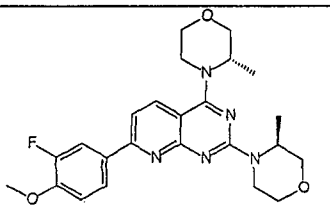
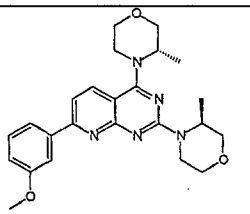
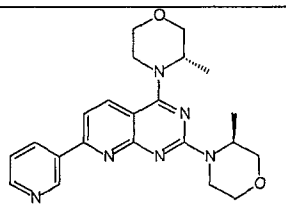
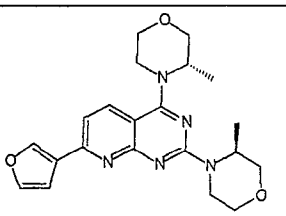
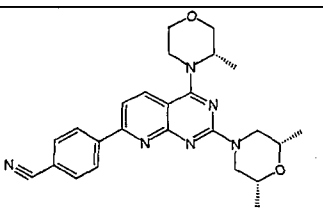
lao	97	3.75	449.3	**c**	
lap	99	3.86	463.3	C	
laq	99	3.87	529.4	D	
lar	99	3.41	407.3	E	
las	98	6.59	449.4	F	
lat	97	4.05	499.3	G	

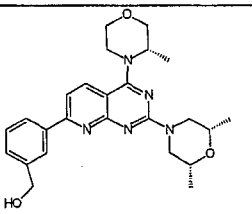
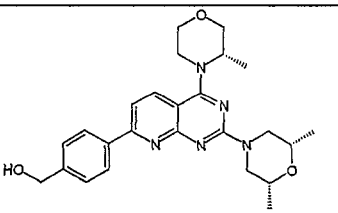
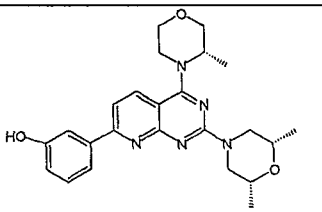
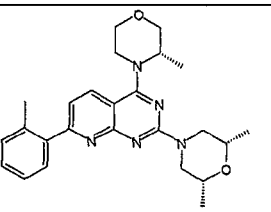
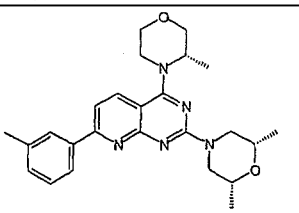
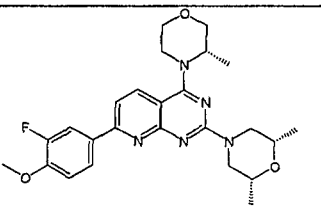
lau	*96*	7	425.3	G	
lav	99	4.28	449.4	H	
law	97	4.33	431.3	I	
lax	99	3.99	450.5	J	
lay	98	4.19	443.3	K	
laz	100	8.94	421.2	L	

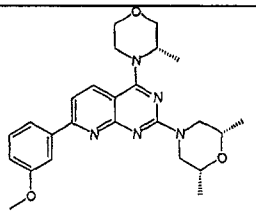
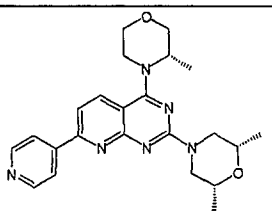
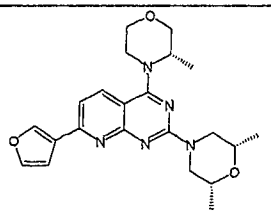
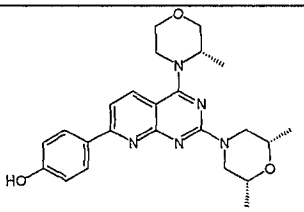
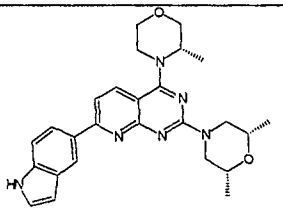
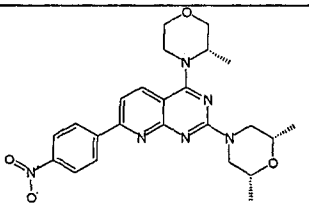
lba	100	4.28	464.5	M	
lbb	98	8.16	450.3	N	
lbc	99	3.99	454.4	0	
lbd	90	8.4	485.3	P	
lbe	99	3.91	507.4	C	
lbf	99	3.39	532.4	**c**	

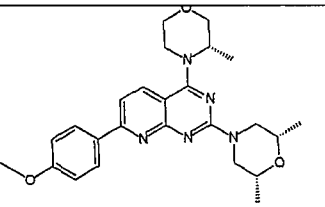
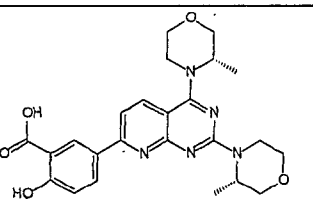
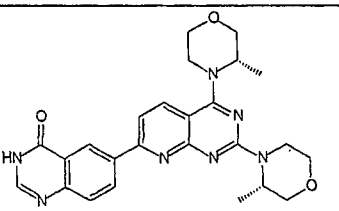
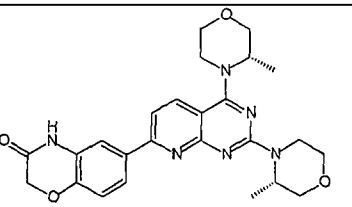
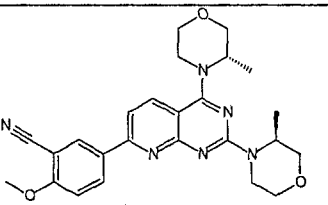
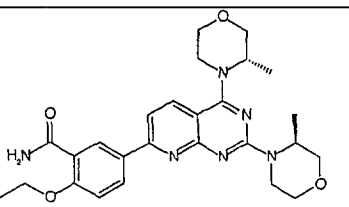
Ibg	97	4.19	494.4	M	
Ibh	98	4.15	474.3	Q	
Ibi	96	4.13	474.4	R	
Ibj	94	3.99	492.3	R	
Ibk	98	4.04	517.4	S	
Ibl	98	4.13	431.2	B	

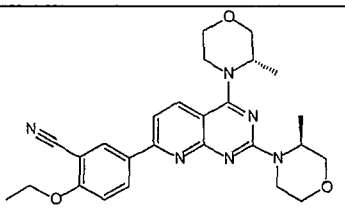
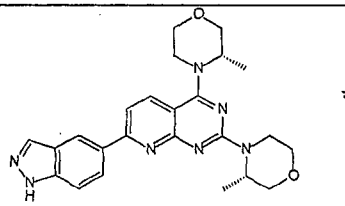
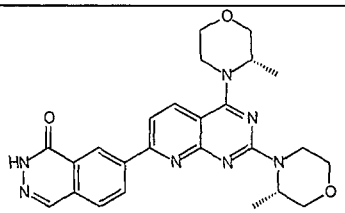
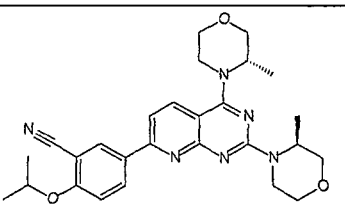
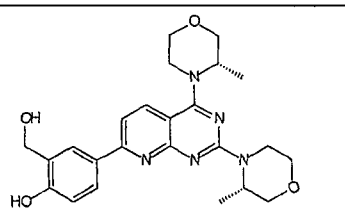
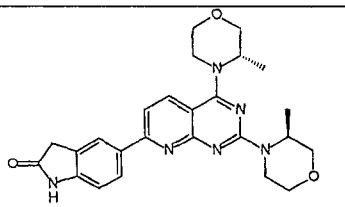
lbm	98	4.27	445.3	B	
lbn	97	4.27	451.2	B	
lbo	99	4.21	436.3	B	
lbp	99	4.40	440.2	B	
lbq	87	4.22	420.3	B	
lbr	93	4.40	420.3	B	

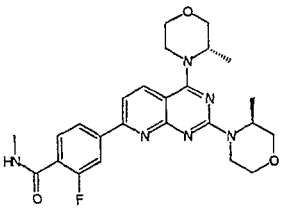
lbs	94	4.30	454.2	B	
lbt	95	4.32	436.3	B	
lbu	99	3.53	407.3	B	
lbv	99	3.94	396.3	B	
lbw	85	4.49	445.3	B	

lbx	99	4.59	450.3	B	
lby	98	4.20	450.3	B	
lbz	87	4.30	436.3	B	
lea	99	4.62	434.4	B	
leb	99	4.74	434.4	B	
lec	92	4.67	463.0	B	

led	99	4.63	450.4	B	
lee	85	3.71	421.3	B	
lcf	98	4.35	410.3	B	
leg	97	4.34	436.3	B	
lch	98	4.48	459.3	B	
lei	87	4.49	465.3	B	

lcj	100	4.50	450.3	B	
lck	99	4.14	466.5	T	
lcl	100	3.8	474.4	P	
lcm	99	4.01	477.3	T	
lcn	99	4.73	474.3	E	
lco	99	4.08	477.3	D	

lcp	87	4.48	461.3	D	
lcq	84	7.44	493.4	L	 *
lcr	*91*	3.85	475.3	T	
lcs	100	4.63	450.4	D	
let	99		464.3	S	
leu	100	3.89	436.2	B	

lev	100	3.89		J	

Notar:

Los siguientes ejemplos se sintetizaron a partir de los correspondientes ácidos borónicos: laa, lab, lac, lad, lae, laf, lag, lah, lai, laj, lak, lal, lam, Ian, lao, lap, laq, las, lat, lau, lav, law, lax, lay, laz, lba, lbb, lbd, lbe, lbk, lbl, lbm, lbn, lbo, lbp, lbq, lbr, lbs, lbt, lbu, lbv, lbw, lbx, lby, lbz, lea, leb, lec, led, lcf, leg, lch, lei, lcj, Id, le, Si, lg, lh, li, lj, Ik, En, lo, lp, lr, It, lw, lx, ly len, lco, lep, les, lev y lz.

Los siguientes ejemplos se sintetizaron a partir de los correspondientes ésteres de boro de pinacolato: la- c, lck, lei, 1cm, lcq, lcr, let, leu, lar, lbf, lee, lm, lq, Es, lu y lv.

Datos NMR para ejemplo ln

^{1}H NMR (300 MHz, $CDC1_3$) 8 ppm 8.88 (ArH, d, J = 2.20 Hz, 1H) , 8.55 (ArH, dd, J = 8.70, 2.45 Hz, 1H) , 8.04 (ArH, d, J = 8.43 Hz, 1H) , 7.42 (ArH, d, J = 8.44 Hz, 1H) , 6.88 (ArH, d, J = 8.70 Hz, 1H) , 5.01- 4.90 (CH,m, 1H) ,4.65 (CH, d, J= 13.12 Hz, 1H) ,4.40 (CH, d,J = 6.68 Hz, 1H) , 4.04 (OCH_3 + CH_2, s, 5H) , 3.96- 3.69 (CH_2, m, 7H) , 3.60 (CH, dt, J= 11.86, 11.60, 2.67 Hz, 1H) , 3.40 (CH, dt, J= 13.01,12.73, 3.60 Hz, 1H) , 1.50 (CH_3, d, 7= 6.78 Hz, 3H) , 1.39 (CH_3, d, J= 6.81 Hz, 3H)

^{13}CNMR(75 MHz, CDCI3) δ ppm 165.41, 165.29, 162.98, 160.10, 160.01, 146.58, 138.51, 134.81, 128.05, 112.42, 110.84, 104.75, 71.29, 70.92, 67.26,66.92, 53.75, 52.87, 46.94, 44.43, 39.33, 14.73 y 14.36.

Datos NMR para ejemplo lu

^{1}HNMR(300MHz,$CDCl_3$) δ ppm8.80(ArH,d, J= 1.91 Hz, 1H) , 8.39 (ArH, dd, J= 8.66,

2.39 Hz, 1H) , 7.96 (ArH, d, *J* = 8.48 Hz, 1H) , 7.35 (ArH, d, *J* = 8.49 Hz, 1H) , 6.59 (ArH, d, *J* = 8.66 Hz, 1H) , 4.91 (CH, dd, *J* = 4.15,1.62 Hz, 1H) , 4.78 (NH_2, s, 2H) , 4.67- 4.55 (CH, m, 1H) , 4.34 (CH, d, *J* = 6.88 Hz, 1H) , 4.04- 3.91 (CH_2, m, 2H) , 3.90- 3.64 (CH_2, m, 7H) , 3.62- 3.49 (CH_2, m, 1H) , 3.44- 3.29 (CH_2, m, 1H) , 1.45 (CH_3, d, *J*= 6.77 Hz, 3H) , 1.34 (CH_3, d, *J* = 6.82 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.54, 163.10, 160.45, 160.13, 159.45, 148.10, 137.82, 134.76, 125.17, 112.16, 108.45, 104.59, 71.44, 71.06, 67.41, 67.07, 52.98, 47.05,44.56, 36.46, 14.84 y 14.75.

Datos NMR para ejemplo lag

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.59 (ArH, dd, *J* = 7.33, 2.43 Hz, 1H) , 8.40 (ArH, ddd, *J* = 8.53, 5.03, 2.47 Hz, 1H) , 7.97 (ArH, d, *J* = 8.42 Hz, 1H) , 7.42 (ArH, d, *J* = 8.46 Hz, 1H) , 7.20- 7.10 (ArH, m, 1H) , 4.84 (CH, dd, *J* = 3.67, 2.96 Hz, 1H) , 4.53 (CH, d, *J* = 12.77 Hz, 1H) , 4.33 (CH_2, d, *J*= 6.83 Hz, 1H) , 3.99- 3.89 (CH_2, m, 2H) , 3.86- 3.77 (CH_2, m, 4H) , 3.75- 3.65 (CH_2, m, 5H) , 3.67- 3.32 (CH_2, m, 3H) , 3.57- 3.45 (CH_2, m, 1H) , 3.36- 3.26 (CH_2, m, 1H) , 1.42 (CH_3, d, J = 6.78 Hz, 3H) , 1.30 (CH_3, d,*J*=6.82 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) 5ppm 165.26, 164.26, 162.74, 160.29, 159.93, 135.52, 135.11, 133.47, 133.34, 130.89, 116.84, 116.51, 113.11, 105.11, 71.26, 70.91, 67.11, 66.91, 62.20, 52.79, 47.02, 44.46, 43.02, 39.36,14.77 y 14.37.

Datos NMR para ejemplo 1 aq

^{1}H NMR (300 MHz, CDCI3) δ ppm 8.61 (ArH, t, *J* = 1.46, 1.46 Hz, 1H) , 8.33 (ArH, d,*J* = 7.84 Hz, 1H) , 8.06 (ArH, d, *J* = 8.37 Hz, 1H) , 7.90 (ArH, s, 1H) , 7.62 (ArH, d, *J* = 7.84 Hz, 1H) , 7.44 (ArH, d, *J* = 8.38 Hz, 1H) , 5.30 (CH_2, s, 1H) , 4.97- 4.84 (CH_2, m, 1H) , 4.64- 4.52 (CH_2, m, 1H) , 4.45- 4.34 (CH_2, m, 1H) , 4.06- 3.94 (CH_2, m, 2H) , 3.93- 3.64 (CH_2, m, 8H) , 3.61- 3.51 (CH_2, m, 1H) , 3.45- 3.30 (CH_2, m, 1H) , 3.19 (CH_2, d, *J*= 4.84 Hz, 2H) , 1.49 (CH_3, d, *J* = 6.78 Hz, 3H) , 1.36 (CH_3, d, J = 6.82 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3) δ ppm 160.22, 140.70, 140.01, 134.25, 131.82, 129.24, 128.02,

126.34, 113.12, 105.41, 104.65, 71.23, 70.87, 66.88, 61.03, 52.85, 47.04,45.34, 44.42, 39.35, 14.78 y 14.38.

Datos NMR para ejemplo lar

^{1}H NMR (300 MHz, CDCI3) δ ppm 8.81- 8.73 (ArH, m, 2H) , 8.14- 7.99 (ArH, m, 3H) , 7.48 (ArH, d, *J*= 8.35 Hz, 1H) , 5.02- 4.89 (CH, m, 1H) , 4.69- 4.59 (CH_2, m, 1H) , 4.41 (CH, d, *J* = 6.84 Hz, 1H) , 4.08- 3.96 (CH_2, m, 2H) , 3.82 (H2, dddd, *J*= 19.69, 14.05, 6.26, 3.77 Hz, 7H) , 3.65- 3.53 (CH_2, m, 1H) , 3.48- 3.31 (CH_2, m, 1H) , 1.51 (CH_3, d, *J* = 6.78 Hz, 3H) , 1.38 (CH_3, d,J=6.83Hz,3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.29, 162.96, 160.03, 159.82, 150.36, 145.80, 135.20, 121.83, 113.02, 105.93, 71.24, 70.87, 67.21, 66.87, 52.88, 46.99, 44.45, 39.35,14.76 y 14.41.

Datos NMR para ejemplo las

^{1}H NMR (300 MHz,$CDCl_3$) δ ppm 8.67 (ArH, t, *J* = 1.54,1.54 Hz, 1H) , 8.29 (ArH, dd, *J* = 6.60,1.28 Hz, 1H) , 8.07 (ArH, d, J= 8.41 Hz, 1H) , 8.03- 7.98 (ArH, m, 2H) , 7.62- 7.49 (ArH, m, 2H) , 4.98- 4.89 (CH, m, br, 1H) , 4.67- 4.59 (CH, m, br, 1H) , 4.41 (CH, d, *J*= 6.78 Hz, 1H) , 4.05- 3.66 (CH_2, m, 10H) , 3.64- 3.34 (CH_2, m, 3H) , 1.75 (s, 1.5H) , 1.50 (CH_3, d, *J* = 6.78 Hz, 3H) ,1.38 (CH_3, *d*,*J*= 6.82 Hz, 3H) .

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 168.86, 165.34, 162.90, 161.21, 160.01, 138 97, 135.00, 133.74, 131.09, 129.23, 128.98, 126.52, 113.20, 105.20, 100.00, 71.23, 70.89, 67.22, 66.90, 52.82, 46.97, 44.45, 39.34, 14.75 y 14.36

Datos NMR para ejemplo lat

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.06 (ArH, d, *J* = 2.05 Hz, 1H) , 7.98 (ArH, d, *J* = 8.41 Hz, 1H) , 7.86- 7.79 (ArH, m, 1H) , 7.46- 7.33 (ArH, m, 3H) , 7.23 (NH, s, 1H) , 4.83 (CH, dd, *J* = 3.58,2.50 Hz, 1H) , 4.56- 4.46 (CH, m, 1H) , 4.32 (CH, d, *J* = 6.74 Hz, 1H) , 3.93- 3.89 (CH_2, m, 2H) , 3.88- 3.77 (CH_2, m, 2H) , 3.76- 3.58 (CH_2, m, 5H) , 3.49 (CH_2, dt, *J* = 11.76,11.38,

2.76 Hz, 1H) , 3.35- 3.20 (CH_2, m, 1H) , 2.89 (SCH_3, s, 3H) , 1.42 (CH_3, d, *J*= 6.78 Hz, 3H) , 1.27 (CH_3, d, J= 5.25, Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.32, 162.87, 161.30, 159.96, 140.41, 137.57, 135.01, 129.92, 124.55, 122.25, 120.57, 113.32, 105.24, 71.25, 70.90, 67.22, 66.91, 52.86, 46.99, 44.42, 39.40, 31.60, 22.66, 14.77 y 14.12.

Datos NMR para ejemplo lax

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.88 (ArH, t, *J* = 1.52,1.52 Hz, 1H) , 8.32- 8.25 (ArH, m, 1H) , 8.13- 8.06 (ArH, m, 1H) , 7.99 (ArH, d, *J*= 8.42 Hz, 1H) , 7.53- 7.39 (ArH, m, 2H) , 4.90- 4.80 (CH, m, 1H) , 4.58- 4.48 (CH, m, 1H) , 4.33 (CH, d, *J*= 6.90 Hz, 1H) , 3.95- 3.65 (CH_2, + OH m, 8H) , 3.64 (CH_2, d, *J* = 2.85 Hz, 2H) , 3.56- 3.45 (CH, m, 1H) , 3.31 (CH, d, *J*= 3.67 Hz, 1H) , 1.42 (CH_3, d, *J*= *6.79* Hz, 3H) , 1.29 (CH_3, d, *J* = 6.81 Hz, 3H) ^{13}CNMR(75MHz,$CDCl_3$) δ ppm 169.20, 165.22, 161.32, 159.85, 139.91, 135.01, 131.39, 129.70, 128.71, 113.31, 70.90, 67.10, 52.80, 47.07, 44.42, 39.36, 14.77 y 14.37.

Datos NMR para ejemplo laz

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.04- 7.95 (ArH, m, 2H) , 7.87 (ArH, d, *J* = 8.54 Hz, 1H) , 7.32 (ArH, d, *J*= 8.55 Hz, 1H) , 6.71- 6.64 (ArH, m, 2H) , 4.92- 4.81 (CH, m, 1H) , 4.57 (CH, d, br, 1H) , 4.29 (CH_2, d, *J* = 7.10 Hz, 1H) , 3.91 (CH_2, m, 2H) , 3.82- 3.58 (CH_2 + NH_2, m, 9H) , 3.48 (CH_2, dd, J= 11.36, 2.76 Hz, 1H) , 3.33 (CH_2, dd, J= 13.48, 3.61 Hz, 1H) , 1.39 (CH_3, d, *J* = 6.78 Hz, 3H) , 1.28 (CH_3, d, *J* = 6.82 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.28, 162.18, 148.68, 135.36, 129.54, 119.67, 114.75, 112.63, 104.43, 104.00, 71.29, 70.94, 67.27, 67.12, 66.95, 52.78, 44.45, 39.15, 14.74 y 14.37.

Datos NMR para ejemplo lba

^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 8.69 (ArH, t, J= 1.58,1.58 Hz, 1H) , 8.44- 8.33 (ArH, m, 1H) , 8.11- 8.03 (ArH, m, 1H) , 7.99 (ArH, d, J= 8.42 Hz, 1H) , 7.57- 7.38 (ArH, m, 2H) , 4.87 (CH_2, dd, *J* = 4.84, 0.43 Hz, 1H) , 4.57 (CH, d, *J* = 12.80 Hz, 1H) , 4.31 (CH_2, t, *J* = 6.72, 6.72 Hz, 1H) , 3.94 (CH_2, dd, *J*= 11.15, 3.26 Hz, 2H) , 3.90 (OCH_3, d, *J*= 6.23 Hz, 3H) , 3.83 -

3.62 (CH_2, m, 7H) , 3.57- 3.45 (CH_2, m, 1H) , 3.39- 3.24 (CH_2, m, 1H) , 1.42 (CH_3, d, *J* = 6.78 Hz, 3H) , 1.30 (CH_3, d, J= 6.81 Hz, 3H)

^{13}CNMR(75 MHz, CDCl3) δ ppm 166.92, 165.41, 162.93, 161.43, 161.01, 139.13, 134.91, 132.51, 130.87, 130.57, 128.87, 113.26, 105.16, 71.29, 70.91, 67.25, 66.91, 52.86, 52.18, 46.96, 44.45, 14.77 y 14.37.

Datos NMR para ejemplo lbc

^{1}H NMR (300 MHz, DMSO) δ ppm 8.37 (ArH, dd, *J* = 7.40, 2.26 Hz, 1H) , 8.20 (ArH, d, *J* = 8.50 Hz, 1H) , 8.14- 8.05 (ArH, m, 1H) , 7.62 (ArH, d, *J*= 8.51 Hz, 1H) , 7.29 (ArH, dd, *J* = 9.77, 8.71 Hz, 1H) , 5.42 (CH, t, *J*= 5.76, 5.76 Hz, 1H) , 4.77 (CH, dd, J= 6.57,1.98 Hz, 1H) , 4.65 (CH_2OH, d, *J* = 5.67 Hz, 2H) , 4.51- 4.37 (CH_2, m, 2H) , 3.98- 3.83 (CH_2, m, 3H) , 3.80- 3.70 (CH_2, m, 2H) , 3.69- 3.56 (CH_2, m, 4H) , 3.45 (CH_2, dt, J= 11.86, 11.77, 2.75 Hz, 1H) , 3.30- 3.16 (CH_2, m, 3H) , 1.38 (CH_3, d, *J*= 6.75 Hz, 3H) , 1.25 (CH_3, d, /= 6.75 Hz, 3H) ^{13}CNMR(75 MHz, DMSO) δ ppm 164.91, 162.60, 160.18, 159.82, 136.10, 134.86, 130.19, 129.99, 128.61, 128.27, 128.15, 115.85, 115.57, 113.00, 104.80, 70.89,70.66, 66.84, 66.67, 52.29, 46.76,44.34, 14.84 y 14.34.

Datos NMR para ejemplo lbd

^{1}H NMR (300 MHz, DMSO) δ ppm 8.63 (ArH, t, *J* = 1.49,1.49 Hz, 1H) , 8.26 (ArH, d, *J* = 7.95 Hz, 1H) , 8.17 (ArH, d, J= 8.46 Hz, 1H) , 7.91- 7.80 (ArH, m, 1H) , 7.62 (ArH, dd, *J* = 14.96, 8.10 Hz, 2H) , 7.37 (NH_2, s, 2H) , 4.69 (CH, dd, *J*= 6.21,1.34 Hz, 1H) , 4.35 (CH_2, d, *J* = 13.74 Hz, 2H) , 3.91- 3.74 (CH_2, m, 3H) , 3.73- 3.46 (CH_2, m, 6H) , 3.36 (CH_2, dt, J = 11.82, 11.71,2.49 Hz, 1H) , 2.41 (CH_2, td, J= 3.46,1.69,1.69 Hz, 1H) , 1.30 (CH_3, d,J= 6.74 Hz, 3H) , 1.17 (CH_3, d, *J*= 6.75 Hz, 3H)

^{13}CNMR(75 MHz) δppm 164.85, 162.63, 159.86, 159.49, 145.34, 139.35, 136.44, 130.73, 129.98, 127.34, 124.96, 113.18, 105.38, 79.87, 79.43, 78.99, 70.89, 70.67, 66.85, 66.67, 52.29, 46.79, 44.37, 14.88 y 14.41.

Datos NMR para ejemplo lbk

^{1}H NMR (300 MHz, $CDC1_3$) δ ppm 8.19 (ArH, dd, *J* = 7.62,2.22 Hz, 1H) , 8.12 (ArH, ddd, *J*

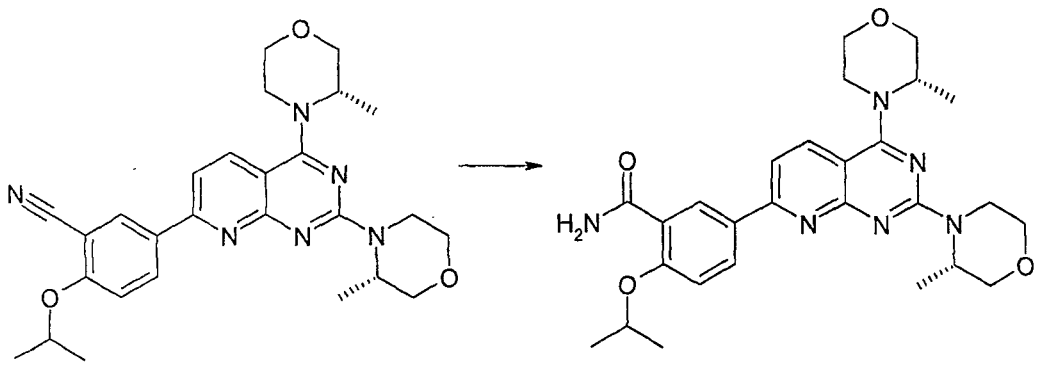
= 8.54, 5.03, 2.25 Hz, 1H) , 8.01 (ArH, d, J = 8.41 Hz, 1H) , 7.38 (ArH, d, J = 8.43 Hz, 1H) , 7.24- 7.19 (ArH, m, 1H) , 6.83 (NH, s, br, 1H) , 4.98- 4.85 (CH, m, 1H) , 4.67- 4.55 (CH, m, 1H) .

4.36 (CH_2, d, J = 6.95 Hz, 1H) , 4.06- 3.93 (CH_2, m, 2H) , 3.91- 3.65 (CH_2, m, 1H) , 3.53 (CH_2, dd, J= 11.40,2.69 Hz, 1H) , 3.44- 3.28 (CH_2, m, 1H) , 3.07 (SCH3, s, 3H) , 1.47 (CH_3, d, J = 6.77 Hz, 3H) , 1.34 (CH_3, d, J = 6.81 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.45, 162.93, 160.61, 160.12, 157.28, 153.99, 136.32, 135.15, 123.51, 116.31, 116.05, 113.26,105.18, 71.39, 71.01, 67.36, 67.01, 53.00,47.07, 44.51, 39.44, 31.71, 22.77, 14.86, y 14.95.

Los compuestos también se sintetizaron según los siguientes procedimientos:

Procedimiento para la síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- isopropoxi- benzamida (Ejemplo 1cw)

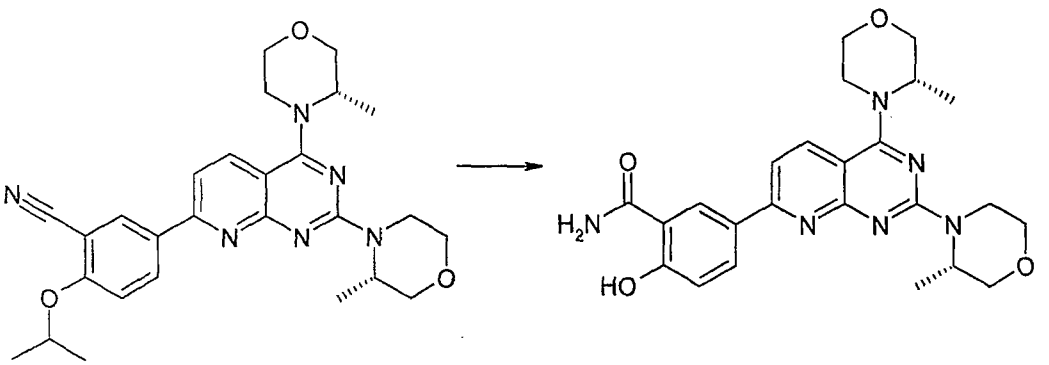


Se agregó por porciones 5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- isopropoxi- benzonitrilo (1 equiv) a H_2S0_4 concentrado (0.1 M substrato en ácido) . La reacción se calentó a 90 °C y se mantuvo a esta temperatura hasta que todo el material de inicio se disolvió para proporcionar una solución roja brillante. La mezcla fue enfriada y se agregó agua (2 volumenes de reacción) por goteo, luego la solución se neutralizó mediante adición cuidadosa de NaOH sólido hasta lograr pH 4- 5. La mezcla fue enfriada y se neutralizó mediante la adición de 2N NaOH y luego se extrajo utilizando EtOAc (2X10 volumenes de reacción) . Los extractos combinados se secaron ($MgSO_4$) , filtraron y concentraron *al vacío* para proporcionar un residuo crudo el cual se purificó mediante cromatografía rápida (SiO_2)

utilizando MeOH/DCM - 0.T00 llegando a 5:95 como eluyente para proporcionar el producto deseado como un polvo amarillo.

5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- isopropoxi- benzamida: (53 % rendimiento, 100 % pureza) m/z (LC- MS,ESP) :507.5 $[M+H]^-$, R/T = 3.01 min)

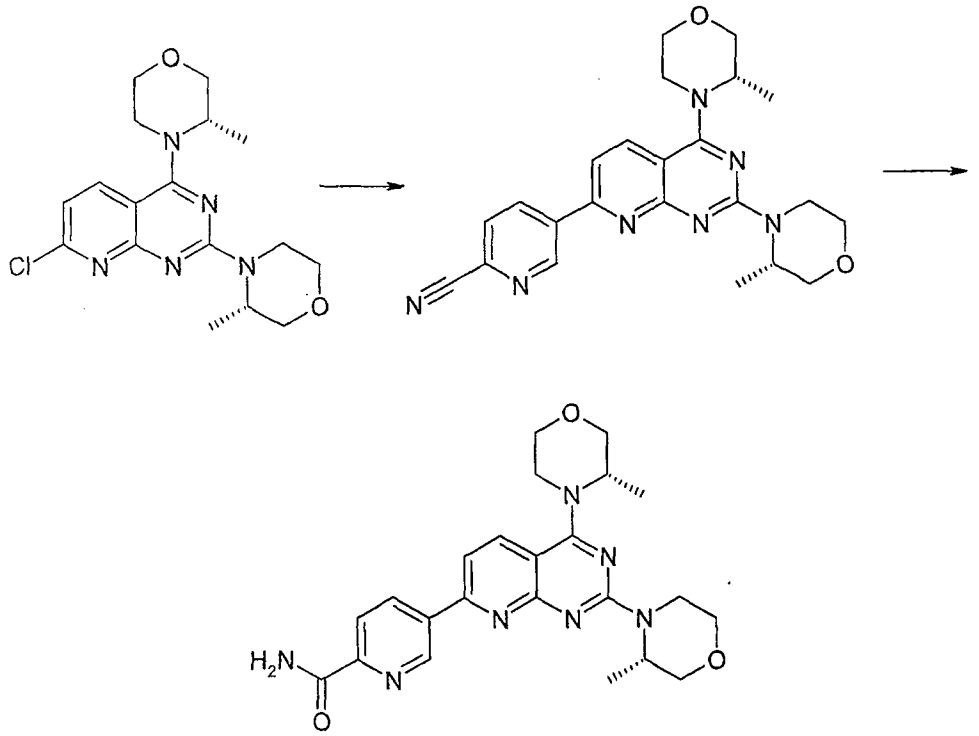
Procedimiento para la síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4~yI) - pirido[2,3- d]pirimidin- 7- il]- 2- hidroxilo- benzamida (Ejemplo lex)



Se agregó 5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- isopropoxi- benzonitrilo (1 equiv) por porciones a H_2SO_4 concentrado (0.1 M substrato en ácido) . La reacción se calentó a 90 °C y se mantuvo a esta temperatura hasta que todo el material de inicio se disolvió para proporcionar una solución de color rojo brillante. La mezcla fue enfriada y se agregó agua (2 volumenes de reacción) por goteo, luego la solución se neutralizó mediante adición cuidadosa de NaOH sólido hasta lograr pH 4- 5. La mezcla fue enfriada y se neutralizó mediante la adición de 2N NaOH y luego se extrajo utilizando EtOAc (2X10 volumenes de reacción) . Los extractos combinados se secaron (MgSO4) , filtraron y concentraron *al vacío* para proporcionar un residuo crudo el cual se purificó mediante cromatografia rápida (SiO_2) utilizando MeOH/DCM - 0:100 llegando a 5:95 como eluyente para proporcionar el producto deseado como un polvo amarillo.

5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- hidroxilo- benzamida: (44 % rendimiento, 100 % pureza) m/z (LC- MS,ESP) :465.4 $[M+H]^-$, R/T = 2.70 min)

Procedimiento para la síntesis de amida del ácido 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- yl]~piridina- 2- carboxílico (Ejemplo 1ey)



La síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridina- 2- carbonitrilo se realizó como sigue:-

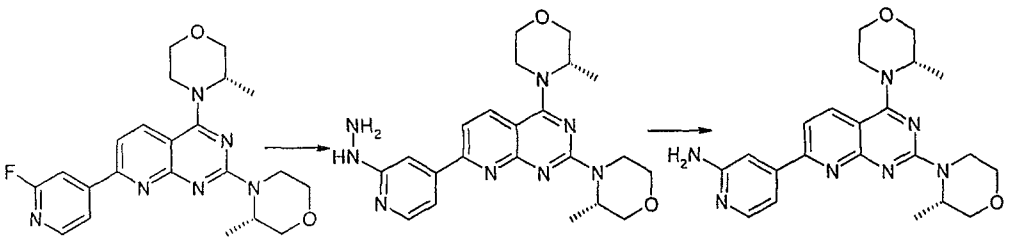
A cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3 equiv) y el ácido borónico apropiado o pinacolato de éster borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) los cuales se disolvieron en N,N- dimetilacetamida (0.17 M de cloro- substrato) . La mezcla se degasificó con nitrógeno, se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 15 minutos. La mezcla se concentró *al vacío* y luego se suspendió en éter t- butilmetílico, se filtró y secó para proporcionar el producto deseado.

5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridina- 2- carbonitrilo: (84 % rendimiento, 93 % pureza) m/z (LC- MS,ESP) :191.3 $[M+H]^+$, R/T = 2.29 min)

Para una suspension de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridina- 2- carbonitrilo (1 equiv) en H_2SO_4 concentrado. La mezcla se calentó a 90 °C hasta formar una solución marrón claro. La mezcla se dejo enfriar y luego se alcalinizó con 50 % por peso de Solución de NaOH. La mezcla acuosa se extrajo utilizando EtOAc (3X2 volumenes de reacción) . Las fracciones orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron *al vacío* para proporcionar un sólido amarillo palido el cual se trituró con EtOAc para proporcionar el producto deseado.

5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridina- 2- ácido carboxílico amida: 93 % rendimiento, 96 % pureza) m/z (LC- MS,ESP) :450.4 $[M+H]^+$, R/T = 3.72 min)

Procedimiento para la síntesis de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- yI]- piridin- 2- ylamina (Ejemplo lcz)



A una solución 1.2 M de compuesto lau (1 equiv) en THF se agregó hidrato de hidrazina (9 volumenes de reacción) . El recipiente de reacción se selló y expuso a radiación microondas (115 °C, ambiente de absorción de medios) durante 2 horas. Al terminar, la mezcla de reacción se extrajo con EtOAc (2X1 volumen de reacción) . Las fracciones orgánicas se combinaron, secaron (MgSO4) , filtraron y concentraron *al vacío* para proporcionar el producto deseado en forma apropiadamente limpia para utilizar en reacciones subsiguientes.

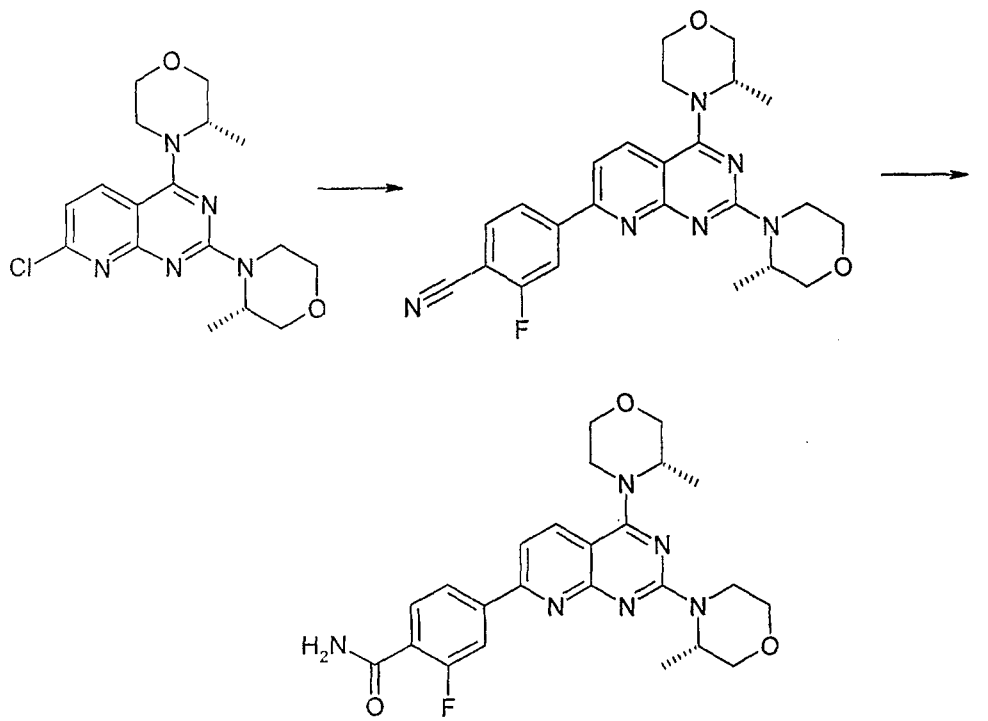
{4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- il}- hidrazina 7- (4,4,5,5- Tetrametil- [l,3,2]dioxaborolan- 2- il) - 2H- ftalazin- l- ona: (77 % rendimiento, 84 % pureza) m/z (LC- MS,ESP) :437.4 $[M+H]^+$, R/T = 2.23 min)

Una solución 0.12 M de {4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3-

d]pirimidin- 7- il]- piridin- 2- il}- hidrazina 7- (4,4,5,5- Tetrametil- [1,3,2]dioxaborolan- 2- il) - 2H- ftalazin- 1- ona (1 equiv) en EtOH se agregó a un autoclave revestido en vidrio el cual contenia Ra- Ni activado. La reacción se mantuvo bajo 5 barios H2 durante 30 horas. Al terminar, la mezcla se filtró a través de una almohadilla de Celite™ y el filtrado se concentró al vacío. El residuo crudo resultante se purificó mediante cromatografía rápida de fase inversa utilizando 5:95 - 0.1 % TFA/MeCN:0.1 % TFA/H_2O como eluyente para proporcionar el producto deseado como un polvo amarillo.

4- [2,4- Bis- ((S) - 3- nietil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- ilamina: (70 % rendimiento, 100 % pureza) m/z (LC- MS,ESP) :422 $[M+H]^+$, R/T = 2.25 min)

Procedimiento para la síntesis de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzamida (Ejemplo 1da) .



Al cloro- sustrato apropiado (1 equiv) se agregó carbonato de potasio (2.5 equiv) y el ácido borónico apropiado o pinacolato de éster borónico (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) los cuales se disolvieron en MeCN/H2O
(0.03 M de cloro- substrato) . La mezcla se degasificó con nitrógeno, se selló y expuso a

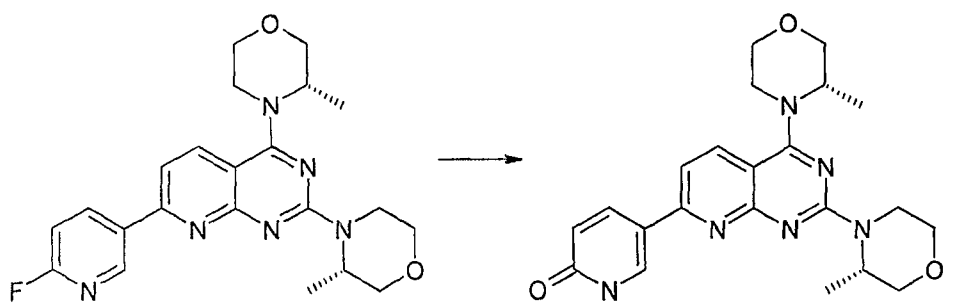
radiación microondas (110 °C, ambiente de absorción de medios) durante 25 minutos. La mezcla se filtró y el precipitado se recolectó, y se recristalizó a partir de $MeCN/H_2O$ para proporcionar el producto deseado.

4- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzonitrilo: (49 % rendimiento, 87 % pureza) m/z (LC- MS,ESP) :449 [M+H]+, R/T = 2.93 min)

Se disolvió 4- [2,4- Bis- ((S) - 3- me1iiil- morfolin- 4- il) - pirido[2,3- d]pirimidm- 7- il]- 2- fluoro- benzonitrilo (1 equiv) en ácido sulfúrico concentrado (0.15 M substrato en ácido) . La reacción se calentó rapidamente a 90 °C durante 5 minutos antes de enfriar la mezcla o apagar, cuidadosamente, con NaOH sólido hasta que la solución fue básica. La mezcla se extrajo con EtOAc/nBuOH (2X1 volumen de reacción – tasa 1:1) . Los extractos orgánicos se combinaron, secaron (MgS04) , filtraron y concentraron al vacío para proporcionar un residuo el cual se purificó adicionalmente utilizando cromatografia rápida (SiO2) con TBME llegando a TBME/MeOH (95:5) como eluyente, para proporcionar el compuesto del título como un sólido amarillo.

4- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzamida Síntesis: (71 % rendimiento, 99 % pureza) m/z (LC- MS,ESP) :467 $[M+H]^+$, R/T = 2.60 min)

Procedimiento para la síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- lH- piridin- 2- ona (Ejemplo ldb) .

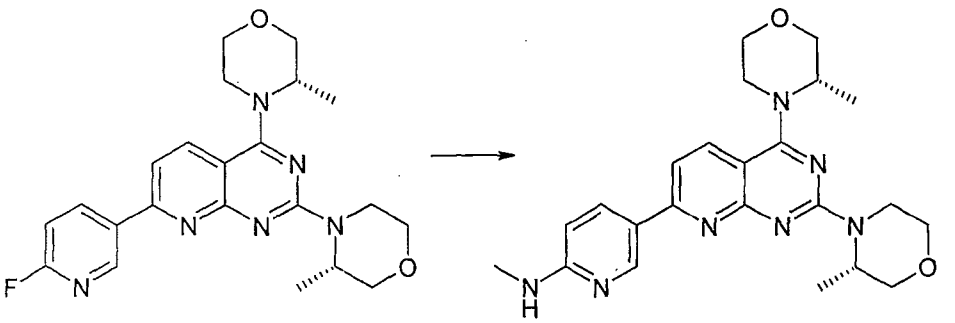


A una solución 0.2 M de compuesto lah (1 equiv) en DMA se agregó una solución acuosa 1.6 M de hidróxido de sodio (5 equiv) . El recipiente de reacción se selló y expuso a

radiación microondas (110°C, ambiente de absorción de medios) durante 10 minutos. La mezcla de reacción se concentró al vacío. El residuo se suspendió en agua y sonicó para proporcionar una solución turbia, lavada con TBME luego enfriada y neutralizada con 2M HCl, formando un precipitado amarillo. El precipitado se filtró y lavó con agua y TBME y se secó para proporcionar el producto deseado.

5- [2,4- Bis- ((S) - 3 - metil- morfolin- 4- il) - pirido [2,3- d]pirimidin- 7- il]- 1 H- piridin- 2- ona: (69 % rendimiento, 96 % pureza) m/z (LC- MS,ESP) :423 [M+H]+, R/T = 3.60 min)

Procedimiento para la síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- yi) - pirido[2,3- d]pirimidin- 7- yI]- lH- piridin- 2- ona (Ejemplo ldc) .



Al compuesto lah (1 equiv) se agregó una solución de 40 % metilamina en metanol (100 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (115°C, ambiente de absorción de medios) durante 30 minutos. La solución se concentró al vacío para proporcionar un sólido amarillo. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

{5- [2,4- Bis- (3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- il}- metilo- amina: (61% rendimiento, 99 % pureza) m/z (LC- MS,ESP) :436 [M+H]+, R/T = 3.34 min)

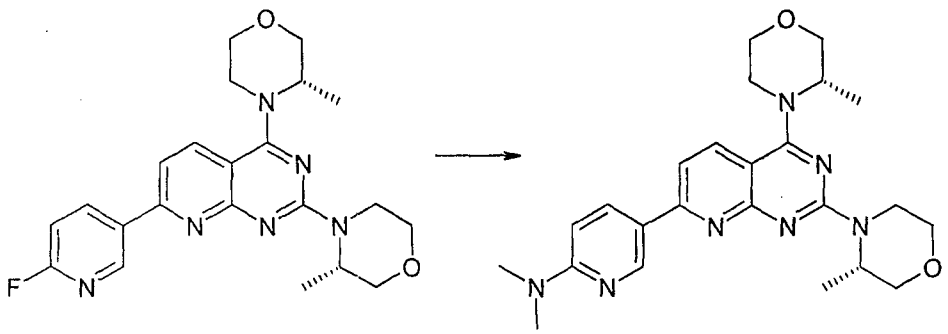
Datos NMR para ejemplo ldc

^{1}H NMR (300 MHz, $CDCl_3$. δ ppm 8.69 (ArH, d, J = 2.06 Hz, 1H) , 8.56 (ArH, dd, J = 9.02, 2.32 Hz, 1H) , 7.97 (ArH, d, J= 8.47 Hz, 1H) , 7.33 (ArH, d, J= 8.48 Hz, 1H) , 6.59 (ArH, d, J = 9.03 Hz, 1H) , 5.92 (NH, s, br, 1H) , 4.90 (CH_2, dd, J = 5.85, 0.41 Hz, 1H) , 4.59 (CH_2, d, J = 12.53 Hz, 1H) , 4.41- 4.29 (CH2, m, 1H) , 4.05- 3.93 (CH2, m, 2H) , 3.90- 3.62 (CH2, m, 8H) , 3.62- 3.50 (CH2, m, 1H) , 3.43- 3.31 (CH2, m, 1H) , 3.00 (NCH3, s, 3H) , 1.47 (CH3, d,/= 6.78

Hz, 3H) , 1.35 (CH3, d, J = 6.82 Hz, 3H)

^{13}CNMR(75 MHz, CDCI3 δ ppm 167.59, 165.30, 162.90, 159.99, 158.84, 144.22, 139.19, 134.85, 123.35, 111.65, 106.51,104.57, 71.28, 70.91,67.24, 66.92, 52.83, 46.96,44.42, 39.34.29.05,14.73 o 14.34.

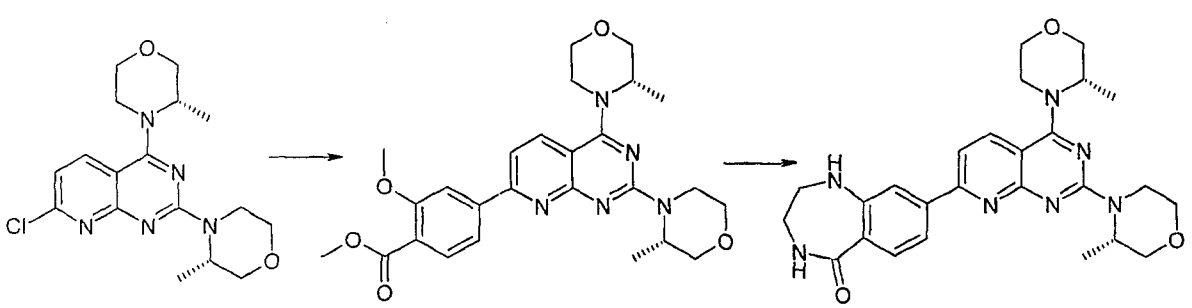
Procedimiento para la síntesis de {5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- yI]- piridin- 2- yI}- dimetil- amina (Ejemplo ldd) .



A una solución del compuesto lah (1 equiv) en THF (0.05 M) se agregó una solución de 33 % dimetilamina en etanol (200 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130°C, ambiente de absorción de medios) durante 40 minutos. La solución se concentró al vacío para proporcionar un sólido amarillo. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

{5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- il}- dimetil- amina: (54 % rendimiento, 97 % pureza) m/z (LC- MS,ESP) :450 $[M+H]^+$, R/T = 3.52 min)

Procedimiento para la síntesis de 8- [2,4- bis- ((S) - 3- metilo- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- l,2,3,4- tetrahidro- benzo[e][l,4]diazepin~5- ona (Ejemplo lde) .



Se suspensió cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , ácido 3- metoxi- 4- metoxicarbonilfenilborónico, éster de pinacol (1.1 equiv) en (1:1) acetonitrilo/agua (0.1 M de cloro- substrato) . La mezcla se sonicó y degasificó durante 15 minutos con nitrógeno. Luego se agregó tetrakistrifenilfosfina (0.05 equiv) y la mezcla se sonicó durante 5 minutos más con nitrógeno. La mezcla se calentó a 100°C durante 3 horas bajo nitrógeno. La reacción fue enfriada y el residuo insoluble se filtró. El filtrado se concentró a la mitad del volumen original y la mezcla de agua restante se extrajo con CH_2Cl_2. Las capas orgánicas se lavaron con agua y salmuera, se combinaron y secaron con sulfato de magnesio, se filtraron y concentraron al vacío para proporcionar un aceite el cual se purificó mediante cromatografia en columna rápida eluyendo con 50 % a 100 % EtOAc/Hexano.

Éster metílico del ácido 4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- benzóico: (67 % rendimiento, 100 % pureza) m/z (LC- MS,ESP) :494 [M+H]+, R/T = 2.86 min)

Una solución de éster metílico del ácido 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2.3- d]pirimidin- 7- il]- 2- metoxi- benzoico (1 equiv) en etilendiamina (0.35 M) se agitó a temperatura ambiente durante 24 horas. Se agregó DMA a la solución (etilendiamina/DMA 1:1.25) . El recipiente de reacción se selló y expuso a radiación microondas (180°C, ambiente de absorción de medios) durante 1 hora. La mezcla de reacción se diluyó con CH_2Cl_2 y se extrajo con agua y se lavó con salmuera. La capa orgánica se secó con sulfato de magnesio, se filtró y concentró al vacío para proporcionar un sólido amarillo el cual luego se purificó mediante HPLC preparativa para proporcionar el producto deseado.

8- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- l,2,3,4- tetrahidro- benzo[e][l,4]diazepin- 5- ona: (49 % rendimiento, 99 % pureza) m/z (LC- MS,ESP) :490 $[M+H]^+$, R/T = 3.52 min)

Datos NMR para ejemplo lde

^{1}H NMR (300 MHz, CDCI3 δ ppm 8.65 (NH, s, br, 1H) , 8.01 (ArH, d, J= 8.38 Hz, 1H) , 7.78 (ArH, s, 1H) , 7.68 (ArH, s, 1H) , 7.44 (ArH, dd, J = 18.50, 8.20 Hz, 2H) , 4.93- 4.77 (CH2, m, 1H) , 4.50 (CH2, s, 1H) , 4.46- 4.32 (CH2, m, 1H) , 4.05- 3.61 (CH2, m, 14H) , 3.53 (CH2, d, J = 2.04 Hz, 1H) 5 3.41- 3.26 (CH2, m, 1H) , 1.47 (CH3, d, J"= 6.76 Hz, 3H) , 1.33 (CH3, d, J= 6.78 Hz, 3H) .

Organizacion y
Digitalizacion CSA Ltda

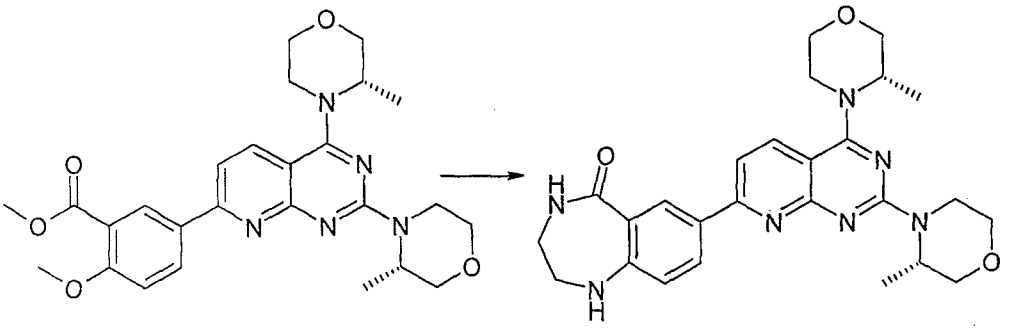
PATENTE DE INVENCIÓN

09-17881

TOMO 3/3

^{13}CNMR(75 MHz,$CDCl_3$ δppm 165.11, 165.07, 165.00, 163.41, 162.64, 161.07, 159.90, 144.87, 135.18, 129.50, 118.02, 116.80, 113.87, 109.20,105.45, 71.20, 70.89, 67.14, 66.89, 52.77, 47.04, 44.76, 44.40, 39.33,14.78 y 13.32.

Procedimiento para la síntesis de 7- [2,4- bis- ((S) - 3- metilo- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- l,2,3,4- tetrahidro- benzo[e] [l,4]diazepin- 5- ona (Ejemplo ldf) .



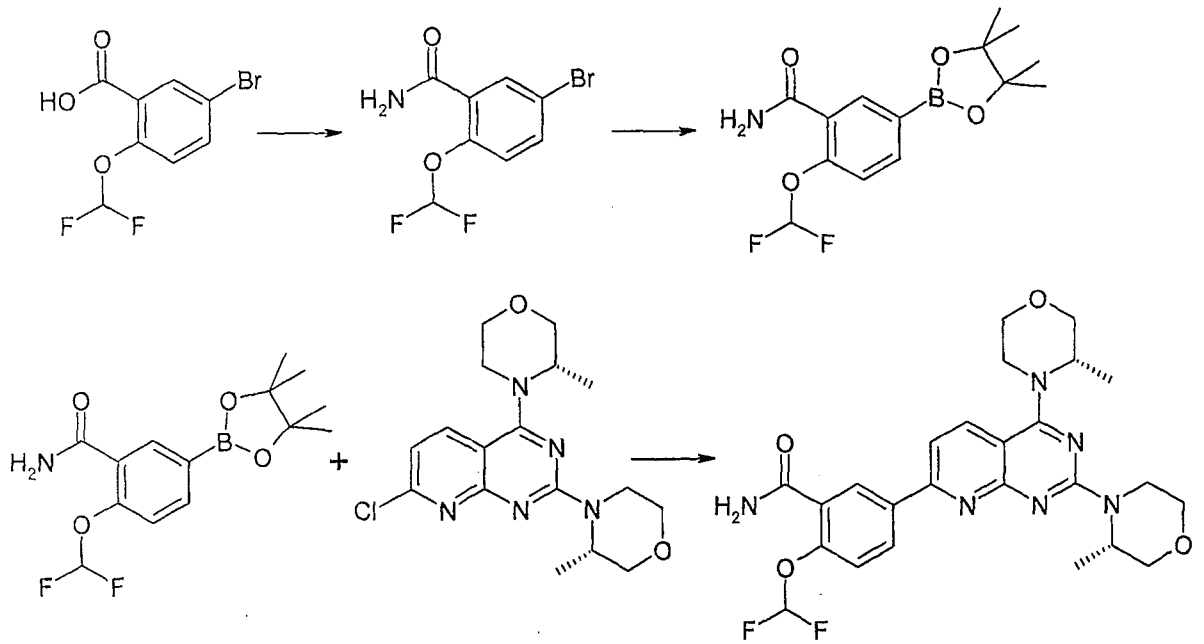
Una solución del compuesto lbg (1 equiv) en etilendiamina (0.35 M) se agitó a temperatura ambiente durante 24 horas. Se agregó DMA a la solución (etilendiamina/DMA 1:1.25) . El recipiente de reacción se selló y expuso a radiación microondas (180°C, ambiente de absorción de medios) durante 1 hora. La mezcla de reacción se diluyó con etilacetato y se extrajo con agua. La capa orgánica se secó con sulfato de magnesio, se filtró y concentró al vacío para proporcionar un residuo el cual luego se purificó mediante cromatografia en columna rápida eluyendo con 0 % a 20 % MeOH/ CH_2Cl_2.

8- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- l,2,3,4- tetrahidro- benzo[e][l.4]diazepin- 5- ona: (40 % rendimiento, 100 % pureza) m/z (LC- MS,ESP) :490 $[M+H]^+$, R/T = 3.49 min)

Datos NMR para ejemplo ldf

^{1}H NMR (300 MHz, CDCI3 δ ppm 8.60 (ArH, d,J = 2.23 Hz, 1H) , 7.93- 7.83 (ArH, m, 2H) , 7.34 (ArH, d,J= 8.56 Hz, 1H) , 6.89 (ArH, d, J= 8.97 Hz, 1H) , 4.82- 4.71 (CH2, m, 1H) , 4.47 (CH_2, dd, J = 7.28, 6.58 Hz, 1H) , 4.30 (CH2, d, J = 6.93 Hz, 1H) , 3.95- 3.55 (CH_2, m, 13H) , 3.55- 3.42 (CH2, m, 1H) , 3.35- 3.21 (CH2, m, 1H) , 1.40 (CH3, d, J= 6.77 Hz, 3H) , 1.26 (CH_3, d, .7=6.80 Hz, 3H) .

Procedimiento para la síntesis de 5- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3-d]pirimidin- 7- il]- 2- difluorometoxi- benzamida (Ejemplo ldg) .



A una solución de ácido 5- bromo- 2- difluorometoxi- benzoico(1 equiv) en THF (0.1 M) se agregó por goteo cloruro de tionilo (5 equiv) a temperatura ambiente. La mezcla de reacción se agitó a 40°C durante 2 horas. La mezcla de reacción se concentró al vacío. El residuo se suspendió en THF seco (0.04 M) y gas de amoniaco se burbujeó lentamente en la mezcla de reacción durante 45 minutos. La mezcla de reacción se concentró al vacío. El residuo se disolvió en CH_2Cl_2 mínimo y se agregó hexano para proporcionar un precipitado blanco que fue recolectado mediante filtración al vacío en forma apropiadamente limpia para utilizar en reacciones subsiguientes.

5- Bromo- 2- difluorometoxi- benzamida: (45 % rendimiento, 73 % pureza) m/z (LC- MS, ESP) :266/268 [M+H]+, R/T = 3.42 min) .

A una solución de 5- bromo- 2- difluorometoxi- benzamida (1 equiv) en dioxan (0.1 M) se agregó bis(pinacolato) diboro (1.1 equiv) , acetato potásico (3.5 equiv) y dppf (0.05 equiv) . La mezcla de reacción se degasificó con nitrógeno durante 15 minutos. Se agregó PdCl2(dppf) (0.05 equiv) a la mezcla de reacción, la cual se degasificó durante 5 minutos más. La mezcla de reacción se agitó a 110°C durante 12 horas bajo nitrógeno. La mezcla de reacción se particionó

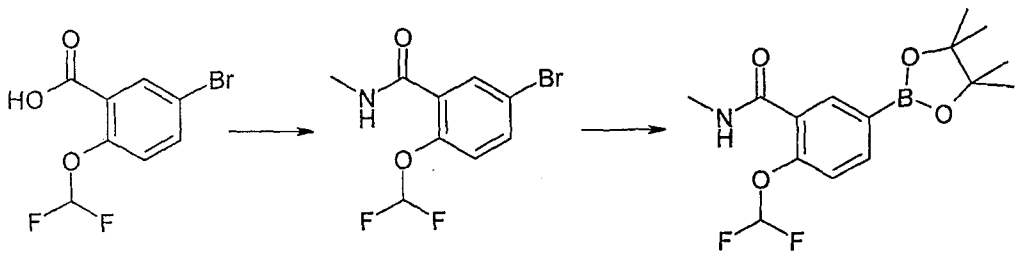
entre EtOAc y agua. La capa acuosa se extrajo con EtOAc y las fases orgánicas combinadas se lavaron con agua, se secaron con sulfato de magnesio, filtraron y concentraron al vacío para proporcionar el producto deseado para utilizar en reacciones subsiguientes

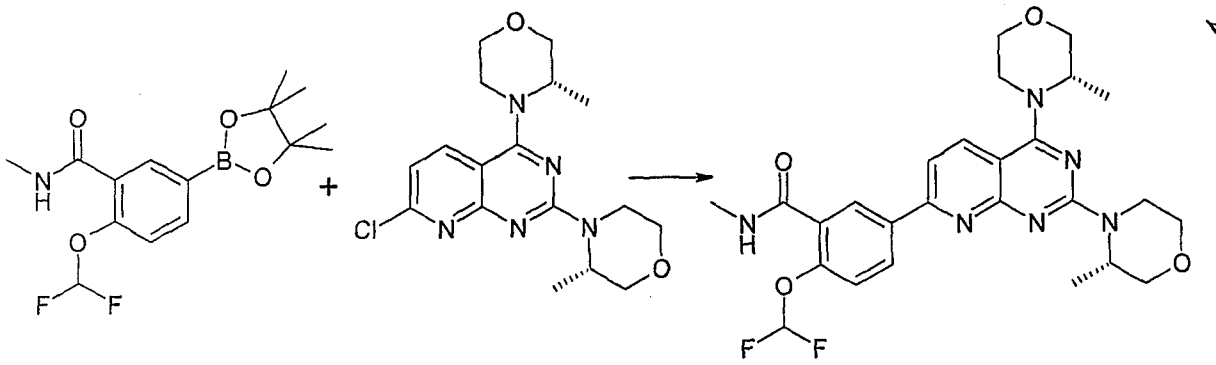
2- Difluorometoxi- 5- (4,4,5,5- tetrametil- [1,352]dioxaborolan- 2- il) - benzamida: (71 % rendimiento, el crudo fue adelantado sin más análisis)

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , 2- difluorometoxi- 5- (4,4,5,5- tetrametil- [1,3,2]dioxaborolan- 2- il) - benzamida (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 100 °C durante 4 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con salmuera, secaron (MgSO4.) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- difluorometoxi- benzamida: (14 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 515 $[M+H]^+$, R/T = 7.40 min

Procedimiento para la síntesis de 5- [2,4- bis- ((S) ~3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- difluorometoxi- N- metilo- benzamida (Ejemplo ldh) .





A una solución de ácido 5- bromo- 2- difluorometoxi- benzóico (1 equiv) en DMF (0.1 M) se agregó trietilamina (4 equiv) . La mezcla de reacción fue enfriada a 0°C y se agregó HBTU (1.2 equiv) . La mezcla de reacción se dejo llegar a temperatura ambiente durante 1 hora y se agregó hidrocloruro de metilamina (2 equiv) . La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se particionó entre EtOAc y agua, y la fase acuosa se extrajo adicionalmente con EtOAc. Las fases orgánicas combinadas se lavaron con agua, se secaron con sulfato de magnesio, filtraron y concentraron al vacío para proporcionar el producto deseado en forma apropiadamente limpia para utilizar en reacciones subsiguientes.

5- Bromo- 2- difluorometoxi- N- metilo- benzamida: (100 % rendimiento, 75 % pureza) m/z (LC- MS, ESP) : 280/282 [M+H]+, R/T = 3.55 min)

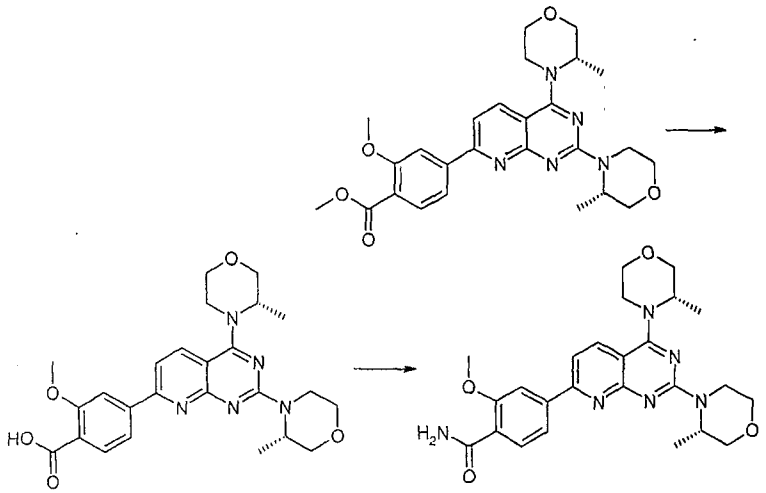
Se preparó 2- Difluorometoxi- N- metilo- 5- (4,4,5,5- tetrametil- [l,3,2]dioxaborolan- 2- il) - benzamida en una forma similar a 2- Difluorometoxi- 5- (4,4,5,5- tetrametil- [l,3,2]dioxaborolan- 2- il) - benzamida utilizando 5- bromo- 2- difluorometoxi- N- metilo- benzamida como el material de inicio.

2- Difluorometoxi- N- metilo- 5- (4,4,5,5- tetrametil- [l,3,2]dioxaborolan- 2- il) - benzamida: (100 % rendimiento, el crudo se tomó hacia adelante sin análisis adicional)

Una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , 2- difluorometoxi- 5- (4,4,5,5- tetrametil- [l,3,2]dioxaborolan- 2- il) - benzamida (1.1 equiv) y tetrakis(trifenilfosfina) paladio (0.05 equiv) en acetonitrilo/agua (0.1 M de cloro- substrato) se agitó a 100 °C durante 2 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con salmuera, secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

5- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- difluorometoxi- N- metilo- benzamida: (53 % rendimiento, 87 % pureza) m/z (LC- MS, ESP) : 421 $[M+H]^+$, R/T = 4.06 min)

Procedimiento para la síntesis de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- yI]- 2- metoxi- benzamida (Ejemplo ldi) .



Se disolvió éster metílico del ácido 4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- benzoico (1 equiv) en metanol (0.2 M) . se agregó solución acuosa de 1M hidróxido de sodio (5.0 equiv) . La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Al terminar, la mezcla de reacción fue neutralizada con 1M HCl acuoso y se concentró al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 10 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Acido 4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- benzóico: (100 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 480 $[M+H]^+$, R/T = 2.69 min)

Se suspendió Acido 4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- benzoico(1 equiv) en THF (0.05 M) . Se agregó cloruro de tionilo por goteo a 40°C. Luego la mezcla de reacción se calentó durante 1 hora a 40°C. Luego se burbujeó gas de amoniaco lentamente en la mezcla de reacción. Se agregó THF para dilución adicional (0.025 M) y la mezcla de reacción se calentó durante una hora a 40°C. Al terminar, la mezcla de reacción

fue enfriada y concentrada al vacío. El residuo se particionó entre agua y CH_2Cl_2. La fase acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

4- [2.4- Bis- ((S) - 3 - metil- morfolin- 4- il) - pirido [2,3 - d]pirimidin- 7- il]- 2- metoxi- benzamida: (88 % rendimiento, 99 % pureza) m/z (LC- MS, ESP) : 479 [M+H]+, R/T = 3.92 min)

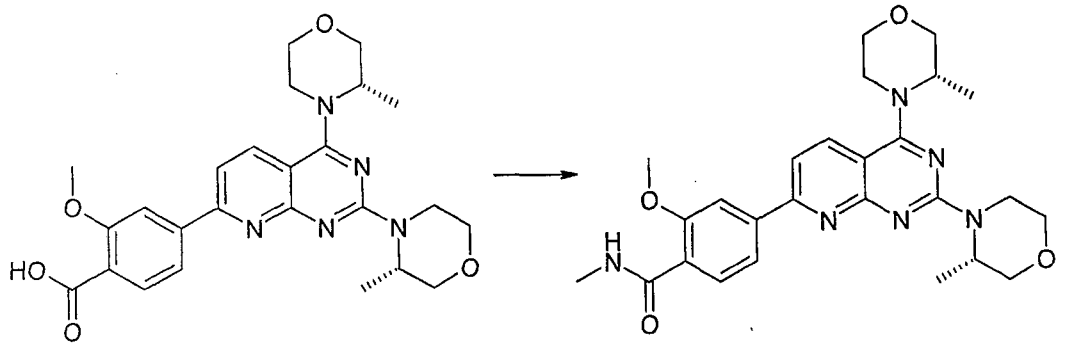
Datos NMR para ejemplo ldi

^{1}H NMR (300 MHz, CDCI3 δ ppm 8.30 (ArH, d, J = 8.17 Hz, 1H) , 8.04 (ArH, dd, J = 6.21, 4.98 Hz, 2H) , 7.80 (NH, br, s, 1H) , 7.67 (ArH, dd, J= 8.21,1.49 Hz, 1H) , 7.49 (ArH, d, J = 8.44 Hz, 1H) , 5.96 (NH, s, br, 1H) , 4.98- 4.85 (CH2, m, 1H) , 4.61 (CH2, d, J= 12.90 Hz, 1H) , 4.39 (CH2, d, J = 6.89 Hz, 1H) , 4.13 (OCH3, s, 3H) , 4.05- 3.64 (CH2, m, 9H) , 3.64- 3.51 (CH2s

m, 1H) , 3.41 (CH2, dd, J= 13.34, 3.62 Hz, 1H) , 1.49 (CH3, d, J= 6.79 Hz, 3H) , 1.36 (CH3, d, J= 6.82 Hz, 3H) .

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 166.78, 165.32, 162.81, 160.99, 160.02, 158.15, 143.57, 134.98, 132.76, 121.80, 120.15,113.62, 111.30, 105.44, 71.27, 70.89, 67.23, 66.90, 56.42, 52.88, 47.01, 44.41, 39.36, 14.77 y 14.40.

Procedimiento para la síntesis de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- N- metilo- benzamida (Ejemplo ldj) .



Se disolvió ácido 4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- benzoico (1 equiv) en THF (0. 1 M) y se agregó HBTU (1.5 equiv) . Se agregó

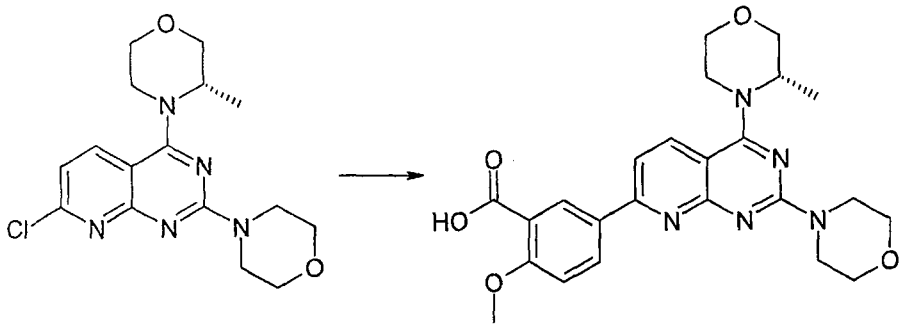
por goteo metilamina en THF (15 equiv) seguido por trietilamina (1.5 equiv) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró al vacío. El residuo se particionó entre agua y CH_2Cl_2. La fase acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

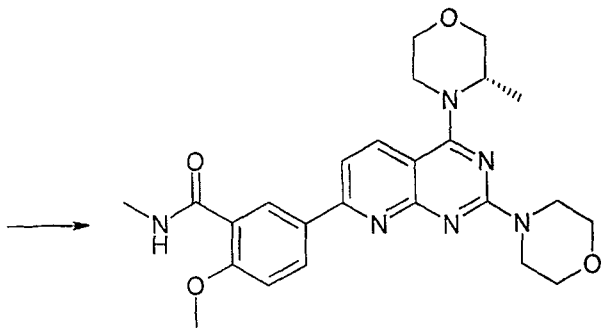
4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[253- d]pirimidin- 7- il]- 2- metoxi- N- metilo- benzamida: (56 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 493 [M+H]+, R/T = 4.00 min)

Datos NMR para ejemplo ldj

!H NMR (300 MHz, $CDCl_3$ δ ppm 8.26 (ArH, d, J = 8.16 Hz, 1H) , 7.98 (ArH, dd, J = 8.74, 4.91 Hz, 2H) , 7.91- 7.81 (NH, m, br, 1H) , 7.60 (ArH, dd, J= 8.21, 1.52 Hz, 1H) , 7.43 (ArH, d, J*= 8.45 Hz, 1H) , 4.93- 4.81 (CH_2, m, 1H) , 4.62- 4.51 (CH2, m, 1H) , 4.39- 4.28 (CH_2, m, 1H) , 4.07 (OCH_3, s, 3H) , 4.00- 3.58 (CH_2, m, 9H) , 3.57- 3.45 (CH_2, m, 1H) , 3.40- 3.27 (CH_2, m, 1H) , 2.99 (NHCH3, d, J = 4.82 Hz, 3H) , 1.43 (CH_3, d, J = 6.78 Hz, 3H) , 1.31 (CH_3, d, J = 6.81 Hz, 3H) .

Procedimiento para la síntesis de 2- metoxi- N- metilo- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- morfolin- 4- il- pirido[2,3- d]pirimidin- 7- il]- benzamida (Ejemplo 1 dk) .





A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.0 equiv) , y éster metílico del ácido 2- metoxi- 5- (4,4,5,5- tetrametil- [1,3,2]dioxaborolan- 2- il) - benzoico(1.05 equiv) en acetonitrilo/agua (1:1) (0.028 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130°C, ambiente de absorción de medios) durante 20 minutos. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 20 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

2- Metoxi- 5 - [4- ((S) - 3 - metil- morfolin- 4- il) - 2- morfolin- 4- y 1- pirido [2,3 - d]pirimidin- 7-

il]- benzoic acid: (91 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 466.4 $[M+H]^+$, R/T = 2.68 min)

Se disolvió ácido 2- Metoxi- 5- [4- ((S) - 3 - metil- morfolin- 4- il) - 2- moifolin- 4- il- pirido[2,3 - d]pirimidin- 7- il]- benzoico (1 equiv) en DMF (0.1 M) y se agregó DIPEA (8 equiv) .

Se agregó HBTU (1.2 equiv) a 0°C y la mezcla de reacción se agitó durante 30 minutos.

Se agregó hidrocloruro de metilamina (5 equiv) y la mezcla de reacción se agitó a 0°C durante 30 minutos y a temperatura ambiente durante 1 hora. La mezcla de reacción se particionó entre agua y etilacetato. La fase acuosa se extrajo con etilacetato. Las fases orgánicas combinadas se lavaron con agua y salmuera, se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna para proporcionar el producto deseado.

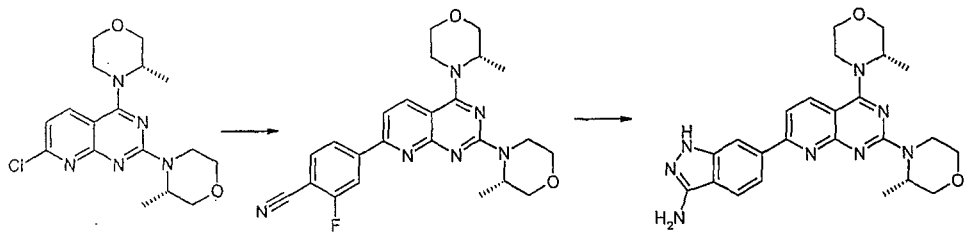
4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- N- metilo- benzamida: (73 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 479.2 $[M+H]^+$, R/T = 3.97 min)

Datos NMR para ejemplo ldk

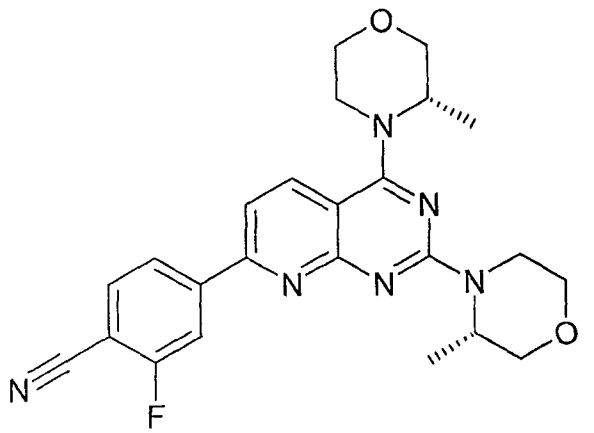
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.71 (ArH, d, J = 2.45 Hz, 1H) , 8.45 (ArH, dd, J = 8.75, 2.48 Hz, 1H) , 7.97 (ArH, d, J = 8.52 Hz, 1H) , 7.78 (NH, s, br, 1H) , 7.51 (ArH, d,J= 8.56 Hz, 1H) , 7.01 (ArH, d, J= 8.84 Hz, 1H) , 4.39 (CH2, d, J= 6.69 Hz, 1H) , 3.96 (OCH3, s, 3H) , 3.95- 3.77 (CH2, m, 7H) , 3.76- 3.58 (CH2, m, 7H) , 2.98 (NCH3, d, J = 4.81 Hz, 3H) , 1.42 (CH3,d,J=6.78Hz,3H) .

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.74, 164.71, 161.22, 160.99, 159.11, 159.04, 135.09, 132.93, 131.23, 131.16, 121.32, 119.02,113.63, 111.84, 104.61, 70.90, 66.90, 56.27, 52.70, 44.70, 44.48,26.70 y 14.85.

Procedimiento para la síntesis de 6- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- yI]- lH- indazoI- 3- ylamina (Ejemplo ldl) .

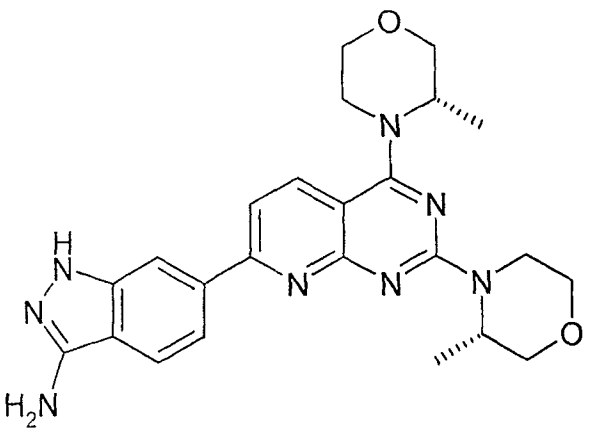


A una mezcla de 7- cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina (1 equiv) , carbonato de potasio (2.5 equiv) , y ácido 4- ciano- 3- fluorofenilborónico (1.2 equiv) en acetonitrilo/agua (1:1) (0.03 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (110 °C, ambiente de absorción de medios) durante 25 minutos bajo atmósfera de nitrógeno. Al terminar, el precipitado fue recolectado mediante filtración al vacío, el cual estuvo en forma apropiadamente pura para ser utilizado sin purificación adicional.



4- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzonitrilo: (49 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 449.2 [M+H]+ R/T = 2.93 min

A una solución 0.2 M de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzonitrilo (1 equiv) en n- BuOH se agregó 0.2 volumenes de reacción de hidrato de hidrazina. Un condensador de reflujo se fijo a la mezcla la cual luego se calentó a 140 °C durante 2 horas después de lo cual se enfrió, y concentró al vacío para proporcionar un residuo naranja el cual se purificó mediante cromatografia rápida (SiO2) utilizando Et_2O:MeOH - 94:6 como eluyente el cual permitió que un sólido amarillo que luego se recristalizó a partir de CH_2Cl_2/Hexanos proporcionara el compuesto del título como un sólido amarillo.

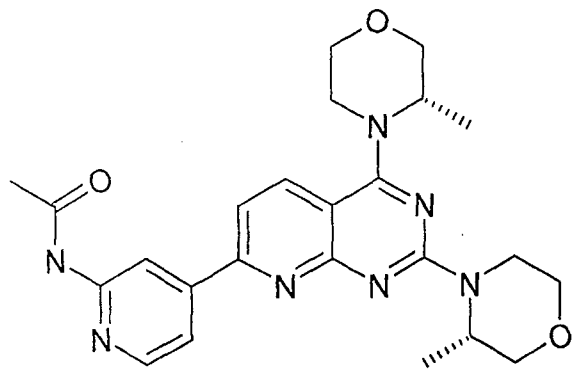


6- [2,4- Bis- ((S) - 3 - metilo- morfolm- 4- il) - pirido [2,3- d]pirirnidin- 7- il] - 1 H- indazol- 3 - ilamina: (90 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 461.2 $[M+H]^+$ R/T = 3.77 min

Datos NMR para ejemplo ldl

(^{1}HNMR (300 MHz, CD_3SOCD_3 δ ppm 11.6 (1H, s, formato) , 8.31- 8.01 (ArH, m, 2H) , 7.74 (ArH, ddd, /= 18.90, 15.23, 8.49 Hz, 3H) , 5.42 (NH2, s, 2H) , 4.88- 4.70 (NH, m, 1H) , 4.44 (CH2, d, J= 10.93 Hz, 2H) , 3.91 (CH2, m, 3H) , 3.81- 3.54 (CH2, m, 6H) , 3.46 (CH2, dt, J = 11.82,11.67, 2.52 Hz, 1H) , 3.38- 3.13 (CH2,m, 1H) ,2.51 (CH, td,J=3.52,1.73,1.73 Hz, 1H) , 1.38 (CH3, d, J= 6.75 Hz, 3H) , 1.26 (CH3, d, J= 6.79 Hz, 3H) . 13CNMR(75 MHz, CD_3SOCD_3) δ ppm 164.43, 162.05, 161.20, 159.29, 149.19, 141.79, 136.12, 135.32, 120.42, 116.81, 114.78, 113.13, 108.47, 104.30, 70.39, 70.15, 66.34, 66.15, 51.81, 46.24, 43.81, 30.89, 22.0, 14.31 y 13.89.

Procedimiento para la síntesis de N- {4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- il}- acetamida (Ejemplo 1dm) .



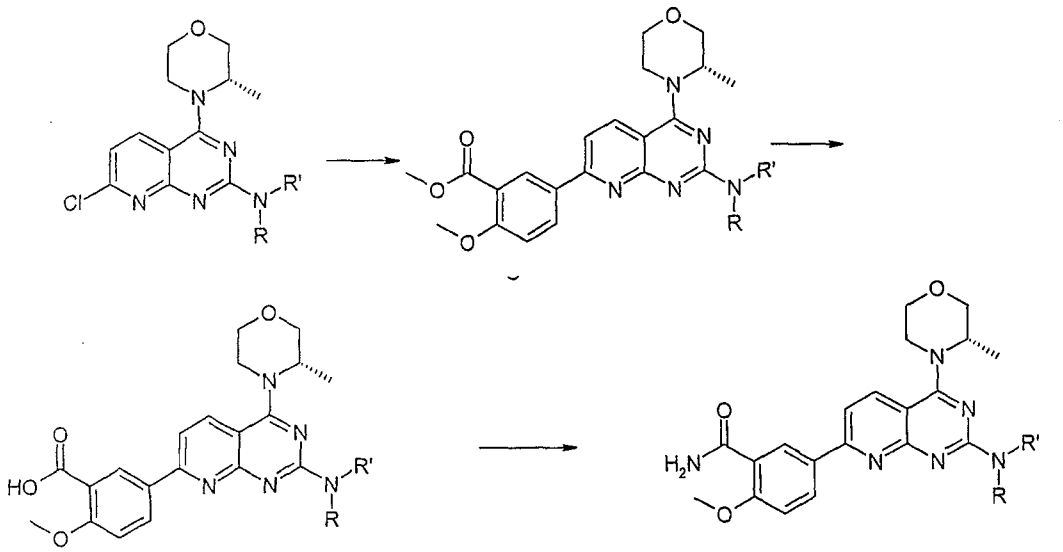
A una solución 0.1 M de 4- [2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- ilamina (ejemplo lcz) (1 equiv) en piridina se agregó anhidrido acético (3 equiv) . Se fijo un condensador de reflujo al recipiente de reacción, el cual luego se calentó a 70 °C durante 2 días. Al terminar, la reacción se purificó, en su forma cruda mediante HPLC preparativa para proporcionar el compuesto del titulo como un sólido blanco.

N- {4- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- il}- acetamida :(95 % rendimiento, 99 % pureza) m/z (LC- MS, ESP) : 464.1 $[M+H]^+$ R/T = 3.77 min

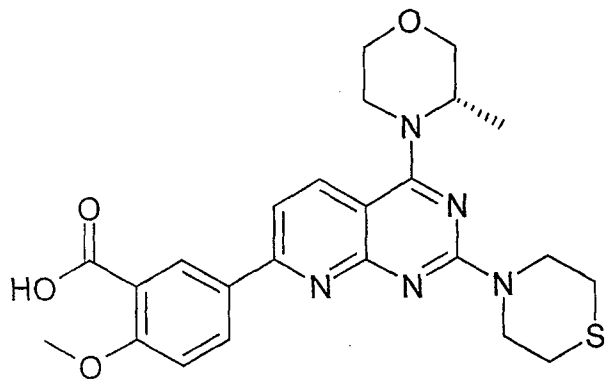
Datos NMR para ejemplo 1dm

^{1}H NMR (300 MHz, $CDCl_3$.δ ppm 8.70 (NH, s, 1H) , 8.37- 8.29 (ArH, m, 2H) , 8.01 (ArH, d, J = 8.36 Hz, 1H) , 7.94 (ArH, dd, J = 5.26,1.54 Hz, 1H) , 7.49 (ArH, d, J = 8.39 Hz, 1H) , 4.87 (CH2, ddd, J= 2.90, 1.56, 0.64 Hz, 1H) , 4.56 (CH2, d,J= 13.43 Hz, 1H) , 4.33 (CH2, d, J = 6.86 Hz, 1H) , 3.99- 3.58 (CH2, m, 10H) , 3.57- 3.45 (CH2, m, 1H) , 3.39- 3.25 (CH2, m, 1H) , 2.19 (CH3, s, 3H) , 1.43 (CH3, d, /= 6.78 Hz, 3H) , 1.31 (CH3, d, J= 6.82 Hz, 3H) 13CNMR(75 MHz, $CDCl_3$ δppm 168.79, 165.32, 162.82, 160.00, 159.87,151.94,148.64, 148.15, 135.18, 118.86, 113.66, 111.94, 106.03,71.27, 70.89, 67.23, 66.89, 52.89,46.98, 44.46, 39.35, 24.81, 14.77 y 14.41.

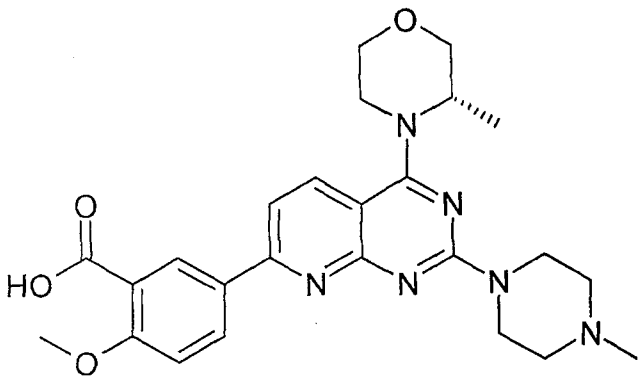
Procedimiento para la síntesis de Ejemplos 1dn a 1dp



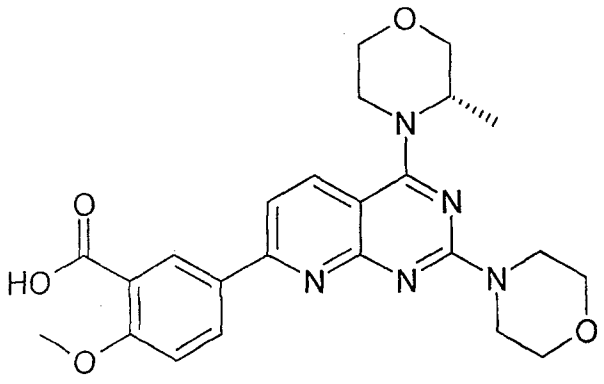
La 7- cloropiridopirimidina apropiada se hizo reaccionar con éster metílico del acido 2- metoxi- 5- (4,4,5,5- tetrametil- [1,3,2]dioxaborolan- 2- il) - benzoico según las condiciones E para proporcionar éster metílico del ácido 2- metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- tiomorfolin- 4- il- pirido[2,3- d]pirimidin- 7- il]- benzoico como el producto deseado (1 equiv) el cual luego se diluyó en MeOH para proporcionar una solución 0.03M. Luego se agregó NaOH (5 equiv de solución1 M) y la mezcla resultante se agitó a temperatura ambiente durante 5 días. Después de este tiempo la reacción se filtró y neutralizó con HCl 1M antes de ser concentrada al vacío para proporcionar un residuo amarillo crudo el cual se diluyó en CH_2Cl_2. La mezcla se filtró y el filtrado resultante se concentró para proporcionar el producto deseado como un aceite.



Acido 2- Metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- tiomorfolin- 4- il- pirido[2,3-d]pirimidin- 7- il]- benzóico: (99 % rendimiento, 95 % pureza) m/z (LC- MS, ESP) : 482.2$[M+H]^+$ R/T = 2.78 min



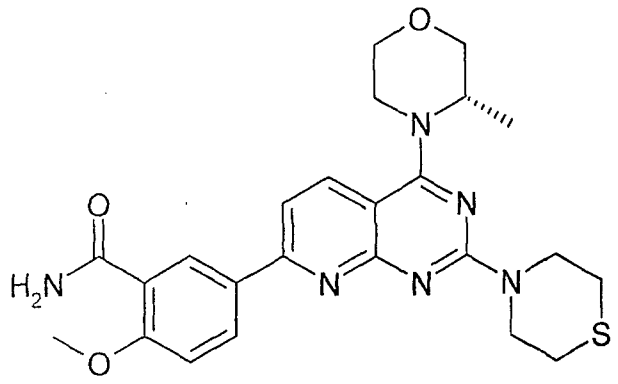
Acido 2- Metoxi- 5- [4- ((S) - 3 - metil- morfolin- 4- il) ~2~(4- metil- piperazin- 1 - il) - pirido [2.3 - d]pirimidin- 7- il]- benzóico: (88 % rendimiento, 96 % pureza) m/z (LC- MS, ESP) : 479.5[M+H]+ R/T = 2.26 min



Acido 2- Metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- morfolin- 4- il- pirido[2,3-

d]pirimidin- 7- il]- benzoico: (91 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) :466.4 $[M+H]^+$ R/T = 2.68 min

A una solución 0.06 M calentada (40°C) del derivado de ácido benzóico apropiado (1 equiv) en THF anhidro se agregó cloruro de tionilo (2.5 equiv) por goteo. La reacción se mantuvo a esta temperatura y agitó durante 1 hora adicional. Después de este tiempo la mezcla se evaporó para proporcionar un aceite marrón, el cual se diluyó en THF seco (suficiente para preparar solución 0.06 M) antes de burbujear gas de amoniaco a través de la mezcla, lo cual se acompaño por una exoterma. Al terminar, la adición de amoniaco se detuvo y la mezcla se concentró al vacío para proporcionar un residuo aceitoso amarillo el cual se disolvió en CH_2Cl_2 (1 volumen de reacción) y se lavó con agua (2X1 volumen de reacción) . El extracto orgánico fue retirado, secado ($MgSO_4$) , filtrado y concentrado al vacío para proporcionar el compuesto del titulo.



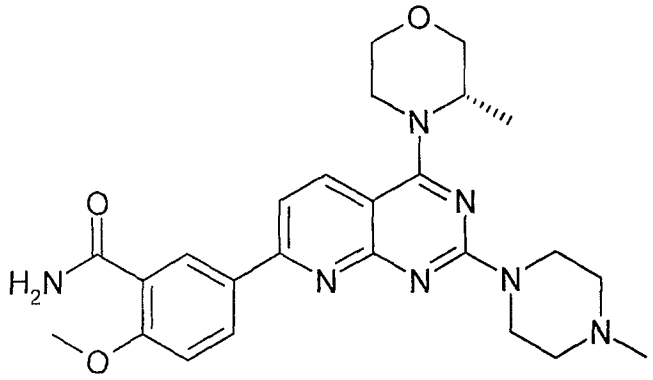
2- Metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- tiomorfolin- 4- il- pirido[2,3- d]pirimidin- 7- il]- benzamida: (30 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 481.1$[M+H]^+$ R/T = 4.02 min

Datos NMR para ejemplo ldn

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.83 (ArH, d, J = 2.46 Hz, 1H) , 8.61 (ArH, dd, J = 8.75, 2.48 Hz, 1H) , 8.00 (ArH, d, J = 8.47 Hz, 1H) , 7.72 (NH, d, J = 0.76 Hz, 1H) , 7.56 (ArH, d, J = 8.50 Hz, 1H) , 7.13 (ArH, d,J= 8.82 Hz, 1H) , 5.88 (NH, d,J= 0.98 Hz, 1H) , 4.42- 4.23 (CH2, m,4) , 4.05 (CH30, s, 3H) , 4.03- 3.94 (CH2, m, 1H) , 3.85 (CH2, ddd, J= 14.51, 8.58,

5.82 Hz, 2H) , 3.78- 3.62 (CH2, m, 3H) , 2.75- 2.65 (CH2, m, 3H) , 1.46 (CH3, d, J= 6.76 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3 δ ppm 166.60, 165.41, 162.87,161.09, 159.89, 159.23, 134.73, 133.71, 131.82,131.68, 120.56, 113.16, 111.89, 104.63, 70.95, 66.91, 56.29, 52.81,46.70, 44.54, 27.45 y 14.70.

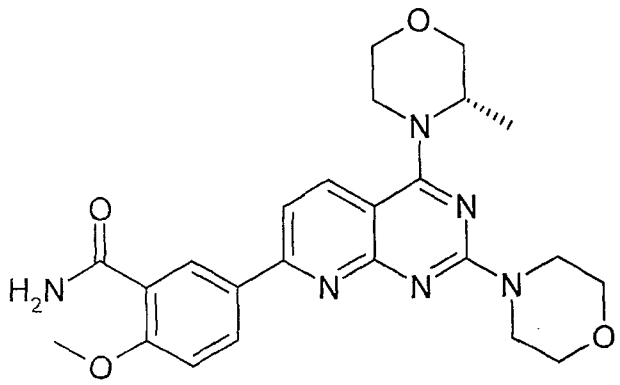


2- Metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- (4- metil- piperazin- l- il) - pirido[2,3-d]pirimidin- 7- il]- benzamida: (12 % rendimiento, 98 % pureza) m/z (LC- MS, ESP) : 481.1$[M+H]^+$

R/T = 43.28 min

Datos NMR para ejemplo ldo

^{1}H NMR (300 MHz, CDCI3 5 ppm 8.78 (ArH, d, J = 2.48 Hz, 1H) , 8.57 (ArH, dd, J = 8.76, 2.52 Hz, 1H) , 8.28 (NH, s, br, 1H) , 7.96 (ArH, d, J = 8.50 Hz, 1H) , 7.68 (NH, s, br, 1H) , 7.54 (ArH, d, J= 8.55 Hz, 1H) , 7.08 (ArH, d, J= 8.84 Hz, 1H) , 4.42- 4.28 (CH2, m, 1H) , 4.09 (CH2, s, br, 2H) , 4.01 (OCH3, s, 3H) , 3.77 (CH2, ddd, J= 36.04,19.80,10.87 Hz, 9H) , 2.76 (CH2, t, J = 5.05, 5.05 Hz, 4H) , 2.47 (NCH3, s, 3H) , 1.42 (CH3, d, J = 6.77 Hz, 3H) .



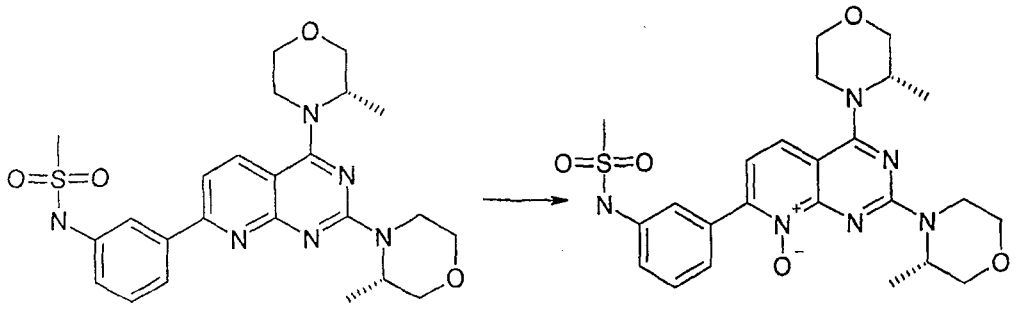
2- Metoxi- 5- [4- ((S) - 3- metil- morfolin- 4- il) - 2- morfolin- 4- il- pirido[2,3- d]pirimidin- 7- il]- benzamida: (61 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 465.4 [M+H]+ R/T = 2.69 min

Datos NMR para ejemplo 1dp

lH NMR (300 MHz,, CDCI3 δ ppm 8.77 (ArH, d, J = 2.44 Hz, 1H) , 8.58 (ArH, dd, J = 8.76, 2.47 Hz, 1H) , 7.94 (ArH, d, J= 8.48 Hz, 1H) , 7.65 (NH, s, br, 1H) , 7.51 (ArH, d, J = 8.53 Hz. 1H) , 7.06 (ArH, d, J= 8.84 Hz, 1H) , 5.91 (NH, s, br, 1H) , 4.32 (CH2, d, J = 6.79 Hz, 1H) , 3.98 (OCH3, s, 3H) , 3.95- 3.86 (CH2, m, 5H) , 3.84- 3.55 (CH2, m, 9H) , 1.40 (CH3, d,J = 6.77 Hz, 3H)

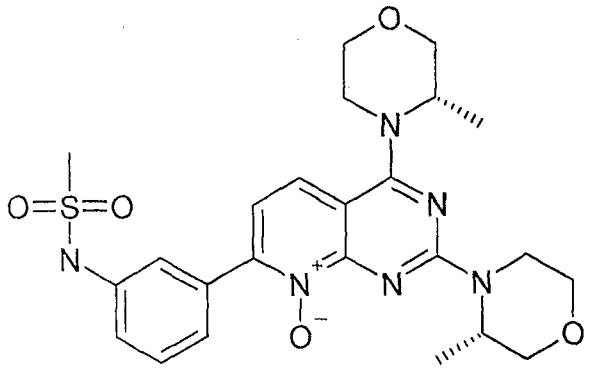
^{13}CNMR(75 MHz, $CDCl_3$ δ ppm 166.63, 165.31,162.78, 160.96,160.31, 159.29, 134.76, 133.68, 131.69, 131.60,120.56, 113.09, 111.88, 104.76, 70.94, 67.04, 66.91, 56.28, 52.76, 44.58. 44.45 y 14.75.

Procedimiento para la síntesis de Ejemplo 1dq



A una solución (0.1 M) del ejemplo lat (1 equiv) en $CHCl_3$ se agregó m- CPBA (5.5

equiv) . Un condensador de reflujo se agregó al aparato y la mezcla se calentó a 60 °C durante 17 horas. Después de este tiempo la reacción se concentró al vacío y se purificó mediante cromatografía rápida (SIO_2) utilizando CH_2Cl_2:MeOH - 95:5 como eluyente para proporcionar el producto deseado.



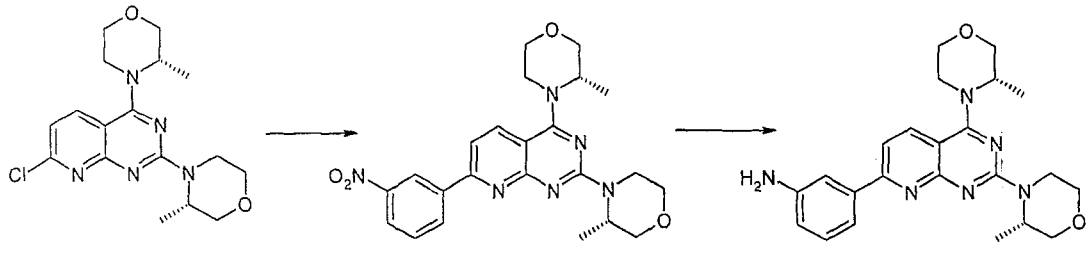
N- {3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - 8- oxi- pirido[2,3- d]pirimidin- 7- il]- fenil}- metanosulfonamida: (39 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 515.5$[M+H]^+$ R/T = 2.95min.

Datos NMR para ejemplo ldq

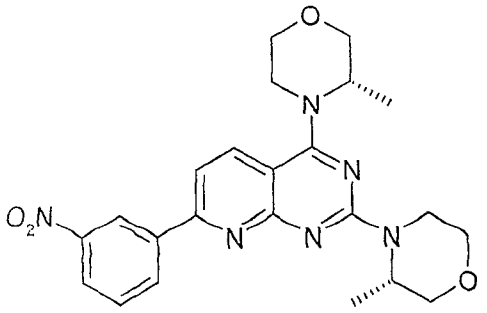
^{1}HNMR(300 MHz, $CDCl_3$ δppm 10.04 (NH, s, br, 1H) , 8.42 (ArH, s, 1H) , 7.55- 7.25 (ArH, m, 4H) , 6.96 (ArH, d, J = 8.67 Hz, 1H) , 4.80 (CH2, s, br, 1H) , 4.51 (CH2, s, br, 1H) , 4.31 (CH2, d, J = 6.71 Hz, 1H) , 4.00- 3.51 (CH2, m, 9H) , 3.49- 3.34 (CH2, m, 1H) , 3.24 (CH2, dd, J = 13.22, 3.30 Hz, 1H) , 2.80 (SCH3, s, 3H) , 1.42 (CH3, d,J= 6.78 Hz, 1H) , 1.19 (CH3, d, J = 6.69 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3 δppm 165.58, 159.69, 158.28, 149.96, 138.59, 134.47, 129.53, 125.86. 123.35, 123.30, 116.17,107.52, 71.33, 71.11, 67.32, 67.10, 53.39, 47.62, 44.87, 39.79. 38.68, 31.90, 22.97 y 15.16.

Procedimiento para la síntesis de Ejemplo ldr

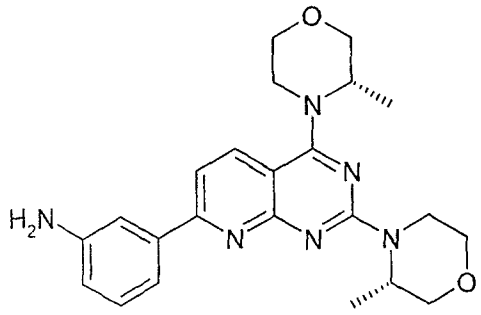


7- Cloro- 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina se acopló con ácido 3- nitrobenzoico utilizando las condiciones de Suzuki D para proporcionar el producto deseado como un polvo amarillo.



2.4- Bis- ((S) - 3 - metil- morfolin- 4- il) - 7- (3 - nitro- fenil) - pirido [2,3 - d]pirimidina: (90 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 451.6[M+H]+ R/T = 3.41min

A una solución 0.1M de 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - 7- (3- nitro- fenil) - pirido[2,3- djpirimidina (1 equiv) en EtOH/H20- 1:1 se agregó cloruro de amonio (8 equiv) y polvo de hierro (8 equiv) . La mezcla de reacción se calentó a 100 °C durante 1 hora antes de enfriar y filtrar a través de una almohadilla delgada de Celite ™. La torta se lavó con EtOH (1 volumen de reacción) . El filtrado se concentró al vacío y luego se particionó entre agua y CH_2Cl_2 (1 volumen de reacción de cada uno) . La fase orgánica fue retirada, secada (MgSO4) , filtrada y concentrada al vacío y luego purificada mediante cromatografia rápida (SiO_2) utilizando MeOH.:CH_2Cl_2 (0:100 - 5:95 - 10- 90) como eluyente para proporcionar el compuesto del titulo como un sólido amarillo.



3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- fenilamina: (88 % rendimiento, 98 % pureza) m/z (LC- MS, ESP) : 421.1[M+HJ+ R/T = 3.76min

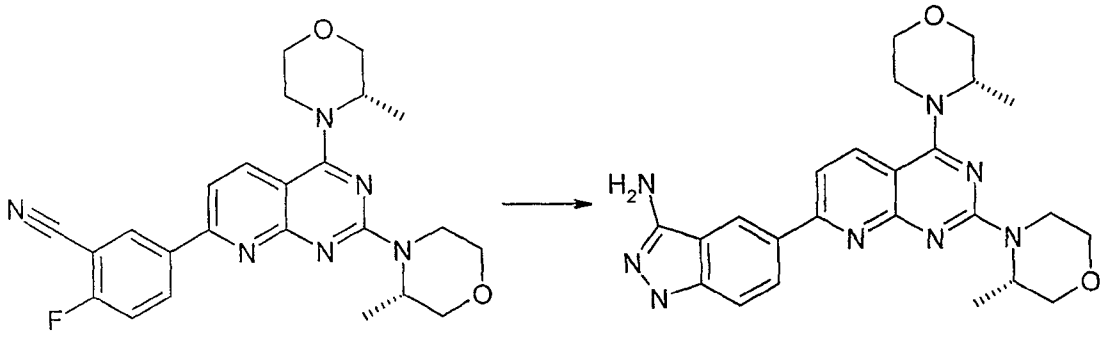
Datos NMR para ejemplo ldr

^{1}H NMR (300 MHz, CDCb δ ppm 7.93 (ArH, d, J = 8.45 Hz, 1H) , 7.62- 7.55 (ArH, m, 1H) , 7.41- 7.32 (m, 1H) , 7.20 (ArH, d, J= 7.32 Hz, 2H) , 6.71 (ArH, ddd, J= 7.88,2.40, 0.86 Hz, 1H) , 4.87 (ArH, dd, J = 3.54, 1.66 Hz, 1H) , 4.57 (NH, d, J = 13.25 Hz, 1H) , 4.30 (NH, s, br, 1H) , 3.98- 3.56 (CH2, m, 11H) , 3.56- 3.44 (CH2, m, 1H) , 3.37- 3.24 (CH2, m, 1H) , 1.40 (CH3, d,

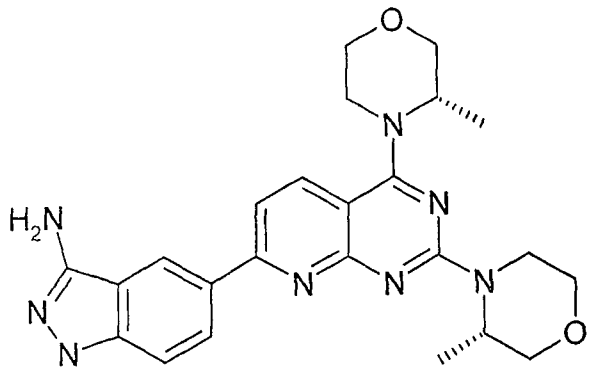
J = 6.77 Hz, 3H) , 1.29 (CH3, d, J = 6.81 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$ δ ppm 165.46,162.87, 162.60,159.96, 146.80, 139.75,134.48, 129.35, 117.99, 116.69, 114.74, 113.48, 104.92, 71.32, 70.93, 67.28, 66.94, 52.80, 46.90, 44.49. 39.33.14.71 y 14.33.

Procedimiento para la síntesis del Ejemplo Ids



A una solución 0.3M de 5- [2,4- bis- ((S) - 3- metil- morfolin~4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- benzonitrilo (ejemplo lav) (1 equiv) en EtOH se agregó hidrato de hidrazina (5 equiv) . La mezcla fue sometida a reflujo durante 90 minutos después de lo cual fue enfriada y particionada entre CH_2Cl_2 y agua (1 volumen de reacción de cada uno) . El extracto orgánico fue retirado. La fase acuosa se extrajo adicionalmente con CH_2Cl_2 (2X1 volumen de reacción) . Luego los extractos orgánicos combinados fueron secados (MgSO4) , filtrados y concentrados al vacío para proporcionar una pasta aguada amarilla la cual se purificó adicionalmente mediante cromatografia rápida (SiO_2) utilizando EtOAC/Hexanos como eluyente para proporcionar el compuesto del titulo como un polvo amarillo.



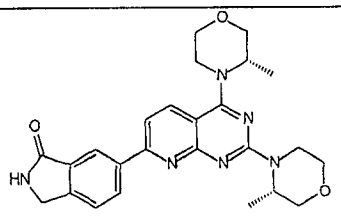
5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 1H- indazol- 3- ilamina: (52 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 461.6[M+H]+ R/T = 2.85min

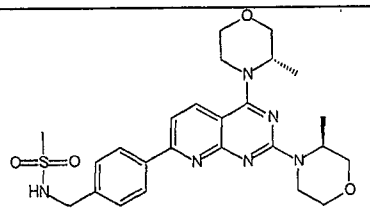
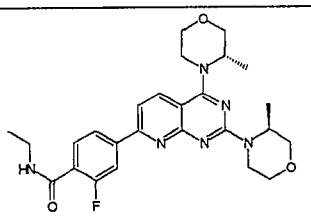
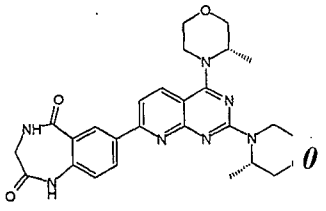
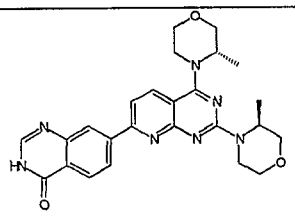
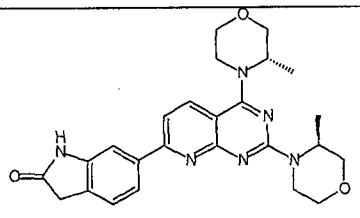
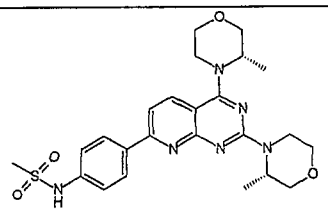
Datos NMR para ejemplo Ids

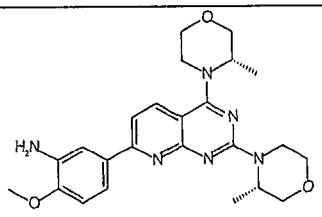
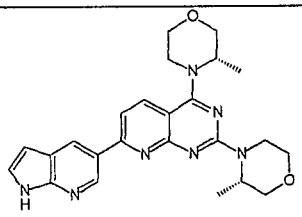
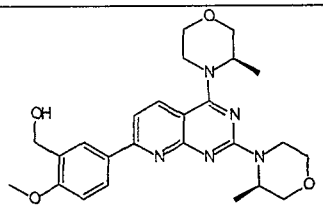
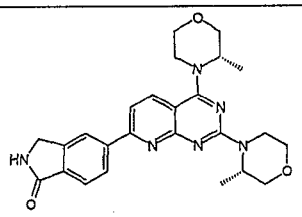
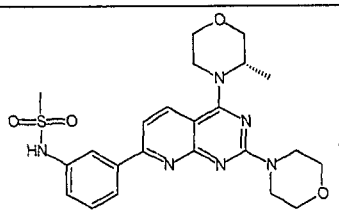
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.52 (ArH, s, 1H) , 8.06 (ArH, dd, J = 8.84,1.50 Hz, 1H) , 7.94 (ArH, d, J = 8.49 Hz, 1H) , 7.42 (ArH, d, J = 8.50 Hz, 1H) , 7.29 (ArH, d, / = 8.79 Hz, 2H) , 4.87 (CH2, dd, J= 3.99, 1.99 Hz, 1H) , 4.60 (CH2, s, br, 1H) , 4.32 (CH2, d, J = 6.78 Hz, 1H) , 3.98- 3.58 (CH2, m, 9H) , 3.51 (CH2, dt, J= 11.78,11.46,2.71 Hz, 1H) , 3.39- 3.25 (CH_2, m, 1H) , 1.42 (CH_3, d, J = 6.77 Hz, 3H) , 1.29 (CH_3, d, J = 6.81 Hz, 3H) (NH no se observa con claridad)

^{13}CNMR(75 MHz, $CDCl_3$ δppm 165.43, 162.97, 162.33, 160.01, 142.86,134.62, 130.11, 127.06, 120.17, 115.21, 112.98, 109.71, 104.51, 71.32, 70.94, 67.28, 66.95, 52.80, 46.95, 44.48, 39.36, 27.01, 14.79 y 14.33.

Tabla

	Pureza (%)	Tiempo de Retención (min)	m/z [M+Hf	Conditionrs	Estructura de Ejemplo
Idt	96	3.96	461.2	U	

ldu	97	4.10	513.1	I	
ldv	99	4.04	495.0	J	
ldw	98	3.70	504.1	V	1 
ldx	99	3.79	474.1	I	
ldy	99	3.79	474.1	W	
ldz	99	4.06	499.2	D	

lea	99	4.16	451.2	D	
leb	98	3.96	446.2	P	
lee	99	7.55	466.2	J	
led	98	3.86	461.2	D	
lee	98	4.04	485.2	D	

Notar:

Los siguientes ejemplos se sintetizaron a partir de los correspondientes ácidos borónicos: ldu, ldv, ldz y lee.

Los siguientes ejemplos se sintetizaron a partir de los correspondientes ésteres de boro de pinacolato: ldw, ldx, lea, leb y lee.

Los siguientes ejemplos se sintetizaron a partir de a mezcla de los correspondientes ácidos borónicos o ésteres de boro de pinacolato: 1dt, 1dy, y 1ed.

Datos NMR para ejemplo lee

^{1}H NMR (300 MHz, CDCb δ ppm 8.15 (ArH, d, J= 7.5 Hz, 2H) , 7.97 (ArH, d, J= 8.46 Hz, 1H) , 7.42 (ArH, d, J= 8.46 Hz, 1H) , 6.98 (ArH, d, J= 9.24 Hz, 1H) , 4.91 (CH_2, d, J= 5.55 Hz, 1H) , 4.77 (CH_2OH, s, 2H) , 4.61 (CH_2, d, J= 12.42 Hz, 1H) , 4.36 - 4.34 (CH_2, m, 1H) , 4.00 - 3.70 (OCH_3 + CH_2, m, 9H) , 3.69 - 3.51 (CH_2, m, 1H) , 3.41 - 3.31 (CH_2, m, 1H) , 1.46 (CH3, d, J= 6.69 Hz, 3H) , 1.35 (CH_3, d, J= 6.87 Hz, 3H) .

^{13}C NMR (75 MHz, CDCb) δ ppm 165.42,162.88,161.87,159.95,159.16,134.54, 131.13, 129.25, 128.89, 128.44, 112.85, 110.27, 104.49, 71.30, 70.92, 67.26, 66.93, 61.98, 55.56, 52.78, 46.91,44.45, 39.32,14.69 o 14.31.

Datos NMR para ejemplo led

^{1}H NMR (300 MHz, CDCI3 δ ppm 8.34 (ArH, s, 1H) , 8.11 (ArH, d, J = 8.02 Hz, 1H) , 8.00 (ArH, d, J = 8.41 Hz, 1H) , 7.90 (ArH, d, J = 7.98 Hz, 1H) , 7.43 (ArH, d, J = 8.42 Hz, 1H) , 7.10 (NH, br, s, 1H) , 4.95- 4.81 (CH2, m, 1H) , 4.57 (CH2, d, J = 13.37 Hz, 1H) , 4.47 (NHCH2, s, 2H) , 4.33 (CH2, d, J= 6.68 Hz, 1H) , 3.99- 3.58 (CH2, m, 9H) , 3.51 (CH2, dt, J= 11.81, 11.45,2.72 Hz, 1H) ,3.31 (CH2,dt,J= 12.91, 12.52, 3.57 Hz, 1H) , 1.42 (CH3,d,J= 6.78 Hz, 3H) , 1.30 (CH3, d, J= 6.81 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3) δ ppm 171.32, 165.36, 162.94, 161.42, 160.04, 144.06, 142.31, 135.01, 133.20, 127.63, 123.83, 123.08, 113.49, 105.35, 71.27, 70.91, 67.24, 66.91, 52.85, 46.96,45.70,44.48, 39.35,14.76 y 14.39.

Datos NMR para ejemplo lef

^{1}H NMR (300 MHz, CDC13.5 ppm 8.08 (ArH, d,J = 1.95 Hz, 1H) , 8.01- 7.94 (ArH, m, 1H) , 7.82 (ArH, td, J = 6.63,1.80,1.80 Hz, 1H) , 7.48 (NH, br, s, 1H) , 7.39 (ArH, dd, J = 12.99, 5.20 Hz, 3H) , 4.34 (CH_2, q, J= 6.63, 6.56, 6.56 Hz, 1H) , 3.97- 3.76 (CH_2, m, 7H) , 3.75- 3.57 (CH_2, m, 7H) , 2.87 (S02CH3, s, 3H) , 1.42 (CH3, d,J = 6.78 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3) 5ppm 165.21, 162.77, 161.34,160.28, 140.30,137.69, 135.07, 129.91, 124.53, 122.37, 120.57, 113.44,105.22, 70.91, 66.97, 66.89, 52.84, 44.58, 44.39,

39.32 y 14.79.

Datos NMR para ejemplo ldz

1H NMR (300 MHz, $CDCl_3$ δ ppm 8.11- 8.03 (ArH, m, 2H) , 7.96 (ArH, d, J = 8.44 Hz, 1H) , 7.38- 7.31 (ArH, m, 1H) , 7.32- 7.24 (ArH, m, 2H) , 4.85 (CH2, d, J = 5.45 Hz, 1H) , 4.54 (CH2, d, J= 12.83 Hz, 1H) , 4.32 (CH2, d, J= 6.78 Hz, 1H) , 3.97- 3.57 (CH_2, m, 9H) , 3.50 (CH_2, dt, J= 11.75, 11.35, 2.73 Hz, 1H) , 3.37- 3.24 (CH2, m, 1H) , 2.95 (SO_2CH_3, s, 3H) , 1.42 (CH_3, d, J = 6.78 Hz, 1H) , 1.29 (CH3, d, J = 6.81 Hz, 3H) (NH no se observó) .

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.36, 162.93, 161.33, 160.00, 138.73, 135.29, 134.86, 129.34, 119.66, 112.95, 104.90, 71.27, 70.92, 67.24, 66.93, 52.82, 46.97, 44.45, 39.58, 33.35, 14.75 y 14.36.

Datos NMR para ejemplo lea

^{1}H NMR (300 MHz, $CDC1_3$.δ ppm 7.87 (ArH, d, J = 8.55 Hz, 1H) , 7.81 (ArH, d, J = 1.80 Hz, 1H) , 7.47 (ArH, dd, J = 8.17,1.85 Hz, 1H) , 7.35 (ArH, d, J = 8.57 Hz, 1H) , 6.69 (ArH, d, J = 8.14 Hz, 1H) , 4.85 (CH2, d, J = 5.96 Hz, 1H) , 4.62- 4.52 (CH2, m, 1H) , 4.28 (CH2, d, J = 6.77 Hz, 1H) , 4.02 (NH2, s, br, 2H) , 3.95 (d, J= 6.54 Hz, 1H) , 3.93 (CH3, s, 3H) , 3.92- 3.57 (CH2, m, 9H) , 3.55 - 3.45 (CH2, m, 1H) , 3.38- 3.25 (CH2, m, 1H) , 1.39 (CH3, d, J= 6.77 Hz, 3H) , 1.29 (CH3.d,J= 6.81 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3) δ ppm 165.48, 162.91, 162.45, 159.98, 147.22, 138.70, 134.14, 128.92, 121.24, 113.97, 112.74, 110.15, 104.11, 71.35, 70.95, 67.32, 66.96, 55.83, 52.79, 46.89,44.44, 39.31, 31.60,22.66 y 14.30.

Datos NMR para ejemplo leb

^{1}H NMR (300 MHz, CD_3COCD_3 δ ppm 11.83 (ArH, s, 1H) , 9.06 (ArH, d, J = 2.07 Hz, 1H) , 8.75 (ArH, d, J = 2.09 Hz, 1H) , 8.30- 8.10 (ArH, m, 1H) , 7.72 (ArH, d, J = 8.55 Hz, 1H) , 7.54 (ArH, s, 1H) , 6.59 (NH, s, 1H) , 4.77 (CH2, dd, J= 6.66,1.89 Hz, 1H) , 4.49- 4.34 (CH2, m, 2H) , 4.03- 3.83 (CH2, m, 3H) , 3.81- 3.55 (CH2, m, 6H) , 3.54- 3.38 (CH2, m, 1H) , 3.23 (CH2, dd, J= 13.19, 3.46 Hz, 1H) , 1.37 (CH3, d, J= 6.74 Hz, 3H) , 1.25 (CH3, d, J= 6.75 Hz, 3H) .

13CNMR(75 MHz, CD3COCD3) 5 ppm 165.41,163.09, 161.32, 160.22,150.21, 143.45, 136.25, 128.14, 128.09, 126.99, 120.44,113.54, 104.90, 101.82, 71.32, 71.09, 67.27, 67.09,

52.78,47.17,44.79 y 15.25.

Datos NMR para ejemplo ldy

^{1}H NMR (300 MHz, CD_3SOCD_3 δ ppm 8.40 (ArH, d, J = 1.37 Hz, 1H) , 8.33 (ArH, dd, J = 8.38,1.63 Hz, 1H) , 8.25 (ArH, d, J = 8.45 Hz, 2H) , 8.17 (ArH, s, 1H) , 7.79 (ArH, d, J = 8.48 Hz, 1H) , 4.84- 4.73 (CH, m, 1H) , 4.45 (CH2, d, J= 13.67 Hz, 2H) , 4.00- 3.84 (CH2, m, 3H) , 3.81- 3.57 (CH2, m, 6H) , 3.46 (CH2, dt, J = 11.84,11.73,2.61 Hz, 1H) , 3.23 (CH2, dt, J = 13.16,12.92, 3.65 Hz, 1H) , 1.39 (CH3, d, J= 6.75 Hz, 3H) , 1.26 (CH3, d, J= 6.75 Hz, 3H) 13CNMR(75 MHz, CD_3SOCD_3 δ ppm 164.30, 162.06, 160.45, 159.32, 159.03, 149.10, 145.91, 143.53, 135.86, 126.40, 125.73,125.30, 123.33, 113.30, 105.06, 70.35, 70.14, 66.31, 66.14, 51.79, 46.27, 43.81, 30.38, 14.35 y 13.89.

[redacted]

Datos NMR para ejemplo ldv

^{1}HNMR (300 MHz, CD3$SOCD_3$ δ ppm 8.39 (ArH, dd, J = 5.45, 3.65 Hz, 1H) , 8.23 (ArH, d, J = 8.47 Hz, 1H) , 8.14- 8.03 (ArH, m, 2H) , 7.81- 7.69 (ArH + NH, m, 2H) , 4.77 (CH_2, dd, J = 6.52.2.00 Hz, 1H) , 4.43 (CH2, d, J= 13.75 Hz, 2H) , 3.99- 3.83 (CH_2, m, 2H) , 3.80- 3.56 (CH_2, m, 6H) , 3.52- 3.15 (CH_2, m, 5H) , 2.50 (CH_2, td, J= 3.67,1.83,1.83 Hz, 2H) , 1.38 (CH_3, d, J = 6.75 Hz, 3H) , 1.25 (CH_3, d, / = 6.75 Hz, 3H) , 1.19- 1.10 (CH_3, m, 3H) .

^{13}C NMR(75 MHz, CD_3SOCD_3 δppm 164.80, 163.51, 162.52, 159.84, 158.73, 158.27, 142.53, 142.43, 136.38, 131.02, 125.84, 123.52,123.48, 115.08, 114.76, 113.45, 105.57, 70.87, 70.64, 66.83, 66.65, 52.32, 46.79, 44.32, 34.59,15.10,14.87 o 14.42.

Datos NMR para ejemplo ldy

[redacted]

^{1}H NMR (300 MHz,, CD_3SOCD_3 δ ppm 10.52 (NH, s, 1H) , 8.19 (ArH, d, J = 8.50 Hz, 1H) , 7.79- 7.68 (ArH, m, 2H) , 7.61 (ArH, d, J = 8.52 Hz, 1H) , 7.35 (ArH, d, J = 7.66 Hz, 1H) , 4.84- 4.69 (CH2, m, 1H) , 4.42 (CH_2, dd, / = 7.38, 5.30 Hz, 2H) , 3.91 (CH_2, dd, J = 14.30,7.97 Hz, 3H) , 3.82- 3.52 (CH2, m, 8H) , 3.45 (CH2, d, J = 2.42 Hz, 1H) , 3.26 - 3.15 (CH2, m, 1H) , 1.37 (CH3, d, J = 6.74 Hz, 3H) , 1.25 (CH3, d, J = 6.76 Hz, 3H) .

^{13}CNMR(75 MHz, CD_3SOCD_3 δ ppm 176.84, 164.89 ,162.55, 160.83, 159.82, 144.90, 138.19, 135.98, 128.66, 125.02, 120.94, 113.09, 108.05, 104.92, 70.90, 70.67, 66.84, 66.67, 52.32, 46.76, 44.30, 36.29, 14.85 y 14.35.

514

Datos NMR para ejemplo ldt

1H NMR (300 MHz, $CDC1_3$ δ ppm 8.58 (ArH, d, J = 7.97 Hz, 1H) , 8.49 (ArH, d, J = 45.95 Hz. 1H) . 7.99 (ArH, d, J= 8.42 Hz, 1H) , 7.50 (ArH, dd, J = 17.31, 8.21 Hz, 1H) , 7.24 (ArH, d. J = 17.82 Hz, 1H) , 5.01- 4.86 (CH2, s, br, 1H) , 4.65- 4.39 (CH2, m, 3H) , 4.33 (CH2, d, J = 6.25 Hz, 1H) , 4.04- 3.58 (CH2, m, 8H) , 3.49 (CH2, d, J = 11.36 Hz, 1H) , 3.31 (CH2, d, J = 2.99 Hz, 1H) , 1.41 (CH3, d, J = 6.72 Hz, 3H) , 1.29 (CH3, d, J = 6.76 Hz, 3H) (1 protón faltante, bastante traslapo visto, tampoco se observó NH)

^{13}CNMR(75 MHz, $CDCI_3$ δ ppm 171.52, 165.39, 162.90, 161.33, 160.01, 145.14, 139.06, 135.02, 132.17, 123.57, 122.56, 113.20, 105.21, 71.29, 70.92,67.25, 66.93, 52.78, 46.95, 45.68,44.51, 39.34,27.00,14.74 y 14.35.

Datos NMR para ejemplo ldu

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.12 (ArH, d, J = 8.32 Hz, 2H) , 8.03 (ArH, d, J = 8.43 Hz, 1H) , 7.51- 7.39 (ArH, m, 3H) , 5.08 (CH2, br, s, 1H) , 4.89 (CH2, d, J= 4.91 Hz, 1H) , 4.58 (CH2. d. J = 12.59 Hz, 1H) , 4.40 (CH2NH, br, s, 2H) , 4.22 (NH, br, s, 1H) , 4.04- 3.64 (CH2, m. 9H) . 3.56 (CH2, dt, J = 11.80, 11.45, 2.75 Hz, 1H) , 3.44- 3.30 (CH2, m, 1H) , 2.87 (S02CH3s. 3H) . 1.48 (CH3, d,J= 6.78 Hz, 3H) , 1.35 (CH3, d, J= 6.81 Hz, 3H)

^{13}C NMR (75 MHz, $CDCI_3$ δ ppm 165.16, 163.70, 162.51, 159.71, 138.71, 138.33, 134.99, 128.40. 128.15, 113.45, 105.20, 71.23, 70.89, 67.18, 66.90, 52.82, 47.07, 46.90, 44.21, 41.25, 39.41,14.78 y 14.38.

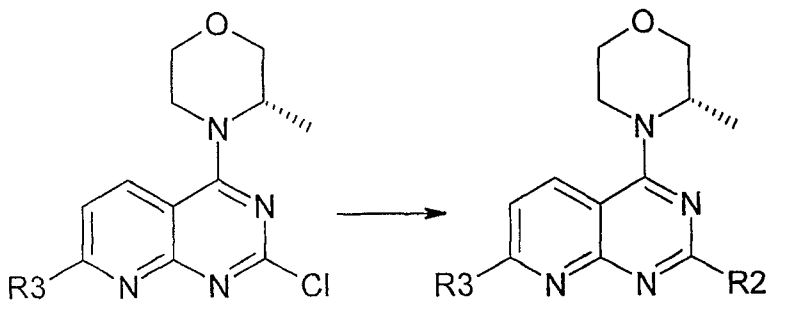
Probados en el Ensayo Biológico: Ej. (lb) 0.00185μM; Ej. (lc) 0.00184uM Ej. (Id) 0.00245nM; Ej. (laz) 0.006865δμM.

Probados en el Ensayo Enzimático Alternativo: Ej. (la) 0.0089μM; Ej. (le) 0.0044μM; Ej. (1f) .005μM; Ej. (lg) 0.011 μM Ej. (lh) 0.0021μM; Ej. (li) 0.0056μM; Ej. (lj) 0.035μM; Ej. (Ik) 0.015μM; Ej. (11) 0.0057μM; Ej. (lm) 0.31μM; Ej. (En) 0.085μM; Ej. (lo) 0.14μM; Ej. (lp) 0.038μM; Ej. (lq) 039μM; Ej. (lr) 0.23μM; Ej. (1s) 0.028μM; Ej. (1t) 0.34μM; Ej. (lu) 0.015μM; Ej. (lv) 0.18μM; Ej. (lw) 0.26μM; Ej. (lx) 0.53μM; Ej. (ly) 0.33μM; Ej. (lz) 0.37μM; Ej. (laa) 0.025μM; Ej. (lab) 0.029μM; Ej. (lac) 0.14μM; Ej. (lad) 0.0069μM; Ej. (lae) 0.38μM; Ej. (laf) 0.054μM; Ej. (lag) 0.029μM; Ej. (lah) 0.012μM; Ej. (lai) 1.1μM; Ej. (laj)

0.49μM; Ej. (lak) 0.017μM; Ej. (lal) 0.23μM; Ej. (lam) 0.21μM; Ej. (Ian) 0.14μM; Ej. (lao) 0.0083μM; Ej. (lap) 0.02μM; Ej. (laq) 0.084μM; Ej. (lar) 0.006μM; Ej. (las) 0.013μM; Ej. (lat) 0.03μM; Ej. (lau) 0.09μM; Ej. (lav) 0.29μM; Ej. (law) 0.062μM; Ej. (lax) 0.0092μM; Ej. (lay) 0.15μM; Ej. (lba) 0.44μM; Ej. (lbb) 0.14μM; Ej. (lbc) 0.083μM; Ej. (lbd) 0.011μM; Ej. (lbe) 0.18μM; Ej. (lbf) 0.06μM; Ej. (lbg) 0.17μM; Ej. (lbh) 0.014μM; Ej. (lbi) 0.032μM; Ej. (lbj) 0.035μM; Ej. (lbk) 0.039μM; Ej. (lbl) 0.0027μM; Ej. (lbm) 0.055μM; Ej. (lbn) 0.04μM; Ej. (lbo) 0.018μM; Ej. (lbp) O.llμM; Ej. (lbq) 0.14μM; Ej. (lbr) 0.056μM; Ej. (lbs) 0.039μM; Ej. (lbt) 0.11μM; Ej. (lbu) 0.016μM; Ej. (lbv) 0.0051μM; Ej. (lbw) 0.036μM; Ej. (lbx) 0.038μM; Ej. (lby) 0.0046μM; Ej. (lbz) 0.018μM; Ej. (lca) 0.35μM; Ej. (lcb) 0.5μM; Ej. (Ice) 0.0064μM; Ej. (lcd) 0.46μM; Ej. (1ce) 0.091 μM; Ej. (lcf) 0.073μM; Ej. (lcg) 0.00026μM; Ej. (lch) 0.22μM; Ej. (lci) 0.15μM; Ej. (lcj) 0.091μM; Ej. (lck) 0.065μM; Ej. (lcl) 0.2μM; Ej. (1cm) 0.16μM; Ej. (lcn) 0.31μM; Ej. (lco) 2.5μM; Ej. (lcp) lμM; Ej. (lcq) 0.25μM; Ej. (lcr) 0.69μM; Ej. (lcs) 7.5μM; Ej. (lct) 0.024μM; Ej. (leu) 0.042μM; Ej. (lcv) 0.3μM; Ej. (lcw) 0.49μM; Ej. (lcx) 0.12μM; Ej. (Ici) 0.72μM; Ej. (lcz) 0.066μM; Ej. (Ida) 1.8μM; Ej. (ldb) 0.03lμM; Ej. (ldc) 0.02μM; Ej. (ldd) 0.073μM; Ej. (lde) 0.0049μM; Ej. (ldg) 0.014μM; Ej. (ldh) 0.041μM; Ej. (ldi) 023μM; Ej. (ldj) 0.25μM; Ej. (ldk) 0.02μM; Ej. (ldl) 0.018μM; Ej. (1dm) 0.0075μM; Ej. (ldn) 0.0055μM; Ej. (ldo) 0.03μM; Ej. (ldp) 0.0067μM; Ej. (ldq) 0.037μM; Ej. (ldt) 0.0026μM; Ej. (ldu) 0.00039μM; Ej. (ldv) 0.72μM; Ej. (ldw) 0.021 μM; Ej. (ldx) 0.035μM; Ej. (ldy) 0.0035uM; Ej. (ldz) 0.099uM; Ej. (lea) 0.057uM; Ej. (leb) 0.17uM; Ej. (lee) 0.013uM; Ej. (led) 0.016uM; Ej. (lee) 0.0048uM.

Probados en ensayo phospho- Ser473 Akt: Ej. (ldf) 0.3813uM; Ej. (ldr) 0.01415uM; Ej. (Ids) 0.06066uM.

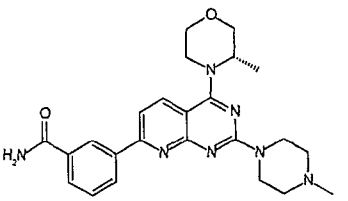
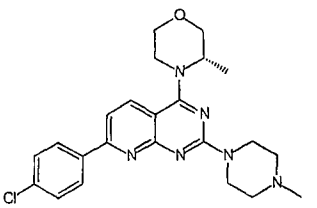
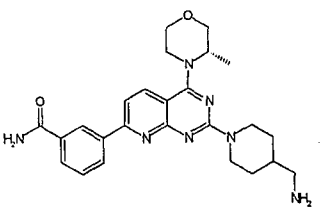
Ejemplo 2

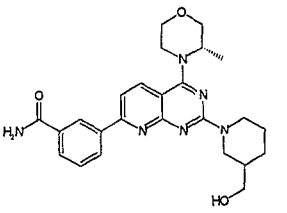
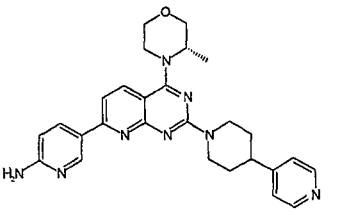
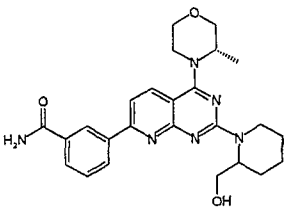
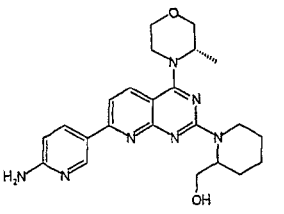
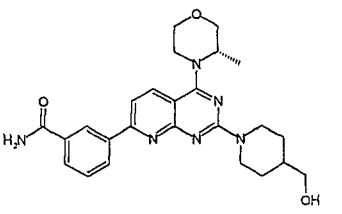


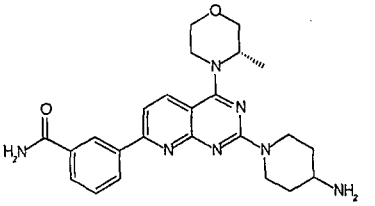
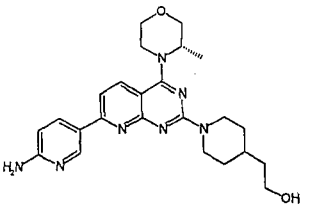
R2= Amino

R3= Arilo o heteroarilo

A una solución (0.2 M) del cloro- sustrato apropiado (1 equiv) en dioxano se agregó diisopropiletilamina (2 equiv) . A esta mezcla luego se agregó la amina apropiada (2 equiv) . Luego la reacción se calentó bajo la influencia de radiación microondas (120 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar, la muestra se concentró al vacío y el residuo resultante se disolvió en CH_2Cl_2 y se lavó con H_2O. La fracción orgánica fue retirada, secada ($MgSO_4$) . El residuo crudo se purificó mediante cromatografía rápida (SiO2) para proporcionar los productos deseados.

	Pureza (%)	Retention time (min)	M/z $[M+H]^+$	Estructura de ejemplo
2a	97	3.28	448.3	
2b	99	3.78	439.3	
2c	99	3.31	462.4	

2d	100	3.76	463.3	
2e	99	3.11	483.3	
2f	99	3.82	463.4	
2g	100	3.39	436.5	
2h	100	3.68	463.4	

2i	98	3.26	448.4	
2j	100	3.38	450.3	

Probados en el Ensayo Enzimático Alternativo: Ej. (2a) 0.7μM; Ej. (2b) 0.56μM; Ej. (2c) 0.6μM; Ej. (2d) 0.27μM; Ej. (2e) 0.35uM; Ej. (2f) 0.17μM; Ej. (2g) 0.064uM; Ej. (2h) 0.29μM; Ej. (2i) 0.64μM; Ej. (2j) 0.2μM.

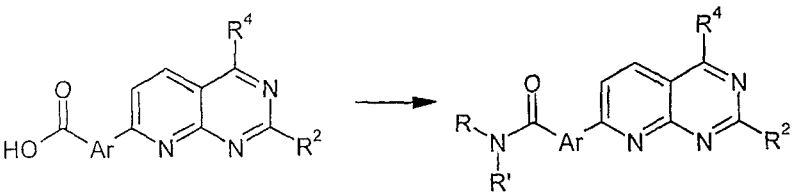
Ejemplo 3:

(Compuestos 3a a 3ab)

R^4 = (S) - 3- metil- morfoline

R^2 = (S) - 3- metil- morfoline

Ar = arilo



Los carboxi- substratos son reportados en el Ejemplo 1.

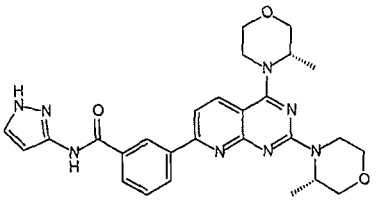
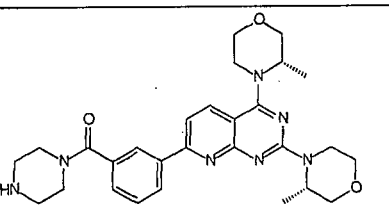
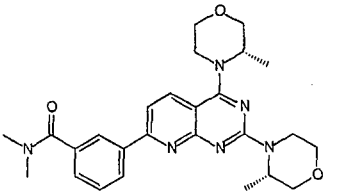
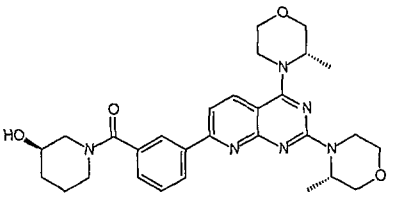
Metodo: Formación de amidas

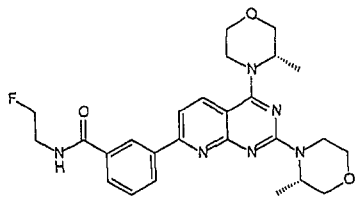
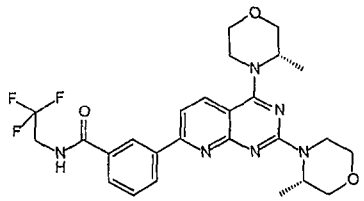
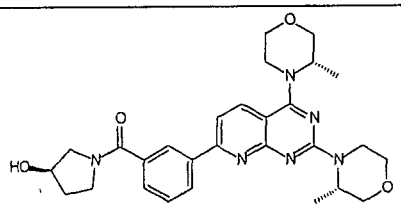
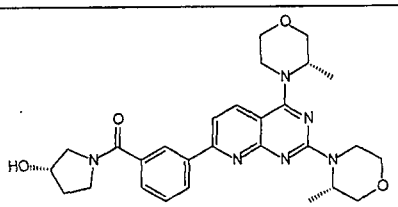
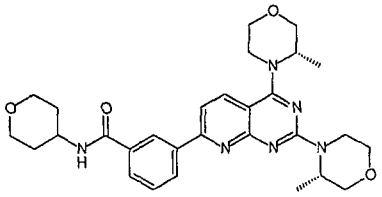
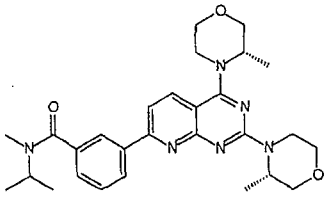
Condiciones A:

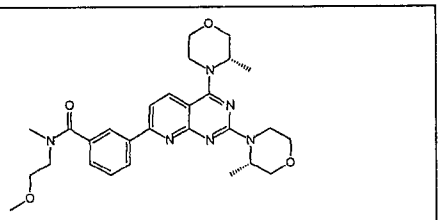
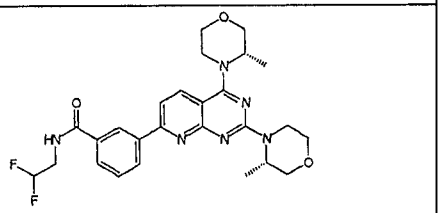
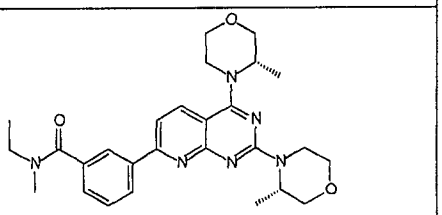
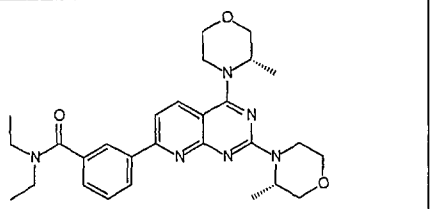
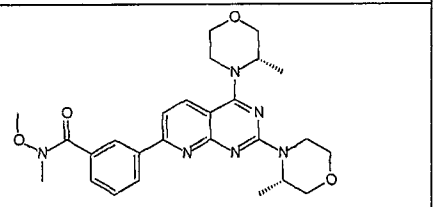
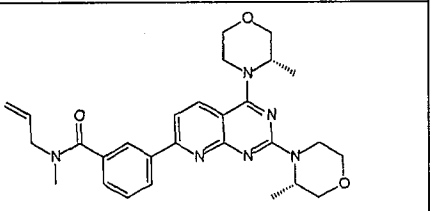
El carboxi- sustrato apropiado (1 equiv) se disolvió en DMF (0.067 M) . HBTU (1.2

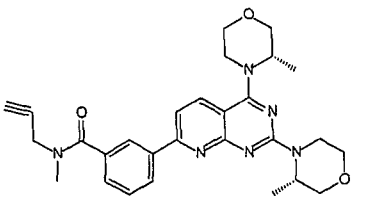
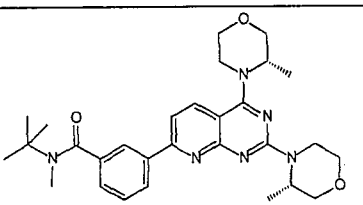
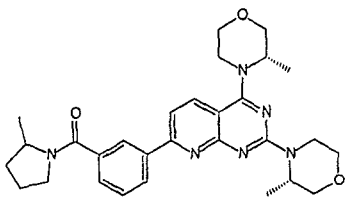
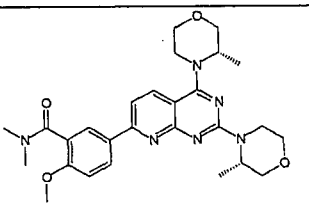
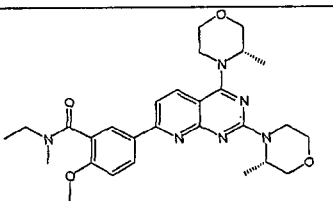
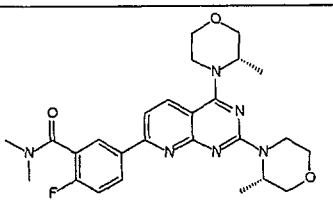
equiv) y se agregó aminas apropiadas (1.05 equiv) junto con 3 gotas de trietilamina a 0°C. Los recipientes de reacción se sellaron y las mezclas se agitaron entre 1 y 12 horas a temperatura ambiente. Al terminar, las muestras se concentraron al vacío. Luego los residuos crudos se purificaron mediante HPLC preparativa para proporcionar los productos deseados.

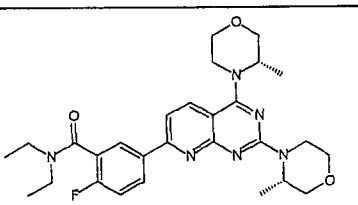
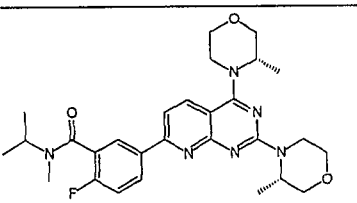
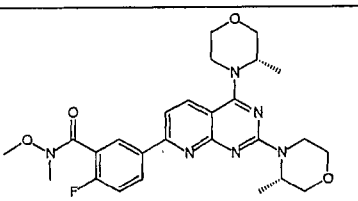
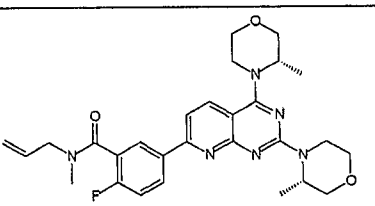
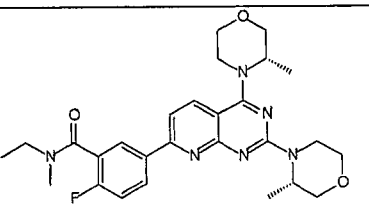
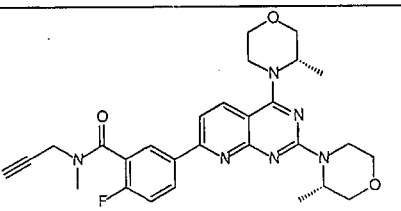
Tabla 3

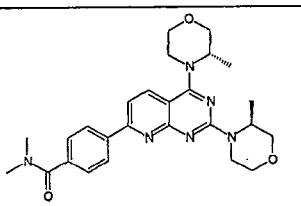
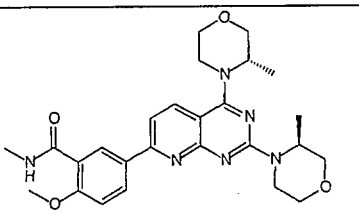
	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
3a	98	7.36	515.3	A	
3b	82	5.31	518.4	A	
3c	96	7.2	477.3	A	
3d	96	6.95	533.4	A	

3e	95	7.33	495.3	A	
3f	95	8.34	531.3	A	
3g	98	6.61	519.4	A	
3h	98	6.64	519.4	A	
3i	99	7.32	533.4	A	
3j	99	8.19	505.4	A	

3k	98	4.15	521.5	A	
3l	99	4.27	513.4	A	
3m	90	4.22	491.3	A	
3n	98	4.35	505.5	A	
3o	95	4.2	493.4	A	
3p	98	4.36	503.4	A	

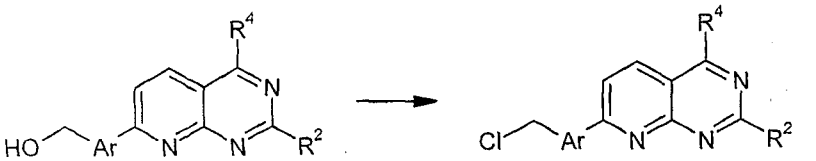
3q	98	4.31	501.4	A	
3r	95	4.62	519.5	A	
3s	99	4.19	517.3	A	
3t	99	3.97	507.4	A	
3u	99	4.07	521.4	A	
3v	96	7.38	495.4	A	

3w	91	8.42	523.3	A	
3x	97	8.44	523.4	A	
3y	97	7.69	511.3	A	
3z	92	8.33	521.3	A	
3aa	86	4.12	509.3	A	
3ab	83	4.19	519.3	A	

3ac	100	7.13	477.4	A	
3ad	100	4.00	493.4	A	

Probados en el Ensayo Enzimático Alternativo: Ej. (3a) 0.048uM; Ej. (3b) 0.32uM; Ej. (3c) 0.09uM; Ej. (3d) 0.28uM; Ej. (3e) 0.0047uM; Ej. (3f) 0.28uM; Ej. (3g) 0.0052uM; Ej. (3h) 0.18uM; Ej. (3i) 0.14uM; Ej. (3j) 0.17uM; Ej. (3k) 0.23uM; Ej. (31) 0.044uM; Ej. (3m) 0.32uM; Ej. (3n) 0.23uM; Ej. (3o) 0.37μM; Ej. (3p) 0.56μM; Ej. (3q) 0.12μM; Ej. (3r) 0.5uM; Ej. (3s) 0.38uM; Ej. (3t) 0.042uM; Ej. (3u) 0.13uM; Ej. (3v) 0.16 μM; Ej. (3w) 0.5μM; Ej. (3x) 0.24uM; Ej. (3y) 0.74uM; Ej. (3z) 0.34uM; Ej. (3aa) 0.026uM; Ej. (3ab) 0.14uM; Ej. (3ac) 1.6uM; Ej. (3ad) 0.066uM.

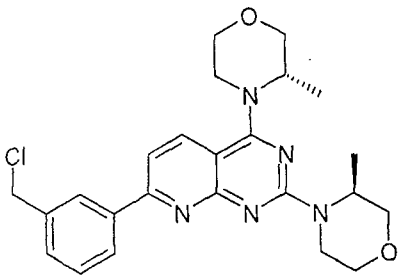
Ejemplo 4



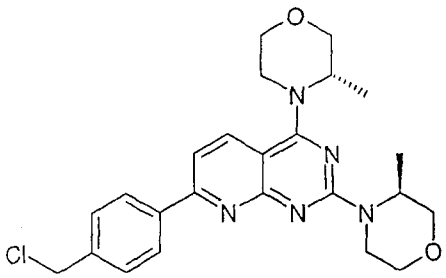
Los sustratos de alcohol bencílico se reportan en el Ejemplo 1.

Se disolvió alcohol bencílico apropiado (1 equiv) en CH_2Cl_2 (0.08 M) . Se agregó trietilamina (1 equiv) a temperatura ambiente, seguido por la adición de cloruro de tionilo (2 equiv) . La mezcla de reacción se agitó a 30°C durante 45 minutos. Al terminar, la mezcla de reacción se particionó entre salmuera y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó

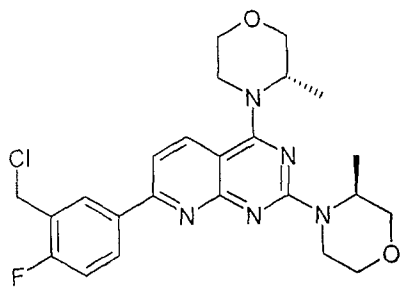
mediante cromatografía en columna sobre gel de sílice eluyendo con 10 a 70 % etilacetato en hexano.



7- (3- Clorometil- fenil) - 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina: (72 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 454 [M+H]+ R/T = 3.15 min

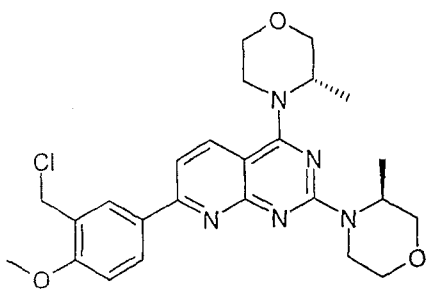


Se disolvió alcohol bencílico apropiado (1 equiv) en CH_2Cl_2 (0.052 M) . Se agregó cloruro de tionilo (3.3 equiv) . La mezcla de reacción se calentó a 55°C y se agregó una solución de trietilamina (1.7 equiv) en CH_2Cl_2 (0.044 M) por goteo durante 10 minutos. La mezcla de reacción se dejo agitar a 30°C durante 10 minutos. Al terminar, la mezcla de reacción se particionó entre salmuera y CH_2Cl_2 y extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 10 a 50 % etilacetato en hexano.
7- (4- Clorometil- fenil) - 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina: (65 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 454 $[M+H]^+$ R/T = 3.15 min



Se disolvió alcohol bencílico apropiado (1 equiv) en CH_2Cl_2 (0.044 M) . Se agregó cloruro de tionilo (3.3 equiv) . La mezcla de reacción se calentó a 55°C y se agregó una solución de trietilamina (1.7 equiv) en CH_2Cl_2 (0.044 M) por goteo durante 10 minutos. La mezcla de reacción se dejo agitar a 30°C durante 30 minutos. Al terminar, la mezcla de reacción se particionó entre salmuera y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se utilizó sin purificación adicional.

7- (3- Clorometil- 4- fluoro- fenil) - 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3-d]pirimidina: (96 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 472 $[M+H]+$ R/T = 3.96 min



Se disolvió alcohol bencílico apropiado (1 equiv) en CH_2Cl_2 (0.086 M) . Se agregó trietilamina (2.5 equiv) y cloruro de tionilo (2.5 equiv) . La mezcla de reacción se calentó a 45 °C durante 3 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 10 a 50 % etilacetato en hexano.

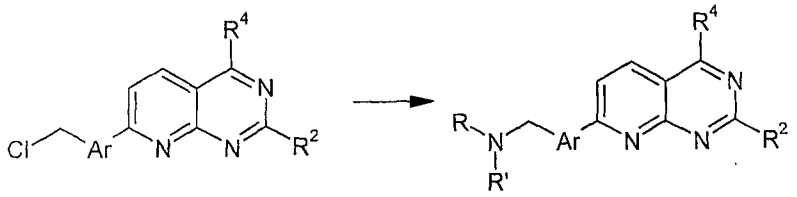
7- (3- Clorometil- 4- metoxi- fenil) - 2,4- bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3-d]pirimidina: (37 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 484 $[M+H]^+$ R/T = 3.21 min

(Compuestos 4a a 4ak)

R^4 = (S) - 3- metil- morfolina

R2 = (S) - 3- metil- morfolina

Ar = arilo



Método: Formación de Bencilaminas. Benciléters y bencilsulfonas .

Condiciones A:

Se disolvió clorobencil- substrate apropiado (1 equiv) en THF (0.067 M) . Se agregó la amina apropiada (80 equiv) así como también trietilamina (1 equiv) . Los recipientes de reacción se sellaron y las mezclas se agitaron durante 3 a 5 horas a 95°C. Al terminar, las muestras se concentraron al vacío. Luego los residuos crudos se purificaron mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones B:

El clorobencil- sustrato apropiado (1 equiv) se disolvió en una solución acuosa de amoniaco/n-butanol (1.5:1) (0.011 M) . El recipiente de reacción se selló y la mezcla se agitó durante 10 minutos a 140°C. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones C:

El clorobencil- sustrato apropiado (1 equiv) e hidróxido de sodio (1 equiv) se disolvieron en etanol (0.011 M) . El recipiente de reacción se selló y la mezcla se agitó durante 3 horas a 50°C. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones D:

El clorobencil- sustrato apropiado (1 equiv) se disolvió en DMF (0.022 M) . Se agregó imidazol (3 equiv) y tert- butóxido de potasio (3 equiv) se agregó. El recipiente de reacción se selló y la mezcla se agitó durante 2 horas a temperatura ambiente. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

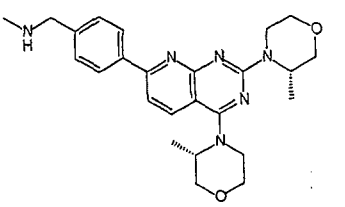
Condiciones E:

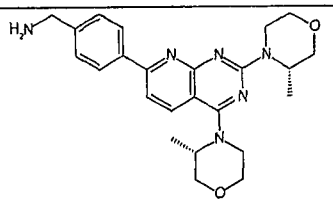
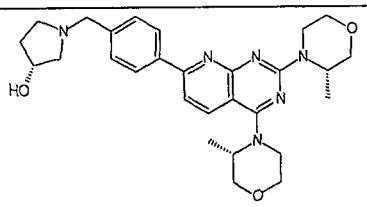
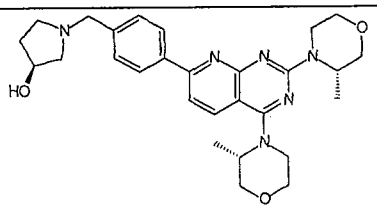
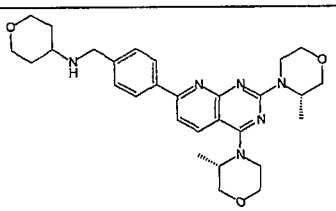
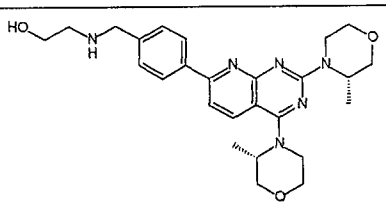
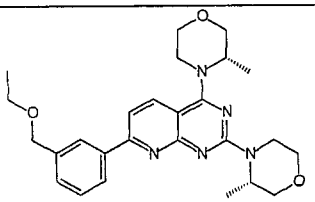
El clorobencil- sustrato apropiado (1 equiv) se disolvió en DMF (0.066 M) . Se agregó sulfinato de sodio (1.3 equiv) . La mezcla se agitó durante 2 horas a 125°C. Al terminar, la muestra se concentró al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

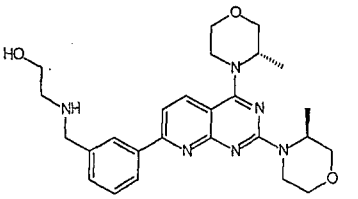
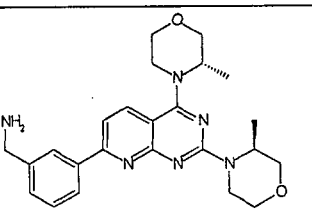
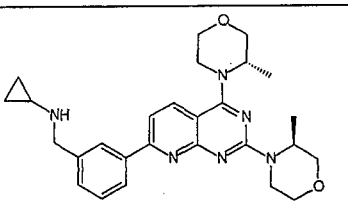
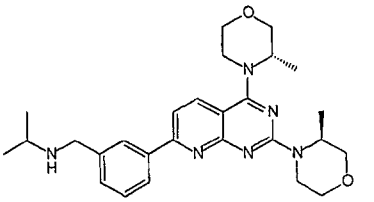
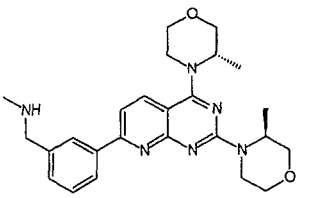
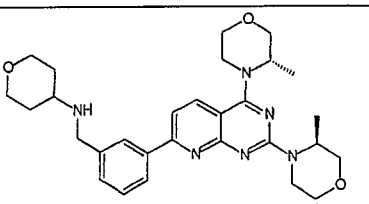
Condiciones F:

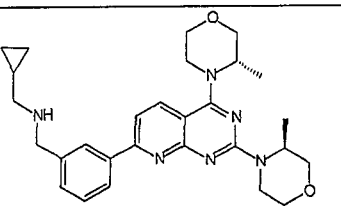
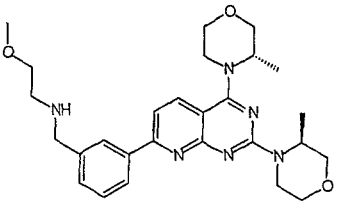
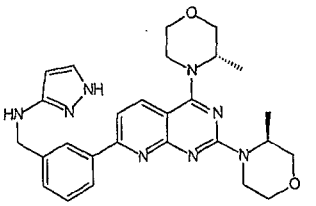
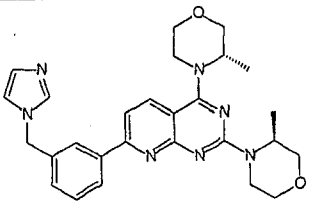
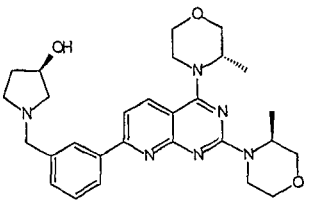
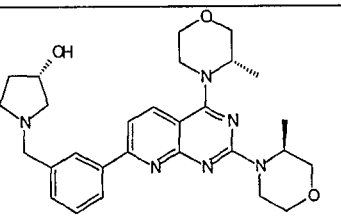
El clorobencil- sustrato apropiado (1 equiv) , carbonato de potasio (2.6 equiv) trietilamina (1 equiv) y la amina apropiada (1.1 equiv) se suspendieron en DMF (0.028 M) . El recipiente de reacción se selló y la mezcla se agitó durante 16 horas a 40°C. Al terminar, la muestra fue filtrada a través de un cartucho de sílice, lavada con CH_2Cl_2 y luego concentrada al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

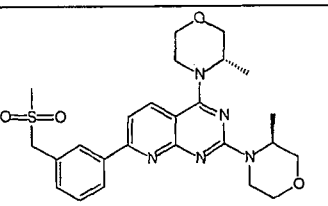
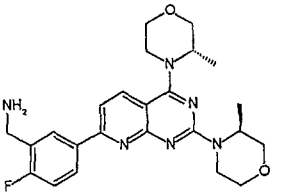
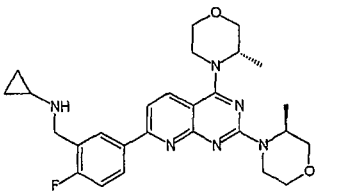
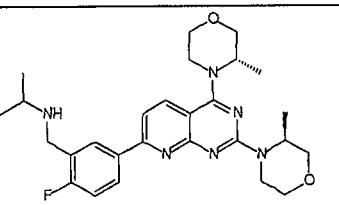
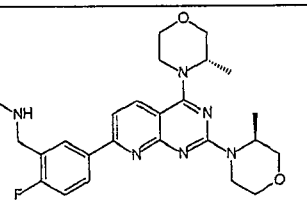
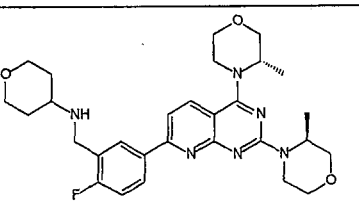
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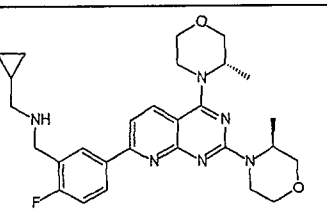
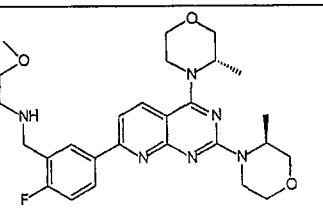
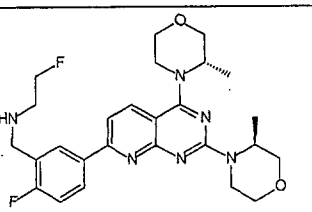
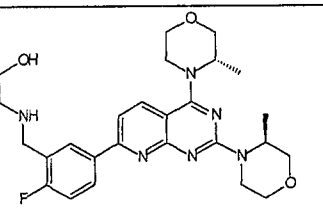
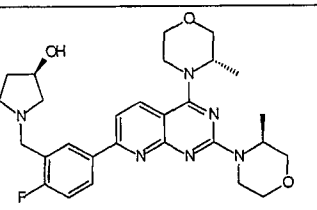
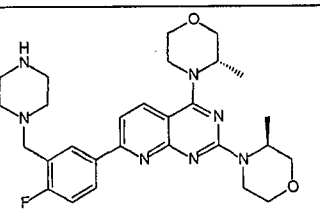
	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
4a	87	3.61	449.3	A	

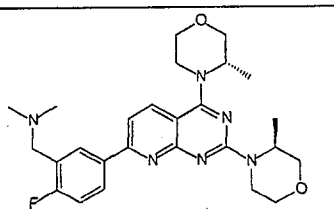
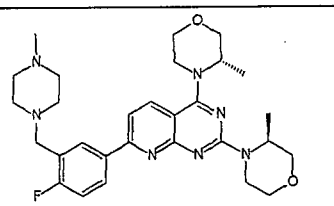
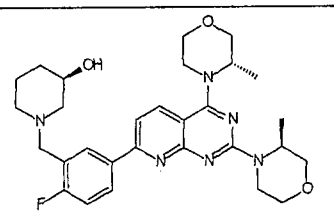
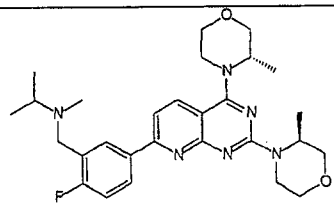
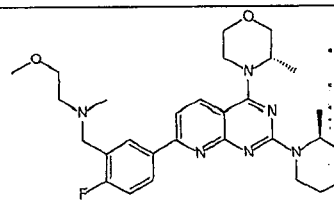
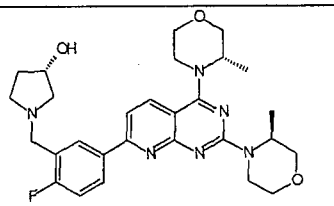
4b	95	3.41	435.2	B	
4c	99	3.4	505.5	A	
4d	100	3.42	505.5	A	
4e	100	3.44	519.5	A	
4f	100	3.39	479.4	A	
4g	95	4.36	464.4	C	

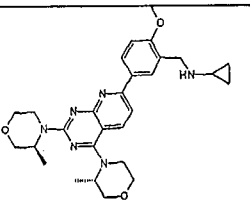
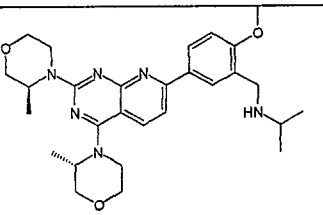
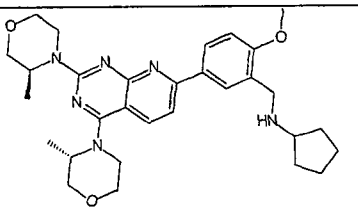
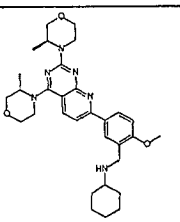
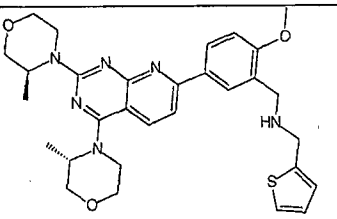
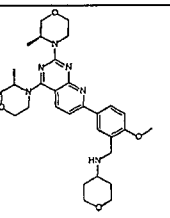
4h	*96*	3.4	479.4	A	
4i	95	3.4	435.4	B	
4j	92	5.6	475.4	A	
4k	94	5.65	477.4	A	
41	97	5.39	449.4	A	
4m	90	5.6	519.5	A	

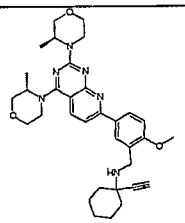
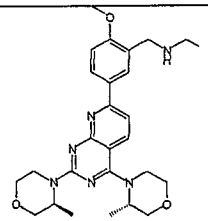
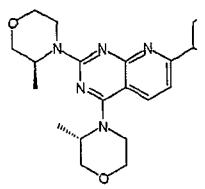
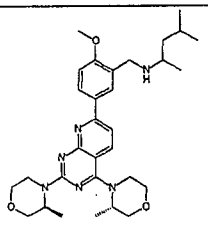
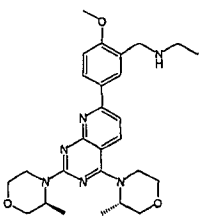
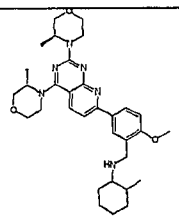
4n	96	5.83	489.5	A	
4o	95	5.56	493.4	A	
4p	26, 69	6.63, 6.78	501.4	A	
4q	99	3.43	486.4	D	
4r	94	3.44	505.5	A	
4s	97	3.44	505.3	A	

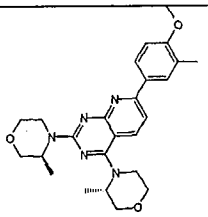
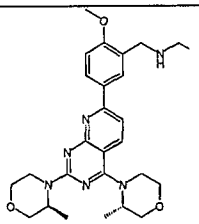
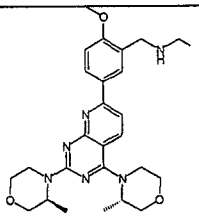
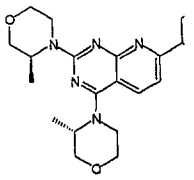
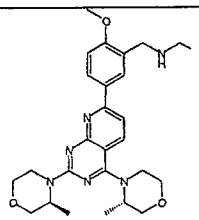
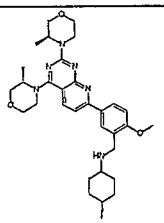
4t	94	6.06	498.7	E	
4u	98	3.42	453.4	B	
4v	99	3.63	493.4	A	
4w	99	3.62	495.4	A	
4x	96	3.55	467.4	A	
4y	99	3.6	537.4	A	

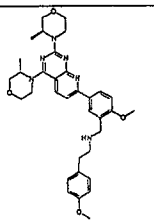
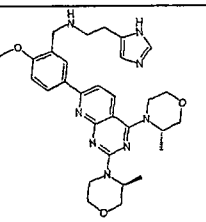
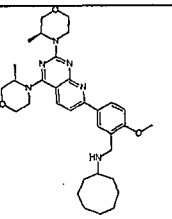
4z	99	3.67	507.4	A	
4aa	97	3.59	511.4	A	
4ab	91	3.58	499.4	A	
4ac	99	3.55	497.4	A	
4ad	99	3.4	523.4	A	
4ae	99	3.47	522.4	A	

4af	99	3.42	481.4	A	
4ag	99	3.49	536.4	A	
4ah	98	3.43	537.5	A	
4ai	99	3.48	509.4	A	
4aj	99	3.46	525.5	A	
4ak	99	3.42	523.5	A	

4al	99	3.55	505.4	F	
4am	99	3.60	507.4	F	
4an	99	3.66	533.4	F	
4ao	99	3.77	547.5	F	
4ap	99	3.70	561.4	F	
4aq	99	3.52	549.5	F	

4ar	99	3.85	571.5	F	
4as	99	3.85	549.5	F	
4at	99	3.76	535.5	F	
4au	99	3.83	549.5	F	
4av	96	3.32	578.5	F	
4aw	99	3.82	561.5	F	

4ax	99	3.59	519.4	F	
4ay	99	3.66	521.4	F	
4az	99	3.65	521.4	F	
4ba	99	3.46	509.4	F	
4bb	99	3.52	523.4	F	
4bc	99	3.84	561.5	F	

4bd	99	3.81	599.5	F	
4be	93	3.29	559.4	F	
4bf	99	3.91	575.5	F	

Datos NMR para ejemplo 4h

^{1} NMR (300 MHz, DMSO) δ ppm 8.21 (ArH, d, J = 8.39 Hz, 2H) , 8.08- 8.01 (ArH, m, 1H) , 7.65 (ArH, d, J = 8.49 Hz, 1H) , 7.49 (ArH, d, / = 4.85 Hz, 2H) , 4.82- 4.72 (CH2, m, 1H) , 4.45 (CH2,+ NHm, 3H) , 3.99- 3.82 (CH2, m, 7H) , 3.69 (CH2, ddd, J= 19.97, 8.86, 5.32 Hz, 8H) , 3.53 (CH2, t, J = 5.65, 5.65 Hz, 2H) , 3.29- 3.15 (CH2, m, 2H) , 1.38 (CH3, d, J= 6.75 Hz, 3H) , 1.25 (CH3, d, J = 6.75 Hz, 3H)

Datos NMR para ejemplo 4r

^{1}NMR (300 MHz, CDC13 5 ppm 8.19 (ArH, s, 1H) , 8.03 (ArH, ddd, /= 8.43, 5.31, 3.28 Hz, 2H) , 7.54- 7.37 (ArH, m, 3H) , 5.00- 4.85 (CH, m, 1H) , 4.68- 4.56 (CH2, m, 1H) , 4.36 (CH2,

ddd, J= 6.83, 4.79,2.16 Hz, 2H) , 4.07- 3.92 (CH2, m, 2H) , 3.91- 3.66 (CH2, m, 11H) , 3.63- 3.49 (CH2, m, 1H) , 3.39 (CH2, dd, J= 13.37, 3.58 Hz, 1H) , 3.04- 2.92 (CH2, m, 1H) , 2.80

(CH2, d,J= 10.30 Hz, 1H) , 2.65 (CH2, dd, J= 10.23,4.92 Hz, 1H) , 2.52- 2.39 (CH2, m, 1H) , 2.21 (CH2, d, J= 7.02 Hz, 1H) , 1.89- 1.73 (CH2, m, 1H) , 1.46 (CH3, d,/= 6.77 Hz, 3H) , 1.35 (CH3,d,J=6.81Hz,3H)

^{13}CNMR(75 MHz, CDC13) δ ppm 165.57, 163.03, 162.50, 160.11, 139.06, 134.83, 130.62, 128.81, 127.10, 113.70, 105.06, 71.44, 71.06, 67.41, 67.25, 67.07, 62.87, 60.08, 52.98, 52.49, 47.07, 44.58, 39.47, 35.02, 14.86 y 14.90.

Datos NMR para ejemplo 4s

^{1}H NMR (300 MHz, CDC13) δ ppm 8.22 (ArH, s, 1H) , 8.11- 7.96 (ArH, m, 2H) , 7.48 (ArH, dd, J= 10.85, 7.98 Hz, 3H) , 4.99- 4.86 (CH, m, 1H) , 4.68- 4.55 (CH, m, 1H) , 4.44- 4.30 (CH2, m, 2H) , 4.06- 3.92 (CH2, m, 2H) , 3.93- 3.65 (CH2, m, 10H) , 3.62- 3.50 (CH2, m, 1H) , 3.39 (CH2, dd,J = 13.39, 3.57 Hz, 1H) , 3.14- 3.01 (CH2, m, 1H) , 2.88 (CH2, d, J= 10.59 Hz, 1H) , 2.77- 2.67 (CH2, m, 1H) , 2.63- 2.43 (CH2, m, 1H) , 2.31- 2.14 (CH2, m, 1H) , 1.92- 1.79 (CH2, m, 1H) , 1.47 (CH3, d, J= 6.77 Hz, 3H) , 1.35 (CH3, d, J = 6.81 Hz, 3H)

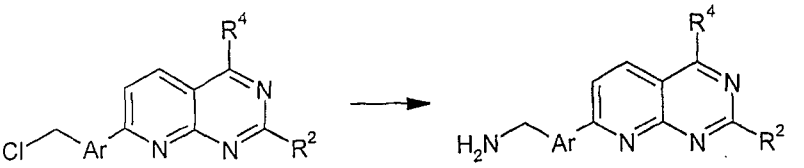
^{13}CNMR(75 MHz, CDCI3)) δ ppm 165.56, 163.03, 162.34, 160.12, 139.16, 134.89, 130.80, 128.94, 128.91, 127.39, 113.69, 105.11, 71.44, 71.21, 71.06, 67.40, 67.06, 62.61, 59.93, 52.98, 52.42,47.08,44.58, 39.47, 34.88, 31.73,22.80,14.86 y 14.91.

Probados en el Ensayo Biológico: Ej. (4f) 0.001967μM.

Probados en el Ensayo Enzimático Alternativo: Ej. (4a) 0.0016uM; Ej. (4b) 0.025μM; Ej. (4c) 0.093 μM; Ej. (4d) 0.013μM; Ej. (4e) 0.0019μM; Ej. (4f) <0.0027uM; Ej. (4g) 0.13μM; Ej. (4h) 0.031μM; Ej. (4i) 0.027μM; Ej. (4j) 0.054uM; Ej. (4k) 0.016uM; Ej. (4l) 0.0091uM; Ej. (4m) 0.015uM; Ej. (4n) 0.0071 μM; Ej. (4o) 0.021 μM; Ej. (4p) 0.17μM; Ej. (4q) 0.13μM; Ej. (4r) 0.04μM; Ej. (4s) 0.029uM; Ej. (4t) 0.09uM; Ej. (4u) 0.027μM; Ej. (4v) O.14μM; Ej. (4w) 0.028uM; Ej. (4x) 0.12μM; Ej. (4y) 0.13uM; Ej. (4z) 0.13uM; Ej. (4aa) 0.21μM; Ej. (4ab). 1.1 uM; Ej. (4ac) 0.087uM; Ej. (4ad) 0.081 μM; Ej. (4ae) 0.16μM; Ej. (4af) 0.58μM; Ej. (4ag) 0.54μM; Ej. (4ah) 0.2uM; Ej. (4ai) 0.22μM; Ej. (4aj) 0.46μM; Ej. (4ak) 0.015uM; Ej. (4al) 0.064μM; Ej. (4am) 0.024uM; Ej. (4an) 0.095uM; Ej. (4ao) 0.064uM; Ej. (4ap) 0.11uM; Ej. (4aq) 0.012uM; Ej. (4ar) 0.06uM; Ej. (4as) 0.091 μM; Ej. (4at) 0.12u.M; Ej. (4au) 0.096uM;

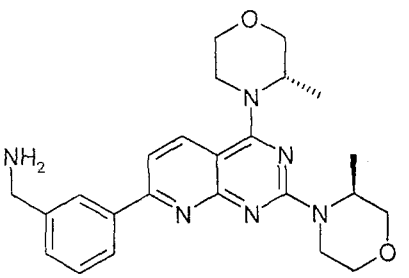
Ej. (4av) 0.0038uM; Ej. (4aw) 0.11uM; Ej. (4ax) 0.1μM; Ej. (4ay) 0.14μM; Ej. (4az) 0.038μM; Ej. (4ba) 0.013uM; Ej. (4bb) 0.032μM; Ej. (4bc) 0.076μM; Ej. (4bd) 0.12uM; Ej. (4be) 0.049uM; Ej. (4bf) 0.059μM.

Ejemplo 5

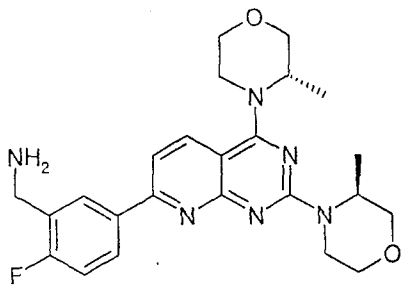


Los sustratos de Bencil- cloruro se reportan en el Ejemplo 4.

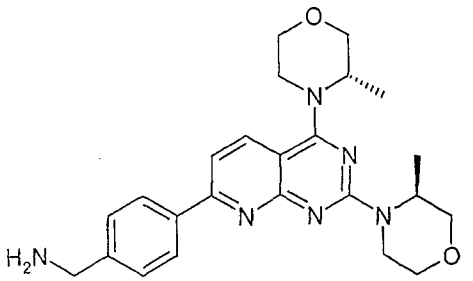
El cloruro de bencilo apropiado (1 equiv) se disolvió en una solución de hidróxido de amonio y n- butanol (1.5:1) (0.01 M) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar, la mezcla de reacción se particionó entre salmuera y etilacetato y se extrajo con etilacetato. Las fases orgánicas combinadas se secaron (MgS04) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 5 % metanol en CH_2Cl_2.



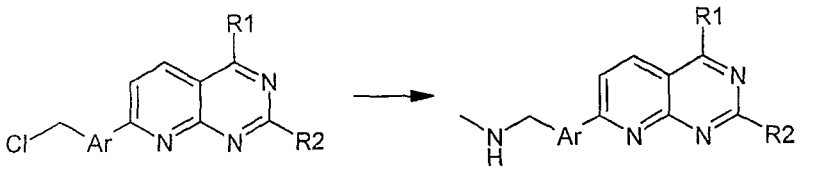
3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- bencilamina: (81 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 435 [M+H]+ R/T = 2.44 min



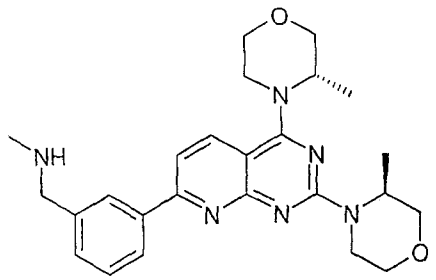
5- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- fluoro- bencilamina: (85 % rendimiento, 98 % pureza) m/z (LC- MS, ESP) : 453 [M+H]+ R/T = 3.21 min



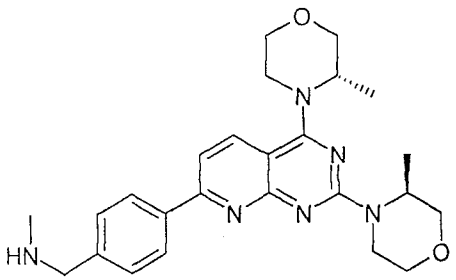
4- [2,4- Bis- (3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- bencilamina: (95 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 435 [M+H]+ R/T = 2.36 min



El cloruro de bencilo apropiado (1 equiv) se disolvió en una solución 2M de metilamina en THF (80 equiv) . Se agregó trietilamina (1 equiv) . La mezcla de reacción se agitó a 95°C durante 2.5 horas. Al terminar, la mezcla de reacción se concentró al vacío y el residuo se diluyó con etilacetato y n- butanol y la fase orgánica se lavó con salmuera, se secó ($MgSO_4$) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 7 % metanol en CH_2Cl_2.



{3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- benzil}- metilo-amina: (77 % rendimiento, 94 % pureza) m/z (LC- MS, ESP) : 449 [M+H]+ R/T = 2.44 min

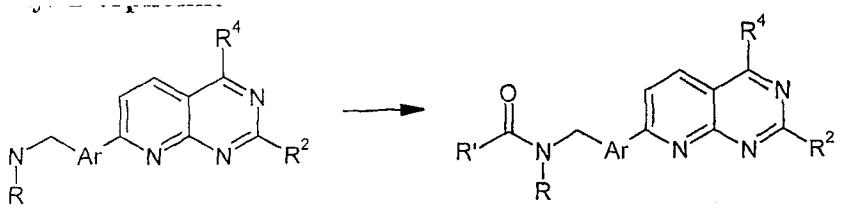


{4- [2,4- Bis- (3 - metil- morfolin- 4- il) - pirido [2,3- d]pirimidm- 7- il]- benzil} - metilo-amina: (93 % rendimiento, 87 % pureza) m/z (LC- MS, ESP) : 449 [M+H]+ R/T = 2.40 min

Procedimientos para la síntesis de Ejemplos 5a a 5z

R4 = (S) - 3- metil- morfolina

R2 = (S) - 3- metil- morfolina



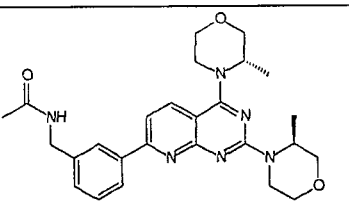
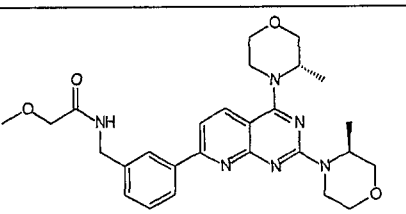
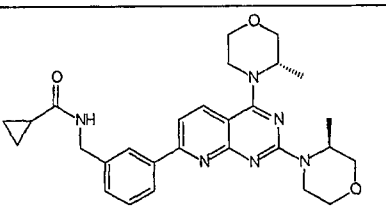
Condiciones A:

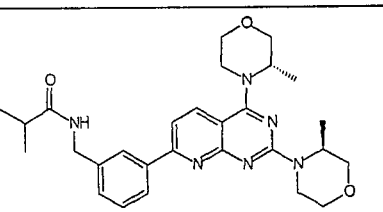
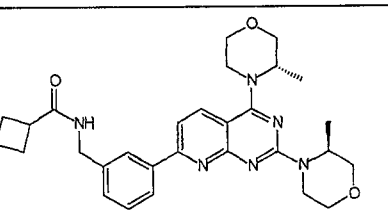
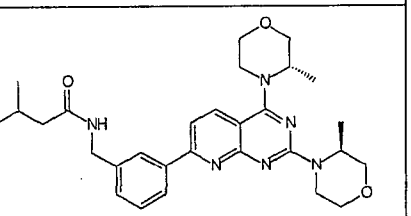
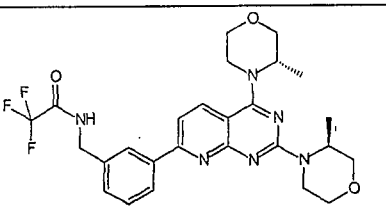
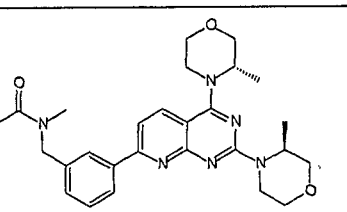
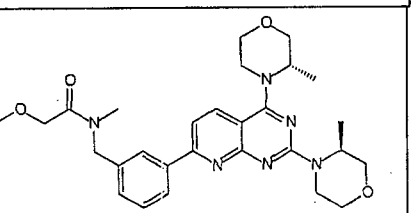
El aminobencil- sustrato apropiado (1 equiv) se disolvió en CH_2Cl_2 (0.035 M) . Luego se agregó el cloruro de acilo apropiado o anhidrido ácido (2 equiv) así como también trietilaraina (1 equiv) . La mezclas se agitaron durante 2 horas a temperatura ambiente. Al terminar, las muestras se concentraron al vacío. Luego los residuos crudos se purificaron mediante HPLC preparativa para proporcionar los productos deseados.

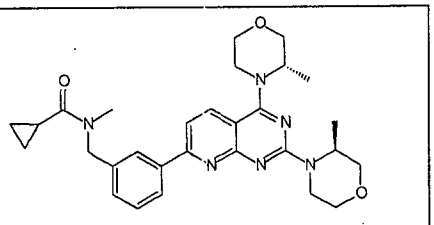
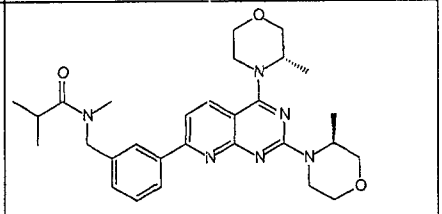
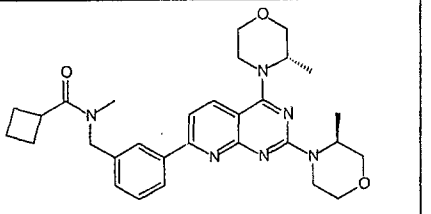
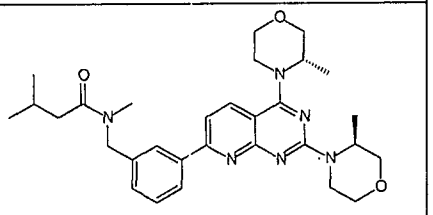
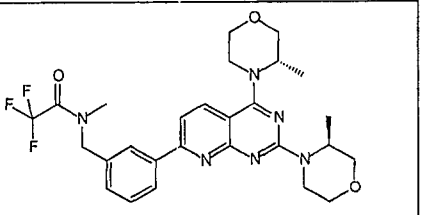
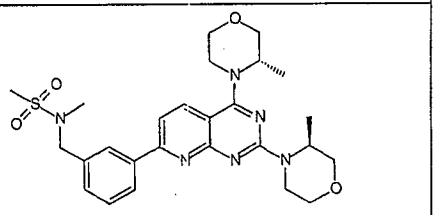
Condiciones B:

El metilaminobencil- substrato apropiado (1 equiv) se disolvió en CH_2Cl_2 (0.035 M) . Se agregó cloruro de acilo apropiado o anhidrido ácido (2 equiv) así como también trietilamina (1 equiv) . Las mezclas se agitaron durante 12 horas a 95 °C. Al terminar, las muestras se concentraron al vacío. Luego los residuos crudos se purificaron mediante HPLC preparativa para proporcionar los productos deseados.

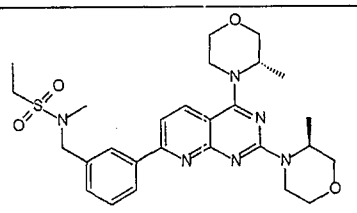
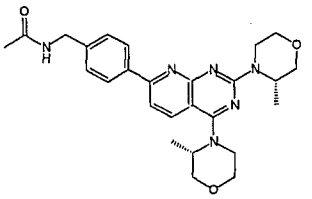
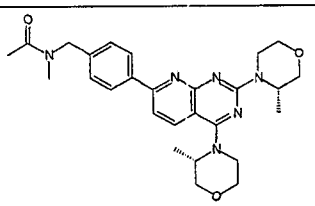
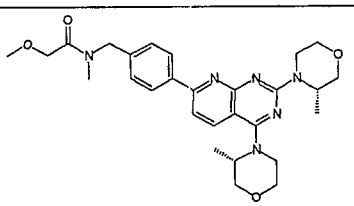
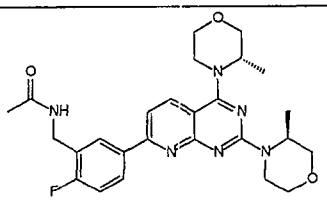
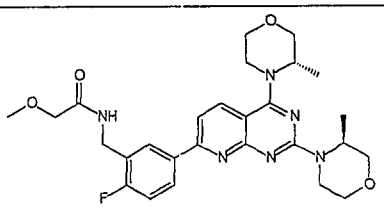
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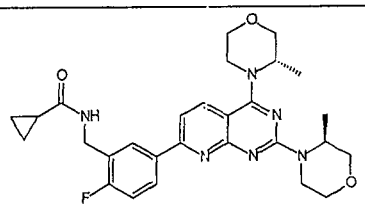
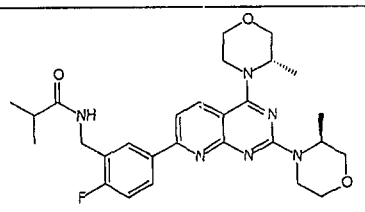
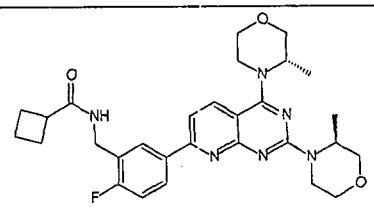
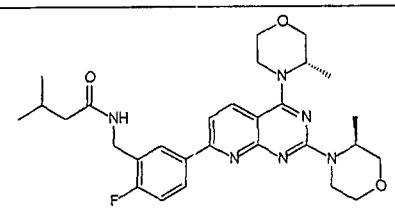
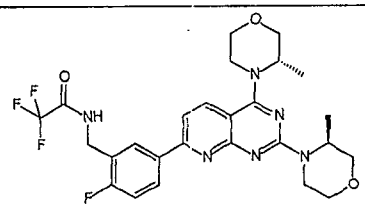
	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
5a	98	4.02	477.4	A	
5b	99	4.12	507.4	A	
5c	99	4.22	503.4	A	

5d	99	4.27	505.4	A	
5e	99	4.34	517.4	A	
5f	99	4.41	519.4	A	
5g	99	4.51	531.3	A	
5h	98	4.17	491.4	B	
5i	99	4.17	521.5	B	

5j	98	4.39	517.4	B	
5k	98	4.48	519.5	B	
51	99	4.58	531.5	B	
5m	99	4.64	533.5	B	
5n	98	4.73	545.4	B	
5o	100	4.38	527.4	C	

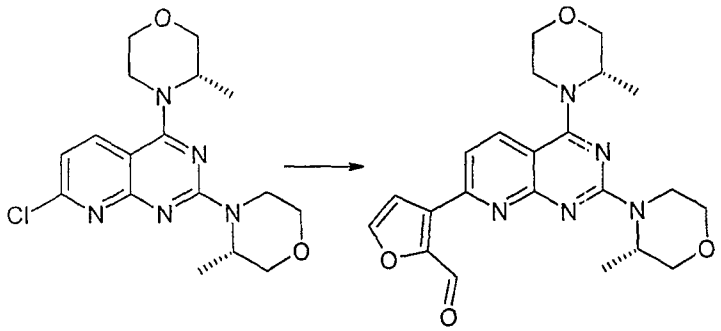
546

5p	99	4.51	541.4	**c**	
5q	99	3.8	477.4	A	
5r	98	3.93	491.4	B	
5s	99	3.93	521.4	B	
5t	100	3.94	495.4	A	
5u	100	4.02	525.4	A	

5v	100	4.16	521.4	A	
5w	100	4.19	523.4	A	
5x	100	4.27	535.4	A	
5y	100	4.32	537.5	A	
5z	98	4.38	549.5	A	

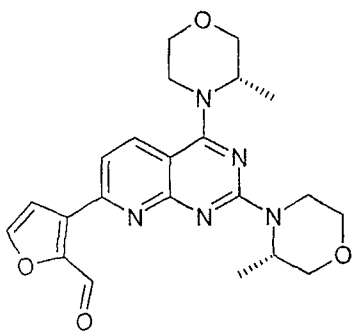
Probados en el Ensayo Enzimático Alternativo: Ej. (5a) 0.023uM; Ej. (5b) 0.054μM; Ej. (5c) 0.12uM; Ej. (5d) 0.12uM; Ej. (5e) 0.12uM; Ej. (5f) 0.37uM; Ej. (5g) 0.12uM; Ej. (5h) 0.19uM; Ej. (5i) 0.2uM; Ej. (5j) 0.31uM; Ej. (5k) 0.89uM; Ej. (51) 0.049uM; Ej. (5m) 1.4uM; Ej. (5n) 0.64uM; Ej. (5o) 0.12uM; Ej. (5p) 0.5uM; Ej. (5q) 0.091uM; Ej. (5r) 0.56uM; Ej. (5s) 0.67uM; Ej. (5t) 0.057uM; Ej. (5u) 0.16μM; Ej. (5v) 0.14μM; Ej. (5w) 0.16μM; Ej. (5x) 0.29uM; Ej. (5y) 0.44μM; Ej. (5z) 1.4μM.

Ejemplo 6



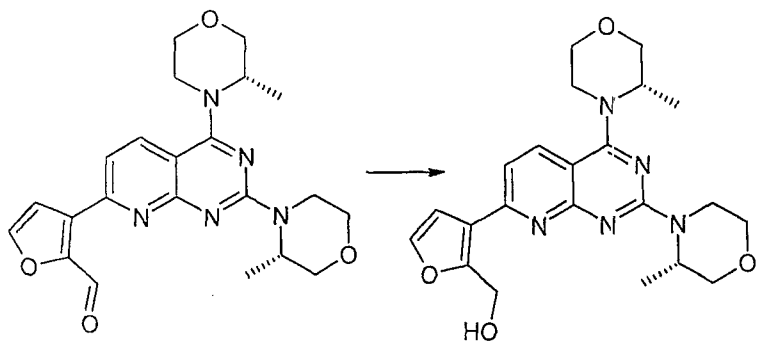
El cloro- substrato se reportó en Ejemplo 1.

El cloro- sustrato apropiado (1 equiv) se disolvió en n- butanol (0.055 M) . Se agregó ácido 2- formilfuran- 3- borónico (1.0 equiv) , carbonato de potasio (1.2 equiv) , y tetrakis(trifenilfosfina) paladio^0 (0.05 equiv) . El recipiente de reacción se selló y se expuso a radiación microondas (110 °C, ambiente de absorción de medios) durante 15 minutos. Al terminar, la mezcla de reacción fue filtrada a través de un cartucho de sílice y el filtrado se concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 40 % etilacetato en hexano para proporcionar el producto deseado.



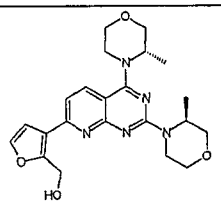
3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- furan- 2- carbaldehido: (26 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 424 [M+H]+ R/T = 2.81 min

(Compuesto 6a)



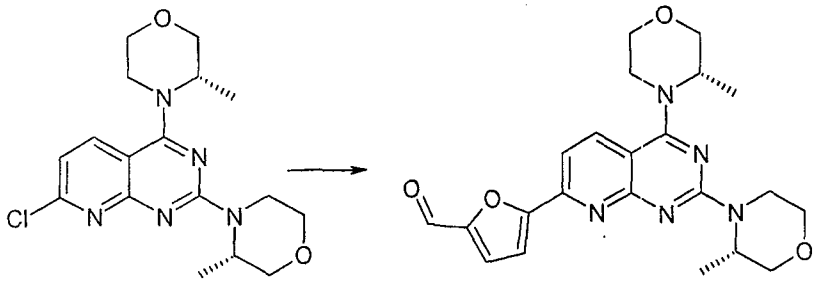
El producto anterior se disolvió en THF (0.018 M) y se agregó borohidruro de sodio (2 equiv) . Esta mezcla se dejo agitar a temperatura ambiente durante 5 minutos. Al terminar, la mezcla de reacción se filtró a través de un cartucho de sílice y el filtrado se concentró al vacío. El residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Tabla 6:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructura de ejemplo
6a	96	6.89	426.3	

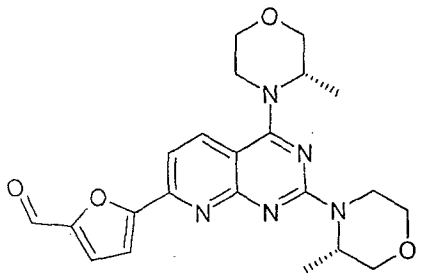
Probados en Ensayo Enzimático Alternativo: Ej. (6a) 0.013μM.

Ejemplo 7



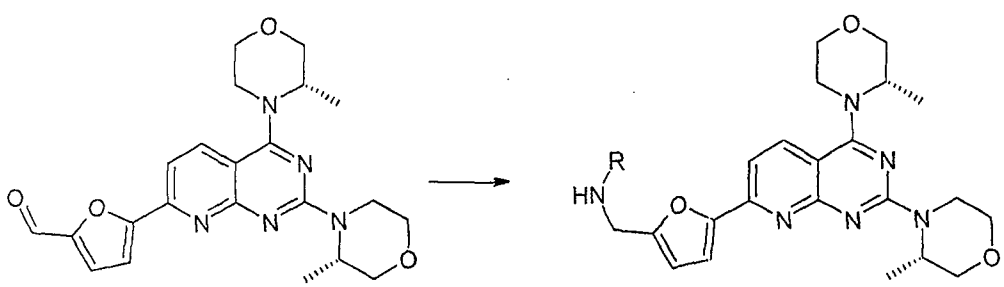
El cloro- substrato se reportó en el Ejemplo 1.

El cloro- sustrato apropiado (1 equiv) se disolvió en dioxano (0.16 M) . Se agregó ácido 5- formil- 2- furilborónico (1.05 equiv) , fosfato de tripotasio (1.5 equiv) y bis(tri- t- butilfosfine) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (170 °C, ambiente de absorción de medios) durante 45 minutos. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2 y extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 40 a 100 % etilacetato en hexano para proporcionar el producto deseado.



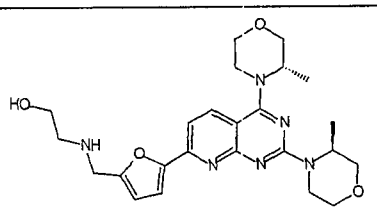
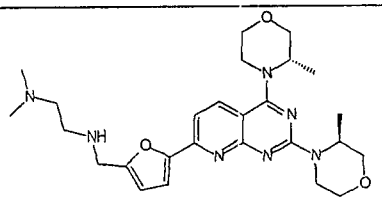
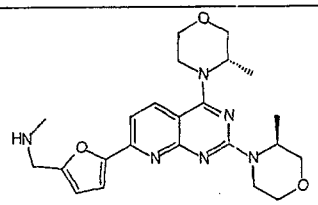
5 - [2,4- Bis- (3 - metil- morfolin- 4- il) - pirido [2,3 - d]pirimidin- 7- il]- furan- 2- carboxaldehido: (100 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 424 [M+H]+ R/T = 2.75 min

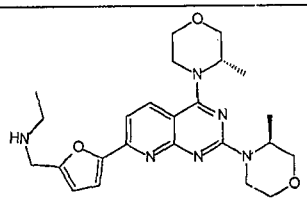
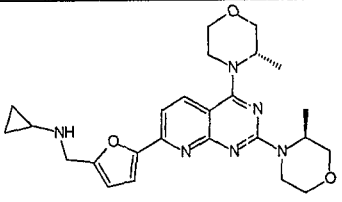
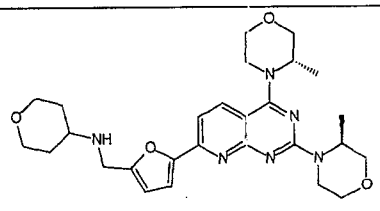
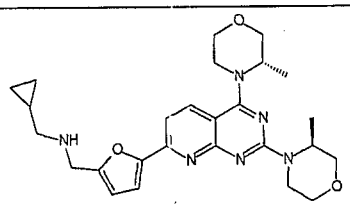
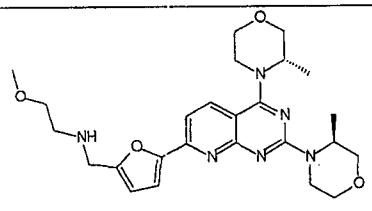
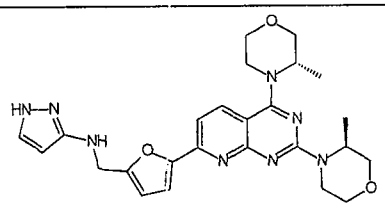
(Compuestos 7a a 7k)

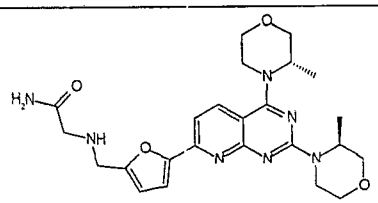
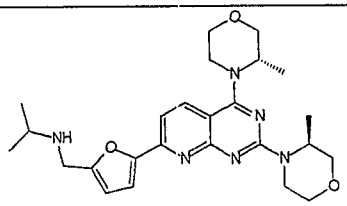


El formilfuran- sustrato apropiado (1 equiv) se disolvió en una solución de THF/CH_2Cl_2 (1:1) (0.036 M) . Se agregó aminas apropiadas (2.2 equiv) , borohidruro de sodio (2.4 equiv) y ácido acético (0.03 equiv) . La mezcla de reacción se agitó a temperatura ambiente durante 24 horas. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con metanol y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Tabla 7:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructura de ejemplo
7a	97	3.2	496.4	
7b	99	3.32	469.4	
7c	99	3.49	439.4	

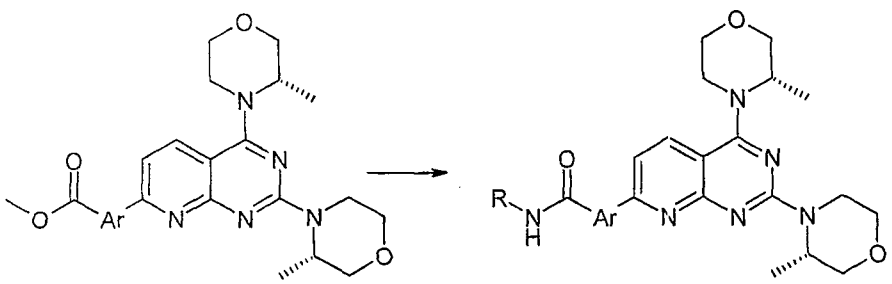
7d	99	3.51	453.4	
7e	99	3.58	465.4	
7f	97	3.53	509.4	
7g	98	3.61	479.4	
7h	99	3.56	483.4	
7i	95	3.86	491.4	

7j	98	3.46	482.4	
7k	99	3.54	467.4	

Probados en el Ensayo Enzimático Alternativo: Ej. (7a) 0.59μM; Ej. (7b) 0.13μM; Ej. (7c) 0.091μM; Ej. (7d) 0.097uM; Ej. (7e) 0.15μM; Ej. (7f) 0.12μM; Ej. (7g) 0.17μM; Ej. (7h) 0.33μM; Ej. (7i) 0.079μM; Ej. (7j) 0.12μM; Ej. (7k) 0.14μM.

Ejemplo 8

(Compuestos 8a a 8b)



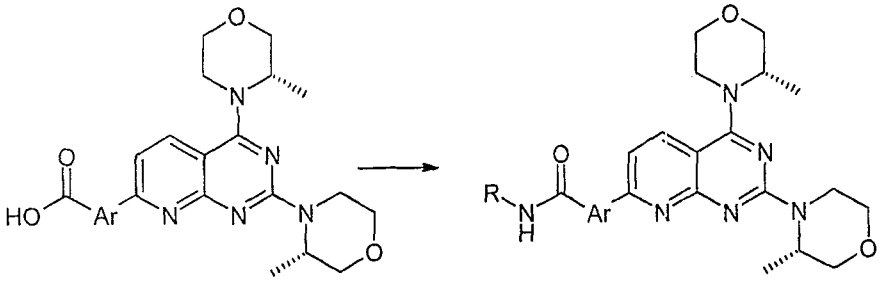
Los éster metilbenzóicos sustratos se reportaron en el Ejemplo 1.

Condiciones A:

El ejemplo lba (1 equiv) se disolvió en dioxano (0.16 M) . se agregó etanolamina (51.0 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 50 minutos. Al terminar, la mezcla de reacción se concentró al vacío. Luego el residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice utilizando un gradiente 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones B:

El ejemplo lbg (1 equiv) se disolvió en dioxano (0.05 M) . Se agregó etanolamina (2.0 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 2 X 20 minutos. Al terminar, la mezcla de reacción se concentró al vacío. La mezcla de reacción se particionó entre agua y CH_2Cl_2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. Luego el residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice utilizando un gradiente 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

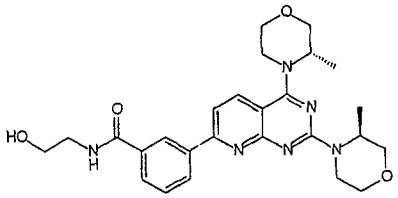
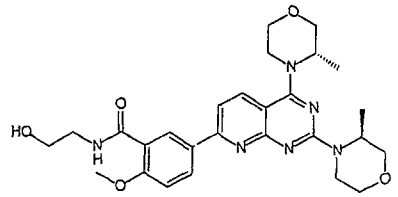
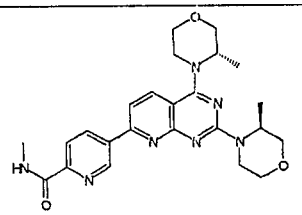
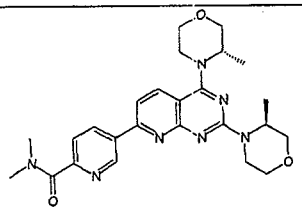


Condiciones C:

A una solución del derivado de ácido carboxílico apropiado (1 equiv) suspendido en CH_2Cl_2 se agregó HBTU (1.3 equiv) seguido por diisopropiletilamina (3 equiv) . La mezcla se enfrió (- 78 °C) y se agregó la amina apropiada (1.1 equiv) . La mezcla se agitó durante 3 hrs antes de ser concentrada hasta sequedad y purificada mediante HPLC preparativa para proporcionar el producto deseado.

Tabla 8:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo

8a	100	3.75	493.5	A	
8b	99	3.86	523.5	B	
8c	97	3.79	465.3	C	
8d	98	3.70	507.4	C	

Datos NMR para ejemplo 8a

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.55 (ArH, s, 1H) , 8.09 (ArH, d, J = 7.85 Hz, 1H) , 7.95 (ArH, d, J = 8.42 Hz, 1H) , 7.86 (ArH, d,J= 7.86 Hz, 1H) , 7.49- 7.33 (ArH, m, 2H) , 4.89- 4.75 (CH, m, 1H) , 4.56- 4.46 (CH, m, 1H) , 4.38- 4.26 (CH2, m, 1H) , 3.97- 3.87 (CH2, m, 2H) , 3.85-

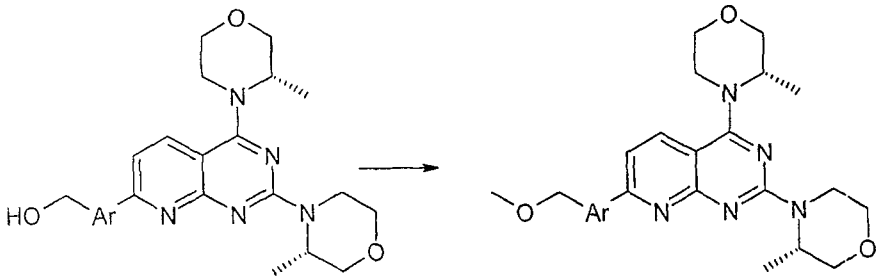
3.75 (CH2, m,4H) , 3.72- 3.55 (CH2, m, 7H) , 3.53- 3.44 (CH2, m, 1H) , 3.34- 3.24 (CH2, m, 1H) ,

1.41 (CH3, d, J= 6.77 Hz, 3H) , 1.28 (CH3, d, J = 6.82 Hz, 3H) .

Probados en el Ensayo Enzimático Alternativo: Ej. (8a) 0.028uM; Ej. (8b) 0.079uM; Ej. (8c) 0.13uM;Ej.(8d) 2μM.

Ejemplo 9

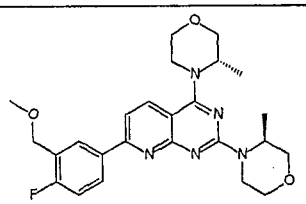
(Compuesto 9a)



El substrato de alcohol bencílico se reportó en el Ejemplo 1.

El ejemplo 1bc (1 equiv) se disolvió en THF (0.022 M) . Se agregó tert- butoxido de sodio (3.0 equiv) y yodometano (10.0 equiv) . El recipiente de reacción se agitó a temperatura ambiente durante 48 horas. Al terminar, la muestra fue filtrada a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

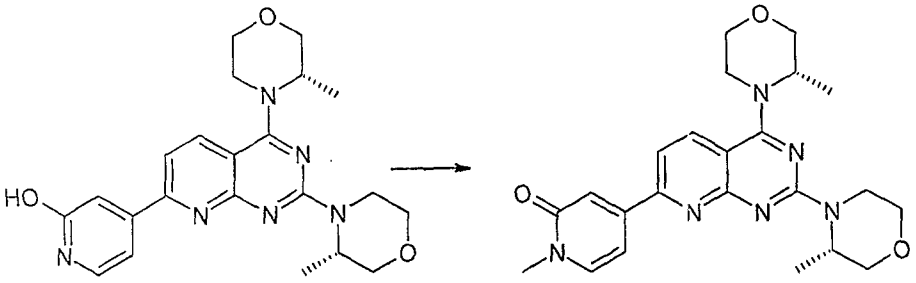
Tabla 9:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructura de ejemplo
9a	100	2.87	468.4	

Probado en el Ensayo Enzimático Alternativo: Ej. (9a) 0.088μM.

Ejemplo 10

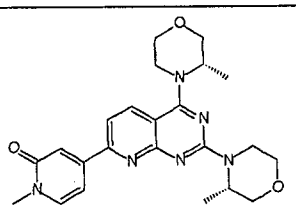
(Compuesto 10a)



El sustrato de piridinona se reportó en el Ejemplo 13.

El ejemplo 13c (1 equiv) se disolvió en DMF (0.1 M) . Se agregó carbonato de potasio (1.1 equiv) y yodometano (1.1 equiv) . El recipiente de reacción se agitó a 100°C durante 2 horas. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

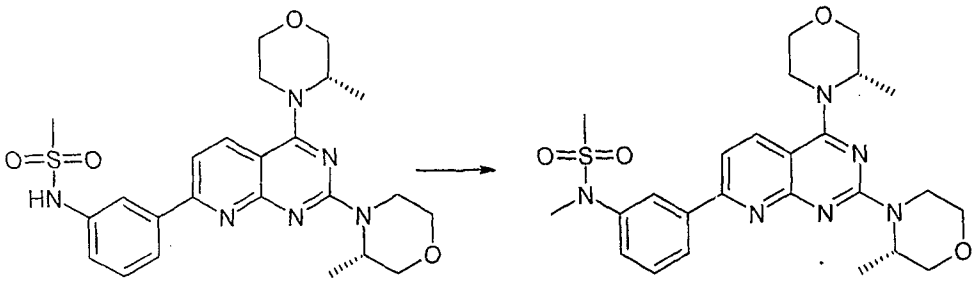
Tabla 10:

	Pureza (%)	Tiempo de retención (min)	m/z [M+Hf	Estructura de ejemplo
10a	100	3.67	437.2	

Probado en el Ensayo Enzimático Alternativo: Ej. (10a) 0.11 μM.

Ejemplo 11

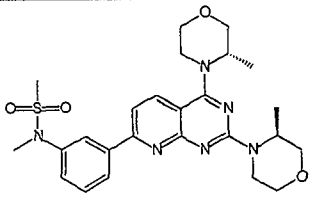
(Compuesto 11a)



El sustrato de sulfonamida se reportó en Ejemplo 1.

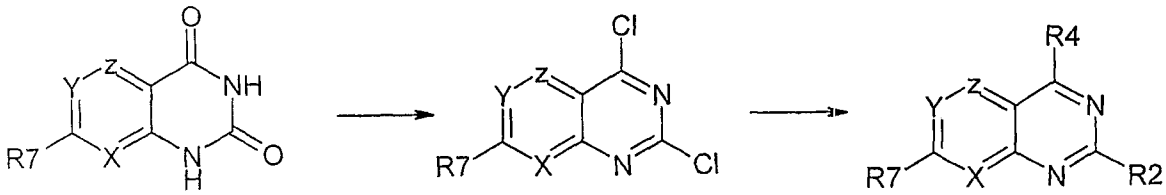
El Ejemplo lat (1 equiv) se disolvió en DMF (0.1 M) . Se agregó carbonato de potasio (2.0 equiv) y yodometano (1.5 equiv) . El recipiente de reacción se calentó a 100°C durante 2 horas. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Tabla 11:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructura de ejemplo
11a	87	4.11	513.3	

Probado en el Ensayo Enzimático Alternativo: Ej. (1 la) 0.37uM.

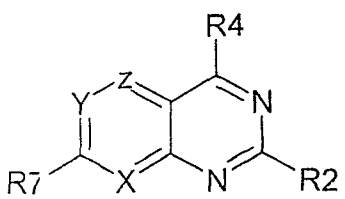
Ejemplo 12



A una solución de la 7- substituida- lH- pteridina- 2,4- diona apropiada (1 equiv) en tolueno anhidro (suficiente para preparar una solución 0.1 M) se agregó base Hunig (3 equiv) . Se fijo un condensador de reflujo al recipiente de reacción y la mezcla se calentó, bajo una atmósfera inerte a 70 °C durante 30 minutos. Después de este tiempo, la reacción se enfrió a 40 °C después de lo cual se agregó $POCl_3$ (3 equiv) . Luego la mezcla se calentó, con agitacion, a 110 °C durante 3 horas. Al terminar, la reacción fue enfriada y concentrada al vacío para proporcionar un residuo alquitranado el cual se disolvió en el volumen mínimo de CH_2Cl_2 y se filtró a través de almohadilla de sílice gruesa. El filtrado resultante se concentró al vacío para proporcionar el producto 2,4- dicloro- 7- substituido- pteridina deseado (típicamente 65- 99 % rendimiento) en forma apropiadamente pura para utilizar sin purificación adicional.

2.4- Dicloro- 7- p- tolil- pteridina;R7=toluilo, R2= Cl, R4=Cl, X=N, Y=C, Z=N: (61 % rendimiento, 99 % pureza) m/z (LC- MS, ESP) : No se ionizó, R/T = 3.27 min

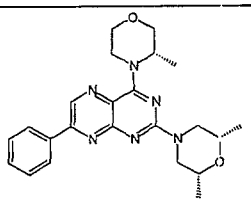
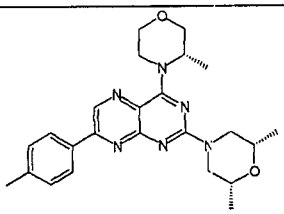
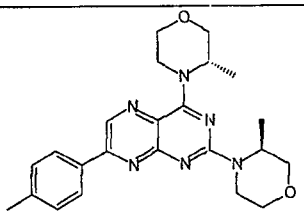
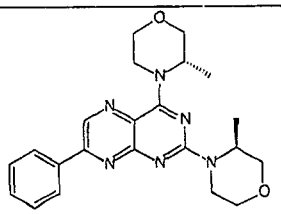
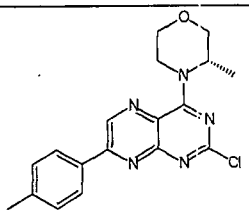
2.4- Dicloro- 7- fenil- pteridina; R7=fenilo, R2= Cl, R4=C1, X=N, Y=C, Z=N: (66 % rendimiento, 99 %pureza) m/z (LC- MS, ESP) : No se ionizó, R/T = 3.10 min



A una solución fria (- 5 °C) de la amina apropiada (1 equiv = R4) en N,N- dimetilacetamida (suficiente para preparar solución 0.2 M) se agregó la 2,4- dicloro- 7- substituida- pteridina apropiada (1 equiv agregada como una solución 0.04 M en N,N- dimetilacetamida) . Después de approx 10 minutos se agregó base Hunig (1 equiv) y la mezcla resultante se agitó a - 5 °C durante 30 minutos. Después de este tiempo, la reacción se dejo calentar a temperatura ambiente, después de lo cual se agregó la amina apropiada (1 equiv = R2) y la base Hunig (1 equiv) . La mezcla resultante se calentó a 60 °C y se mantuvo a esta temperatura, con agitacion, durante 16

horas. Al terminar, la mezcla se dejo enfriar a temperatura ambiente antes de ser purificada mediante HPLC preparativa para proporcionar el producto deseado.

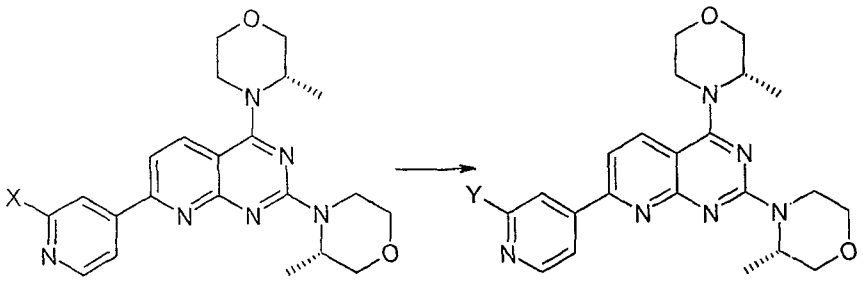
Tabla 12

	Pureza(%)	Tiempo de retención (min)	m/z [M+Hf	Estructura de ejemplo
12a	99	5.33	421.5	
12b	96	5.55	435.4	
12c	95	10.29	421.3	
12d	94	9.48	407.2	
12e	94	9.48	356.2	

Probados en el Ensayo Enzimático Alternativo: Ej. (12a) 0.02669uM; Ej. (12b) 0.2147uM; Ej. (12c) 0.04872uM; Ej. (12d) 0.0263uM; Ej. (12e) 0.5414uM.

Ejemplo 13

(Compuestos 13a a 13f)



Los substratos de pridina se reportaron en el Ejemplo 1.

Condiciones A:

El ejemplo lw (1 equiv) se disolvió en una solución de THF seco/metanol (1:1) (0.057 M). Se agregó hidruro de sodio (4.5 equiv). La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos bajo nitrógeno. El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 40 minutos. Al terminar la muestra se concentró al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones B:

El ejemplo lw (1 equiv) se disolvió en THF seco (0.057 M). Se agregó dimetiletanolamina (10.0 equiv) e hidruro de sodio (5.0 equiv). La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos bajo nitrógeno. El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 20 minutos. Al terminar, la muestra se concentró al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones C:

El ejemplo lau (1 equiv) se disolvió en DMSO (0.59 M). Se agregó solución acuosa 8N de hidróxido de sodio (50.0 equiv). El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 20 minutos. Al

terminar, se agregó cuidadosamente HCl acuoso concentrado. La mezcla se neutralizó con solución acuosa 2N de hidróxido de sodio. La suspensión se diluyó con metanol luego se filtró a través de un embudo sinterizado. El filtrado se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones D:

El E emplo lau (1 equiv) se disolvió en NMP (0.1 M) . Se agregó cianuro de potasio (20.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 46 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH2Cl2. La fase acuosa se extrajo con CH2Cl2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 50 a 100 % etilacetato en hexano para proporcionar el producto deseado.

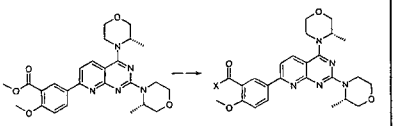
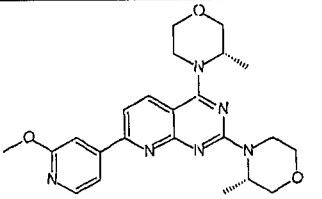
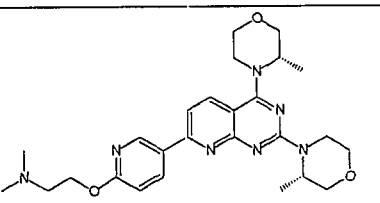
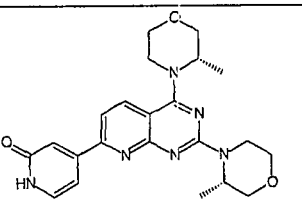
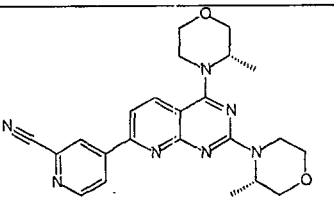
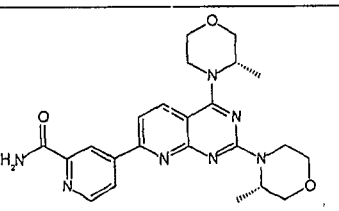
Condiciones E:

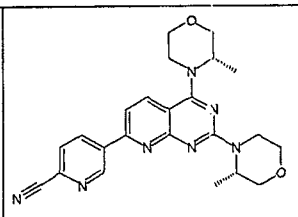
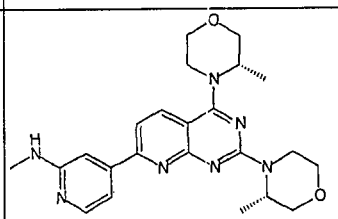
El ejemplo lau (1 equiv) se disolvió en NMP (0.1 M) . Se agregó cianuro de potasio (20.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 46 horas. Al terminar, la mezcla de reacción se particionó entre agua y CH_2Cl_2. La fase acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 50 a 100 % etilacetato en hexano primero, luego eluyendo con 10 % metanol en CH_2Cl_2. Luego las fracciones crudas fueron adicionalmente purificadas mediante HPLC preparativa para proporcionar el producto deseado.

Condiciones F:

El ejemplo lah (1 equiv) se disolvió en NMP (0.1 M) . Se agregó cianuro de potasio (8.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (180 °C, ambiente de absorción de medios) durante 40 minutos. Al terminar, la muestra fue filtrada a través de un cartucho de sílice, se lavó con EtOAc y luego se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Tabla 13

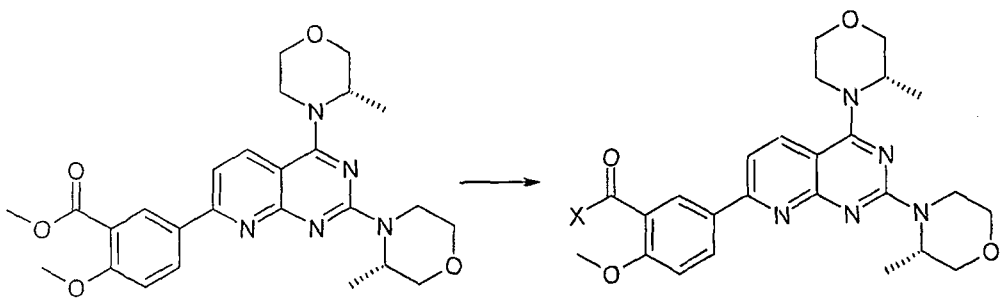
	Pureza (%)	Tiempo de retención(min)	m/z [M+Hf	Condiciones	Estructura de ejemplo
					
13a	99	4	437.3	A	
13b	99	3.42	494.4	B	
13c	97	5.77	423.4	C	
13d	97	3.96	432.4	D	
13e	98	6.62	450.2	E	

13f	99	3.93	432.3	F	
13g	89	5.03	478.4		

Probados en el Ensayo Enzimático Alternativo: Ej. (13a) 0.2uM; Ej. (13b) 0.33uM; Ej. (13c) 0.14uM; Ej. (13d) 0.48uM; Ej. (13e) 0.19uM; Ej. (13f) 0.16uM; Ej. (13g) 0.11μM.

Ejemplo 14

(Compuestos 14a- 14b)



El sustrato de éster se reportó en el Ejemplo 1.

Hidrolisis de éster:

Condiciones A

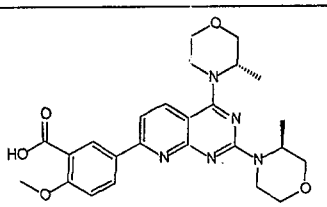
El ejemplo lbg (1 equiv) se disolvió en metanol (0.2 M) . Se agregó solución acuosa 1M de hidróxido de sodio (5.0 equiv) . La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Al terminar, la mezcla de reacción fue neutralizada con 1M HCl acuoso y concentrada al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 10 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

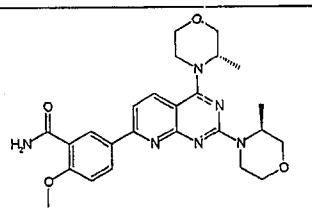
Formación de amidas:

Condiciones B

El ejemplo lbg (1 equiv) se suspendió en THF (0.05 M) . Se agregó cloruro de tionilo (2.5 equiv) por goteo a 40°C. La mezcla de reacción se calentó durante 1 hora a 40°C. Luego se burbujeó gas de amoniaco lentamente en la mezcla de reacción. Luego se agregó THF para dilución adicional (0.025 M) y la mezcla de reacción se calentó durante una hora a 40°C. Al terminar, la mezcla de reacción fue enfriada y concentrada al vacío. El residuo se particionó entre agua y CH_2Cl_2. La fase acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Tabla 14:

	Pureza (%)	Tiempo de retencion (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
14a	98	3.95	480.5	A	

14b	98	7.09	479.4	B	

Datos NMR para ejemplo 14a

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.82- 8.69 (ArH, m, 1H) , 8.68- 8.56 (ArH, m, 1H) , 8.03- 7.90 (ArH, m, 1H) , 7.52- 7.39 (ArH, m, 1H) , 7.18- 7.05 (ArH, m, 1H) , 4.92- 4.80 (CH, m, 1H) , 4.61- 4.47 (CH, m, 1H) , 4.37- 4.27 (CH2, m, 1H) , 4.07 (OCH3, s, 3H) , 4.00- 3.87 (CH2, m, 2H) .

3.85- 3.60 (CH2, m, 6H) , 3.57- 3.24 (CH2, m, 3H) , 1.41 (CH3, d, J = 6.65 Hz, 3H) , 1.30 (CH3, d,J=6.74Hz,3H)

^{13}CNMR(75 MHz, CDC13) δppm 165.33, 134.98, 134.96, 132.64, 132.61, 132.58, 119.77, 112.83, 112.11, 100.01, 71.29, 70.90, 67.24, 66.91, 52.80, 46.96, 44.44, 39.34 y 14.74.

Datos NMR para ejemplo 14b

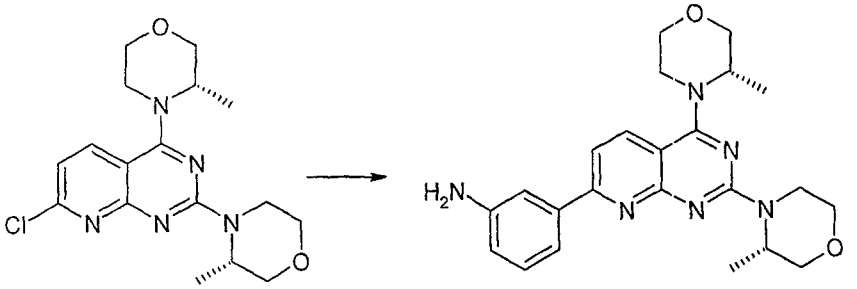
^{1}H NMR (300 MHz, CDC13) δ ppm 8.83 (ArH, d, J = 2.46 Hz, 1H) , 8.64 (ArH, dd, J = 8.76, 2.49 Hz, 1H) , 8.01 (ArH, d, J = 8.47 Hz, 1H) , 7.71 (NH, s, br, 1H) , 7.57 (ArH, d, J = 8.50 Hz, 1H) , 7.13 (ArH, d, J= 8.83 Hz, 1H) , 5.79 (NH, s, br, 1H) , 5.00- 4.84 (CH, m, 1H) , 4.62 (CH, dd, J- 13.82, 0.70 Hz, 1H) , 4.37 (CH2, d, J= 6.77 Hz, 1H) , 4.05 (OCH3, s, 3H) , 4.03- 3.94 (CH2, m,2H) , 3.91- 3.79 (CH2, m, 3H) , 3.79- 3.63 (CH2, m, 4H) , 3.64- 3.51 (CH2, m, 1H) .

3.44- 3.30 (CH2, m, 1H) , 1.47 (CH3, d, J= 6.78 Hz, 3H) , 1.35 (CH3, d, J= 6.81 Hz, 3H)

13CNMR(75 MHz, $CDCl_3$) δ ppm 166.58, 165.45, 162.87, 159.99, 159.22, 134.71, 133.75, 131.84, 131.65, 120.52, 113.07, 111.87, 104.80, 102.94, 71.33, 70.94, 67.29, 66.94, 56.28, 52.80, 46.93, 44.49, 39.33, 14.72 y 14.34.

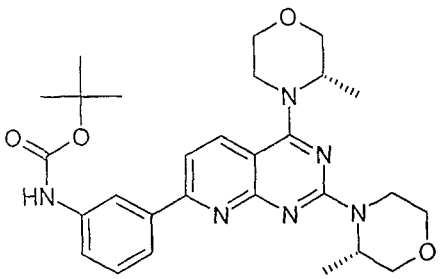
Probados en el Ensayo Enzimático Alternativo: Ej. (14a) 0.00015uM; Ej. (14b) 0.0032uM.

Ejemplo 15



El cloro- substrato se reportó en el Ejemplo 1.

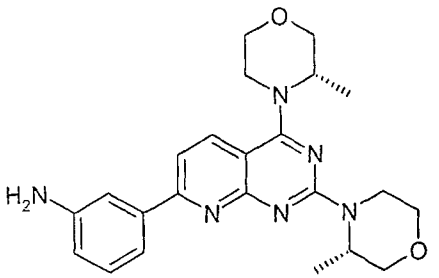
A una mezcla de 7- cloro- 4- ((S) - 3- metil- morfolin- 4- il) - 2- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidina (1 equiv) , carbonato de potasio (1.2 equiv) , y ácido 3- BOC- aminofenilborónico (1.2 equiv) en acetonitrilo/agua (1:1) (0.08 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 10 minutos bajo atmósfera de nitrógeno. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con con etilacetato y luego se concentraron al vacío. El residuo crudo se utilizó como tal en la siguiente reacción.



Ester tert- butílico de ácido {3- [2,4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- fenil}- carbámico: (95 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 520.9 [M+H]+ R7T = 3.23 min

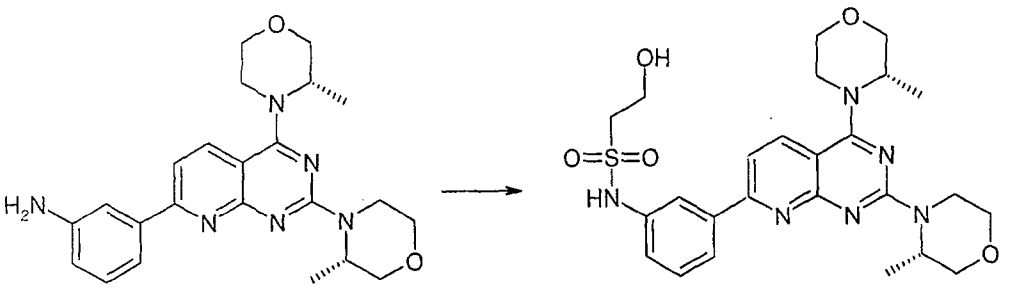
El producto anterior (1 equiv) se disolvió en una solución TFA/ CH_2Cl_2 (1:20) (0.018 M) . La mezcla de reacción se agitó a temperatura ambiente durante 15 horas. La mezcla de reacción luego se concentró al vacío. El residuo se particionó entre agua y CH_2Cl_2. La fase acuosa se neutralizó con hidróxido de sodio acuoso 1N. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y concentraron al vacío. El residuo crudo se utilizó como tal en la siguiente

reacción.

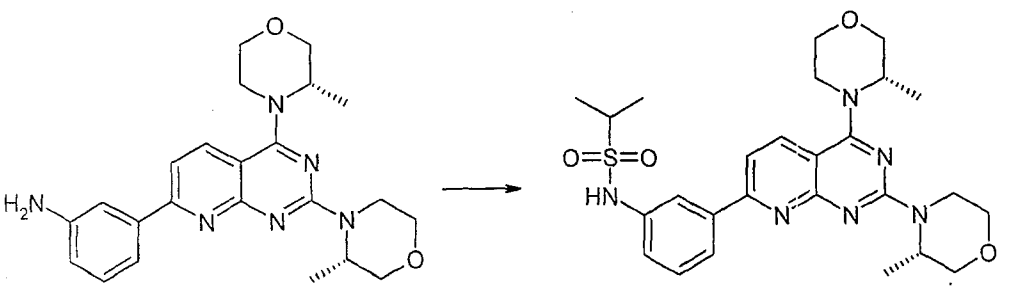


3- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- fenilamina: (100 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 520.9 [M+H]+ R/T = 2.72 min

(Compuesto 15a)

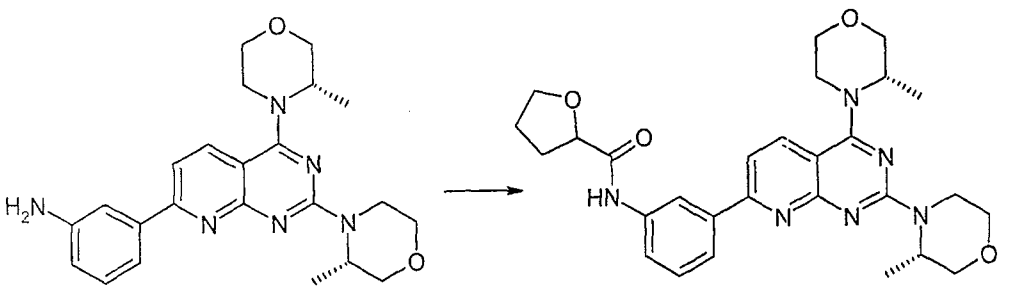


El producto anterior (1 equiv) se disolvió en THF (0.013 M) . Se agregó suavemente cloruro de cloroetanosulfonilo (3.5 equiv) a la mezcla de reacción a 0°C y la mezcla de reacción se agitó a temperatura ambiente durante 15 horas. Luego se agregó hidróxido de sodio acuoso (50 equiv) y la mezcla de reacción se calentó a 40°C durante 12 horas. La mezcla de reacción se concentró al vacío. El residuo crudo se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 a 5 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.



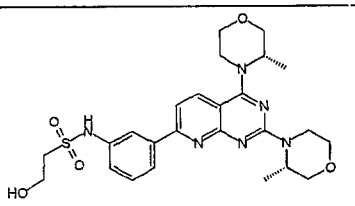
3- [2,4- Bis- ((S) - 3 - metil- morfolin- 4- il) - pirido [2,3 - d]pirimidin- 7- il]- fenilamina (1 equiv) se disolvió en THF (0.1 M) . Se agregó piridina (10 equiv) y cloruro de isopropilsulfonilo

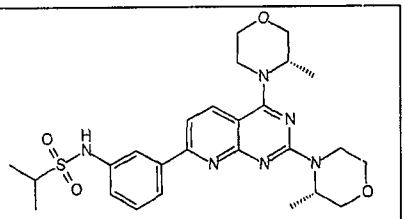
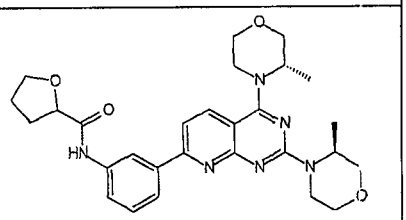
(10 equiv) a la mezcla de reacción a temperatura ambiente. Luego la mezcla de reacción seagitó a 90°C durante 4 horas. La mezcla de reacción se particionó entre CH_2Cl_2 y agua. La fase orgánica se secó ($MgSO_4$) , filtró y concentró al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 60 % EtOAc en hexano para proporcionar el producto deseado.



3- [2.4- Bis- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- fenilamina equiv) se disolvió en CH_2Cl_2 (0.24 M) . Se agregó ácido tetrahidro- 2- furóico (1.1 equiv) , HBTU (2.0 equiv) y trietilamina (2 equiv) y luego la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se particionó entre CH_2Cl_2 y agua. La fase orgánica se secó (MgSO4) , filtró y concentraró al vacío. El residuo crudo se purificó mediante cromatografia en columna sobre gel de sílice eluyendo con 0 a 4 % MeOH en TBME para proporcionar el producto deseado.

Tabla 15

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructuras de ejemplo
15a	98	3.99	529.4	

15b	96	8.28	527.3	
15c	99	4.19	519.3	

^{1}HNMR(300 MHz) , $CDCl_3$ δ ppm 8.00- 7.94 (ArH, m, 2H) , 7.81 (ArH, td,J = 7.12,1.52, 1.52 Hz, 1H) , 7.45- 7.32 (ArH, m, 3H) , 6.84 (NH, s, br, 1H) , 4.93- 4.80 (CH2, m, 1H) , 4.55 (CH2, d, J= 12.97 Hz, 1H) , 4.38- 4.25 (CH2, m, 1H) , 4.01- 3.57 (CH2, m, 9H) , 3.57- 3.45 (CH2, m, 1H) , 3.36- 3.32 (CH2,m,2H) , 1.42 (CH3, d,J= 6.78 Hz, 3H) , 1.37- 1.26 (3 XCH3,m, 9H)

^{13}CNMR(75 MHz, CDC13) δ ppm 165.36, 162.85, 161.36,159.98,140.27,137.89,134.92, 129.80,124.03,121.31,119.64,113.30,105.19, 71.28, 70.91, 67.25, 66.91, 52.89, 52.87, 44.42, 39.33, 31.60,22.66,16.60, 14.75 o 14.36.

Datos NMR para ejemplo 15c

^{1}H NMR (300 MHz, $CD3COCD_3$ δ ppm 8.52 (ArH, s, 1H) , 8.24 (ArH, d, J = 8.48 Hz, 1H) , 7.91- 7.80 (ArH, m, 2H) , 7.62 (ArH, d, /= 8.47 Hz, 1H) , 7.46 (ArH, t,J= 7.94, 7.94 Hz, 1H) , 6.48 (NH, br, s, 1H) , 4.84- 4.70 (CH2, m, 1H) , 4.53- 4.33 (CH2, m, 3H) , 4.09- 3.79 (CH2, m, 5H) , 3.80- 3.56 (CH2, m, 5H) , 3.49- 3.40 (CH2, m, 1H) , 3.23 - 3.28 (CH2, m, 1H) , 2.20 (CH2,

d, J=6.66 Hz, 1H) , 2.11- 1.81 (CH2,m,4H) , 1.39 (CH3, d,J= 6.75 Hz, 3H) , 1.26(CH3,d, J = 6.75 Hz, 3H) .

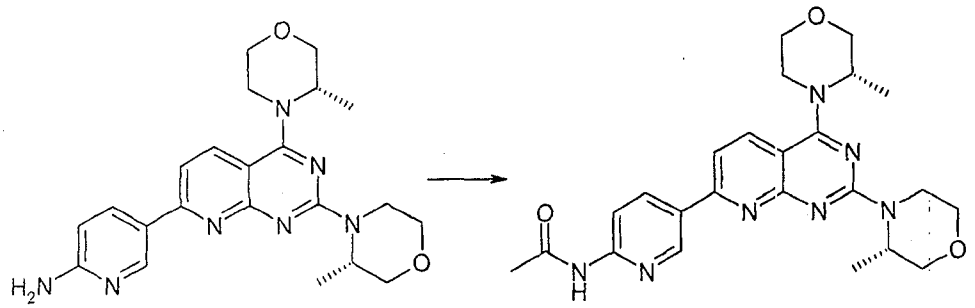
^{13}CNMR(75 MHz, CD3COCD3) δ ppm 171.66, 160.37, 147.37, 145.71, 138.93, 138.46, 135.69, 128.98, 126.26, 126.11, 122.52, 121.58, 118.91, 118.37, 104.46, 77.93, 70.31, 70.13, 68.81, 66.28, 66.15, 51.77, 46.41, 43.85, 29.98, 25.06, 14.39 y 13.92.

Probados en el Ensayo Enzimático Alternativo: Ej. (15a) 0.0043uM; Ej. (15c) 0.33uM.

Probados en ensayo phospho- Ser473 Akt: Ej. (15b) 0.5051 μM.

Ejemplo 16

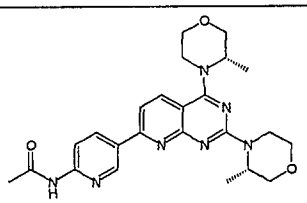
(Compuesto 16a)



El sustrato de aminopiridina se reportó en el Ejemplo 1.

El Ejemplo 1u (1 equiv) se disolvió en piridina (0.11 M) . Se agregó anhídrido acético (5.0 equiv) y la mezcla de reacción se calentó a 70°C durante 6 horas. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

Tabla 16:

	Pureza (%)	Tiempo de retención (min)	m/z [M+Hf	Estructura de ejemplo
16a	100	3.8	464.4	

Datos NMR para ejemplo 16a

^{1}H NMR (300 MHz,CDCl3) δ ppm 8.18- 8.12 (ArH, m, 2H) , 8.05 (ArH, d, J = 8.42 Hz, 1H) , 7.52- 7.40 (ArH, m, 3H) , 4.96 (CH, d, br, J = 4.93 Hz, 1H) , 4.66 (CH, d, br, J= 12.90 Hz, 1H) , 4.40 (d, br, J = 6.71 Hz, 1H) , 4.07- 3.54 (CH2, m, 11H) , 3.47- 3.35 (CH, m, 1H) , 1.51

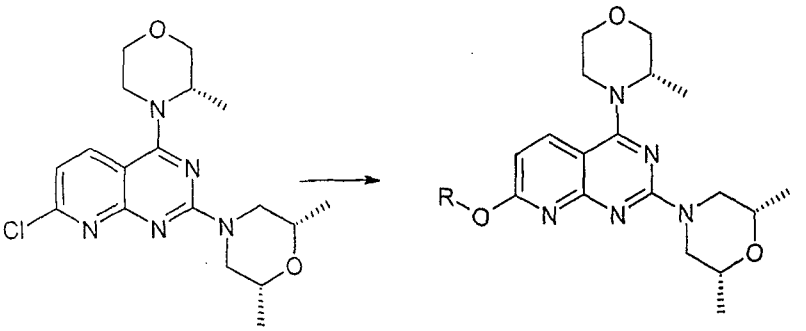
(CH3, d, J = 6.79 Hz, 3H) , 1.39 (CH3, d, J = 6.82 Hz, 3H)

^{13}CNMR(75 MHz, CDC13) δ ppm 165.41, 162.93, 161.83,160.02, 137.14,136.13,134.84, 129.19, 128.77, 112.99,105.03, 71.29, 70.91, 67.26, 66.91, 52.85, 46.95, 44.46, 39.34, 14.73 y 14.37.

Probados en el Ensayo Enzimático Alternativo: Ej. (16a) 0.034) μM.

Ejemplo 17

(Compuesto 17a)

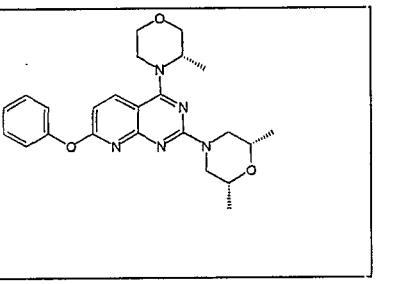


El cloro- substrato se reportó en Ejemplo 1.

El cloro- sustrato apropiado (1 equiv) se disolvió en tolueno (0.07 M) . Se agregó fenol (1.0 equiv) , acetato de paladio (0.05 equiv) , BINAP (0.05 equiv) y fosfato de tripotasio (1.0 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar, la muestra se concentró al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar el producto deseado.

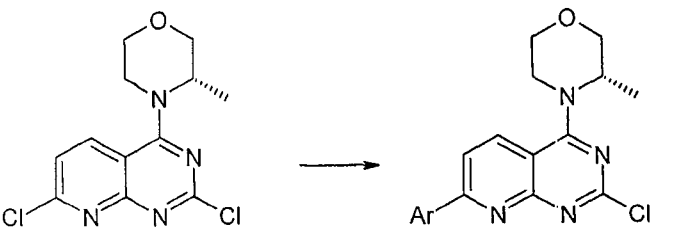
Tabla 17:

	Pureza(%)	Tiempo de retencion(min)	m/z $[M+H]^+$	Estructura de ejemplo

17a	93	4.70	436.4	

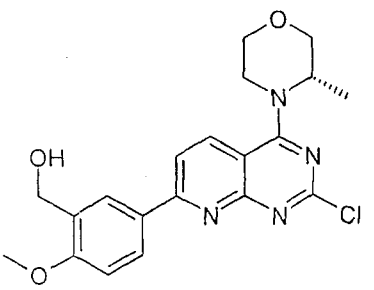
Probados en el Ensayo Enzimático Alternativo: Ej. (17a) 0.52uM.

Ejemplo 18



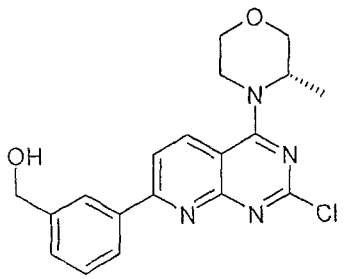
El cloro- substrato se reportó en Ejemplo 1.

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , y el ácido borónico apropiado (1.1 equiv) en acetonitrilo/agua (1:1) (0.033 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . La suspensión se sonicó mientras se degasificó con nitrógeno durante 5 minutos luego se calentó a 95 °C durante 2 horas. Al terminar, la mezcla de reacción se dejo enfriar a temperatura ambiente. La mezcla de reacción se concentró al vacío a volumen original medio. El residuo crudo se extrajo con CH_2Cl_2 y las fases orgánicas combinadas se lavaron con salmuera, secaron (MgSO4) , filtraron y concentraron al vacío para proporcionar un sólido amarillo. El residuo fue sonicado en éter dietílico, recolectado mediante filtración al vacío para proporcionar el producto deseado como un polvo amarillo.



{5- [2- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi-

fenil}- metanol: (78 % rendimiento, 100 % pureza) m/z (LC- MS, ESP) : 401 $[M+H]^+$ R/T = 3.47 min



{ 3 - [2- Cloro- 4- ((S) - 3 - metil- morfolin- 4- il) - pirido [2,3 - d]pirimidin- 7- il]- fenil} - metanol: (90 % rendimiento, 90 % pureza) m/z (LC- MS, ESP) : 371 [M+H]+ R/T = 4.06 min

Alternativamente, a una mezcla agitada de bis(pinacolato) diboro (1.05 equiv) y acetato potásico (3 equiv) en N- metilpirrolidina (13.5 equiv) , purgada con nitrógeno, se agregó el alcohol bromobencílico correspondiente (1 equiv) seguido por $PdCl_2(dppf)$ (0.02 equiv) . Luego la mezcla se calentó a 60 °C y se mantuvo durante 10 min, luego se calentó a 70 °C y se mantuvo durante 15min y finalmente se calentó a 80 °C y se mantuvo durante 1h. Luego se agregó el cloro- sustrato apropiado (1 equiv) seguido por $PdCl_2(dppf)$ (0.02 equiv) y N- metilpirrolidina (4.5 equiv) . Luego la temperatura se mantuvo a 75 °C, luego se agregó 4.3M carbonato de potasio acuoso (3.5 equiv) durante 13min, luego se agregó agua (12 equiv) y la reacción se agitó a 75 °C durante 90min. Luego se agregó agua (144 equiv) lentamente durante 70min con agitacion mientras la temperatura se redujo a 66 °C. Luego la temperatura de la mezcla agitada se mantuvo a 64 °C durante 30min, luego se enfrió a 20 °C durante 2.5h, y se mantuvo a 20 °C durante la noche. La pasta aguada resultante fue filtrada, y el sólido lavado primero con una mezcla 3:1 agua:N- metilpirrolidona (18 equiv de agua) , luego lavado con agua (24 equiv) y luego lavado con etilacetato (4 x 4.4equiv) . Luego el sólido se secó en un horno de vacío a 50 °C para dejar el compuesto del título en una forma limpia apropiada para utilizar sin purificación adicional. Por ejemplo, {5- [2- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- 2- metoxi- fenil}- metanol: (73 % rendimiento)

(Compuestos 18a a 18do)



Condiciones A:

El cloro- sustrato apropiado (1 equiv) se disolvió en DMA (0.04 M) . Luego se agregó fosfato de tripotasio (1.5 equiv) y el nucleofilo apropiado (amina secundaria) (1.5 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (200 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones B:

El cloro- sustrato apropiado (1 equiv) se suspendió en una solución de propan- 2- ol y amoniaco acuoso (1:3) (0.02 M) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 20 minutos. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones C:

El cloro- sustrato apropiado (1 equiv) se disolvió en dioxano (0.04 M) .
Luego se agregó diisopropiletilamina (5.0 equiv) y el nucleofilo apropiado (amina secundaria) (1.5 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 20 minutos. Al terminar, las muestras se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones D:

El cloro- sustrato apropiado (1 equiv) se disolvió en dioxano (0.04 M) . Luego se agregó fosfato de tripotasio (3.0 equiv) , xantfos (0.05 equiv) , acetato de paladio (0.05 equiv) y el nucleofilo apropiado (amina) (1.5 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 20 minutos. Al

terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones E:

El cloro- sustrato apropiado (1.0 equiv) se disolvió en dioxano (0.04 M) . Luego se agregó diisopropiletilamina (5.0 equiv) y el nucleofilo apropiado (amina secundaria, con cadena lateral amino BOC- protegido) (1.5 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 20 minutos. Al terminar, las muestras se concentraron al vacío. Luego se agregó al residuo crudo una solución 4 M de HCl en dioxano (0.15 M) .las mezclas de reacción se agitaron a temperatura ambiente durante 3 horas. Al terminar, la muestras se alcalinizaron con una solución de hidróxido de sodio 2N. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones F:

El nucleofilo apropiado (imidazol sustituido) (10.0 equiv) se disolvió en DMF (0. 4 M) . Luego se agregó hidruro de sodio (5.0 equiv) . La mezcla de reacción se agitó a temperatura ambiente durante 10 minutos bajo nitrógeno y se agregó una solución del cloro- sustrato apropiado (1.0 equiv) en DMF (0.075 M) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, eluyeron con CH_2Cl_2 y luego se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones G:

El cloro- sustrato apropiado (1 equiv) se disolvió en dioxano (0.04 M) . Luego se agregó diisopropiletilamina (5.0 equiv) y el nucleofilo apropiado (amina secundaria) (4.5 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 40 minutos. Al terminar, las muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos

deseados.

Condiciones H:

El cloro- sustrato apropiado (1 equiv) se disolvió en dioxano (0.04 M) . Luego se agregó diisopropiletilamina (5.0 equiv) y el nucleofilo apropiado (amina secundaria) (10.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 60 minutos. Al terminar, las muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones I:

El cloro- sustrato apropiado (1 equiv) se disolvió en una solución de DMA al 1% en dioxano (0.04 M) . Luego se agregó diisopropiletilamina (5.0 equiv) y el nucleofilo apropiado (amina secundaria) (10.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (180 °C, ambiente de absorción de medios) durante 60 minutos. Al terminar, las muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones J:

El cloro- sustrato apropiado (1 equiv) se disolvió en una solución de DMA al 1% en dioxano (0.04 M) . Luego se agregó diisopropiletilamina (7.0 equiv) y el nucleofilo apropiado (amina secundaria) (3.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 60 minutos. Al terminar, las muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones K:

El cloro- sustrato apropiado (1 equiv) se disolvió en DMF (0.075 M) . Luego se agregó carbonato de potasio (5.0 equiv) y el nucleofilo apropiado (alcohol) (10.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (120 °C, ambiente de absorción de medios) durante 20 minutos. Al terminar, las muestras se concentraron al vacío.

Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones L:

El cloro- sustrato apropiado (1 equiv) se disolvió en DMF (0.075 M) . Luego se agregó carbonato de potasio (5.0 equiv) y el nucleofilo apropiado (alcohol) (20.0 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 40 minutos. Al terminar, la muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones M:

El cloro- sustrato apropiado (1 equiv) se disolvió en DMA (0.13 M) . Luego se agregó diisopropiletilamina (2.0 equiv) y el nucleofilo apropiado (amina) (2.0 equiv) . El recipiente de reacción se calentó a 100 °C durante 3 horas. Al terminar, la mezcla de reacción se particionó entre diclorometano y agua y la capa acuosa se extrajo adicionalmente con diclorometano. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y el filtrado se concentró al vacío para proporcionar un residuo amarillo el cual se purificó mediante recristalización a partir de éter dietílico.

Condiciones N:

5- [2- Cloro- 4- ((S) - 3- metil- morfolin- 4- il) - pirido[2,3- d]pirimidin- 7- il]- piridin- 2- ilamina (1 equiv) se disolvió en DMA (0.21 M) . Luego se agregó diisopropiletilamina (1.0 equiv) y el nucleofilo apropiado (amina) (1.1 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar, la mezcla de reacción se particionó entre diclorometano y agua y la capa acuosa se extrajo adicionalmente con CH_2CL_2. Las fases orgánicas combinadas se secaron (MgSO4) , filtraron y el filtrado se concentró al vacío para proporcionar un residuo amarillo el cual se purificó mediante cromatografía en columna sobre gel de sílice eluyendo con 0 % a 10 % MeOH en CH_2Cl_2 para proporcionar el producto deseado.

Condiciones O:

El cloro- sustrato apropiado (1 equiv) se disolvió en DMA (0.16 M) . Luego se agregó diisopropiletilamina (1.0 equiv) y el nucleofilo apropiado (amina) (1.2 equiv) . El recipiente de reacción se calentó a 80 °C durante 48 horas. Al terminar, la mezcla de reacción se particionó entre etilacetato y agua y la capa orgánica se lavó con salmuera. Las fases orgánicas combinadas se secaron ($MgSO_4$) , filtraron y el filtrado se concentró al vacío para proporcionar un residuo el cual se purificó mediante HPLC preparativa para proporcionar el producto deseado.

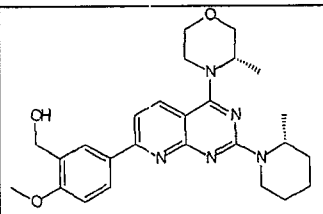
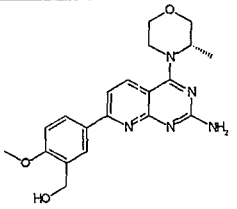
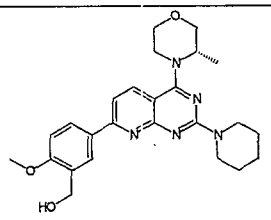
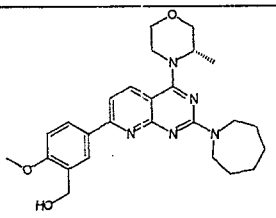
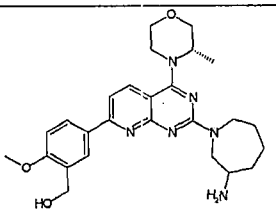
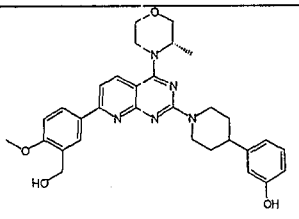
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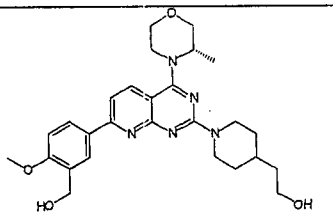
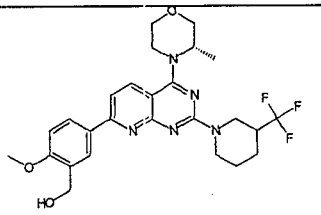
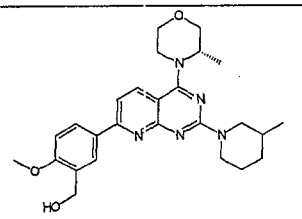
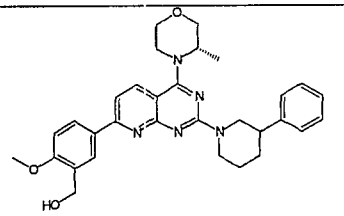
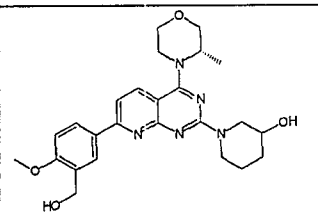
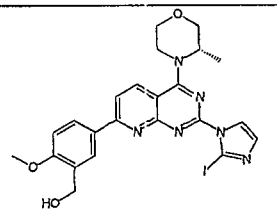
El cloro- sustrato apropiado (1 equiv) se disolvió en Anisol (0.25 M) (10 vol) . Luego se agregó diisopropiletilamina (1.3 equiv) y el nucleofilo apropiado (amina) (1.3 equiv) . El recipiente de reacción se calentó a 125 °C y agitó durante 1 1h. Al terminar, la mezcla de reacción se dejo enfriar a 50 °C. Se agregó solución de ácido cítrico al 20% (7 vol) , se agitó durante 5min y luego se dejo separar particionada. La capa acuosa fue retirada y retenida. Luego la capa orgánica fue extraida con una alícuota adicional de solución acuosa de ácido cítrico al 20% (3 vol) . La capa orgánica se descartó y las capas acuosas se combinaron. Las capas acuosas combinadas se lavaron primero con Anisol (5 vol) , luegose agregó lentamente solución acuosa de hidróxido de sodio al 50% (1.23 vol) . La fase acuosa resultante se extrajo con etilacetato (10 vol) . La capa acuosa se descartó y la capa orgánica se lavó primero con solución acuosa de hidróxido de sodio al 10% (5 vol) y luego agua (5 vol) . Luego la capa orgánica fue luego aguada con un depurador (*depurador*) de siliciclo Si- tiourea a 50 °C durante 2h, luego el depurador se filtró y lavó con etilacetato (2x1 vol) . La fase orgánica fue enfriada a 20 °C, sembrada para comenzar cristalización y agitada hasta obtener una pasta aguada. La pasta aguada se calentó a 50 °C al vacío y el etilacetato (3 vol) se retiró mediante destilación al vacío. Se agregó 2- metilpentano (3.4vol) y la mezcla se calentó a 60 °C y luego se enfrió lentamente a 20 °C durante 2h. La pasta aguada resultante fue filtrada, y el sólido se lavó con 1:1 etilacetato:pentano (2 x 0.5vol) . Luego el sólido se secó en un horno de vacío a 50 °C para dejar el producto deseado. Por ejemplo, se obtuvo el compuesto 1a (50.4% rendimiento) . El producto crudo (1 equiv) se disolvió en DMSO (5 vol con base en el peso del producto) a 50 °C. Se agregó agua (2 vol) y la mezcla agitó a 50 °C hasta cristalizar el producto. La pasta aguada se calentó a 60 °C y luego se agregó agua (3vol) lentamente durante 30 min manteniendo la temperatura a 60 °C. La mezcla se enfrío lentamente a

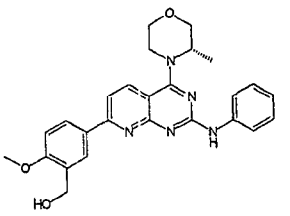
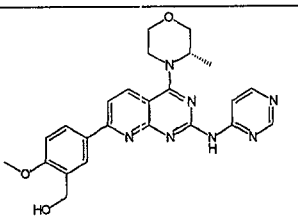
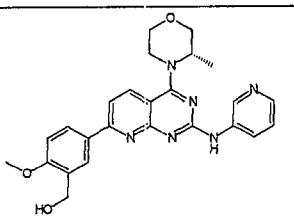
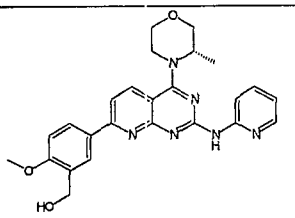
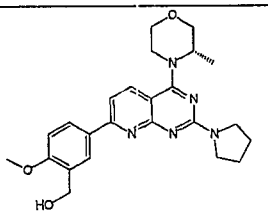
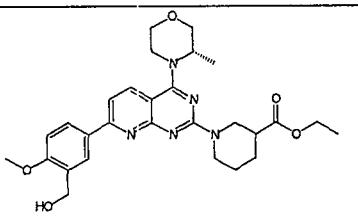
20 °C durante 2h, y luego se mantuvo a 20 °C durante 30min. La pasta aguada resultante fue filtrada, y el sólido fue lavado con 2:1 agua: DMSO (0.5:1 vol) , y luego agua (3 x 2vol) . Luego el sólido fue secado en un horno de vacío a 50 °C para dejar el producto deseado.

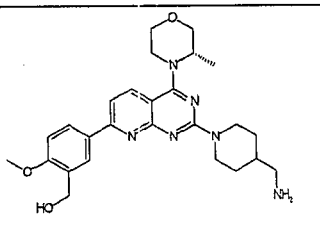
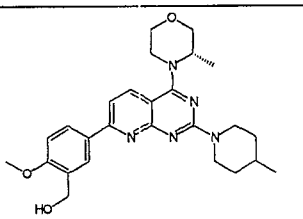
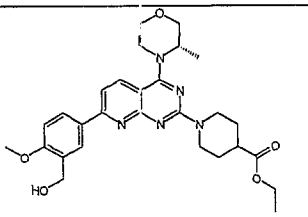
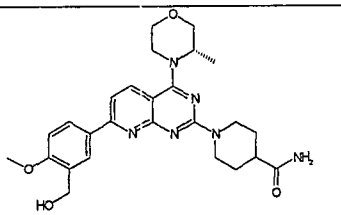
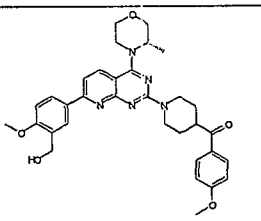
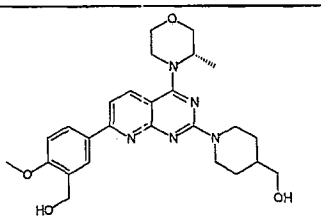
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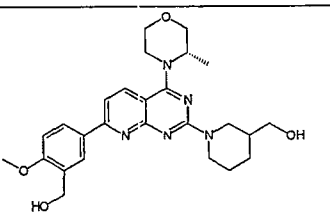
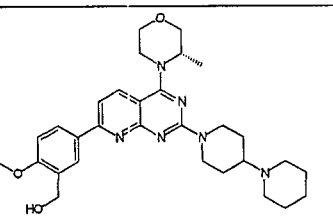
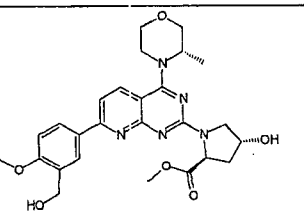
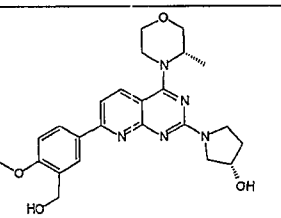
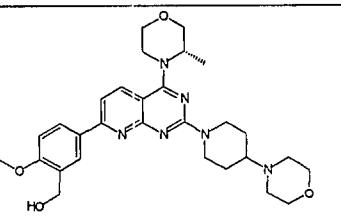
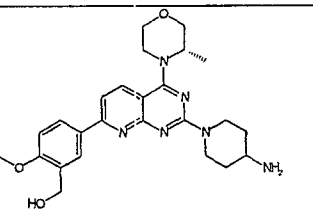
	Pureza (%)	Tiempo de retención(min)	m/z [M+Hf	Condiciones	Estructura de ejemplo

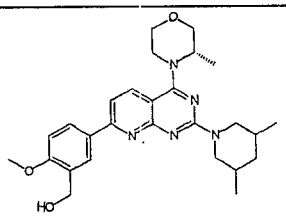
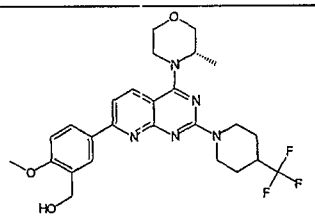
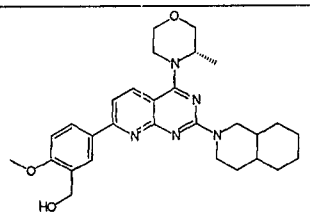
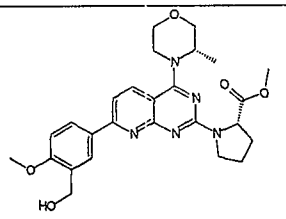
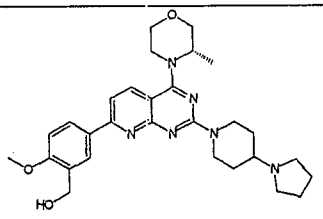
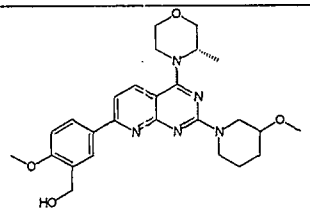
18a	91	4.43	464.5	A	
18b	98	3.89	382.4	B	
18c	96	4.36	450.4	C	
18d	97	4.48	464.4	C	
18e	93	3.56	479.4	C	
18f	97	4.45	542.4	C	

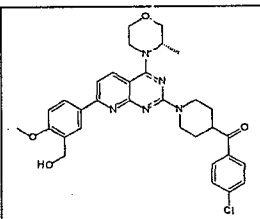
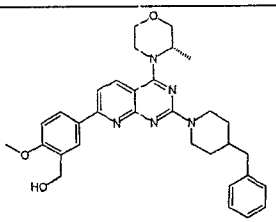
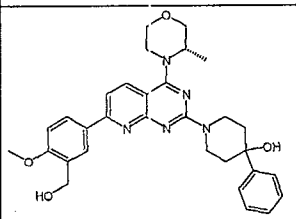
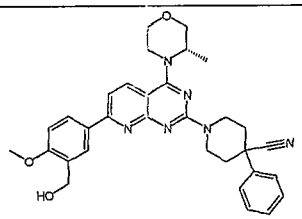
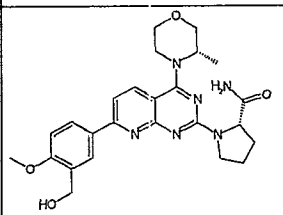
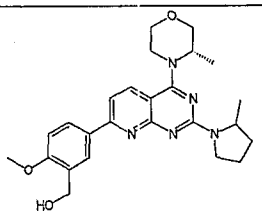
18g	97	4.11	494.4	C	
18h	98	4.60	518.4	**C**	
18i	96	4.54	464.4	**C**	
18j	98	4.83	526.4	**C**	
18k	93	3.96	466.4	**C**	
181	79	8.73	559.5	D	

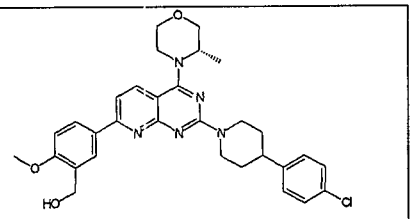
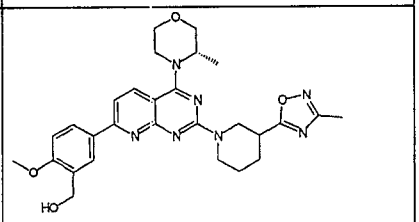
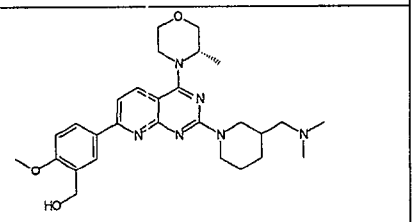
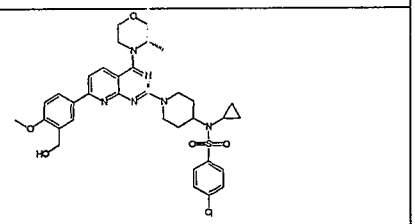
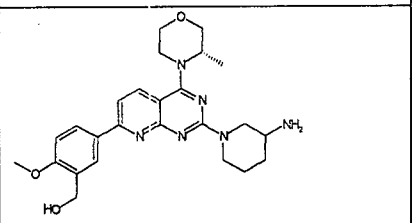
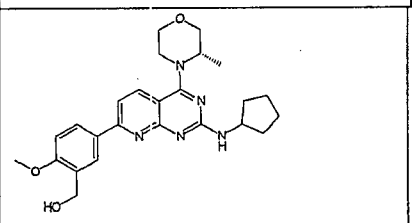
18m	94	4.28	458.5	D	
18n	99	3.86	460.5	D	
18o	92	6.48	459.3	D	
18p	91	9.79	459.3	D	
18q	91	8.03	436.3	C	
18r	86	8.77	522.4	C	

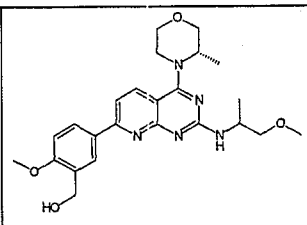
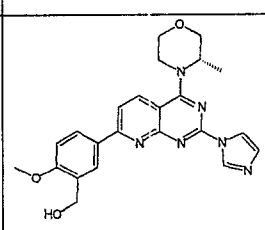
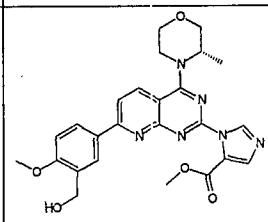
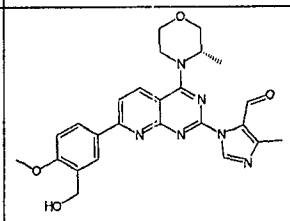
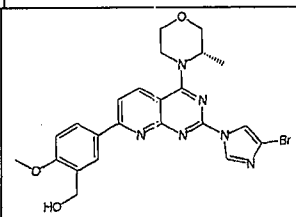
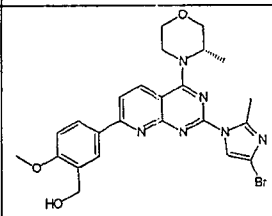
18s	81	5.59	479.4	C	
18t	88	9.14	464.4	C	
18u	91	8.76	522.4	**c**	
18v	92	6.73	493.4	**c**	
18w	87	9.69	584.5	**c**	
18x	80	7.26	480.4	C	

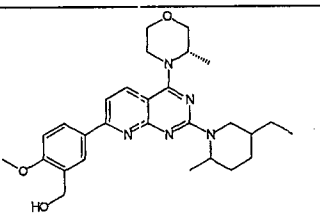
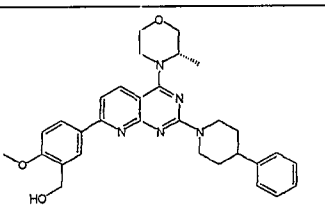
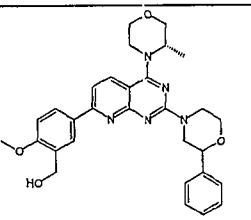
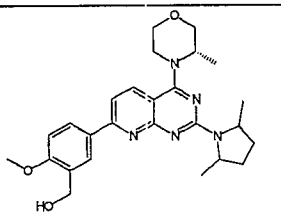
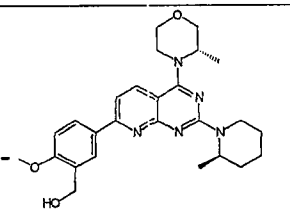
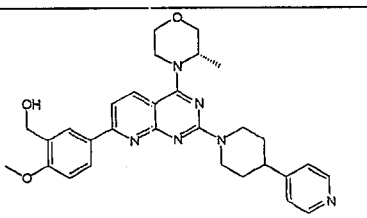
18y	85	7.41	480.4	C	
18z	95	5.67	533.4	C	
18aa	88	6.79	510.3	C	
18ab	93	6.81	452.3	C	
18ac	93	5.44	535.4	C	
18ad	99	5.40	465.5	E	

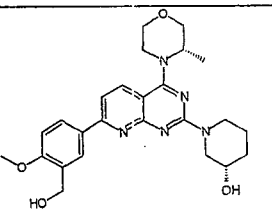
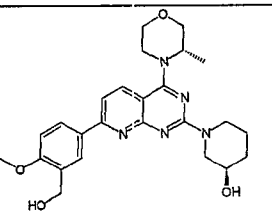
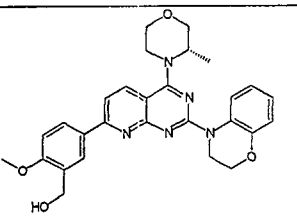
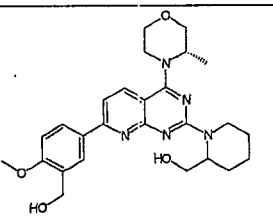
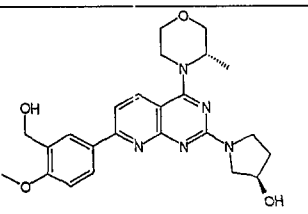
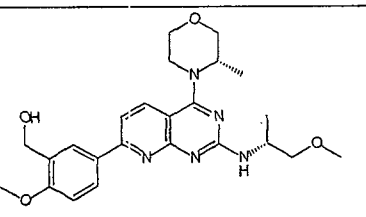
18ae	94	9.86	478.4	C	
18af	94	9.11	518.3	C	
18ag	72,25	10.37,10.81	504.4	C	
18ah	94	7.56	494.3	C	
18ai	96	5.55	519.4	C	
18aj	99	7.82	480.4	C	

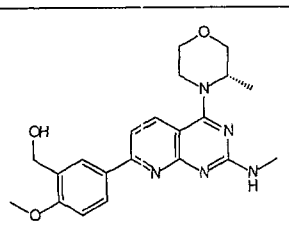
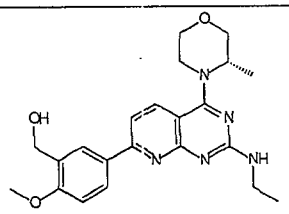
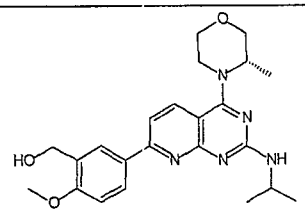
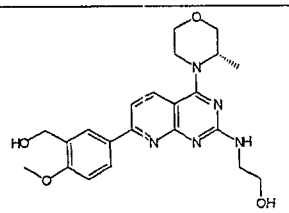
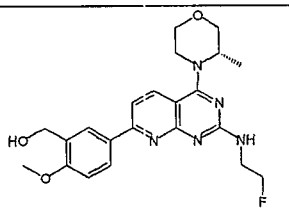
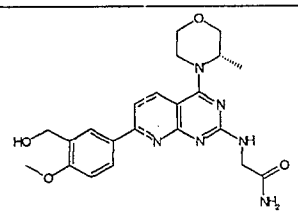
18ak	96	10.49	588.4	C	
18al	96	10.92	540.4	C	
18am	97	8.84	542.4	C	
18an	95	9.74	551.4	C	
18ao	96	6.18	479.3	C	
18ap	92	8.46	450.3	C	

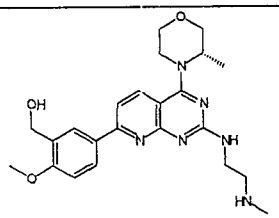
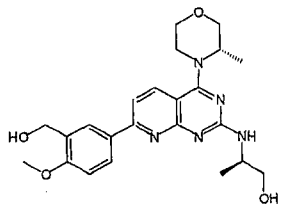
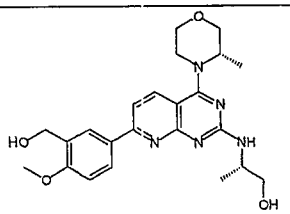
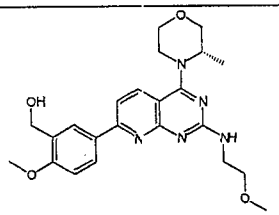
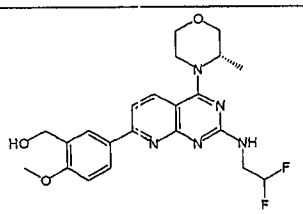
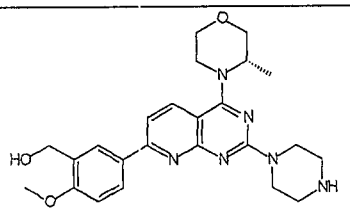
18aq	97	10.99	560.4	C	
18ar	89	8.12	532.4	**c**	
18as	91	5.71	507.4	**c**	
18at	99	10.88	679.4	**c**	
18au	85	5.37	465.4	E	
18aw	98	4.30	450.5	**c**	

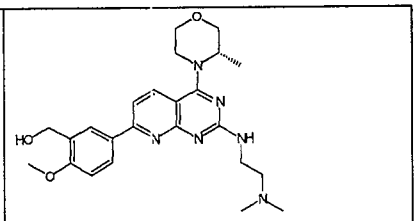
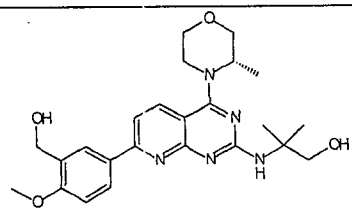
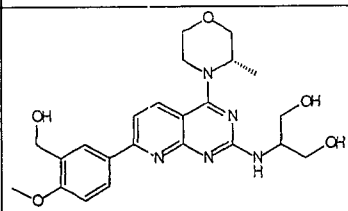
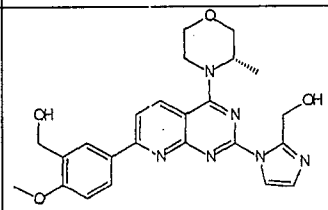
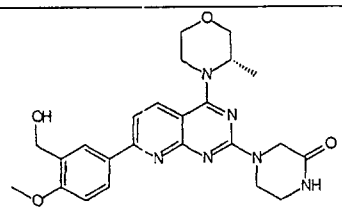
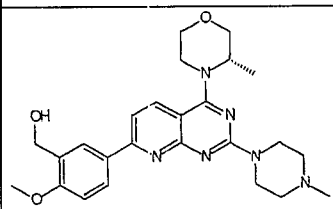
18ax	99	4.02	454.5	**c**	
18ay	100	3.83	433.4	F	
18az	92	9.32	491.4	F	
18ba	93	4.54	475.4	F	
18bb	100	5.06	511.4	F	
18bc	97	10.48	525.3	F	

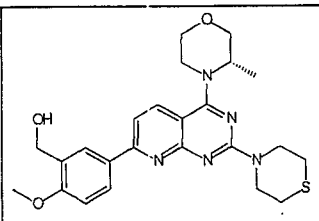
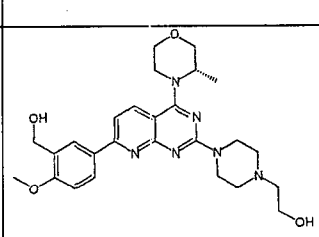
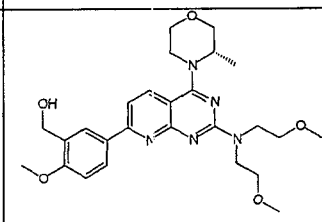
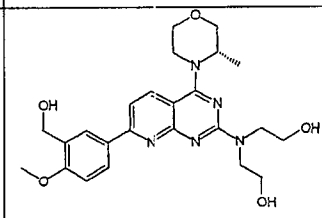
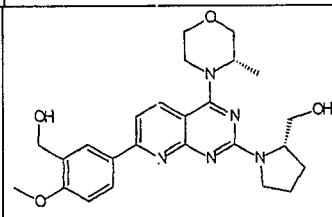
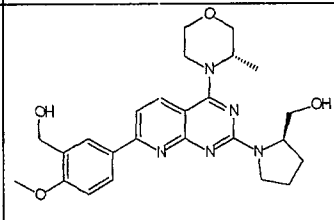
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18be	99	4.67	526.6	C	
18bf	99	4.48	528.5	C	
18bg	98	4.38	464.5	C	
18bh	98	4.37	464.5	C	
18bi	100	3.56	527.5	C	

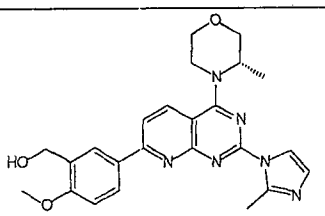
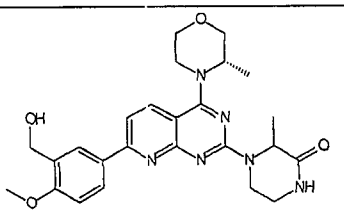
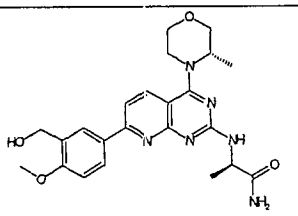
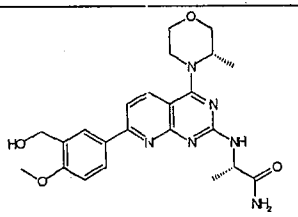
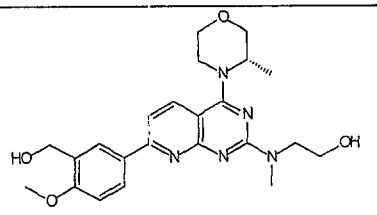
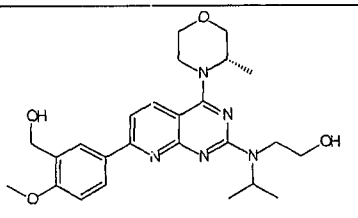
18bj	99	3.84	466.4	**C**	
18bk	99	3.83	466.4	**C**	
18bl	95	9.06	500.5	**C**	
18bm	98	7.65	480.5	**C**	
18bn	97	3.78	452.5	C	
18bo	95	4.03	454.4	C	

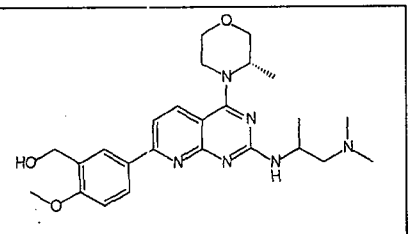
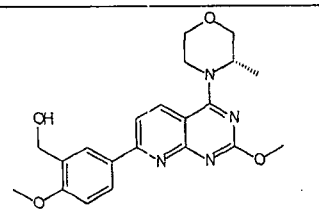
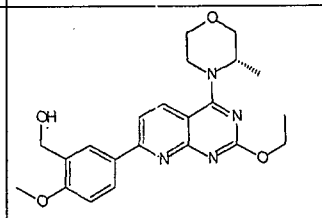
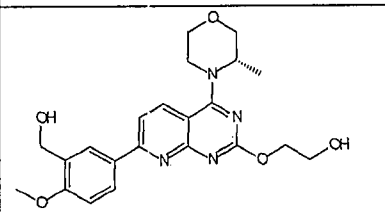
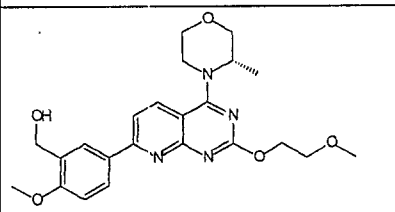
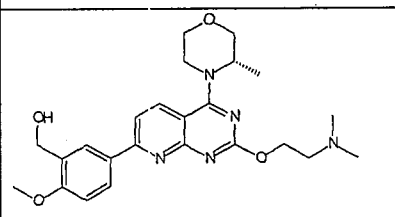
18bp	98	4.01	396.4	H	
18bq	99	4.14	410.4	G	
18br	99	4.30	424.4	H	
18bs	93	5.27	426.4	C	
18bt	94	7.18	428.3	H	
18bu	84	5.95	439.3	I	

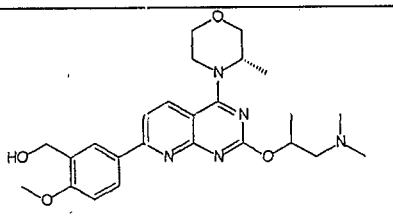
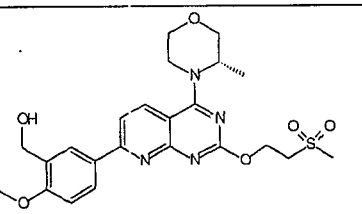
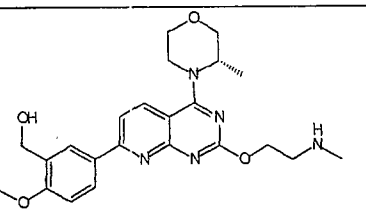
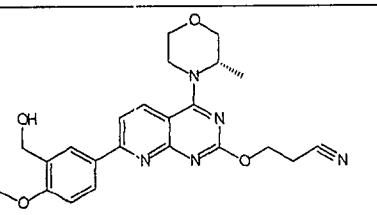
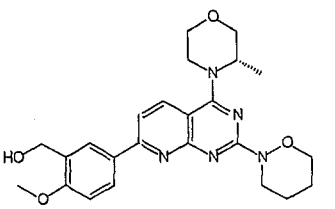
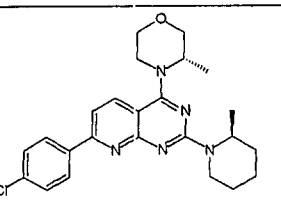
18bv	91	4.91	439.4	C	
18bw	94	5.38	440.4	G	
18bx	94	5.40	440.4	G	
18by	92	5.44	440.4	C	
18bz	*91*	5.52	446.3	H	
18ca	90	4.92	451.4	C	

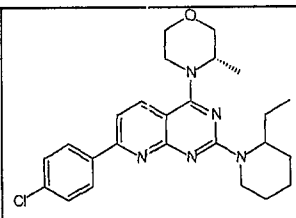
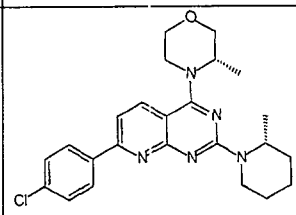
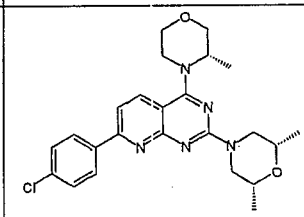
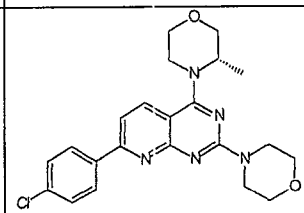
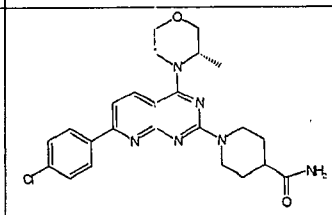
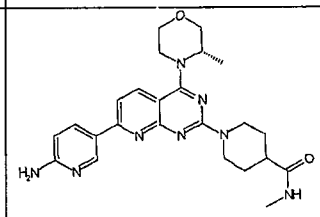
18cb	93	4.95	453.4	C	
18cc	96	5.50	454.4	H	
18cd	92	5.18	456.4	H	
18ce	96	5.37	463.4	G	
18cf	91	5.31	465.4	G	
18cg	92	4.95	465.4	C	

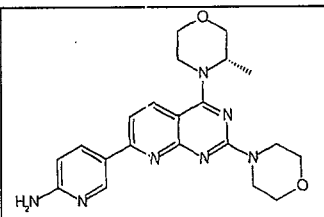
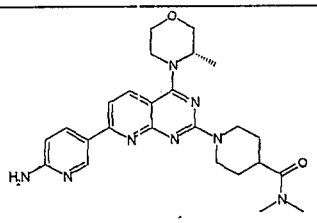
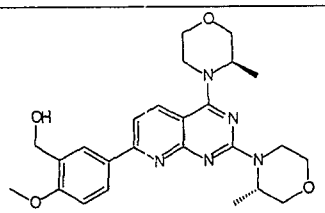
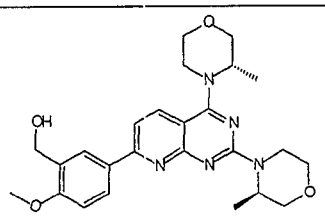
18ch	93	5.73	468.3	C	
18ci	99	4.95	495.4	C	
18cj	97	5.79	498.4	G	
18ck	91	5.28	470.3	G	
18cl	93	5.57	466.3	C	
18cm	92	5.58	466.3	C	

18cn	97	6.87	447.3	F	
18co	93	6.70	479.2	C	
18cp	92	6.18	453.2	J	
18cq	92	6.18	453.1	J	
18cr	92	6.72	440.2	C	
18cs	97	7.84	468.3	I	

18ct	98	5.38	467.3	I	
18cu	98	6.63	397.2	K	
18cv	88	7.17	411.2	L	
18cw	100	6.24	427.2	K	
18cx	83	6.87	441.2	L	
18cy	93	5.45	454.2	K	

18cz	97	5.72	468.3	K	
18da	98	7.96	489.3	K	
18db	98	6.73	440.3	K	
18dc	96	8.26	436.2	K	
18dd	95	4.05	452.4	J	
18de	93	5.36	438.2	A	

18df	93	11.22	452.3	A	
18dg	96	4.86	438.4	A	
18dh	100	4.66	454.4	A	
18di	100	4.37	426.4	A	
18dj	98	7.86	467.4	M	
18dk	97	4.77	463.2	N	

18dl	99	4.78	408.1	N	
18dm	97	4.89	477.3	N	
18dn	97	4.03	466.2	0	
18do	99	3.99	466.2	0	

Datos NMR para ejemplo 18b

^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 8.85 (ArH, d, J= 2.46 Hz, 1H) , 8.64 (ArH, dd, J= 8.75, 2.48 Hz, 1H) , 8.30 (OH, s, br, 1H) , 8.04 (ArH, d, J= 8.47 Hz, 1H) , 7.59 (ArH, d, J= 8.54 Hz, 1H) , 7.14 (ArH, d, J= 8.83 Hz, 1H) , 5.03- 4.91 (CH2, m, 1H) , 4.66 (CH2, dd, J= 13.05, 0.77 Hz, 1H) . 4.41 (CH2, d, J= 6.75 Hz, 1H) , 4.07 (OCH3, s,3H) , 4.04- 3.98 (CH2, m, 1H) , 3.97- 3.68 (CH2, m, 11H) , 3.60 (CH2, d,J= 2.75 Hz, 1H) , 3.41 (CH2, s, 1H) , 1.50 (CH3, d, J = 6.77 Hz, 3H) . 1.39 (CH3, d, J= 6.81 Hz, 3H)

Datos NMR para ejemplo 18k

^{1}HNMR(300MHz, $CHCl_3$) δ ppm 10.59- 10.51 (OH,m, 1H) , 8.18 (ArH, dd, J=4.42, 2.17 Hz, 2H) , 7.99 (ArH, d, J = 8.45 Hz, 1H) , 7.44 (ArH, d, J = 8.48 Hz, 1H) , 7.01 (ArH, d, J = 9.22 Hz, 1H) , 4.81 (CH2OH, s, 2H) , 4.37- 4.11 (CH2, m, 3H) , 4.09- 3.65 (OCH3+ CH2, m, 13H) , 2.02- 1.94 (CH2, m, 1H) , 1.73 - 1.38 (CH2, m, 1H) , 1.50 (CH3, d, J- 6.77 Hz, 3H) 13CNMR(75 MHz, $CDCl_3$) δ ppm 162.05, 161.84, 161.81, 159.16, 150.47, 134.52, 129.29, 128.68, 128.43, 127.47, 117.04, 112.75, 110.28, 104.93, 104.30, 70.96, 67.12, 66.95, 66.77, 61.97, 55.57, 52.75, 50.99, 44.48 y 14.72.

Datos NMR para ejemplo 18v

^{1}H NMR (300 MHz, CDCl3) δ ppm 8.07 (ArH, dd, J = 7.09,2.14 Hz, 2H) , 7.89 (ArH, d, J = 8.47 Hz, 1H) , 7.33 (ArH, d, J= 8.49 Hz, 1H) , 6.91 (ArH, d,J= 9.31 Hz, 1H) , 6.88 (NH, S, Br, 1H) . 5.34 (NH, s, Br, 1H) , 4.95 (CH2, dd, J = 12.22, 0.66 Hz, 2H) , 4.70 (CH2OH, s, 2H) , 4.34- 4.20 (CH, m, 1H) , 3.93- 3.53 (OCH3, + CH2, m, 10H) , 2.91 (CH2, d, J= 12.29 Hz, 2H) , 2.38 (CH2, s, 2H) , 1.89 (CH2, dd, J= 6.92, 6.38 Hz, 2H) , 1.76- 1.54 (CH2, m, 3H) , 1.38 (CH3, d,J=6.76Hz,3H)

^{13}CNMR(75MHz,CDCl3) δppm 176.91, 165.39, 162.98, 161.80, 160.14, 159.13, 134.52, 131.20, 129.28, 128.84, 128.44, 119.99, 112.70, 110.26, 104.34, 70.97, 67.10, 66.94, 61.97, 55.57. 52.76, 44.52, 43.73, 43.69, 43.16, 26.88, y 14.70.

Datos NMR para ejemplo 18ab

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (ArH, d, J = 7.14 Hz, 2H) , 8.00 (ArH, d, J= 8.47 Hz, 1H) , 7.43 (ArH, d, J= 8.42 Hz, 1H) , 7.01 (ArH, d, ./= 9.13 Hz, 1H) , 4.82 (CH2OH, s, 2H) , 4.71- 4.59 (CH2, m, 1H) , 4.47- 4.35 (CH2, m, 1H) , 3.97 (OCH3, s, 3H) , 3.85 (CH2, ddd, J = 17.63,13.74, 9.24 Hz, 8H) , 2.12 (CH2, s, Br, 5H) , 1.50 (CH3d, J= 6.75 Hz, 3H) . 13C NMR (75 MHz, $CDCl_3$) ppm 159.35,159.10,134.61,131.26,129.22,128.89,128.54, 112.41,110.21,104.39, 71.06, 66.95, 61.99, 55.56, 52.80, 44.51, 27.01 y 14.78.

Datos NMR para ejemplo 18ax

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.27- 8.17 (ArH, m, 2H) , 8.00 (ArH, d, J = 8.50 Hz, 1H) , 7.45 (ArH, d, J= 8.51 Hz, 1H) , 7.01 (ArH, d,J= 8.65 Hz, 1H) , 5.40 (NH, br, s, 1H) , 4.81

(CH2OH, s, 2H) , 4.49- 4.35 (CH2, m, 1H) , 3.97 (OCH3, s, 3H) , 3.93- 3.64 (CH2, m, 6H) , 3.58-
3.48 (CH2. m, 2H) , 3.43 (OCH3, s, 3H) , 1.49 (CH3, d, J= 6.71 Hz, 3H) , 1.34 (CH3, d, J = 6.68 Hz, 3H)

^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.67, 161.56, 160.64, 159.19, 134.53,129.27, 128.83, 128.39, 112.53, 110.30, 76.23, 70.98, 67.00, 62.02, 59.18, 55.57, 52.73, 44.31,18.23, 18.20 y 14.85.

Datos NMR para ejemplo 18bn

^{1}H NMR (300 MHz, CDC13) δ ppm 8.23- 8.15 (ArH, m, 2H) , 7.99 (ArH, d, J = 8.45 Hz, 1H) , 7.42 (ArH, d, /= 8.46 Hz, 1H) , 7.00 (ArH, d, J= 8.35 Hz, 1H) , 4.81 (CH2OH, s, 2H) , 4.65 (CH, s. br, 1H) , 4.05- 3.64 (OCH3 + CH2, m, 13H) , 3.24 (OH, s, 1H) , 1.50 (CH3, d, J= 6.73 Hz, 3H) .

^{13}CNMR(75 MHz, CDCI3) δ ppm 165.18, 162.87,159.34, 159.06, 134.57, 131.25, 129.26, 128.84, 128.47, 112.36, 110.20, 104.35, 71.00, 70.97, 66.94, 61.91, 55.55, 52.82, 44.43, 27.01 y 14.87.

Datos NMR para ejemplo 18bo

^{1}H NMR (300 MHz, CDCI3) δ ppm 8.28- 8.17 (ArH, m, 2H) , 8.00 (ArH, d, J = 8.49 Hz, 1H) , 7.45 (ArH, d,J= 8.50 Hz, 1H) , 7.02 (ArH, d,J= 8.60 Hz, 1H) , 5.51- 5.34 (CH,m, 1H) ,4.81 (CH2OH, s, 2H) , 4.47- 4.34 (CH, m, 1H) , 4.00 (CH2, d,J= 1.94 Hz, 1H) , 3.97 (OCH3, s, 3H) , 3.93- 3.89 (CH2, m, 2H) , 3.83- 3.63 (CH2, m, 4H) , 3.53 (CH2, d,br, J = 4.02 Hz, 2H) , 3.43 (OCH3, s, 3H) , 1.50 (CH3, á,J= 6.73 Hz, 3H) , 1.34 (CH3, d, J= 6.69 Hz, 3HJCNMR(75 MHz, CDC13) 8ppm 165.69, 161.55,160.67,159.19,134.52,131.15,129.26, 128.84, 128.41,119.72, 112.58. 110.30, 70.98, 67.12, 67.00, 62.05, 59.18, 55.58, 52.73, 14.32, 18.20 y 14.84.

Datos NMR para ejemplo 18dj

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.10- 8.03 (ArH, m, 2H) , 7.95 (ArH, d, J = 8.41 Hz, 1H) , 7.42- 7.30 (ArH, m, 3H) , 5.52- 5.27 (NH2, m, br,2H) , 4.98 (CH2, dd, J= 12.74, 0.96 Hz, 2H) , 4.31- 4.29 (CH, m, 1H) , 3.97- 3.55 (CH2, m, 8H) , 3.07- 2.86 (CH2, m, 2H) , 2.45- 2.35 (CH2, m, 1H) , 1.99- 1.88 (CH2, m, br, 2H) , 1.70 (CH2, m, 2H) , 1.41 (CH3, d, J= 6.76 Hz, 3H)

13CNMR(75 MHz, $CDCl_3$) δ ppm 176.75,170.03,165.35,162.99, 161.12, 160.17,137.17, 136.10,134.83,129.19,128.76,112.81,104.86,100.00, 70.95, 67.12, 66.91, 52.83,44.50, 43.72, 43.68, 43.10, 28.88 o 14.73.

Datos NMR para ejemplo 18dk

^{1}R NMR (300 MHz, $CDCl_3$ δ ppm 8.67 (ArH, d, J = 1.86 Hz, 1H) , 8.38 (ArH, dd, J = 8.76, 2.36 Hz, 1H) , 8.29 (NH, s, señal debil, 1H) , 7.91 (ArH, d, J= 8.45 Hz, 1H) , 7.27 (ArH, d, J = 8.46 Hz, 1H) , 6.58 (ArH, d, J = 8.75 Hz, 1H) , 5.54- 5.45 (CH2, m, 1H) , 4.97 (NH2, br, s, 2H) , 4.37- 4.24 (CH2, m, 1H) , 3.97- 3.54 (CH2, m, 6H) , 3.09- 2.87 (CH2, m, 2H) , 2.77 (NHCH3, d, J = 4.82 Hz, 3H) , 2.42- 2.24 (CH2, m, 1H) , 1.87 (CH2, d, J = 0.84 Hz, 2H) , 1.79- 1.59 (CH2, m, 2H) , 1.40 (CH3, d, J = 6.76 Hz, 3H) .

Datos NMR para ejemplo 18dl

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.68 (ArH, d, J = 1.98 Hz, 1H) , 8.49 (ArH, dd, J = 8.87, 2.32 Hz, 1H) , 8.38 (NH, s, br,señal debil 1H) , 7.99 (ArH, d, J= 8.47 Hz, 1H) , 7.34 (ArH, d, J = 8.49 Hz, 1H) , 6.67 (ArH, d, J = 8.85 Hz, 1H) , 4.38 (CH2, d, J = 6.77 Hz, 1H) , 4.05- 3.82 (CH2, m, 7H) , 3.81- 3.62 (CH2, m, 7H) , 1.47 (CH3, d, J= 6.77 Hz, 3H) .
^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 165.16, 162.79, 160.31, 159.09, 158.45, 143.98, 139.12, 135.00, 124.48, 111.80, 110.03, 104.70, 70.92, 67.00, 66.90, 52.81, 44.57, 44.40 y 14.78.

Datos NMR para ejemplo 18dm

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.67 (ArH, d,J= 2.05 Hz, 1H) , 8.36 (ArH, dd, J = 8.76, 2.27 Hz, 1H) , 7.90 (ArH, dd, J = 8.45, 2.12 Hz, 1H) , 7.26 (ArH, dd, J = 8.47, 0.73 Hz, 1H) , 6.57 (ArH, d, J= 8.76 Hz, 1H) , 5.10- 4.87 (NH2, m, 2H) , 4.37- 4.22 (CH2, m, 1H) , 3.96- 3.51 (CH2, m, 6H) , 3.08 (NCH3 + CH2, s, 4H) , 2.95- 2.91 (NCH3, s, 3H) , 2.80- 2.59 (CH2, m, 1H) , 1.76 (CH2, d, J= 2.61 Hz, 3H) , 1.64- 1.44 (CH, m, 1H) , 1.38 (CH3, t, J= 6.34, 6.34 Hz, 3H) .
^{13}CNMR(75 MHz, $CDCl_3$) δ ppm 173.59, 165.46, 165.31,163.03, 160.17, 158.89, 145.99, 138.35, 134.76, 124.89, 111.71, 109.15, 104.41, 70.96, 66.96, 52.81, 46.85, 44.38, 39.43, 37.26, 35.56, 28.06, 24.95 y 14.71.

Datos NMR para ejemplo 18dn

^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.10 (ArH, d, J= 7.89 Hz, 2H) , 7.97 (ArH, d, J= 8.49 Hz, 1H) , 7.42 (ArH, d, J= 8.46 Hz, 1H) , 6.98 (ArH, d, J= 8.55 Hz, 1H) , 4.88 (CH2> d, J= 5.25 Hz, 1H) , 4.77 (CH2OH, s, 2H) , 4.56 (CH2, d, J= 13.38 Hz, 1H) , 4.38 - 4.36 (CH2, m, 1H) , 4.02 - 3.51 (OCH3 + CH2, m, 11H) , 3.43 - 3.33 (CH2, m, 1H) , 1.47 (CH3, d, J= 6.77 Hz, 3H) , 1.35 (CH3, d, J= 6.78 Hz, 3H) .

^{13}CNMR(75 MHz, CD3COCD3) δ ppm 165.11, 162.27, 161.87, 159.54,159.23, 134.74, 130.76, 129.41, 128.86, 128.39, 113.09, 110.32, 104.45, 71.20, 70.95, 67.17, 66.91, 61.80, 55.57, 52.82, 47.05, 44.44, 39.45, 14.74 y 14.44.

Datos NMR para ejemplo 18do

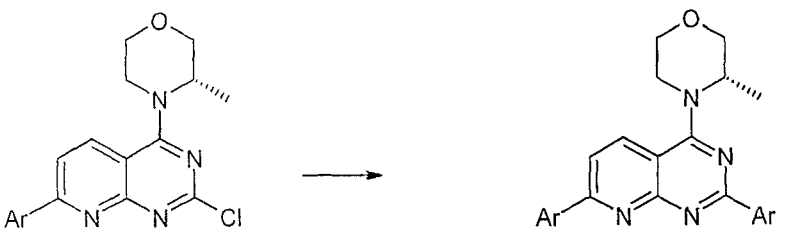
^{1}H NMR (300 MHz, $CDCl_3$ δ ppm 8.10 (ArH, d, J= 8.76 Hz, 2H) , 7.98 (ArH, d, /= 8.49 Hz, 1H) , 7.42 (ArH, d, J= 8.46 Hz, 1H) , 6.97 (ArH, d, J= 8.37 Hz, 1H) , 4.88 (CH2, d, J= 5.46 Hz, 1H) , 4.77 (CH2OH, s, 2H) , 4.58 - 4.49 (CH2, m, 1H) , 4.39 - 4.36 (CH2, d J= 7Al Hz, 1H) , 4.02 - 3.51 (OCH3 + CH2, m, 11H) , 3.43 - 3.33 (CH2, m, 1H) , 1.48 (CH3, d, J= 6.78 Hz, 3H) , 1.35 (CH3, d, J= 6.78 Hz, 3H) .

^{13}CNMR(75 MHz, $CD3COCD_3$) δ ppm 165.05, 161.87, 159.45, 159.24, 134.78, 130.70, 129.44, 128.86, 128.38, 113.14, 110.33, 104.43, 71.19, 70.95, 67.16, 66.90, 61.77, 55.57, 52.82, 47.08, 44.44, 39.47, 14.76 y 14.44.

Probados en el Ensayo Enzimático Alternativo: Ej. (18a) 0.03 uM; Ej. (18b) 0.1 uM; Ej. (18c) 0.066uM; Ej. (18d) 0.15uM; Ej. (18e) 0.039uM; Ej. (18f) 0.038uM; Ej. (18g) 0.031uM; Ej. (18h) 0.23uM; Ej. (18i) 0.03uM; Ej. (18j) 0.088uM; Ej. (18k) 0.019uM; Ej. (18l) 0.097uM; Ej. (18m) 0.042uM; Ej. (18n) 0.31uM; Ej. (18o) 0.51 uM; Ej. (18p) 0.25uM; Ej. (18q) 0.11 uM; Ej. (18r) 0.18uM; Ej. (18s) 0.037uM; Ej. (18t) 0.054uM; Ej. (18u) 0.073uM; Ej. (18v) 0.014uM; Ej. (18w) 0.25uM; Ej. (18x) 0.014uM; Ej. (18y) 0.023 uM; Ej. (18z) 0.088nM; Ej. (18aa) 0.019uM; Ej. (18ab) 0.012uM; Ej. (18ac) 0.014uM; Ej. (18ad) 0.078uM; Ej. (18ae) 0.034uM; Ej. (18af) 0.23uM; Ej. (18ag) 0.25uM; Ej. (18ah) 0.03 uM; Ej. (18ai) 0.063uM; Ej. (18aj) 0.022nM; Ej. (18ak) 0.42uM; Ej. (18al) 0.36uM; Ej. (18am) 0.077uM; Ej. (18an) 0.14pM; Ej. (18ao) 0.073uM; Ej. (18ap) 0.013uM; Ej. (18aq) 0.19uM; Ej. (18ar) 0.079uM; Ej. (18as) 0.08uM; Ej. (18at) 0.78uM; Ej. (18au) 0.1 ImM; Ej. (18av) 0.27uM; Ej. (18aw) 0.058(iM; Ej. (18ax) 0.026uM; Ej. (18ay) 0.087uM; Ej. (18az) 0.092uM; Ej. (18ba) O.luM; Ej. (18bb) 0.65uM; Ej. (18bc) 0.043uM; Ej. (18bd) 0.19uM; Ej. (18be) 0.79uM; Ej. (18bf)

0.077uM; Ej. (18bg) 0.047uM; Ej. (18bh) 0.04uM; Ej. (18bi) 0.32uM; Ej. (18bj) 0.024uM; Ej. (18bk) 0.022uM; Ej. (18bl) 0.61uM; Ej. (18bm) 0.025uM; Ej. (18bn) O.OluM; Ej. (18bo) 0.058uM; Ej. (18bp) 0.049uM; Ej. (18bq) 0.072uM; Ej. (18br) 0.03uM; Ej. (18bs) 0.042(iM; Ej. (18bt) 0.062uM; Ej. (18bu) 0.047uM; Ej. (18bv) O.lluM; Ej. (18bw) 0.03luM; Ej. (18bx) 0.035uM; Ej. (18by) 0.039uM; Ej. (18bz) O.OluM; Ej. (18ca) 0.0026uM; Ej. (18cb) 0.25uM; Ej. (18cc) 0.018uM; Ej. (18cd) 0.025uM; Ej. (18ce) 0.37uM; Ej. (18cf) 0.013uM; Ej. (18cg) 0.067uM; Ej. (18ch) 0.078uM; Ej. (18ci) 0.068uM; Ej. (18cj) 0.055uM; Ej. (18ck) 0.0095pM; Ej. (18cl) 0.023uM; Ej. (18cm) 0.029uM; Ej. (18cn) 0.013uM; Ej. (18co) 0.0052uM; Ej. (18cp) 0.0057uM; Ej. (18cq) 0.027uM; Ej. (18cr) 0.0063uM; Ej. (18cs) 0.0047uM; Ej. (18ct) 0.097nM; Ej. (18cu) 0.08uM; Ej. (18cv) 0.043uM; Ej. (18cw) 0.034uM; Ej. (18cx) 0.024uM; Ej. (18ci) 0.12uM; Ej. (18cz) 0.079uM; Ej. (18da) 0.71uM; Ej. (18db) 0.0031uM; Ej. (18dc) 0.21 uM; Ej. (18dd) 0.028uM; Ej. (18de) 0.26uM; Ej. (18df) 0.4nM; Ej. (18dg) 0.3 pM; Ej. (18dh) O.l5uM; Ej. (18di) 0.15uM; Ej. (18dj) 0.052uM; Ej. (18dm) 0.061uM; Ej. (18dn) 0.0094uM; Ej. (18do) 0.026uM. Probados en ensayo phospho- Ser473 Akt: Ej. (18dk) 0.682 uM; Ej. (18dl) 0.295 uM.

Ejemplo 19



Los cloro- substratos se reportaron en el Ejemplo 18.

(Compuestos 19a a 19x)

Condiciones A:

A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (3.5 equiv) , y el ácido borónico apropiado (1.0 equiv) en acetonitrilo/agua (1:1) (0.026 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y se calentó a 95 °C durante 2 horas. Al terminar, las muestras se filtraron a través de un cartucho de sílice. se lavaron con CH_2Cl_2 y metanol y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

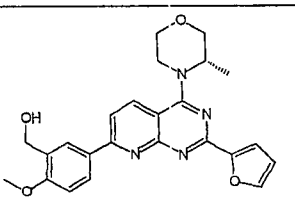
Condiciones B:

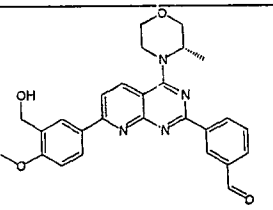
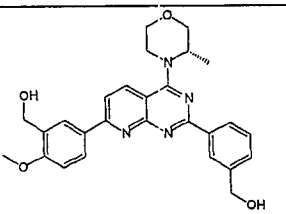
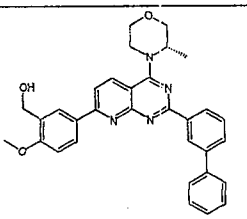
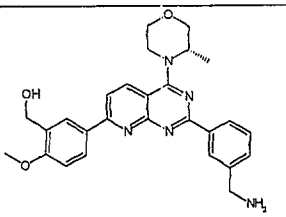
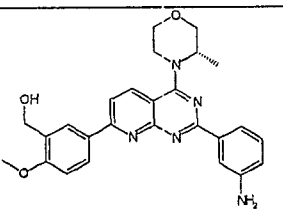
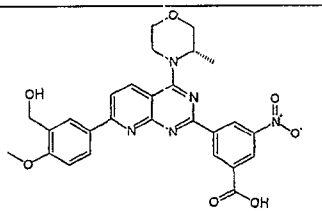
A una mezcla del cloro- sustrato apropiado (1 equiv) , fluoruro de cesio (3.5 equiv) , y el ácido borónico apropiado (1.0 equiv) en acetonitrilo (0.026 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y calentó a 95 °C durante 2 horas. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con CH_2Cl_2 y metanol y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

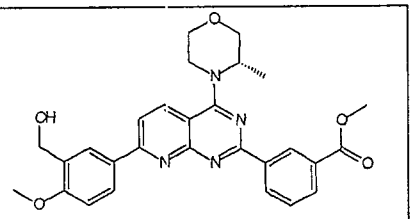
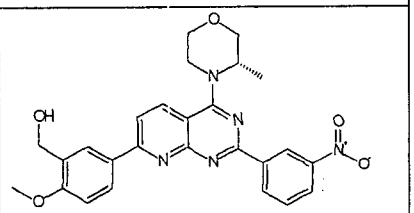
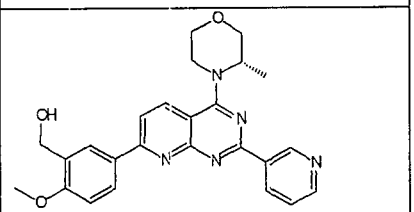
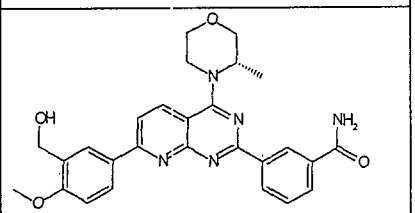
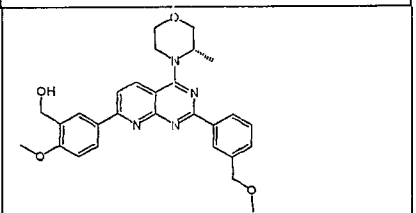
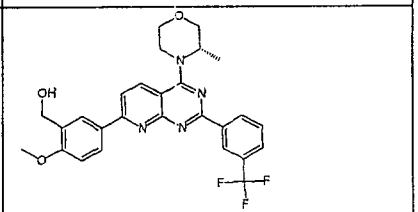
Condiciones C:

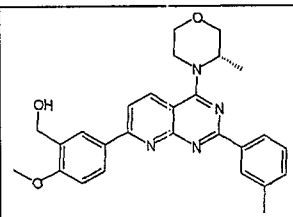
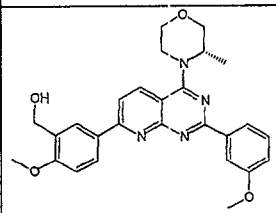
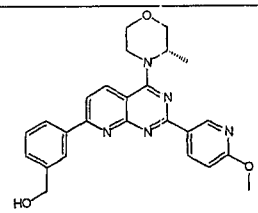
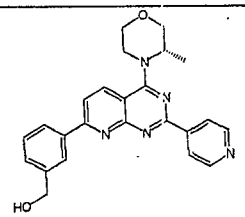
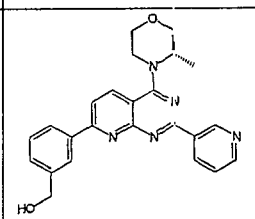
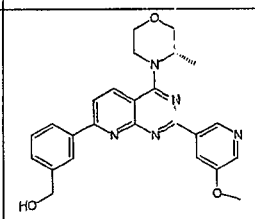
A una mezcla del cloro- sustrato apropiado (1 equiv) , carbonato de potasio (2.5 equiv) , y el pinacolato de éster borónico apropiado o ácido borónico (1.1 equiv) en acetonitrilo/agua (1:1) (0.041 M de cloro- substrato) se agregó tetrakis(trifenilfosfina) paladio (0.05 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (150 °C, ambiente de absorción de medios) durante 30 minutos bajo atmósfera de nitrógeno. Al terminar, las muestras se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

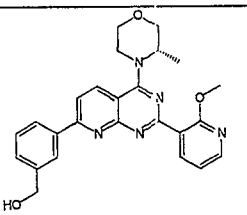
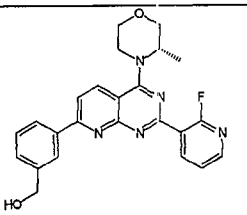
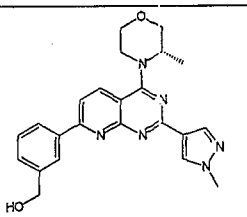
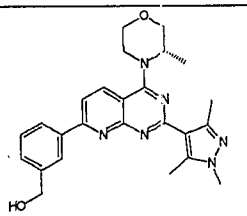
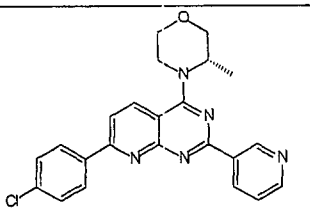
Tabla 19:

	Pureza (%)	Tiempo de retención (min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
19a	93	7.66	433.2	A	

19b	88	8.95	471.3	A	
19c	79	7.54	473.3	A	
19d	92	11.14	519.3	A	
19e	99	6.14	472.3	A	
19f	90	7.43	458.3	A	
19g	84	10.52	532.3	A	

19h	75	9.58	501.3	B	
19i	94	11.13	488.3	A	
19j	84	7.36	444.3	A	
19k	88	7.33	486.3	A	
191	88	8.75	487.3	A	
19m	93	11.64	511.3	A	

19n	87	9.26	457.3	A	
19o	89	9.05	473.3	A	
19p	97	4.31	444.3	C	
19q	95	4.13	414.2	**c**	
19r	94	4.14	414.2	C	
19s	97	4.43	444.2	C	

19t	98	4.28	444.2	**c**	
19u	87	4.41	432.2	**c**	
19v	98	4.07	417.2	**c**	
19w	96	4.12	445.3	**c**	
19x	99	5.66	418.2	A	

Datos NMR para ejemplo 19j

^{1}R NMR (300 MHz, DMSO) δ ppm 9.63 (ArH, d, J = 1.49 Hz, 1H) , 8.84- 8.69 (ArH, m5 2H) , 8.49- 8.37 (ArH, m, 1H) , 8.19 (ArH, dd, J = 8.61, 2.35 Hz, 1H) , 8.00 (ArH, d, J = 8.76 Hz, 1H) , 7.57 (ArH, ddd, J= 7.99,4.81, 0.71 Hz, 1H) , 7.15 (ArH, d,/= 8.71 Hz, 1H) , 5.23 (ArH. dd, J= 2.03, 1.13 Hz, 1H) ,5.23 (CH, m, 1H) , 4.78 (CH, d, J= 6.83 Hz, 1H) , 4.61

(CH2OH, s, 2H) , 4.22 (CH2, d,J= 13.08 Hz, 1H) , 4.03- 3.92 (CH2, m, 1H) , 3.98 (OCH3, s, 3H) , 3.88- 3.61 (CH2, m, 3H) , 2.50 1.49 (CH3, d, J= 6.79 Hz, 3H)
13CNMR(75 MHz, DMSO) 8 ppm 164.91, 161.77, 161.25, 160.36, 158.71, 151.75, 149.97, 136.10, 133.86, 131.45, 129.97, 127.92, 126.79, 124.08, 117.24, 110.92, 108.15, 70.77, 66.83, 66.80, 58.39, 56.04, 52.15, 44.39 y 15.24.

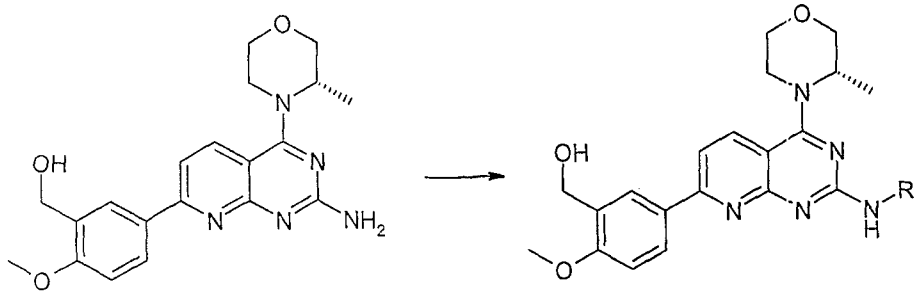
Datos NMR para ejemplo 19x

^{1}H NMR (300 MHz, CDCl3) δ ppm 9.86- 9.80 (ArH, m, 1H) , 9.00- 8.91 (ArH, m, 1H) , 8.77 (ArH, dd, J = 4.80,1.71 Hz, 3H) , 8.28 (ArH, ddd, J = 9.24, 8.03, 5.57 Hz, 1H) , 7.83 (ArH, d, J = 8.64 Hz, 2H) , 7.60- 7.53 (ArH, m, 2H) , 7.53- 7.43 (CH, m, 1H) , 4.72 (CH2, d, J = 6.93 Hz, 1H) . 4.33- 4.23 (CH2, m, 1H) , 4.00- 3.80 (CH2, m, 4H) , 1.65 (CH3, d,J= 6.81 Hz, 3H)
13CNMR(75 MHz, CDCl3) 5 ppm 164.55, 161.73, 161.53, 151.52, 150.66, 136.99, 136.34, 134.91,133.42, 129.34, 129.12, 123.19, 119.66, 117.15, 108.64, 106.49, 70.98, 67.02, 52.92, 44.49 y 15.16.

Probados en el Ensayo Enzimático Alternativo: Ej. (19a) 0.048uM; Ej. (19b) 0.018uM; Ej. (19c) 0.052uM; Ej. (19d) 0.25uM; Ej. (19e) 0.1 luM; Ej. (19f) 0.096uM; Ej. (19g) 0.0087uM; Ej. (19h) 0.77uM; Ej. (19i) 0.28uM; Ej. (19j) 0.057uM; Ej. (19k) 0.077uM; Ej. (191) 0.12uM; Ej. (19m) 0.41uM; Ej. (19n) 0.22uM; Ej. (19o) 0.19uM; Ej. (19p) 0.24uM; Ej. (19q) 0.14uM; Ej. (19r) 0.012uM; Ej. (19s) 2uM; Ej. (19t) 0.097uM; Ej. (19u) 0.055uM; Ej. (19v) 0.07uM; Ej. (19w) 0.086uM; Ej. (19x) 0.81 uM.

Ejemplo 20

El amino substrato se reportó en el Ejemplo 18.
(Compuestos 20a a 20c)



Condiciones A:

El amino sustrato apropiado (1 equiv) se suspendió en THF (0.04 M) . Se agregó sulfonil cloruro apropiado (2.0 equiv) . El recipiente de reacción se selló y se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar, las muestras se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

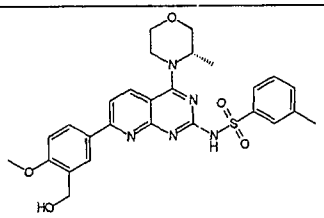
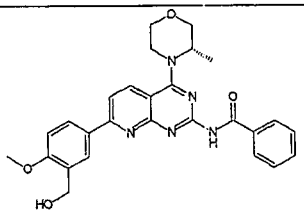
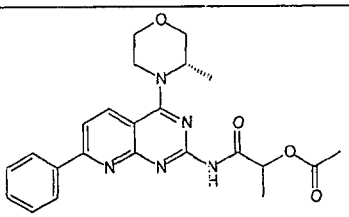
Condiciones B:

El amino sustrato apropiado (1 equiv) se suspendió en DMF (0.04 M) . Se agregó cloruro de acilo apropiado (1.2 equiv) y carbonato de potasio (2.4 equiv) se agregó. El recipiente de reacción se selló y expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 10 minutos. Al terminar las muestras se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Condiciones C:

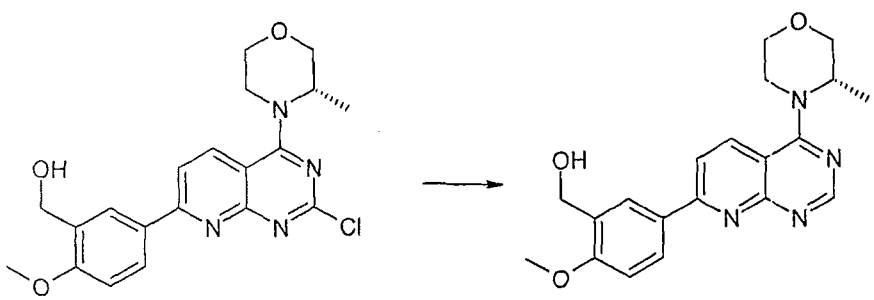
El amino sustrato apropiado (1 equiv) se suspendió en DMF (0.09 M) . Se agregó cloruro de acilo apropiado (3.0 equiv) . El recipiente de reacción se selló y expuso a radiación microondas (130 °C, ambiente de absorción de medios) durante 15 minutos. Al terminar, las muestras se concentraron al vacío. Luego el residuo crudo se purificó mediante HPLC preparativa para proporcionar los productos deseados.

Tabla 20:

	Pureza (%)	Tiempo de retención(min)	m/z $[M+H]^+$	Condiciones	Estructura de ejemplo
20a	93	4.67	536.5	A	
20b	97	4.58	486.4	B	
20c	85	4.56	436.3	C	

Probados en el Ensayo Enzimático Alternativo: Ej. (20a) 1.4uM; Ej. (20b) 0.67uM; Ej. (20c) 0.024uM.

Ejemplo 21

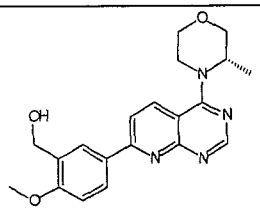


El cloro- substrato se reportó en el Ejemplo 18.

(Compuesto 21a)

El cloro- sustrato apropiado (1 equiv) se disolvió en etanol (0.025 M) . Se agregó formato de sodio (11.0 equiv) y paladio on carbono (0.5 equiv) . El recipiente de reacción se selló y calentó a 100 °C durante 12 horas. Al terminar, la muestra fue filtrada a través de Celite™, y el filtrado se concentró al vacío. Luego el residuo crudo se purificó mediante cromatografía de fase inversa eluyendo con un gradiente de 5 a 95 % acetonitrilo en 0.1 % ácido fórmico/agua, para proporcionar el producto deseado.

Tabla 21:

	Pureza (%)	Tiempo de retención (min)	m/z [M+Hf	Estructura de ejemplo
21a	97	5.94	367.3	

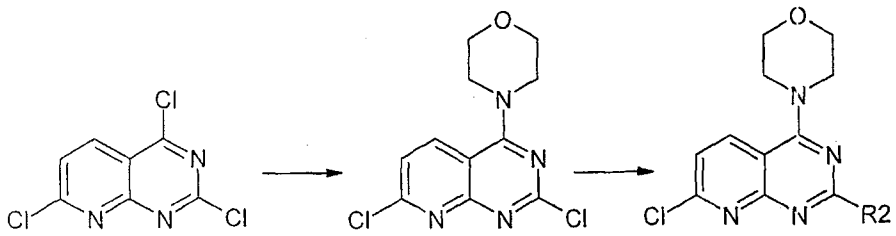
Datos NMR para ejemplo 21a

^{1}H NMR (300 MHz, DMSO) δ ppm 8.70 (ArH, s, 1H) , 8.42 - 8.37 (ArH, m, 2H) , 8.16 (ArH, dd, J = 8.59, 2.34 Hz, 1H) , 8.01 (ArH, d, J = 8.79 Hz, 1H) , 7.14 (ArH, d, J = 8.69 Hz, 1H) , 5.20 (CH, t, J = 5.67, 5.67 Hz, 1H) , 4.59 (CH2, d, J = 5.61 Hz, 2H) , 4.05 - 3.93 (CH2, m, 2H) , 3.89 (OCH3, s, 3H) , 3.80- 3.59 (CH2) m, 4H) , 3.57 (s, 1H) , 3.31 (s, 1H) , 2.50 (td, J= 3.64, 1.80,1.80 Hz, 1H) , 1.42 (CH3, d, J= 6.79 Hz, 3H)

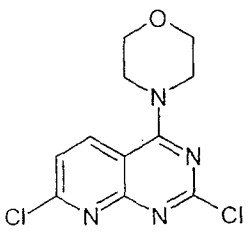
^{13}C NMR (75 MHz, DMSO) δ ppm 164.04, 161.48, 160.52, 158.69, 157.38, 136.11, 131.43, 129.96, 127.87, 126.77, 117.33, 110.93, 109.11, 70.71, 66.83, 58.37, 56.03, 52.14, 44.28 y 15.17.

Probados en el Ensayo Enzimático Alternativo: Ej. (21a) 0.2uM.

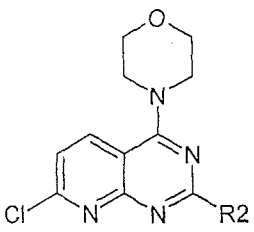
Ejemplo Comparativo 1



Utilizando el método del ejemplo 1, a una solución agitada fria (0- 5°C) (0.1 M) del tricloro sustrato apropiado (1 equiv) en CH2Cl2 se agregó diisopropiletilamina (1 equiv) por goteo. Luego se agregó la amina apropiada (1 equiv) a la mezcla de reacción por porciones durante el periodo de 1 hora. La solución se mantuvo a temperatura ambiente con agitación durante 1 hora más antes de lavar la mezcla con agua (2x1 volumen de reacción) . Los extractos acuosos se combinaron y extrajeron con CH_2Cl_2 (2x1 volumen de reacción) . Luego los extractos orgánicos se combinaron, secaron (sulfato de sodio) , filtraron y concentraron al vacío para proporcionar un residuo aceitoso el cual se solidificó ante secado prolongado. El sólido se trituró con éter dietílico y luego se filtró y la torta se lavó con éter dietílico frio para dejar compuesto del título en una forma apropiadamente limpia para utilizar sin purificación adicional.

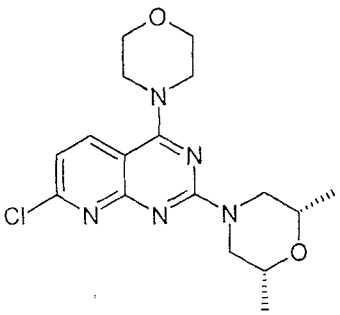


2,7- Dicloro- 4- morfolin- 4- il- pirido[2,3- d]pirimidina - Rl= morfolina: (92% rendimiento, 90% pureza) m/z (LC- MS, ESP) : 285 $[M+H]^+$ R/T = 3.90 min

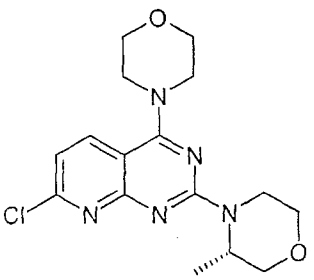


A una solución (0.2 M) del dicloro- sustrato apropiado (1 equiv) en acetamida de dimetilo anhidro bajo una atmósfera inerte se agregó diisopropiletilamina (1 equiv) seguido por la amina apropiada (1 equiv) . La mezcla resultante se calentó durante 48 horas a 70 °C antes de ser enfriada a temperatura ambiente. La reacción se diluyó con CH_2Cl_2 (1 volumen de reacción) y

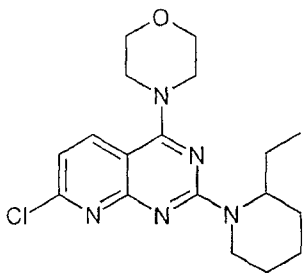
luego se lavó con agua (3x1 volumenes de reacción) . El extracto orgánico se concentró al vacío para proporcionar un jarabe el cual se disolvió en EtOAC (1 volumen de reacción) y se lavó con solución de salmuera saturada antes de ser secado, filtrado (sulfato de sodio) y concentrado al vacío para proporcionar un aceite. El residuo crudo se purificó mediante cromatografia rápida (SiO_2, eluida con EtOAc:Hex (7:3) llegando a (1:1)) para proporcionar el compuesto del titulo como un sólido amarillo que fue apropiadamente limpio para utilizar sin purificación adicional.



7- Cloro- 2- ((2S,6R) - 2,6- dimetil- morfolin- 4- il) - 4- morfolin- 4- il- pirido[2,3- djpirimidina – R1= morfolina, R2=cis- dimetilmorfolina: (42% rendimiento, 100% pureza) m/z (LC- MS, ESP) : 364 $[M+H]^+$ R/T = 2.96 min



7- Cloro- 2- ((S) - 3- metil- morfolin- 4- il) - 4- morfolin- 4- il- pirido[2,3- d]pirimidina Rl = morfolina, R2= (S) - 3- Metil- morfolina: (70 % rendimiento, 97 % pureza) m/z (LC- MS, ESP) : 350 $[M+H]^+$ R/T = 3.44 min



7- Cloro- 2- (2- etilo- piperidin- 1 - il) - 4- morfolin- 4- il- pirido[2,3- d]pirímidina Rl =

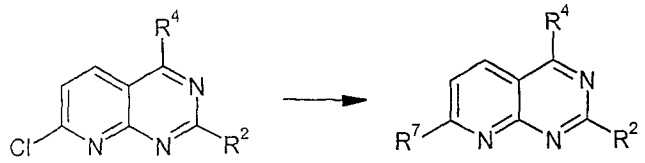
morfolina, R2= 2- Etilo- piperidina: (56 % rendimiento, 95 % pureza) m/z (LC- MS, ESP) : 362 $[M+H]^+$R/T =3.78 min

Ejemplos comparativos 1a, 1b, 1e, 1j, y 1k

R^4 = morfolina

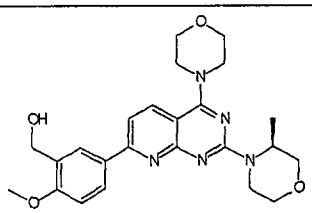
R^2 = (S) - 3- metil- morfolina o cis- dimetilmorfolina o 2- Etil- piperidina

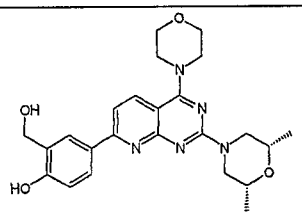
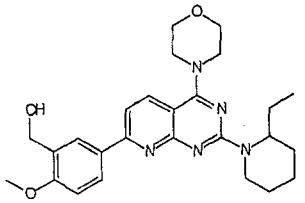
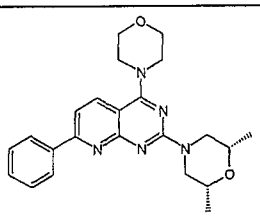
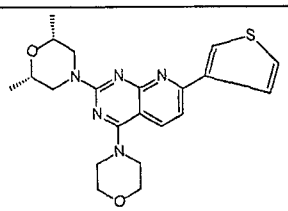
R^7 = arilo o heteroarilo



El cloro- sustrato apropiado (1 equiv) se disolvió en una solución (0.02M) de tolueno/etanol (1:1) . Luego se agregó carbonato de sodio (2 equiv) y el pinacolato de éster borónico apropiado o ácido borónico (1 equiv) seguido por tetrakis(trifenilfosfina) paladio (0.1 equiv) . El recipiente de reacción se selló y la mezcla se expuso a radiación microondas (140 °C, ambiente de absorción de medios) durante 30 minutos. Al terminar, las muestras se filtraron a través de un cartucho de sílice, se lavaron con EtOAc y luego se concentraron al vacío. Luego el producto crudo se purificó mediante HPLC preparativa para proporcionar los ejemplos comparativos deseados.

Se prepararon los siguientes ejemplos comparativos

	Pureza(%)	Tiempo de retención (min)	m/z $[M+H]^+$	Estructura de ejemplo comparativa
1a	99	4.13	452.3	

Ib	95	3.95	452.3	
Ic	99	9.01	464.4	
Ij	88	8.57	406.5	
Ik	93	8.12	412.3	

Ejemplo 22

Ensayo Biológico

Para ensayos de actividad enzimática de mTOR, la proteína mTOR se aisló a partir de extracto citoplásmico de células HeLa mediante inmunoprecipitación, y la actividad se determinó esencialmente como se describió previamente utilizando PHAS- 1 recombinante como un sustrato (ref. 21) .

Los ejemplos la- 1l, 1ak, 1al, 1ap, 1at, 1az, 31, 4a, 4c, 4d, 4f, 4i, 4w, 4x, 5q se probaron y exhibieron valores IC50 contra mTOR de menos de 200 nM. Por ejemplo la medición de 5q dio

un IC50 de 46nm.

Los ejemplos comparativos también se probaron y cuando se compararon con los ejemplos correspondientes, los valores IC50 exhibidos para los Ejemplos comparativos fueron mayores que aquellos de los Ejemplos correspondientes (es decir IC50 Ejemplo comparativo 1a > IC50 Ejemplo 1a) . Por ejemplo la medición del IC50 del Ejemplo 1k fue 5nm mientras el Ejemplo comparativo 1k tuvo un IC50 de 33nm. Por lo tanto, los compuestos del presente invento son más activos en el ensayo mTOR.

Ejemplo 23

Ensayo Enzimático Alternativo

El ensayo utilizó tecnología AlfaScreen (Gray et al, Analytical Biochemistry, 2003, 313: 234- 245) para determiner la capacidad de los compuestos de prueba para inhibir la fosforilación mediante MTOR recombinante.

Un truncado sobre el extremo C de mTOR que incluye los residuos aminoácidos 1362 a 2549 de mTOR (No. de Acceso EMBL. L34075) se expresó establemente como como una fusión etiquetada- FLAG en células HEK293 como lo describió Vilella- Bach et al, Journal de Biochemistry, 1999, 274, 4266- 4272. La línea celular estable de mTOR FLAG- etiquetada HEK 293 (1362- 2549) se mantuvo rutinariamente a 37°C con CO2 al 5% hasta una confluencia de 70- 90 % en medio de crecimiento Eagle modificado de Dulbecco (DMEM; Invitrogen Limited, Paisley, UK No. de Catálogo. 41966- 029) conteniendo 10% de suero fetal de ternero inactivado por calor (FCS; Sigma, Poole, Dorset, UK, No. de Catálogo. F0392) , L- glutamina al 1% (Gibco, No. de Catálogo. 25030- 024) y 2 mg/ml Geneticina (sulfato G418; Invitrogen Limited, UK No. de Catálogo. 10131- 027) . Después de la expression en la línea celular HEK293 mamífera, la proteína expresada se purificó utilizando la etiqueta FLAG epítopo utilizando técnicas de purificación estándares.

Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron en agua según lo requerido para proporcionar un rango de concentraciones finales de ensayo. Aliquotas (2 ul) de cada dilución de compuesto se colocaron en un pozo de una placa de poliestireno blanco de bajo volumen de 384 pozos Greiner (Greiner Bio- one) . Una mezcla de 10 µl de enzima mTOR purificada recombinante, sustrato péptido biotinilado (Biotin- Ahx- Lys- Lys- Ala- Asn- Gln- Val- Fhe- Leu- Gly- Fhe- Thr- Tyr- Val- Ala- Pro- Ser- Val- Leu-

Glu- Ser- Val- Lys- Glu- NH2; Bachem UK Ltd) , ATP (20 μM) en una solución amortiguadora [comprendiendo amortiguador Tris- HCl pH7.4 (50 mM) , EGTA (0.1 mM) , albúmina de suero bovino (0.5 mg/ml) , DTT (1.25 mM) y cloruro de manganeso (10 mM)] se agregaron a las placas de ensayo e incubaron con compuesto durante 2 horas a temperatura ambiente.

Cada reacción se detuvo mediante la adición de 5 μl de una mezcla de EDTA (50 mM) , albúmina de suero bovino (BSA; 0.5 mg/ml) y amortiguador Tris- HCl con pH7.4 (50 mM) Anticuerpo Monoclonal p70 S6 Quinasa (T389) 1A5 (Cell Signalling Technology, No. de Catálogo. 9206B) y nanoesferas donantes AlfaScreen Streptavidina y nanoesferas aceptadoras Proteína A (200ng/pozo Perkin Elmer, No. de Catálogo. 6760002B y 6760137R respectivamente) . Las placas de ensayo se dejaron durante 16 horas aproximadamente a temperatura ambiente antes de la medición. Las señales resultantes provenientes de la excitación de luz laser a 680 nm se midieron utilizando un instrumento Packard Envision.

El péptido biotinilado fosforilado es formado *in situ* como un resultado de fosforilación mediada por mTOR. El péptido biotinilado fosforilado que está asociado con nanoesferas donantes de AlfaScreen Streptavidina forma un complejo con el Anticuerpo Monoclonal p70 S6 Kinase (T389) 1A5 que está asociado con nanoesferas aceptadoras Proteína A Alphascreen. Ante excitación de luz láser a 680 nm, el complejo nanoesfera donante: nanoesfera aceptadora produce una señal que se puede medir. Por consiguiente, la presencia de actividad de la mTOR quinasa resulta en una señal de ensayo. En presencia de un inhibidor de la mTOR quinasa, La intensidad de la señal es reducida.

Los pozos de control que produjeron una señal máxima correspondiente a actividad enzimática máxima se crearon utilizando DMSO al 5% en cambio del compuesto de prueba. Los pozos de control que produjeron una señal minima correspondiente a enzima completamente inhibida se crearon mediante la adición de EDTA (83 mM) en cambio del compuesto de prueba.

La inhibición enzimática de mTOR para un compusto de prueba dado se expresó como un valor IC50.

Los compuestos probados en este ensayo exhibieron valores IC50 contra mTOR menores de 40μm.

Los siguientes compuestos exhibieron valores IC50 contra mTOR menores de 1 μm: lbp, lca, lcb, lcd, 12e, 18df, 1m, 1q, lr, 17, 19h, 19m, 18n, 18o, 18ak, 18al, 18at, lt, 18bb, 18be, 18bi, 18bl, lx, ly, lba, lz, 20b, lae, 7a, 7h, 18ce, 5f, 4af, 4ag, 4aj, 5y, 3b, 5j, 5k, 5p, 3w, 3y, 3z, 1 la, 18da, 3m,

3o, 3p, 3r, 3s, laj, 5r, 5s, lcn, 2a, 2b, lcq, 1er, 2d, 3ad, 2h, lew y 1dd, con los siguientes compuestos exhibiendo valores IC50 contra mTOR menores de 300nM: le, lbq, lbt, lch, lci, 4ap, 4at, 4aw, 4ax, 4ay, 4bd, 12b, 18de, 18dh, 18di, 18dg, 21a, lo, 18b, 18d, 18h, 19d, 19e, 19i, 191, 19n, 19o, 18p, 18q, 18r, 18w, 18af, 18ag, 18an, 18aq, 18au, 18av, lv, 18ay, 18ba, 18bd, lbg, lw, lac, 4p, 9a, lbb, lav, 7b, 7e, 7f, 7g, 7k, 7j, 5c, 5d, 5e, 5g, 4v, 4x, 4y, 4z, 4aa, 4ae, 4ah, 4ai, 5u, 5v, 5w. 5x, 3d, 3f, 18bv, 18cb, 3h, 5h, 5i, 51, 5o, 3i, 3j, 3v, 3x, 3u, 3ab, lal, lam, lan, lbe, 18ci, 18dc, 13a. 19p, 19q, 3k, 3n, 3q, 13f, 13b, 4g, lau, 5q, lay, 18dj, 13c, 13e, 10a, lcl, 2c, 2e, les, 2i, 8d, 13g y leu, con los siguientes compuestos exhibiendo valores IC50 contra mTOR menores de l00nM: lb. la, ld, lbl, lbm, lbn, lf, lbo, li, lg, lh, lbr, lbs, lbu, lbv, le, lj, lbw, lbx, lby, lbz, Ice, Ice, lk, lef, leg. 11, lej, 4al, 4am, 4an, 4ao, 4aq, 4ar, 4as, 4au, 4av, 4az, 4ba, 4bb, 4bc, 4be, 4bf, 12c, 12d, 12a, 18a. 6a. las, lax, ln, lp, ls, lck, 18c, 18e, 18f, 18g, 18i, 18j, 18k, lar, 19a, 19b, 19c, 19f, 19g, 19j, 19k. 181, 18m, lbd, laq, 18s, 18t, 18u, 18v, 18x, 18y, 18z, 18aa, 18ab, 18ac, 18ad, 18ae, 18ah, 18ai, 18aj, 18am, 18ao, 18ap, 18ar, 18as, 18aw, 18ax, 18az, 18bc, 18bf, 18bg, 18bk, 18bh, 18bj, 15a, 18bm, 8b, 4h, 14a, 8a, laa, lab, lad, laf, lag, 14b, lbc, 4i, lah, 4j, 41, 4m, 4n, 4o, 18bn, 18bo, 4u, lbh, 16a, lat, 7c, 7d, 7i, 3a, 3c, 5a, 5b, 4w, 4ac, 4ad, 5t, 3e, 3g, 18bp, 18bq, 18br, 18bs, 18bt, 18bu, 18bw, 18by, 18bz, 18ca, 18cc, 18cd, 18cf, 18cg, 18ch, 18ci, 18cj, 18ck, 18cl, 4ak, 18bx, 18cm, 18cv, lbi, lbj, 4a, law, 3t, 3aa, lap, lbf, 18cn, 18co, 18cp, 18cs, 18ct, 18cu, 18cw, 18cx, 18cz, 18cq, 19r, 19t, 31,19u, 19v, 19w, 20c, lu, 4b, 4q, 4t, 4c, 4e, 4f, 18dd, 4d, laz, 4r, 4s, 2f, 2g, 2j y lcv. Por ejemplo, el compuesto 4aa tiene un IC50 de 151nM.

Los ejemplos comparativos también se probaron y cuando se compararon con los ejemplos correspondientes, los valores IC50 exhibidos para los ejemplos comparativos fueron mayores que aquellos de los ejemplos correspondientes. Por ejemplo el Ejemplo 1k fue medido con un valor IC50 de 15nm mientras el Ejemplo comparativo 1k fue medido con un valor IC50 de 225nm. Por lo tanto, los compuestos del presente invento son más activos para reducir crecimiento celular.

Ejemplo 24

Ensayo de proliferación celular (GI_{50})

El crecimiento celular se evaluó utilizando el ensayo de sulforhodamina B (SRB) (A) . Células T47D (ECACC, 85102201) fueron pasadas de manera rutinaria en RPMI (Invitrogen, 42401018) más 10% de suero fetal de ternero (FCS) , L- glutamina al 1% (Gibco BRL, 25030) hasta una

confluencia no mayor de 80 %. Para realizar el ensayo, células T47D fueron sembradas a $2.5x10^3$ celulas/pozo en 90µl RPMI plus 10% de suero fetal de ternero, L- glutamina al 1% en placas de 96 pozos (Costar, 3904) y se incubaron a 37°C (+5 % CO2) en un incubador humidificado. Una vez las células se han adherido completamente (típicamente después de 4- 5 horas de incubación) la placa fue retirada del incubador y se agregó 10 µL de diluyente agregado a los pozos de control (Al- 12 y B1- 12) . El compuesto se prepare en una dilución semi- logarítmica de seis puntos a 10x la concentración final requerida ej., para un rango de 6 puntos entre 30µM hasta l00nM en eapas semi- logarítmicas, la dilución empezó en 300µM en placa de concentración. La dosificación se completó mediante la adición de 10µL de compuesto a alta concentración a C1- 12 hasta la concentración más baja en H1- 12. Luego las placas se incubaron durante 120 horas antes de análisis SRB.

Al terminar la incubation, el medio fue retirado y las células se fijaron con 100µl ácido tricloroacético helado al 10% (w/v) . Las placas se incubaron a 4°C durante 20 minutos y luego se lavaron cuatro veces con agua. Luego cada pozo de células fue teñido con 100µl de SRB al 0.4 % (w/v) (Sulforhodamina B, Sigma, Poole, Dorset, UK, Número de catálogo S- 9012) en ácido acético al 1% durante 20 minutos antes de lavar cuatro veces con ácido acético al 1%. Luego las placas se secaron durante 2 horas a temperatura ambiente. El tinte de las células teñidas fue solubilizado mediante la adición de 100µl de l0mM Tris Base en cada pozo. Las placas fueron agitadas suavemente y dejadas a temperatura ambiente durante 30 minutos antes de medir la densidad óptica a 564nM sobre un lector de placas de microtítulos Microquant. La concentración de inhibitor que produce una reducción de 50 % en crecimiento (GI50) se determinó mediante análisis de intensidad del teñido de las células tratadas como un porcentaje de los pozos de control de vehículo utilizando el software Excelfit

(A) Skehan, P., Storung, R., Scudiero, R., Monks, A., McMahon, 1, Vistica, D., Warren, J. T., Bokesch, H., Kenny, S. y Boyd, M. R. (1990) Nuevo ensayo de citotoxicidad colorimétrica para clasificàción de fármacos anticancerígenos. J. Nati. Cáncer Inst. 82,1107- 1112.

Los Ejemplos 1a- 11 fueron probados y exhibieron valores GI_{50} menores de 300 nM.

Los ejemplos comparativos también se probaron y cuando se compararon con los ejemplos correspondientes, los valores GI_{50} exhibidos para los ejemplos comparativos fueron mayores que aquellos de los ejemplos correspondientes (es decir GI_{50} Ejemplo comparativo 1a >

GI50 Ejemplo 1a) . Por ejemplo el Ejemplo lk se midió determinando un GI_{50} de 32nm mientras el Ejemplo comparativo 1k se midió determinando un GI_{50} de 268nm. Por lo tanto, los compuestos del presente invento son más activos para reducir el crecimiento celular.

Ejemplo 25

Ensayo in vitro Akt phospho- Ser473

Este ensayo determina la capacidad de los compuestos de prueba para inhibir fosforilación de Serina 473 en Akt como se evaluó utilizando tecnología Acumen Explorer (Acumen Bioscience Limited) , un lector de placas que se puede utilizar para cuantificar rápidamente características de imágenes generadas mediante escaneo por láser.

Una línea celular de adenocarcinoma de mama humano MDA- MB- 468 (LGC Promochem, Teddington, Middlesex, UK, No. de Catálogo. HTB- 132) se mantuvo rutinariamente a 37°C con C02 al 5% hasta una confluencia de 70- 90 % en DMEM conteniendo FCS inactivado por calor al10 % y L- glutamina al 1 %.

Para el ensayo, las células fueron separadas del matraz de cultivo utilizando 'Accutase' (Innovative Cell Technologies Inc, San Diego, CA, USA; No. de Catálogo. AT104) utilizando métodos estándares de cultivo de tejidos y se resuspendieron en medio para proporcionar $1.7x10^5$ células por ml. Se sembraron alicuotas (90 ¡0,1) en cada uno de los 60 pozos internos de una placa negra de 96 pozos Packard (PerkinElmer, Bostón, MA, USA; No. de Catálogo. 6005182) para proporcionar una densidad de ~15000 células por pozo. Alicuotas (90 µl) de medio de cultivo se colocaron en los pozos externos para prevenir los efectos de borde. Las células se incubaron durante la noche a 37°C con CO2 al 5% para permitirles adherirse.

El día 2, las células fueron tratadas con compuestos de prueba e incubadas durante 2 horas a 37°C con CO_2 al 5%. Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron serialmente según lo requerido con medio de crecimiento para proporcionar un rango de concentraciones que fueron 10 veces las concentraciones de prueba finales requeridas. Alicuotas (10µl) de cada dilución de compuesto se colocaron en un pozo (por tripicado) para proporcionar las concentraciones finales requeridas. Como un control de respuesta mínimo, cada placa contenia pozos con una concentración final de 100 µM LY294002 (Calbiochem, Beeston, UK, No. de Catálogo. 440202) . Como un control de respuesta máximo, los pozos contenian DMSO al 1% en cambio del compuesto de prueba. Después de la incubación,

los contenidos de las placas fueron fijados mediante tratamiento con una solución de formaldehído acuoso al 1.6 %(Sigma, Poole, Dorset, UK, No. de Catálogo. F1635) a temperatura ambiente durante 1 hora.

Todos los pasos de aspiración y lavado subsiguientes se realizaron utilizando una lavadora de placa de 96 pozos Tecan (velocidad de aspiración 10 mm/sec) . La solución fijadora fue retirada y los contenidos de las placas se lavaron con solución salina amortiguado con fosfato (PBS; 50 µl; Gibco, No. de Catálogo. 10010015) . Los contenidos de las placas se trataron durante 10 minutos a temperatura ambiente con un alícuota (50 µl) de un amortiguador de permeabilización celular que consta de una mezcla de PBS y Tween- 20 al 0.5%. El amortiguador de "permeabilización" fue retirado y los sitios de unión no específicas fueron bloqueados mediante tratamiento durante 1 hora a temperatura ambiente de una alícuota (50 µl) de un buffer bloqueador que consta de lecha descremada seca al 5% ['Marvel' (marca registrada) ; Premier Beverages, Stafford, GB] en una mezcla de PBS y Tween- 20 al 0.05%. El buffer bloqueador fue retirado y las células se incubaron durante 1 hora a temperatura ambiente con solución de anticuerpo de conejo anti phospho- Akt (Ser473) de conejo (50lµ por pozo; Cell Signalling, Hitchin, Herts, U.K., No. de Catálogo 9277) que se ha diluido 1:500 en buffer bloqueador'. Las células fueron lavadas tres veces en una mezcla de PBS yTween- 20 al 0.05%. Subsecuentemente, las células fueron incubadas durante 1 hora a temperatura ambiente con IgG anti- conejo de cabra rotulado Alexafluor 488 r (50 µl por pozo; Sondas moleculares, Invitrogen Limited, Paisley, UK, No. de Catálogo. Al 1008) que se ha diluido 1:500 en buffer bloqueador". Las células se lavaron 3 veces con una mezcla de PBS y Tween- 20 al 0.05%. Una alícuota de PBS (50 µl) se agregó a cada pozo y las places se sellaron con selladores negros de placa y la señal de fluorescencia se detectó y analizó.

Los datos de respuesta de dosis de fluorescencia obtenidos con cada compuesto se analizaron y el grado de inhibición de Serina 473 en Akt se expreso como un valor IC50.

Los compuestos probados en este ensayo exhibieron valores IC50 contra mTOR menores de 10µm.

Los siguientes compuestos exhibieron valores IC50 contra mTOR menores de lµm: lbu, lce, 12b, 18de, 18dg, 18j, lar, 19e, 19h, 19i, 191, 19m, 19n, 19o, 18n, 18o, 18z, 18aa, 18ag, 18ai, 18al, lv, 18az, lah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, law, 3u, lbf, 18ct, 19q, 19s, 19u, 19v, 19w, lau, 5r, 4t, 18dj, lcl, 2d, 2e, les, 2h,

2j o lew, con los siguientes compuestos exhibiendo valores IC50 contra mTOR menores de 300nM: lbo, lbp, lj, lbx, lby, lef, lci, lej, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, ln, lp, lq, 18e, 18h, 19b, 19c, 19f, 19k, 18p, lbd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, lab, 4p, 9a, lav, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, lam, lao, 18cn, 18cx, lbk, 13b, 4g, 5s, 4q, 18dd, lep, lcq, 2f, 2g, 13g, lev o let, con los siguientes compuestos exhibiendo valores IC50 contra mTOR menores de 100nM: Ib, la, le, ld, lbl, lbm, lf, li, lg, lh, lbr, lbs, lbv, le, lbz, Ice, lk, leg, 11,4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, las, ls, 18c, 18d, 18f, 18g, 18í, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, Iba, 8a, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41,4m, 4n, 4o, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5 a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, Ico y 3ad. Por ejemplo, el compuesto 18di tiene un IC50 de 151nM.

Los ejemplos comparativos también se probaron y cuando se compararon con los ejemplos correspondientes, los valores IC50 exhibidos para los ejemplos comparativos fueron mayores que aquellos de los ejemplos correspondientes. Por ejemplo el Ejemplo 1k se midió determinando un IC50 de 83nm mientras el Ejemplo comparativo 1k se midió determinando un IC50 de 412nm. Por lo tanto, compuestos del presente invento son más activos para reducir el crecimiento celular.

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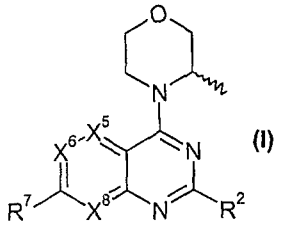
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REIVINDICACIONES

1. Un compuesto de la fórmula I:



(I)

. o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos de X^5, X^6 o X^8 es N, y los demás son CH;

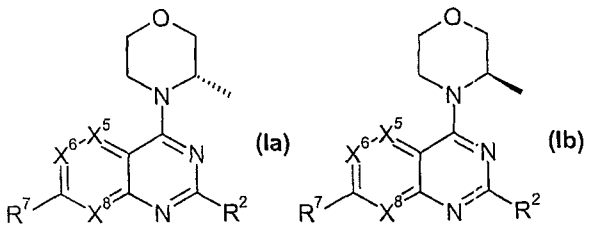
R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{cl}$, $NR^{N7b}S0_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} o R^{S1} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido. un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} o R^{N2} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{NS} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} se seleccionan a partir de H y un grupo C1- 4 alquilo;

R^2 se selecciona a partir de H, halo, OR^{02}, SR^{s2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{02} y R^{S2b} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C1- 7 alquilo opcionalmente sustituido; RN5 y RN6 se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente substituido, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos.

2. Un compuesto de la fórmula 1a ó 1b:



, o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos de X^5, X^6 y X^8 es N, y los demás son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{cl}$, $NR^{N7b}S0_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} y R^{S1} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} y R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

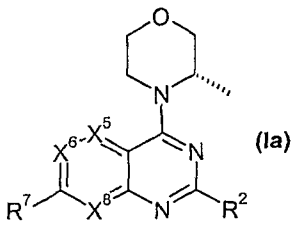
R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros

opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} se seleccionan a partir de H y un grupo C1- 4 alquilo;

R^2 se selecciona a partir de H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{02} y R^{S2b} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; RN5 y RN6 se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, y un grupo C5- 20 arilo opcionalmente sustituido, o RN5 y RN6 junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos.

3. Un compuesto de la fórmula Ia:



o una sal farmacéuticamente aceptable del mismo, en donde:

uno o dos de X^5, X^6 y X^8 es N, y los demás son CH;

R^7 se selecciona a partir de halo, OR^{01}, SR^{S1}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{cl}$, $NR^{N7b}S0_2R^{S2a}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, donde R^{01} y R^{S1} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N1} y R^{N2} se seleccionan independientemente a partir de H, un

grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N1} o R^{N2} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{C1} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N8}R^{N9}$, donde R^{N8} y R^{N9} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N8} y R^{N9} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos;

R^{S2a} se selecciona a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N7a} y R^{N7b} se seleccionan a partir de H o un grupo 1- 7 alquilo opcionalmente sustituido;

R^2 se selecciona a partir de H, halo, OR^{02}, SR^{S2b}, $NR^{N5}R^{N6}$, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, en donde R^{02} y R^{S2b} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido; R^{N5} y R^{N6} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo heteroarilo de 5 a 20 miembros opcionalmente sustituido, o un grupo C5- 20 arilo opcionalmente sustituido, o R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido conteniendo entre 3 y 8 átomos cíclicos.

4. Un compuesto según cualquiera de las reivindicaciones 1 a 3, en donde solamente uno entre X^5, X^6 y X^8 es N.

5. Un compuesto según cualquiera de las reivindicaciones 1 a 3, en donde X^6 es CH y X^5 y

X^8 son N.

6. Un compuesto según cualquiera de las reivindicaciones 1 a 4, en donde X^8 es N.

7. Un compuesto según cualquiera de las reivindicaciones anteriores, en donde R^7 se selecciona a partir de un grupo C5- 20 arilo opcionalmente sustituido, OR^{01}, $NR^{N1}R^{N2}$, $NR^{N7a}C(0)\ R^{c1}$ y $NR^{N7b}S0_2R^{s2a}$

8. Un compuesto según cualquiera de las reivindicaciones 1 a 6, en donde R^7 es un grupo fenilo o piridilo opcionalmente sustituido.

9. Un compuesto según cualquiera de las reivindicaciones 1 a 6, en donde R^7 es OR^{01}, y R^{O1} es un grupo C1- 7 alquilo, el cual se puede sustituir.

10. Un compuesto según cualquiera de las reivindicaciones 1 a 6, en donde R^7 es $NR^{N1}R^{N2}$, y R^{N2} es H.

11. Un compuesto según la reivindicación 10, en donde R^{N1} es C3- 7 cicloalquilo.

12. Un compuesto según la reivindicación 10, en donde R^{N1} es C5- 6 arilo.

13. Un compuesto según cualquiera de las reivindicaciones 1 a 6, en donde R^7 es $NR^{N7a}C(0)\ R^{c1}$, y R^{N7a} preferiblemente es H.

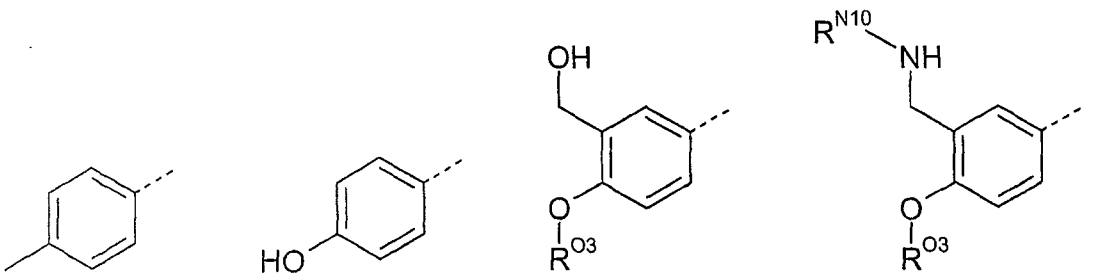
14. Un compuesto según la reivindicación 13, en donde R^{C1} se selecciona a partir de un grupo C5- 20 arilo opcionalmente sustituido, C3- 20 heterociclilo, C1- 7 alquil o $NR^{N8}R^{N9}$, donde R^{NS} es hidrógeno, o R^{N9} es C1- 7 alquilo.

15. Un compuesto según cualquiera de las reivindicaciones 1 a 6, en donde R^7 es $NR^{N7b}S0_2R^{S2a}$, o R^{N7b} es H.

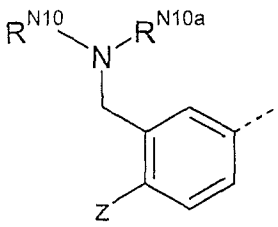
16. Un compuesto según la reivindicación 15, en donde R^{S2a} es C1- 7 alquil.

17. Un compuesto según la reivindicación 8 en donde R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales son preferiblemente seleccionados de halo, hidroxilo, ciano, C1- 7 alquilo, C1- 7 alcoxilo, sulfonamino (por ejemplo - NHS(=0) 2C1- 7alquil) amino (por ejemplo - NH2, C5- 6 arilamino, C1- 7 alquilamino, y di- (C1- 7alquil) amino) , y amido (por ejemplo - CONH2, - CONHC1- 7 alquilo, - CON(C]-7alquil) 2 o - CONH heterociclilo) y en donde los grupos sustituyentes alquilo, alcoxilo, o arilo se pueden opcionalmente adicionalmente sustituir por uno o más grupos seleccionados a partir de halo, hidroxilo, C1- 7 alquilo, C1- 7 alcoxilo, C5- 6 arilo, - NHS(=O) $_2$C1- 7 alquilo, C5- 6 arilamino, di- (C1- 7alquil) amino y C1- 7 alquilamino.

18. Un compuesto según la reivindicación 8 en donde R^7 es un grupo fenilo opcionalmente sustituido seleccionado de



y



en donde

Z es H, F ó OR^{03};

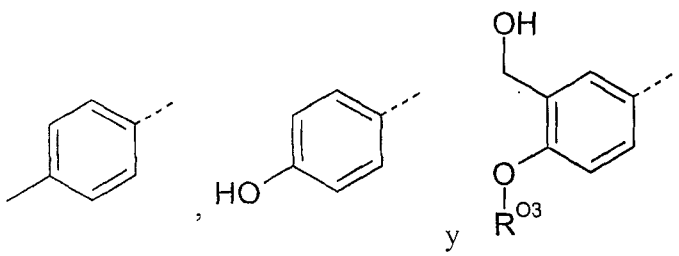
R^{03} se selecciona a partir de hidrógeno o un grupo C1- 6 alquilo opcionalmente sustituido;

R^{N10} se selecciona a partir de hidrógeno, C(0) R^{C2}, C(S) R^{C3}, $S0_2R^{S3}$, un grupo C5- 20

heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido, o un C1- 10 alquilo opcionalmente sustituido donde R^{C2} y R^{C3} se seleccionan a partir de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C1- 7 alquilo opcionalmente sustituido o $NR^{N11}R^{N12}$, donde R^{Nn} o R^{N12} se seleccionan independientemente a partir de H, un grupo C1- 7 alquilo opcionalmente sustituido, un grupo C5- 20 heterociclilo opcionalmente sustituido, un grupo C5- 20 arilo opcionalmente sustituido o R^{N11} y R^{N12} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos; y R^{S3} es seleccionado de H, un grupo C5- 20 arilo opcionalmente sustituido, un grupo C5- 20 heteroarilo opcionalmente sustituido, o un grupo C1- 7 alquilo opcionalmente sustituido C1- 7;

R^{N10a} se selecciona a partir de hidrógeno o un grupo C1- 10 alquilo opcionalmente sustituido; o R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 3 y 8 átomos cíclicos.

19. Un compuesto según la reivindicación 8, en donde R^7 es un grupo fenilo opcionalmente sustituido seleccionado de

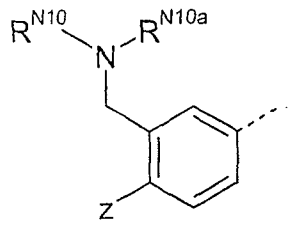


y

en donde

R^{03} se selecciona a partir de hidrógeno o un grupo C1- 6 alquilo opcionalmente sustituido.

20. Un compuesto según la reivindicación 8, en donde R^7 es



en donde

Z es H, F u OR^{O3}

R^{N10} se selecciona a partir de hidrógeno, - C(0) CH_3, - C(0) CH_2OH, - CH_3, - CH_2CH_3, - CH_2CH_2OH,

$CH(CH_3)_2$, - CH_2CH_2OMe, - $CH_2C(CH_3)_2$, - $CH_2CH_2C(CH_3)_2$, - $CH(CH_3)$ $CH_2C(CH_3)_2$, $CH_2CH_2CH_2N(CH_3)_2$, ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, - CH_2 ciclopropilo, metilciclohexilo, cianociclohexilo, pirazolilo, hidroxipirrolidinilo, - CH_2 imidazole;

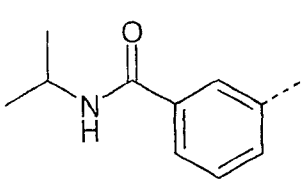
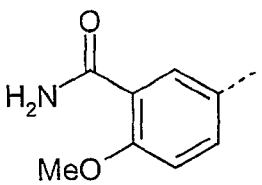
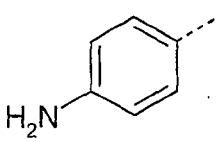
R^{N10a} es hidrógeno; o

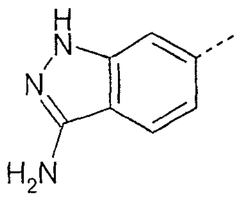
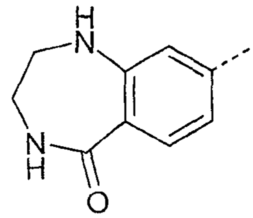
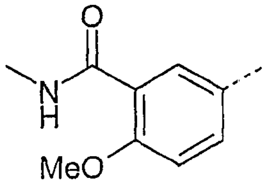
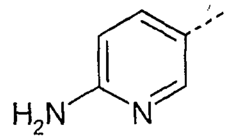
R^{N10} y R^{N10a} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico opcionalmente sustituido que contiene entre 5 y 6 átomos cíclicos;

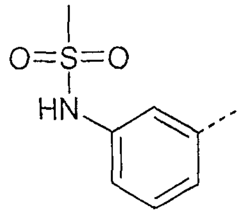
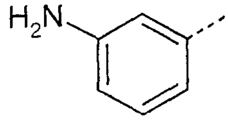
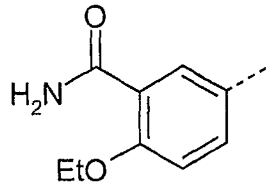
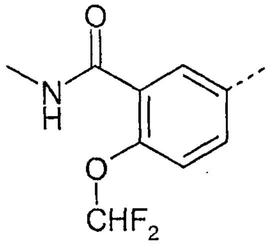
y donde los sustituyentes opcionales se seleccionan a partir de halo, hidroxilo, C1- 7alquiloxilo.

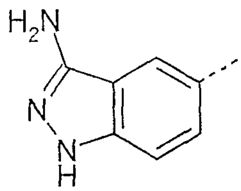
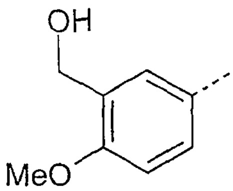
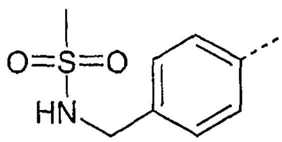
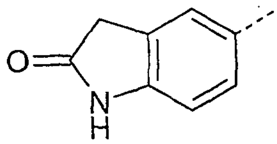
21. Un compuesto según la reivindicación 8 en donde R^7 es un grupo fenilo opcionalmente sustituido, en donde los sustituyentes opcionales se seleccionan a partir de fluoro, hidroxilo, ciano, nitro, metilo, metoxilo, - OCH_2CH_3, - NH_2, - $NHS0_2CH_3$, - $CH_2NHS0_2CH_3$, - $OCHF_2$, - CH_2OH, - $C0_2H$ - $CONH_2$, - CONHMe, - CONHEt, - $CONHCH(CH_3)_2$, - $CONHCH_2CH_2F$, - $CONHCH_2CHF_2$, - $CONHCH_2CH_2OH$, - CONMeEt, - $CONMe_2$, N- metilpiperazinilcarbonilo y 4- hidroxipiperidinilcarbonilo

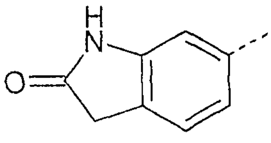
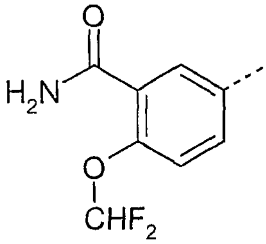
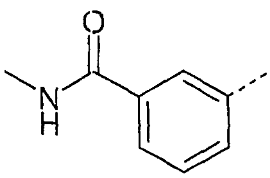
22. Un compuesto según la reivindicación 7 en donde R^7 se selecciona a partir de

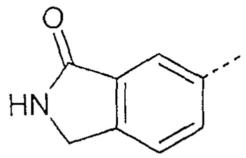

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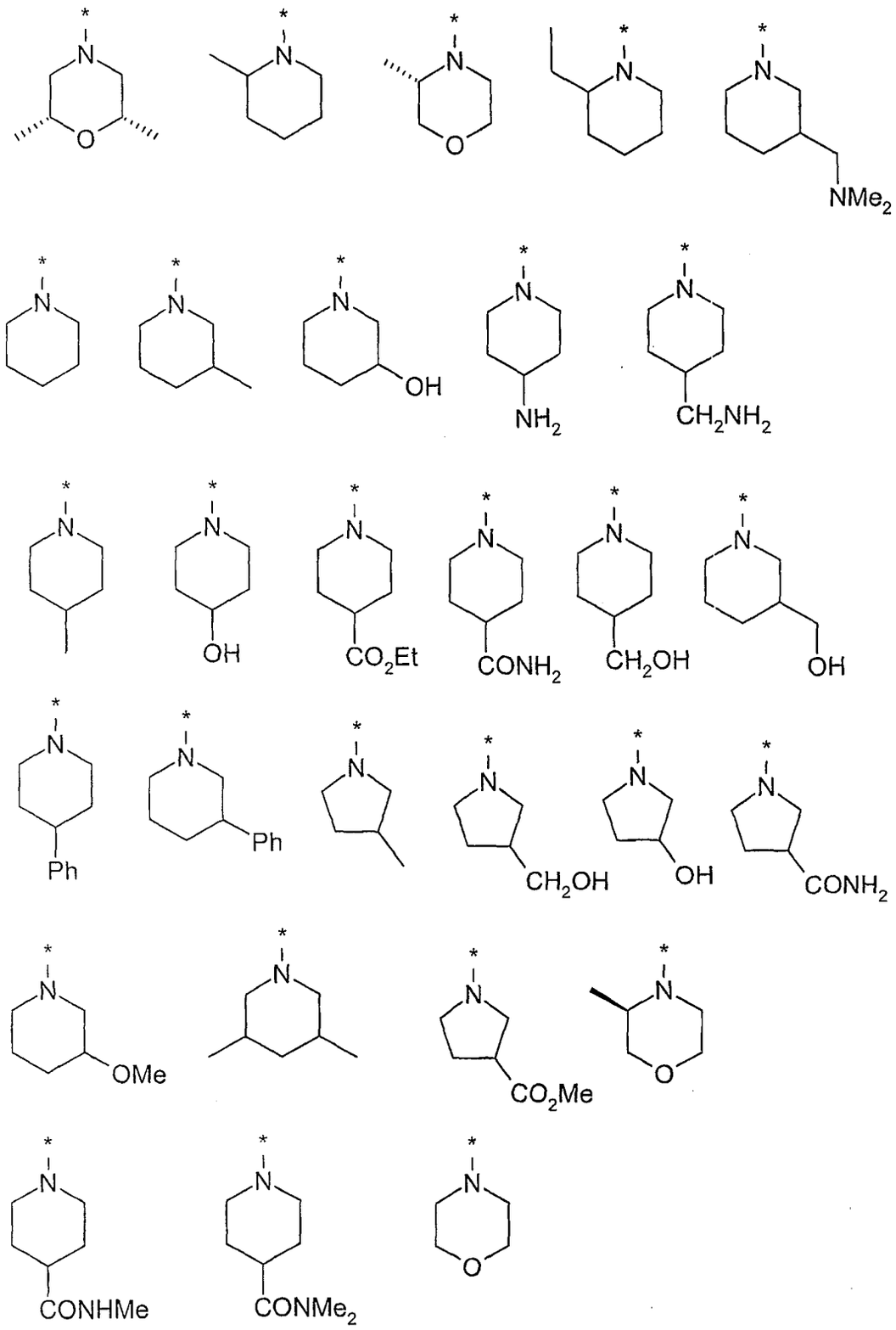
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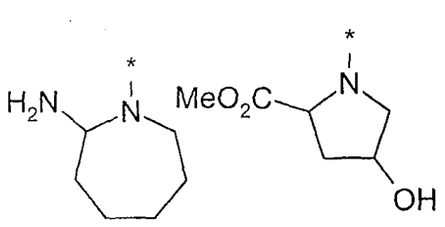
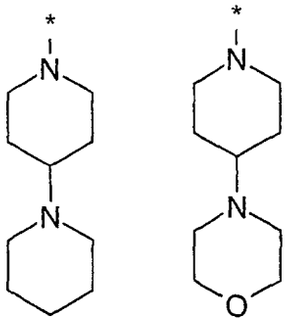
y

23. Un compuesto según cualquiera de las reivindicaciones anteriores, en donde R^2 es $NR^{N5}R^{N6}$, donde R^{N5} y R^{N6} junto con el nitrógeno al cual están unidos forman un anillo heterocíclico que contiene entre 3 y 8 átomos cíclicos, el cual puede opcionalmente ser sustituido.

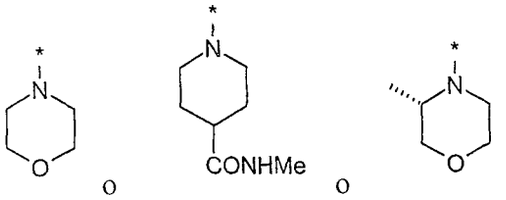
24. Un compuesto según la reivindicación 23, en donde R^2 se selecciona a partir de morfolino, tiomorfolino, piperadinilo, piperazinilo, homopiperazinilo y pirrolidinilo.

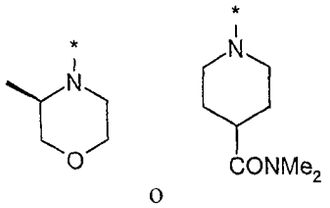
25. Un compuesto según la reivindicación 23 en donde R^2 es



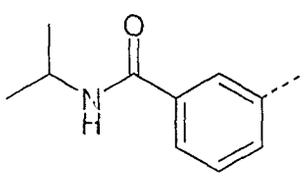
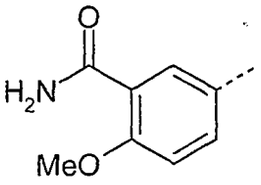
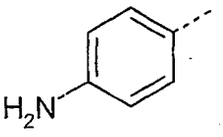


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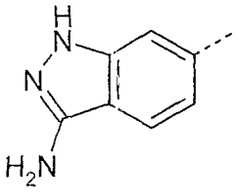
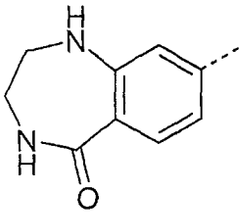
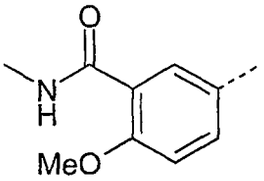
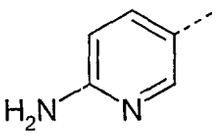
26. Un compuesto según la reivindicación 23, en donde R^2 es

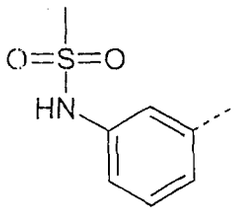
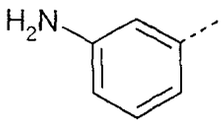
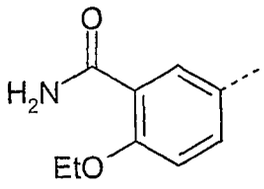
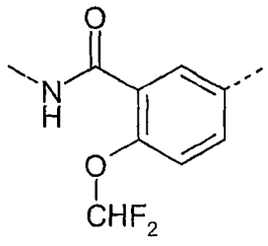
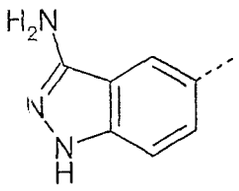
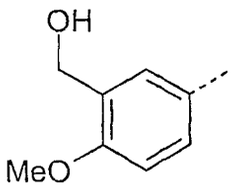
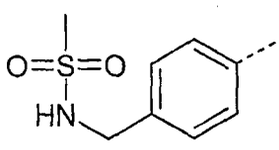
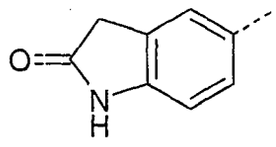
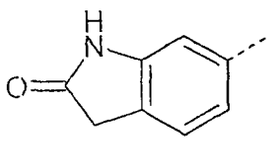
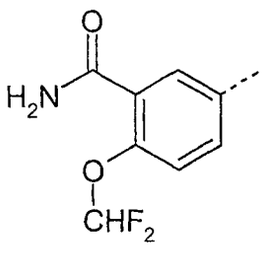
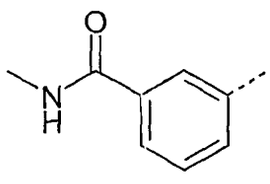
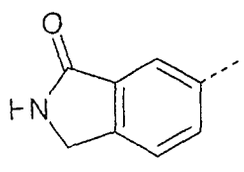

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27. Un compuesto según la reivindicación 7 en donde R^7 se selecciona a partir de

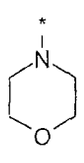
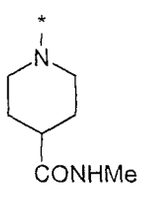
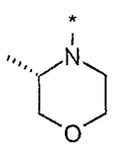
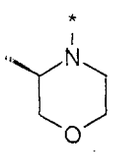
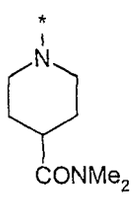

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y en donde R2 es


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28. Un compuesto según la reivindicación 1 seleccionado de cualquiera de los Ejemplos.

29. Un compuesto según la reivindicación 1 seleccionado de cualquiera de los Ejemplos lbu,

lce, 12b, 18de, 18dg, 18j, lar, 19e, 19h, 19i, 191, 19m, 19n, 19°, 18n, 18°, 18z, 18aa, 18ag, 18ai, 18al, lv, 18az, lah, 7e, 7i, 7j, 5d, 5f, 4v, 4ab, 4aj, 5t, 5u, 5w, 5x, 5y, 5z, 3f, 3g, 18bp, 18bs, 18bv, 18by, 18cb, 18cv, law, 3u, lbf, 18ct, 19q, 19s, 19u, 19v, 19w, lau, 5r, 4t, 18dj, lcl, 2d, 2e, les, 2h, 2[illegible], lew, lbo, lbp, lj, lbx, lby, lef, lci, lej, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, ln, lp, lq, 18e, 18h, 19b, 19c, 19f, 19k, 18p, lbd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, lab, 4p, 9a, lav, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, lam, lao, 18cn, 18cx, lbk, 13b, 4g, 5s, 4q, 18dd, lep, lcq, 2f, 2g, 13g, lev, let, Ib, la, le, Id, lbl, lbm, lf, li, lg, lh, lbr, lbs, lbv, le, lbz, Ice, lk, leg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, las, ls, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, Iba, 8a, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41, 4m, 4n, 4o, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, lco, 3ad, lcr, lew, ley, ldv, 15c, leí, lem, lcn, lcq, lev, lex, ldi, ldj, leb, lej, lck, let, leu, lez, ldb, ldc, ldd, lde, ldg, ldh, ldk, ldl, ldm, ldn, Ido, ldp, ldq, ldt, ldu, ldw, ldy, ldz, lea, lee, led, lee, 18dm, 18dn y 18do.

30. Un compuesto según la reivindicación 1 seleccionado de cualquiera de Ejemplos lbo, lbp, lj, lbx, lby, lef, lci, lej, 4an, 4ap, 4av, 12d, 18dh, 18di, 6a, ln, lp, lq, 18e, 18h, 19b, 19c, 19f, 19k, 18p, lbd, 18w, 18ab, 18af, 18aj, 18aq, 18as, 18av, 18ay, 18bb, 18bc, 18bf, 18bl, lab, 4p, 9a, lav, 3a, 5b, 5c, 5e, 5g, 4aa, 4ad, 4ah, 5v, 3e, 18bq, 18bt, 18bz, 18ca, 18cd, 18cg, 18ci, 18bx, 5n, lam, lao, 18cn, 18cx, lbk, 13b, 4g, 5s, 4q, 18dd, lep, lcq, 2f, 2g, 13g, lev, let, Ib, la, le, Id, lbl, lbm, lf, li, lg, lh, lbr, lbs, lbv, le, lbz, lee, lk, leg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, las, ls, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, lbg, 8b, 4h, Iba, 8a, laa, lac, lae, laf, lag, 14b, lbc, 4i, 4j, 4k, 41, 4m, 4n, 4o, 18bn, 18bo, 4u, lbb, lat, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, lak, lal, lap, lbe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, laz, 4r, 4s, lcn, lco, 3ad, lcl, lem, lcn, lcq, lev, lex, ldi, ldj, leb, lej, lck, let, leu, lez, ldb, ldc, ldd, lde, ldg, ldh, ldk, ldl, ldm, ldn, Ido, ldp, ldq, ldt, ldu, ldw, ldy, ldz, lea, lee, led, lee, 18dm, 18dn o 18do.

31. Un compuesto según la reivindicación 1 seleccionado de cualquiera de Ejemplos Ib, la, le, Id, Ibl, Ibm, If, Ii, Ig, Ih, Ibr, Ibs, Ibv, Ie, Ibz, Ice, Ik, Ieg, 11, 4al, 4am, 4ao, 4aq, 4as, 4at, 4au, 4aw, 4ax, 4ay, 4az, 4ba, 4bb, 4bc, 4bd, 4be, 4bf, 12c, 12a, 18a, las, ls, 18c, 18d, 18f, 18g, 18i, 18k, 19j, 18m, 18q, 18r, 18s, 18t, 18u, 18v, 18x, 18y, 18ac, 18ad, 18ae, 18ah, 18ak, 18am, 18an, 18ap, 18ar, 18au, 18aw, 18ax, 18ba, 18bd, 18be, 18bg, 18bi, 18bk, 18bh, 18bj, 18bm, Ibg, 8b, 4h, Iba, 8a, Iaa, Iac, Iae, Iaf, Iag, 14b, Ibc, 4i, 4j, 4k, 41, 4m, 4n, 4o, 18bn, 18bo, 4u, Ibb, Iat, 7b, 7c, 7d, 7f, 7g, 7k, 5a, 4w, 4x, 4y, 4z, 4ac, 4af, 4ai, 18br, 18bw, 18cc, 18cf, 18ch, 18cj, 18ck, 18cl, 4ak, 18cm, 4a, 3i, 3y, Iak, Ial, Iap, Ibe, 18co, 18cr, 18cs, 18db, 19p, 31, lu, 4b, 5q, 4c, 4e, 4f, 4d, Iaz, 4r, 4s, Icn, Ico, 3ad, Icj, Ick, Ict, Ieu, Iez, Idb, Idc, Idd, Ide, Idg, Idh, Idk, Idl, Idm, Idn, Ido, Idp, Idq, Idt, Idu, Idw, Idy, Idz, Iea, Iee, Ied, Iee, 18dm, 18dn y 18do.

32. Un compuesto según la reivindicación 1 seleccionado de cualquiera de Ejemplos la, lu, lal, lap, lat, laz, Ico, Ide, Idg, Idh, Idk, Idl, Idp, Idq, Idr, Ids, Idt, Idu, Idy, Iee, Iee, 12d, 14b, 18dn y 18do

33. Una composición farmacéutica comprendiendo un compuesto según cualquiera de las reivindicaciones 1 a 32, y un vehículo o diluyente farmacéuticamente aceptable.

34. Un compuesto según cualquiera de las reivindicaciones 1 a 32 para utilizar en un método de tratamiento del cuerpo humano o animal.

35. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32 en la preparación de un medicamento para el tratamiento de una enfermedad aliviada mediante la inhibición de mTOR.

36. Un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, para utilizar como un medicamento.

37. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para utilizar en la

producción de un efecto inhibitorio de mTOR en un animal de sangre caliente (homeotermos) tal como el hombre.

38. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para utilizar en la producción de un efecto anti- cancerígeno en un animal de sangre caliente tal como el hombre.

39 El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para utilizar en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama y páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

40. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en la producción de un efecto inhibitorio de mTOR en un animal de sangre caliente tal como el hombre.

41. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en la producción de un efecto anti- cancerígeno en un animal de sangre caliente tal como el hombre.

42. El uso de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

43. Un método para producir un efecto inhibitorio de mTOR en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal

una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo.

44. Un método para producir un efecto anti- cancerígeno en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo.

45 Un método para tratar melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios, en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo.

46. Una composición farmacéutica la cual comprende un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en la producción de un efecto inhibitorio de mTOR en un animal de sangre caliente tal como el hombre.

47. Una composición farmacéutica la cual comprende un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en la producción de un efecto anti- cancerígeno en un animal de sangre caliente tal como el hombre.

48. Una composición farmacéutica la cual comprende un compuesto según cualquiera de las reivindicaciones 1 a 32, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o vehículo farmacéuticamente aceptable para utilizar en el tratamiento de melanoma, glioma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico,

cáncer pulmonar, leucemias, malignidades linfoides, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, endometrio, mama o páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios en un animal de sangre caliente tal como el hombre.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003179

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/519

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 277 738 A1 (YAMANOUCHI PHARMA CO LTD [JP]; LUDWIG INST CANCER RES [US]; IMP CANCER) 22 January 2003 (2003-01-22) the whole document	1-48
Y	HAYAKAWA ET AL: "Synthesis and biological evaluation of 4-morpholino-2-phenylquinazol ines and related derivatives as novel PI3 kinase p110alpha inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 14, no. 20, 11 July 2006 (2006-07-11), pages 6847-6858, XP005633132 ISSN: 0968-0896 the whole document	1-48

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 October 2007	29/10/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Klein, Didier

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003179

645

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 990 117 A (PAMUKCU RIFAT [US] ET AL) 23 November 1999 (1999-11-23) the whole document	1-48
A	US 4 560 685 A (ROCH JOSEF [DE] ET AL) 24 December 1985 (1985-12-24) the whole document	1-48
P,Y	WO 2007/060404 A (KUDOS PHARM LTD [GB]; HUMMERSONE MARC GEOFFREY [GB]; GOMEZ SYLVIE [GB]) 31 May 2007 (2007-05-31) the whole document	1-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/003179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017881- -00000-0000

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Act. 411 PRESENTACION Folios: 646

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ENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [✓] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Vacarro

Firma Responsable

Fecha 23-02-09

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Bogotá,
2020

Doctor(a)
RAISBECK J. IAN

REFERENCIA	Radicación No.	09 17881
	Solicitud internacional	PCT/2007/003179
	Fecha inicio fase nacional	23/03/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	6209

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALEX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 05 JUN. 2009
jfernand

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAMSBECK J. IAN

REFERENCIA	Radicación No.	9 17881
	Solicitud internacional	PCT/2007/003179
	Fecha inicio fase nacional	23/03/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	6203

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 05 JUN. 2009
jfernand