Organizacion y Digitalizacion CSA Ltda
CSA716719

1/3

17337/09

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

Organizacion y Digitalizacion CSA Ltda

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-17337

21/57

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE MORFOLINO PIRIMIDINA, ÚTILES EN EL TRATAMIENTO DE DESORDENES PROLIFERATIVOS

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-151 85 Södertalje

APODERADO: J. IAN RAISBECK

BOGOTÁ 20 de febrero de 2009

P2009/000023

OLARTERAISBECK
OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017337- -00000-0000
Fecha: 2009-02-20 17:09:26 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 925

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000023**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: ASTRAZENECA AB
Dirección: S-151 85 Södertalje
Nacionalidad o Domicilio: Suecia
Lugar de Constitución: Suecia
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 DJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2007/003173 Fecha Agosto 21, 2007

Publicación Internacional No. WO 2008/023159 Fecha Febrero 28, 2008

(6) **Título (54)** **DERIVADOS DE MORFOLINO PIRIMIDINA, ÚTILES EN EL TRATAMIENTO DE DESORDENES PROLIFERATIVOS**

Clasificación Internacional (51) C07D 401/04, C07D 239/42, C07D 401/12, C07D 401/14, C07D 403/04, C07D 403/12, C07D 405/12, C07D 409/12, C07D 413/12, C07D 417/12, A61K 31/506, A61K 31/5377, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Agosto 24, 2006	0616747.2
US	Julio 9, 2007	60/948,544

(9) **Comprobante de pago No.** 09-13,934 **Fecha** Febrero 20 de 2009

(10) **ANEXOS**

[X]	Comprobante de pago de la tasa de presentación de la solicitud.
[X]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[X]	Poderes, si fuere el caso. Adjunto copia simple. Ver expediente No. 07-074.694
[ ]	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.

3

LISTA DE INVENTORES

PCT/GB2007/003173

1. **Maurice, Raymond, Verschoyle FINLAY,**
   AstraZeneca R & D Alderley,
   Alderley Park, Macclesfield Cheshire SK10 4GT
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   Nacionalidad: Británica

2. **Jeffrey MORRIS,**
   AstraZeneca R & D Alderley,
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   Gran Bretaña
   Nacionalidad: Británica

3. **Kurt Gordon PIKE,**
   AstraZeneca R & D Alderley,
   Alderley Park, Macclesfield Cheshire SK10 4GT
   Gran Bretaña
   Nacionalidad: Británica

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 13,934
FECHA : FEBRERO 20 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-017337- -00000-0000
Fecha: 2009-02-20 17:09:26 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 925

***** 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	105792013	20/02/2009	2,613,000.00

***** 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._____

No. 11426

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

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

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

Certificación Notarial

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

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

Ex oficio:

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

Traductor Oficial
JORGE E. SERNA H.

6

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

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

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 10-054

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

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

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

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

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

   Notary Public in Stockholm

Certified

5. **at** Stockholm 6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. No 4071

9. **Seal/stamp:** 10. **Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro
Zayda Cabal
Simón Arbeláez
Alexander Agudelo
Camilo A. Rodríguez
Lina Moreno
Catalina Barbosa
Of Counsel
Guillermo Cabal
Graciela Adel
Jacqueline Chaparro
Cruz E. de Mongabure

Power of Attorney

The undersigned,

AstraZeneca AB

domiciled in

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

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

Poder

El suscrito,

AstraZeneca AB

domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

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

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTOBER 2007

City,Country/Ciudad,País: SODERTALJE

NOTARIOS PUBLICOS Y DE COMERCIO
ANNE-MARIE BOOS

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

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

hereby certify that

ANDERS BURÉN

duly authorized to sign for

ASTRAZENECA AB

has issued and signed the foregoing document.

Fee 340:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

10

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date,	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That	1. Que
of legal age and domiciled in	mayor de edad y domiciliado
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.	4. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):	5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):
1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB	
2. AUTHORISATION IN FAVOUR OF SIGNATORY	

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)

NOTARIUS PUBLICUS
ANNE MARIE BONER

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

Certificado de Existencia

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

AstraZeneca AB

Registro No. 556011-7482

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

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

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

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

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

JORGE E. SERNA SIERRA

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

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

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

Certificación Notarial

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

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

Ex oficio:

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

Apostilla adjunta:

Traductor Oficial
JORGE E. SIERRA
Licencia 876 - 1971 Ministerio

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País: Suecia

El presente documento público

2. Ha sido firmado por: Anne-Marie Bonde

3. Actuando en calidad de: Notario Público

4. Lleva el sello / estampilla de: Notario Público de Estocolmo.

Certificado

5. En: Estocolmo

6. El: Día 26 de Octubre de 2007

7. Por: Björn Sandin, Notario Público

8. Bajo el No. 4070

9. Sello / estampilla: Björn Sandin, Notario Público de Estocolmo.

10. Firma: (Firmado)

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 10-053

Traductor Oficial
JORGE E. SIERRA REYES
Licencia [illegible]

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

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

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

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

   Notary Public in Stockholm

Certified

5. at Stockholm 6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4070

9. **Seal/stamp:** 10. **Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

Bolagsverket

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

Certificate of Good Standing

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

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

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

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

Anna-Karin Östin

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

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

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

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

hereby certify that

ANNA-KARIN ÖSTIN

duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

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

Fee 340:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

17

No. 11426
The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Ms. Anna-Karin Bjöck

Swedish Companies Registration Office, Sundsvall

has issued and signed the foregoing attestation in his/her official capacity

For Stockholm this 17th day of August
SEK 60:- PAID

Agneta Rådelius

SIGNATURE OF Agneta Rådelius
AND STAMP OF : Sc. MFA
SIGNATURE : Mohamed Hussein
DATE : 20-08-07

(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 2008/023159 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *C07D 409/12* (2006.01)
C07D 239/42 (2006.01) *C07D 413/12* (2006.01)
C07D 401/12 (2006.01) *C07D 417/12* (2006.01)
C07D 401/14 (2006.01) *A61K 31/506* (2006.01)
C07D 403/04 (2006.01) *A61K 31/5377* (2006.01)
C07D 403/12 (2006.01) *A61P 35/00* (2006.01)
C07D 405/12 (2006.01)

(21) International Application Number:
PCT/GB2007/003173

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

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0616747.2 24 August 2006 (24.08.2006) GB
60/948,544 9 July 2007 (09.07.2007) 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, MK, ML, MN, MR, MT, MW, MX, MY, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG only)*: **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE).

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

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FINLAY, Maurice, Raymond, Verschoyle** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **MORRIS, Jeffrey** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

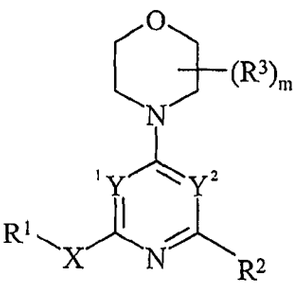
(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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(54) Title: MORPHOLINO PYRIMIDINE DERIVATIVES USEFUL IN THE TREATMENT OF PROLIFERATIVE DISORDERS



(I)

(57) Abstract: A compound of formula (I) or a pharamaceutically acceptable salt thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by an mTOR kinase and/or one or more PI3K enzyme.

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MORPHOLINO PYRIMIDINE DERIVATIVES USEFUL IN THE TREATMENT OF PROLIFERATIVE DISORDERS

The present invention relates to morpholino pyrimidine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by an mTOR kinase and/or one or more PI3K enzyme.

It is now well understood that deregulation of oncogenes and tumour-suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell proliferation or increased cell survival. It is also known that signalling pathways mediated by the PI3K/mTOR families have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative factor in a wide spectrum of human cancers and other diseases.

The mammalian target of the macrolide antibiotic Rapamycin (sirolimus) is the enzyme mTOR. This enzymes belongs to the phosphatidylinositol (PI) kinase-related kinase (PIKK) family of protein kinases, which also includes ATM, ATR, DNA-PK and hSMG-1. mTOR, like other PIKK family members, does not possess detectable lipid kinase activity, but instead functions as a serine/threonine kinase. Much of the knowledge of mTOR signalling is based upon the use of Rapamycin. Rapamycin first binds to the 12 kDa immunophilin FK506-binding protein (FKBP12) and this complex inhibits mTOR signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). The mTOR protein consists of a catalytic kinase domain, an FKBP12-Rapamycin binding (FRB) domain, a putative repressor domain near the *C*-terminus and up to 20 tandemly-repeated HEAT motifs at the *N*-terminus, as well as FRAP-ATM-TRRAP (FAT) and FAT *C*-terminus domain (Huang and Houghton, Current Opinion in Pharmacology, 2003, 3, 371-377).

mTOR kinase is a key regulator of cell growth and has been shown to regulate a wide range of cellular functions including translation, transcription, mRNA turnover, protein stability, actin cytoskeleton reorganisation and autophagy (Jacinto and Hall, Nature Reviews Molecular and Cell Biology, 2005, 4, 117-126). mTOR kinase integrates signals from growth factors (such as insulin or insulin-like growth factor) and nutrients (such as amino acids and glucose) to regulate cell growth. mTOR kinase is activated by growth factors through the PI3K-Akt pathway. The most well characterised function of mTOR kinase in mammalian cells is regulation of translation through two pathways, namely activation of ribosomal S6K1

to enhance translation of mRNAs that bear a 5'-terminal oligopyrimidine tract (TOP) and suppression of 4E-BP1 to allow CAP-dependent mRNA translation.

Generally, investigators have explored the physiological and pathological roles of mTOR using inhibition with Rapamycin and related Rapamycin analogues based on their specificity for mTOR as an intracellular target. However, recent data suggests that Rapamycin displays variable inhibitory actions on mTOR signalling functions and suggest that direct inhibition of the mTOR kinase domain may display substantially broader anti-cancer activities than that achieved by Rapamycin (Edinger *et al.*, Cancer Research, 2003, 63, 8451-8460). For this reason, potent and selective inhibitors of mTOR kinase activity would be useful to allow a more complete understanding of mTOR kinase function and to provide useful therapeutic agents.

There is now considerable evidence indicating that the pathways upstream of mTOR, such as the PI3K pathway, are frequently activated in cancer (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501; Bjornsti and Houghton, Nature Reviews Cancer, 2004, 4, 335-348; Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). For example, components of the PI3K pathway that are mutated in different human tumours include activating mutations of growth factor receptors and the amplification and/or overexpression of PI3K and Akt.

In addition there is evidence that endothelial cell proliferation may also be dependent upon mTOR signalling. Endothelial cell proliferation is stimulated by vascular endothelial cell growth factor (VEGF) activation of the PI3K-Akt-mTOR signalling pathway (Dancey, Expert Opinion on Investigational Drugs, 2005, 14, 313-328). Moreover, mTOR kinase signalling is believed to partially control VEGF synthesis through effects on the expression of hypoxia-inducible factor-1α (HIF-1α) (Hudson *et al.*, Molecular and Cellular Biology, 2002, 22, 7004-7014). Therefore, tumour angiogenesis may depend on mTOR kinase signalling in two ways, through hypoxia-induced synthesis of VEGF by tumour and stromal cells, and through VEGF stimulation of endothelial proliferation and survival through PI3K-Akt-mTOR signalling.

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.

In addition to tumourigenesis, there is evidence that mTOR kinase plays a role in an array of hamartoma syndromes. Recent studies have shown that the tumour suppressor proteins such as TSC1, TSC2, PTEN and LKB1 tightly control mTOR kinase signalling. Loss of these tumour suppressor proteins leads to a range of hamartoma conditions as a result of elevated mTOR kinase signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Syndromes with an established molecular link to dysregulation of mTOR kinase include Peutz-Jeghers syndrome (PJS), Cowden disease, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, Lhermitte-Duclos disease and Tuberous Sclerosis (TSC) (Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). Patients with these syndromes characteristically develop benign hamartomatous tumours in multiple organs.

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.

It is also believed that a number of these morpholino pyrimidine derivatives may have inhibitory activity against the phosphatidylinositol (PI) 3-kinases family of kinases.

Phosphatidylinositol (PI) 3-kinases (PI3Ks) are ubiquitous lipid kinases that function both as signal transducers downstream of cell-surface receptors and in constitutive intracellular membrane and protein trafficking pathways. All PI3Ks are dual-specificity enzymes with a lipid kinase activity that phosphorylates phosphoinositides at the 3-hydroxy position, and a less well characterised protein kinase activity. The lipid products of PI3K-catalysed reactions comprising phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P_3], phosphatidylinositol 3,4-bisphosphate [PI(3,4)P_2] and phosphatidylinositol 3-monophosphate [PI(3)P] constitute second messengers in a variety of signal transduction pathways, including those essential to cell proliferation, adhesion, survival, cytoskeletal rearrangement and vesicle trafficking. PI(3)P is constitutively present in all cells and its levels do not change dramatically following agonist stimulation. Conversely, PI(3,4)P_2 and PI(3,4,5)P_3 are nominally absent in most cells but they rapidly accumulate on agonist stimulation.

The downstream effects of PI3K-produced 3-phosphoinositide second messengers are mediated by target molecules containing 3-phosphoinositide binding domains such as the pleckstrin homology (PH) domain and the recently identified FYVE and phox domains. Well-characterised protein targets for PI3K include PDK1 and protein kinase B (PKB). In addition, tyrosine kinases like Btk and Itk are dependent on PI3K activity.

The PI3K family of lipid kinases can be classified into three groups according to their physiological substrate specificity (Vanhaesebroeck *et al.*, Trends in Biol. Sci., 1997, 22, 267). Class III PI3K enzymes phosphorylate PI alone. In contrast, Class II PI3K enzymes phosphorylate both PI and PI 4-phosphate [PI(4)P]. Class I PI3K enzymes phosphorylate PI, PI(4)P and PI 4,5-bisphosphate [PI(4,5)P_2], although only PI(4,5)P_2 is believed to be the physiological cellular substrate. Phosphorylation of PI(4,5)P_2 produces the lipid second messenger PI(3,4,5)P_3. More distantly related members of the lipid kinase superfamily are Class IV kinases such as mTOR (discussed above) and DNA-dependent kinase that phosphorylate serine/threonine residues within protein substrates. The most studied and understood of the PI3K lipid kinases are the Class I PI3K enzymes.

Class I PI3Ks are heterodimers consisting of a p110 catalytic subunit and a regulatory subunit. The family is further divided into Class Ia and Class Ib enzymes on the basis of regulatory partners and the mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (p110α, p110β and p110δ) that dimerise with five distinct regulatory subunits (p85α, p55α, p50α, p85β and p55γ), with all catalytic subunits being able

to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3Ks are generally activated in response to growth factor-stimulation of receptor tyrosine kinases *via* interaction of their regulatory subunit SH2 domains with specific phospho-tyrosine residues of activated receptor or adaptor proteins such as IRS-1. Both p110α and p110β are constitutively expressed in all cell types, whereas p110δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the Class Ib enzyme is activated in response to G-protein coupled receptor systems (GPCRs) and its expression appears to be limited to leukocytes and cardiomyocytes.

There is now considerable evidence indicating that Class Ia PI3K enzymes contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501). For example, the p110α subunit is amplified in some tumours such as those of the ovary (Shayesteh *et al.*, Nature Genetics, 1999, 21, 99-102) and cervix (Ma *et al.*, Oncogene, 2000, 19, 2739-2744). More recently, activating mutations within the catalytic site of the p110α catalytic subunit have been associated with various other tumours such as those of the colorectal region and of the breast and lung (Samuels *et al.*, Science, 2004, 304, 554). Tumour-related mutations in the p85α regulatory subunit have also been identified in cancers such as those of the ovary and colon (Philp *et al.*, Cancer Research, 2001, 61, 7426-7429). In addition to direct effects, it is believed that activation of Class Ia PI3Ks contributes to tumourigenic events that occur upstream in signalling pathways, for example by way of ligand-dependent or ligand-independent activation of receptor tyrosine kinases, GPCR systems or integrins (Vara *et al.*, Cancer Treatment Reviews, 2004, 30, 193-204). Examples of such upstream signalling pathways include over-expression of the receptor tyrosine kinase erbB2 in a variety of tumours leading to activation of PI3K-mediated pathways (Harari *et al.*, Oncogene, 2000, 19, 6102-6114) and over-expression of the ras oncogene (Kauffmann-Zeh *et al.*, Nature, 1997, 385, 544-548). In addition, Class Ia PI3Ks may contribute indirectly to tumourigenesis caused by various downstream signalling events. For example, loss of the effect of the PTEN tumour-suppressor phosphatase that catalyses conversion of $PI(3,4,5)P_3$ back to $PI(4,5)P_2$ is associated with a very broad range of tumours *via* deregulation of PI3K-mediated production of $PI(3,4,5)P_3$ (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Furthermore,

augmentation of the effects of other PI3K-mediated signalling events is believed to contribute to a variety of cancers, for example by activation of Akt (Nicholson and Anderson, Cellular Signalling, 2002, 14, 381-395).

In addition to a role in mediating proliferative and survival signalling in tumour cells, there is evidence that Class Ia PI3K enzymes contribute to tumourigenesis in tumour-associated stromal cells. For example, PI3K signalling is known to play an important role in mediating angiogenic events in endothelial cells in response to pro-angiogenic factors such as VEGF (Abid *et al.*, Arterioscler. Thromb. Vasc. Biol., 2004, 24, 294-300). As Class I PI3K enzymes are also involved in motility and migration (Sawyer, Expert Opinion Investig. Drugs, 2004, 13, 1-19), PI3K enzyme inhibitors should provide therapeutic benefit *via* inhibition of tumour cell invasion and metastasis. In addition, Class I PI3K enzymes play an important role in the regulation of immune cells contributing to pro-tumourigenic effects of inflammatory cells (Coussens and Werb, Nature, 2002, 420, 860-867).

These findings suggest that pharmacological inhibitors of Class I PI3K enzymes will be of therapeutic value for the treatment of various diseases including different forms of the disease of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In particular, inhibitors of Class I PI3K enzymes 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.

PI3Kγ, the Class Ib PI3K, is activated by GPCRs, as was finally demonstrated in mice lacking the enzyme. Thus, neutrophils and macrophages derived from PI3Kγ-deficient animals failed to produce PI(3,4,5)P_3 in response to stimulation with various chemotactic substances (such as IL-8, C5a, fMLP and MIP-1a), whereas signalling through protein tyrosine kinase-coupled receptors to Class Ia PI3Ks was intact (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053; Li *et al.*, Science, 2002, 287(5455), 1046-1049; Sasaki *et al.*, Science 2002, 287(5455), 1040-1046). Furthermore, PI(3,4,5)P_3-mediated phosphorylation of PKB was not initiated by these GPCR ligands in PI3Kγ-null cells. Taken together, the results demonstrated that, at least in resting haematopoietic cells, PI3Kγ is the sole PI3K isoform that is activated by GPCRs *in vivo*. When murine bone marrow-derived neutrophils and peritoneal

macrophages from wild-type and PI3Kγ$^{-/-}$ mice were tested *in vitro*, a reduced, but not completely abrogated, performance in chemotaxis and adherence assays was observed. However, this translated into a drastic impairment of IL-8 driven neutrophil infiltration into tissues (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053.). Recent data suggest that PI3Kγ is involved in the path finding process rather than in the generation of mechanical force for motility, as random migration was not impaired in cells that lacked PI3Kγ (Hannigan *et al.*, Proc. Nat. Acad. of Sciences of U.S.A., 2002, 99(6), 3603-8). Data linking PI3Kγ to respiratory disease pathology came with the demonstration that PI3Kγ has a central role in regulating endotoxin-induced lung infiltration and activation of neutrophils leading to acute lung injury (Yum *et al.*, J. Immunology, 2001, 167(11), 6601-8). The fact that although PI3Kγ is highly expressed in leucocytes, its loss seems not to interfere with haematopoiesis, and the fact that PI3Kγ-null mice are viable and fertile further implicates this PI3K isoform as a potential drug target. Work with knockout mice also established that PI3Kγ is an essential amplifier of mast cell activation (Laffargue *et al.*, Immunity, 2002, 16(3), 441-451).

Thus, in addition to tumourigenesis, there is evidence that Class I PI3K enzymes play a role in other diseases (Wymann *et al.*, Trends in Pharmacological Science, 2003, 24, 366-376). Both Class Ia PI3K enzymes and the single Class Ib enzyme have important roles in cells of the immune system (Koyasu, Nature Immunology, 2003, 4, 313-319) and thus they are therapeutic targets for inflammatory and allergic indications. Recent reports demonstrate that mice deficient in PI3Kγ and PI3Kδ are viable, but have attenuated inflammatory and allergic responses (Ali *et al.*, Nature, 2004, 431(7011), 1007-11). Inhibition of PI3K is also useful to treat cardiovascular disease *via* anti-inflammatory effects or directly by affecting cardiac myocytes (Prasad *et al.*, Trends in Cardiovascular Medicine, 2003, 13, 206-212). Thus, inhibitors of Class I PI3K enzymes are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

Several compounds that inhibit PI3Ks and phosphatidylinositol (PI) kinase-related kinase (PI3KKs) have been identified, including wortmannin and the quercetin derivative LY294002. These compounds are reasonably specific inhibitors of PI3Ks and PI3KKs over other kinases but they lack potency and display little selectivity within the PI3K families.

Accordingly, it would be desirable to provide further effective mTOR and/or PI3K inhibitors for use in the treatment of cancer, inflammatory or obstructive airways diseases, immune or cardiovascular diseases.

Morpholino pyrimidine derivatives and PI3K inhibitors are known in the art.

International Patent Application WO 2004/048365 discloses compounds that possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. These compounds are arylamino- and heteroarylamino-substituted pyrimidines which differ from the compounds of the present invention with respect to their arylamino- and heteroarylamino substituents. These substituents are not equivalent to the $-XR^1$ substituents of the present invention.

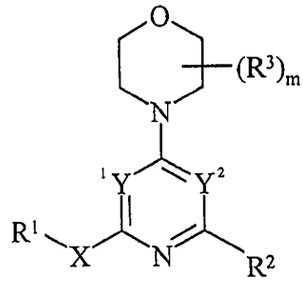
Inhibitors of PI3K activity useful in the treatment of cancer are also disclosed in European Patent Application 1 277 738 which mentions 4-morpholino-substituted bicyclic heteroaryl compounds such as quinazoline and pyrido[3,2-*d*]pyrimidine derivatives and 4-morpholino-substituted tricyclic heteroaryl compounds but not monocyclic pyrimidine derivatives.

A number of compounds such as 4-morpholin-4-yl-6-(phenylsulfonylmethyl)-2-pyridin-4-yl-pyrimidine and 4-{6-[(phenylsulfonyl)methyl]-2-pyridin-2-ylpyrimidin-4-yl}morpholine have been registered in the Chemical Abstracts database but no utility has been indicated and there is no suggestion that these compounds have mTOR and/or PI3K inhibitory activity or useful therapeutic properties.

Surprisingly, we have found that certain morpholino pyrimidine derivatives possess useful therapeutic properties. Without wishing to be bound by theoretical constraints, it is believed that the therapeutic usefulness of the derivatives is derived from their inhibitory activity against mTOR kinase and/or one or more PI3K enzyme (such as the Class Ia enzyme and/or the Class Ib enzyme). Because signalling pathways mediated by the PI3K/mTOR families have a central role in a number of cell processes including proliferation and survival, and because deregulation of these pathways is a causative factor in a wide spectrum of human cancers and other diseases, it is expected that the derivatives will be therapeutically useful. In particular, it is expected that the derivatives will have anti-proliferative and/or apoptotic properties which means that they will be useful in the treatement of proliferative disease such as cancer. The compounds of the present invention may also be useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

Generally, the compounds of the present invention possess potent inhibitory activity against mTOR kinase but the compound may also possess potent inhibitory activity against one or more PI3K enzyme (such as the Class Ia enzyme and/or the Class Ib enzyme).

In accordance with an aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

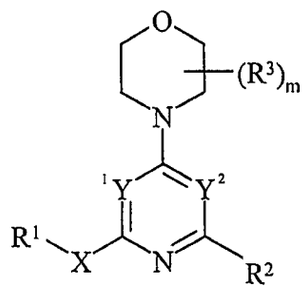
cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ and $\mathbf{R^{19}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R**^{5} are independently hydrogen or C_{1-6}alkyl;

or **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R**^{7} are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

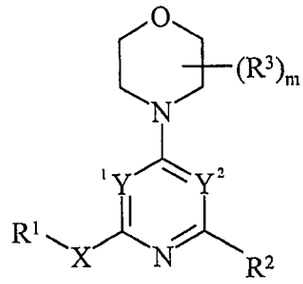
R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-}

$_{6}$alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^{8} provided that one of ^{1}Y and Y^{2} is N and the other is CR^{8};

X is a linker group selected from -CR^{4}=CR^{5}-, -CR^{4}=CR^{5}CR^{6}R^{7}-, -CR^{6}R^{7}CR^{5}=CR^{4}-, -C≡C-, -C≡CCR^{6}R^{7}-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^{7}-, -OCR^{6}R^{7}-, -SCR^{6}R^{7}-, -S(O)CR^{6}R^{7}-, -S(O)$_{2}$CR^{6}R^{7}-, -C(O)NR^{4}CR^{6}R^{7}-, -NR^{4}C(O)CR^{6}R^{7}-, -NR^{4}C(O)NR^{5}CR^{6}R^{7}-, -NR^{4}S(O)$_{2}$CR^{6}R^{7}-, -S(O)$_{2}$NR^{4}CR^{6}R^{7}-, -C(O)NR^{4}-, -NR^{4}C(O)-, -NR^{4}C(O)NR^{5}-, -S(O)$_{2}$NR^{4}- and –NR^{4}S(O)$_{2}$-;

R^{1} is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^{9}, -OR^{9}, -SR^{9}, -SOR^{9}, -SO$_{2}$R^{9}, -COR^{9}, -CO$_{2}$R^{9}, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_{2}$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_{2}$R^{10};

or **X-R**^{1} is –CR^{6}R^{7}OH;

R^{2} is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by –NR^{17}CONR^{18}R^{19} and optionally substituted by one or more substituent group

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independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, and -$NR^{11}COCONR^{12}R^{16}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and -$NR^{13}SO_2R^{14}$;

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}

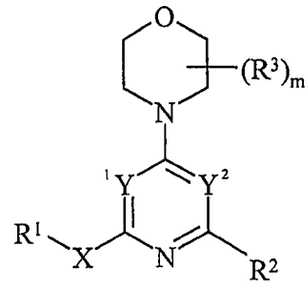
$_{6}$alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

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$\mathbf{R}^1$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

or $\mathbf{X}$-$\mathbf{R}^1$ is $-CR^6R^7OH$;

$\mathbf{R}^2$ is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each $\mathbf{R}^3$, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

$\mathbf{R}^4$ and $\mathbf{R}^5$ are independently hydrogen or C_{1-6}alkyl;

or $\mathbf{R}^1$ and $\mathbf{R}^4$ together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

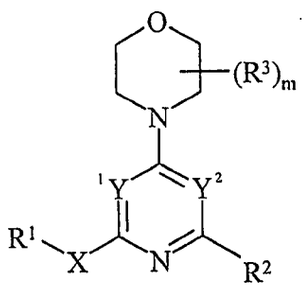
R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy,

hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

for use as a medicament in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group

independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, - SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, –$NR^{11}COR^{12}$, and -$NR^{11}COCONR^{12}R^{16}$;

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ and –$NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or **R^1** and **R^4** together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R^7** are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and **R^{10}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and **R^{18}** are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}

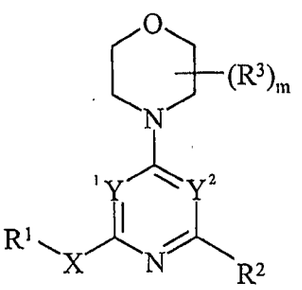
$_{6}$alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R**^{5} are independently hydrogen or C_{1-6}alkyl;

or **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

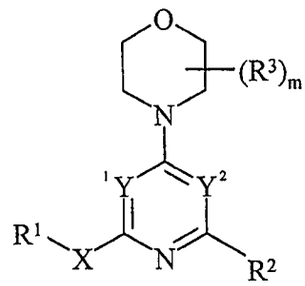
R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy,

hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^5-, -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡C-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7-, -S(O)$_2$NR^{4}CR^{6}R^7-, -C(O)NR^4-, -NR^{4}C(O)-, -NR^{4}C(O)NR^5-, -S(O)$_2$NR^4- and –NR^{4}S(O)$_2$-;

R^1 is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -SO$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_2$R^{10};

or **X-R**^{1} is –CR^{6}R^{7}OH;

$\mathbf{R^2}$ is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each $\mathbf{R^3}$, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl;

or $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro,

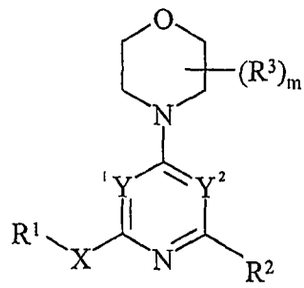
hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ and $\mathbf{R^{19}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with another aspect of the present invention, there is provided the use of a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^5-, -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡C-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -S(O)$_2$NR^{4}CR^{6}R^7-, -C(O)NR^4-, -NR^{4}C(O)-, -NR^{4}C(O)NR^5-, -S(O)$_2$NR^4- and –NR^{4}S(O)$_2$-;

R^1 is a group selected from C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -SO$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_2$R^{10};

or **X-R**^{1} is –CR^{6}R^{7}OH

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is substituted by –NR^{17}CONR^{18}R^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, - SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, and -NR^{11}COCONR^{12}R^{16};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -R^{13}CO$_2$R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R**^{5} are independently hydrogen or C$_{1-6}$alkyl;

or **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent

groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

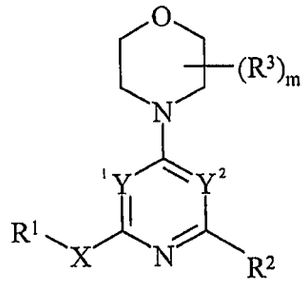
$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ and $\mathbf{R^{19}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl

in the manufacture of a medicament for use in the treatment of proliferative disease.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

$^1\mathbf{Y}$ and $\mathbf{Y^2}$ are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-(O)_2NR^4-$ and $-NR^4S(O)_2-$;

$\mathbf{R^1}$ is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O_2R^9, -COR^9, -CO_2R^9, -$CONR^9R^{10}$, -NR^9R^{10}, –NR^9COR^{10}, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{15}$, -$NR^9COCONR^{10}R^{15}$ and $NR^9SO_2R^{10}$;

$\mathbf{R^2}$ is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by –$NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, and -$NR^{11}COCONR^{12}R^{16}$;

each $\mathbf{R^3}$, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO2R^{14}$ and –$NR^{13}SO_2R^{14}$;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl;

or $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}

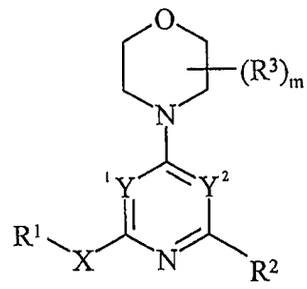
$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^5-, -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡C-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7-, -S(O)$_2$NR^{4}CR^{6}R^7-, -C(O)NR^4-, -NR^{4}C(O)-, -NR^{4}C(O)NR^5-, -(O)$_2$NR^4- and –NR^{4}S(O)$_2$-;

R^1 is a group selected from hydrogen, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and NR^{9}SO$_2$R^{10};

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is substituted by –NR^{17}CONR^{18}R^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, and -NR^{11}COCONR^{12}R^{16};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO2R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R**^{5} are independently hydrogen or C$_{1-6}$alkyl;

or **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent

groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

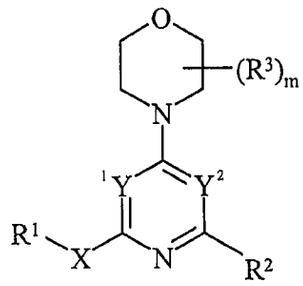
R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

$^1\mathbf{Y}$ and $\mathbf{Y^2}$ are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-(O)_2NR^4-$ and $-NR^4S(O)_2-$;

$\mathbf{R^1}$ is a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $NR^9SO_2R^{10}$;

or $\mathbf{X\text{-}R^1}$ is $-CR^6R^7OH$;

$\mathbf{R^2}$ is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, and $-NR^{11}COCONR^{12}R^{16}$;

each $\mathbf{R^3}$, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, SOR^{13}, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO2R^{14}$ and $-NR^{13}SO_2R^{14}$;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl;

or $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-}

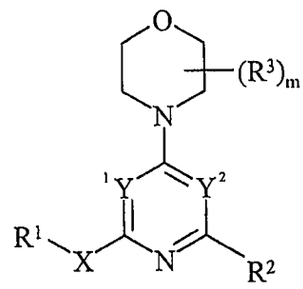
$_{6}$alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl..

In accordance with a further aspect of the present invention, there is also provided a compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^5-, -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡C-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -S(O)$_2$NR^{4}CR^{6}R^7-, -C(O)NR^4-, -NR^{4}C(O)-, -NR^{4}C(O)NR^5-, -S(O)$_2$NR^4- and –NR^{4}S(O)$_2$-;

R^1 is a group selected from C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and NR^{9}SO$_2$R^{10};

or **X-R**^{1} is –CR^{6}R^{7}OH;

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is substituted by –NR^{17}CONR^{18}R^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, and -NR^{11}COCONR^{12}R^{16};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO2R^{14} and –NR^{13}SO$_2$R^{14};

R^4 and **R**^{5} are independently hydrogen or C$_{1-6}$alkyl;

or **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent

groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl,

cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R}^{18}$ and $\mathbf{R}^{19}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention. Solvates and mixtures thereof also form an aspect of the present invention. For example, a suitable solvate of a compound of formula (I) is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

The present invention relates to the compounds of formula (I) as herein defined as well as to salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (I) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of compounds of formula (I) as herein defined which are sufficiently basic to form such salts. Such acid addition salts include but are not limited to furmarate, methanesulfonate, hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulfuric acid. In addition where compounds of formula (I) are sufficiently acidic, salts are base salts and examples include but are not limited to, an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example

triethylamine, ethanolamine, diethanolamine, triethanolamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, dibenzylamine or amino acids such as lysine.

The compounds of formula (I) may also be provided as *in vivo* hydrolysable esters. An *in vivo* hydrolysable ester of a compound of formula (I) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl, 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl, and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example formyl, acetyl, benzoyl, phenylacetyl, substituted benzoyl and phenylacetyl; C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-C_{1-4}alkylcarbamoyl and *N*-(di-C_{1-4}alkylaminoethyl)-*N*-C_{1-4}alkylcarbamoyl (to give carbamates); di-C_{1-4}alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, C_{1-4}alkylaminomethyl and di-(C_{1-4}alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting *in vivo* hydrolysable esters include, for example, $R^A C(O)OC_{1-6}$alkyl-CO-, wherein R^A is for example, benzyloxy-C_{1-4}alkyl, or phenyl. Suitable substituents on a phenyl group in such esters include, for example, 4-C_{1-4}piperazino-C_{1-4}alkyl, piperazino-C_{1-4}alkyl and morpholino-C_{1-4}alkyl.

The compounds of the formula (I) may be also be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula (I). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

In this specification the generic term "C_{p-q}alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only (i.e. *n*-propyl and isopropyl) and references to individual branched-chain alkyl groups such as "*tert*-butyl" are specific for the branched chain version only.

The prefix C_{p-q} in C_{p-q}alkyl and other terms (where p and q are integers) indicates the range of carbon atoms that are present in the group, for example C_{1-4}alkyl includes C_1alkyl (methyl), C_2alkyl (ethyl), C_3alkyl (propyl as *n*-propyl and isopropyl) and C_4alkyl (n-butyl, sec-butyl, isobutyl and *tert*-butyl).

The term C_{p-q}alkoxy comprises –O-C_{p-q}alkyl groups.

The term C_{p-q}alkanoyl comprises –C(O)alkyl groups.

The term halo includes fluoro, chloro, bromo and iodo.

"Carbocyclyl" is a saturated, unsaturated or partially saturated monocyclic, bicyclic or tricyclic ring system containing from 3 to 14 ring atoms, wherein a ring CH_2 group may be replaced with a C=O group. "Carbocyclyl" includes "aryl", "C_{p-q}cycloalkyl" and "C_{p-q}cycloalkenyl".

"aryl" is an aromatic monocyclic, bicyclic or tricyclic carbcyclyl ring system.

"C_{p-q}cycloalkenyl" is an unsaturated or partially saturated monocyclic, bicyclic or tricyclic carbocyclyl ring system containing at least 1 C=C bond and wherein a ring CH_2 group may be replaced with a C=O group.

"C_{p-q}cycloalkyl" is a saturated monocyclic, bicyclic or tricyclic carbocyclyl ring system and wherein a ring CH_2 group may be replaced with a C=O group.

"Heterocyclyl" is a saturated, unsaturated or partially saturated monocyclic, bicyclic or tricyclic ring system containing from 3 to 14 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group. "Heterocyclyl" includes "heteroaryl", "cycloheteroalkyl" and "cycloheteroalkenyl".

"Heteroaryl" is an aromatic monocyclic, bicyclic or tricyclic heterocyclyl, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen where a ring nitrogen or sulfur may be oxidised.

"Cycloheteroalkenyl" is an unsaturated or partially saturated monocyclic, bicyclic or tricyclic heterocyclyl ring system, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group.

"Cycloheteroalkyl" is a saturated monocyclic, bicyclic or tricyclic heterocyclic ring system, particularly having 5 to 10 ring atoms, of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulfur or oxygen, which ring may be carbon or nitrogen linked and wherein a ring nitrogen or sulfur atom may be oxidised and wherein a ring CH_2 group may be replaced with a C=O group.

This specification may make use of composite terms to describe groups comprising more than one functionality. Unless otherwise described herein, such terms are to be interpreted as is understood in the art. For example carbocyclylC_{p-q}alkyl comprises C_{p-q}alkyl substituted by carbocyclyl, heterocyclylC_{p-q}alkyl comprises C_{p-q}alkyl substituted by heterocyclyl, and bis(C_{p-q}alkyl)amino comprises amino substituted by 2 C_{p-q}alkyl groups which may be the same or different.

HaloC_{p-q}alkyl is a C_{p-q}alkyl group that is substituted by 1 or more halo substituents and particuarly 1, 2 or 3 halo substituents. Similarly, other generic terms containing halo such as haloC_{p-q}alkoxy may contain 1 or more halo substituents and particluarly 1, 2 or 3 halo substituents.

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HydroxyC$_{p-q}$alkyl is a C$_{p-q}$alkyl group that is substituted by 1 or more hydroxyl substituents and particularly by 1, 2 or 3 hydroxy substituents. Similarly other generic terms containing hydroxy such as hydroxyC$_{p-q}$alkoxy may contain 1 or more and particularly 1, 2 or 3 hydroxy substituents.

C$_{p-q}$alkoxyC$_{p-q}$alkyl is a C$_{p-q}$alkyl group that is substituted by 1 or more C$_{p-q}$alkoxy substituents and particularly 1, 2 or 3 C$_{p-q}$alkoxy substituents. Similarly other generic terms containing C$_{p-q}$alkoxy such as C$_{p-q}$alkoxyC$_{p-q}$alkoxy may contain 1 or more C$_{p-q}$alkoxy substituents and particularly 1, 2 or 3 C$_{p-q}$alkoxy substituents.

Where optional substituents are chosen from "1 or 2", from "1, 2, or 3" or from "1, 2, 3 or 4" groups or substituents it is to be understood that this definition includes all substituents being chosen from one of the specified groups i.e. all substitutents being the same or the substituents being chosen from two or more of the specified groups i.e. the substitutents not being the same.

"Proliferative disease(s)" includes malignant disease(s) such as cancer as well as non-malignant disease(s) such as inflammatory diseases, obstracutive airways diseases, immune diseases or cardiovascular diseases.

Suitable values for any R group or any part or substitutent for such groups include:

for C$_{1-4}$alkyl:	methyl, ethyl, propyl, butyl, 2-methylpropyl and *tert*-butyl;
for C$_{1-6}$alkyl:	C$_{1-4}$alkyl, pentyl, 2,2-dimethylpropyl, 3-methylbutyl and hexyl;
for C$_{3-6}$cycloalkyl:	cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;
for C$_{3-6}$cycloalkylC$_{1-4}$alkyl:	cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl;
for aryl:	phenyl and naphthyl;
for arylC$_{1-4}$alkyl:	benzyl, phenethyl, naphthylmethyl and naphthylethyl;
for carbocylyl:	aryl, cyclohexenyl and C$_{3-6}$cycloalkyl;
for halo:	fluoro, chloro, bromo and iodo;
for C$_{1-4}$alkoxy:	methoxy, ethoxy, propoxy and isopropoxy;
for C$_{1-6}$alkoxy:	C$_{1-4}$alkoxy, pentyloxy, 1-ethylpropoxy and hexyloxy;
for C$_{1-6}$alkanoyl:	acetyl, propanoyl and 2-methylpropanoyl;
for heteroaryl:	pyridyl, imidazolyl, quinolinyl, cinnolyl, pyrimidinyl, thienyl, pyrrolyl, pyrazolyl, thiazolyl, thiazolyl, triazolyl, oxazolyl,

	isoxazolyl, furanyl, pyridazinyl, pyrazinyl, indolyl, benzofuranyl, dibenzofuranyl and benzothienyl;
for heteroarylC_{1-4}alkyl:	pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, theinylethyl, pyridylmethyl, pyridylethyl, pyrazinylmethyl, pyrazinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrimidinylpropyl, pyrimidinylbutyl, imidazolylpropyl, imidazolylbutyl, quinolinylpropyl, 1,3,4-triazolylpropyl and oxazolylmethyl;
for heterocyclyl:	heteroaryl, pyrrolidinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, piperidinyl, piperazinyl, azetidinyl, morpholinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, indolinyl, dihydro-*2H*-pyranyl and tetrahydrofuranyl.

It should be noted that examples given for terms used in the description are not limiting.

Particular values of m, X, ^{1}Y and Y^2, R^1, R^2 and R^3 are as follows. Such values may be used where appropriate, in connect with any aspect of the invention, or part thereof, and with any of the definitions, claims or embodiments defined herein.

m

In one aspect of the invention m is 0, 1, 2 or 3.

In another aspect m is 0, 1 or 2.

In a further aspect m is 0 or 1.

In yet another aspect m is 0 so that R^3 is absent.

In yet another aspect m is 1 and R^3 is methyl.

^{1}Y and Y^2

In one aspect of the invention ^{1}Y is N and Y^2 is CR^8.

In another aspect ^{1}Y is N and Y^2 is CH.

In yet another aspect ^{1}Y is CR^8 and Y^2 is N.

In a further aspect ^{1}Y is CH or CF and Y^2 is N.

In yet a further aspect ^{1}Y is CH and Y^2 is N.

X

In one aspect of the invention X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-C(O)NR^4-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$.

In another aspect **X** is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7$, $-C(O)NR^4-$ and $-NR^4C(O)-$.

In a further aspect X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4-$, and $-NR^4C(O)-$.

In a further aspect X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$.

In yet another aspect X is a linker group selected from $-SCR^6R^7-$, $-S(O)CR^6R^7-$ and $-S(O)_2CR^6R^7-$.

In another aspect X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NR^4-$ and $-NR^4C(O)-$.

In another aspect X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)_2CH_2-$, $-C(O)NR^4-$, and $-NR^4C(O)-$.

In another aspect X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$.

In another aspect X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-SCH_2-$, $-S(O)CH_2-$ and $-S(O)_2CH_2-$.

In a further aspect X is a linker group selected from $-NHCH_2-$, $-N(CH_3)CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NH-$, $-C(O)N(CH_3)-$, $-NHC(O)-$ and $-N(CH_3)C(O)-$.

In a further aspect X is a linker group selected from $-NHCH_2-$, $-N(CH_3)CH_2-$, $-OCH_2-$, $-SCH_2-$, $-S(O)CH_2-$, $-S(O)_2CH_2-$, $-C(O)NH-$, $-C(O)N(CH_3)-$, $-NHC(O)-$ and $-N(CH_3)C(O)-$.

In yet a further aspect X is a linker group selected from $-NHCH_2-$, $-N(CH_3)CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$.

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In yet a further aspect X is a linker group selected from -$NHCH_2$-, -$N(CH_3)CH_2$-, -OCH_2-, -SCH_2- and -$S(O)_2CH_2$-.

In another aspect X is -SCH_2- or -$S(O)_2CH_2$-.

In another aspect X is -SCH_2-, -$SCH(CH_3)$- or -$SC(CH_3)_2$-.

In another aspect X is -$S(O)CH_2$-, -$S(O)CH(CH_3)$- or -$S(O)C(CH_3)_2$-.

In another aspect X is -$S(O)_2CH_2$-, -$S(O)_2CH(CH_3)$- or -$S(O)_2C(CH_3)_2$-.

In another aspect X is -$S(O)_2CH_2$-.

In another aspect X is -$S(O)_2C(CH_3)_2$-.

R^1

In one aspect of the invention R^1 is a group selected from C_{1-4}alkyl, C_{3-10}cycloalkyl, aryl, C_{3-10}cycloalkylC_{1-4}alkyl, arylC_{1-4}alkyl, cycloheteroalkyl, heteroaryl, cycloheteroalkylC_{1-4}alkyl, heteroarylC_{1-4}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and -NR^9COR^{10}.

In another aspect, R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, oxetanyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10}.

In another aspect, R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10}.

In a further aspect, R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl, furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$.

In a further aspect, R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$.

In another aspect R^1 is a group selected from methyl, ethyl, isopropyl, cyclopropyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2NC(O)CH_3$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

In yet another aspect R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2NMe_2$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 3,5-difluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, oxetan-3-yl, 2-oxopyrolidin-3-yl, 1-methylimidazol-5-ylmethyl , 1-methylpyrrolidin-3-yl , thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

In another aspect R^1 is methyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, 3,5-difluorophenyl, pyridin-4-yl or cyclopropyl.

In another aspect R^1 is methyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, pyridin-4-yl or cyclopropyl.

In another aspect R^1 is methyl or cyclopropyl.

In another aspect R^1 is methyl.

X-R^1

In one embodiment X-R^1 is $-C(CH_3)_2OH$ or $-CH_2OH$.

In one embodiment X-R^1 is $-CH_2OH$.

R^2

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from carbocyclyl or heterocyclyl which group is substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In one aspect of the invention R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by –$NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridyl substituted by –$NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridyl substituted by –$NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

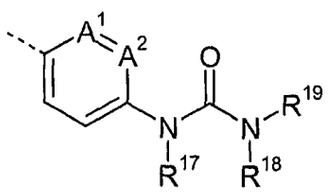
In another aspect R^2 is phenyl or pyridyl substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$.

In another aspect R^2 is phenyl or pyridyl optionally substituted by -$NR^{17}CONR^{18}R^{19}$.

In another aspect R^2 is phenyl or pyridyl optionally substituted by –$NHCONR^{18}R^{19}$.

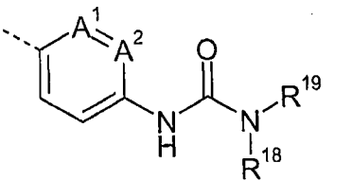
In another aspect R^2 is phenyl or pyridyl optionally substituted by –$NHCONHR^{19}$.

In another aspect R^2 is



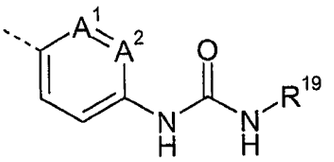
wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

In another aspect R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

In another aspect R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

R^4

In one aspect of the invention R^4 is hydrogen or methyl.

In another aspect R^4 is hydrogen.

R^4 and R^1

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4- to 10-membered heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O

and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a piperidine, morpoline,

azetidine, azepine, diazepane and thiomorpholine ring which ring is optionally substituted by one or more substituent groups selected from halo, hydroxy, oxo and C_{1-6}alkyl.

In another aspect of the invention, when **X** is $-NR^4C(O)-$ $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a piperidine, morpoline, azetidine, azepine, diazepane and thiomorpholine ring which ring is optionally substituted by one or more substituent groups selected from halo, hydroxy, oxo and C_{1-6}alkyl.

In another aspect of the invention, when **X** is $-NR^4C(O)-$ $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 1-methyl-piperidine, 4-hydroxy-piperidine, morpoline, 3-methylmorpoline, 3-hydroxyazetidine, azepine, 1,4-diazepane and a thiomorpholine-1,1-dioxide ring.

$\underline{\mathbf{R^5}}$

In one aspect of the invention R^5 is hydrogen or methyl.

In another aspect R^5 is hydrogen.

In another aspect R^5 is methyl.

$\underline{\mathbf{R^6}}$

In one aspect of the invention R^6 is hydrogen or methyl.

In another aspect R^6 is hydrogen.

In another aspect R^6 is methyl.

$\underline{\mathbf{R^7}}$

In one aspect of the invention R^7 is hydrogen or methyl.

In another aspect R^7 is hydrogen.

In another aspect R^7 is methyl.

$\underline{\mathbf{R^8}}$

In one aspect of the invention R^8 is hydrogen or halo.

In another aspect R^8 is hydrogen or fluoro.

In a further aspect R^8 is hydrogen.

$\underline{\mathbf{R^9}}$

In one aspect of the invention R^9 is hydrogen or C_{1-4}alkyl optionally substituted by 1, 2 or 3 substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-4}alkoxy, amino, C_{1-4}alkylamino and bis(C_{1-4}alkyl)amino.

In another aspect R^9 is hydrogen or C_{1-4}alkyl optionally substituted by 1, 2 or 3 halo substituents.

In a further aspect R^9 is hydrogen, methyl or trifluoromethyl.

$\underline{R^{10}}$

In one aspect of the invention R^{10} is hydrogen.

$\underline{R^{11}}$

In one aspect of the invention R^{11} is hydrogen or a group selected from C_{1-4}alkyl, aryl and cycloheteroalkyl which group is optionally substituted by 1, 2 or 3 groups selected from halo, hydroxy and cyano.

In another aspect R^{11} is hydrogen, methyl optionally substituted with hydroxy or cyano, phenyl or pyrrolidinyl.

In another aspect R^{11} is hydrogen or methyl.

$\underline{R^{12}}$

In one aspect of the invention R^{12} is hydrogen or methyl.

$\underline{R^{17}}$

In one aspect of the invention R^{17} is hydrogen or a group selected from C_{1-4}alkyl, aryl and cycloheteroalkyl which group is optionally substituted by 1, 2 or 3 groups selected from halo, hydroxy and cyano.

In another aspect R^{17} is hydrogen, methyl optionally substituted with hydroxy or cyano, phenyl or pyrrolidinyl.

In another aspect R^{17} is hydrogen or methyl.

In another aspect R^{17} is hydrogen.

$\underline{R^{18}}$

In one aspect of the invention R^{18} is hydrogen or methyl.

In one aspect of the invention R^{18} is hydrogen

$\underline{R^{19}}$

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-}

$_{6}$alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, phenyl, naphthyl, pyrrolyl, imidazolyl, isoxazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, azaindolyl, indolyl, quinolinyl, benzimidazolyl, benzofuranyl, dibenzofuranyl, benzothienyl, phenylC_{1-6}alkyl, naphthylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, imidazolylC_{1-6}alkyl, isoxazolylC_{1-6}alkyl, pyrazolylC_{1-6}alkyl, furanylC_{1-6}alkyl, thienylC_{1-6}alkyl, pyridinylC_{1-6}alkyl, pyrimidinylC_{1-6}alkyl, pyridazinylC_{1-6}alkyl, azaindolylC_{1-6}alkyl, indolylC_{1-6}alkyl, quinolinylC_{1-6}alkyl, benzimidazolylC_{1-6}alkyl, benzofuranylC_{1-6}alkyl, dibenzofuranylC_{1-6}alkyl, benzothienylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, phenyl, naphthyl, pyrrolyl, imidazolyl, isoxazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, azaindolyl, indolyl, quinolinyl, benzimidazolyl, benzofuranyl, dibenzofuranyl, benzothienyl, phenylC_{1-6}alkyl, naphthylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, imidazolylC_{1-6}alkyl, isoxazolylC_{1-6}alkyl, pyrazolylC_{1-6}alkyl, furanylC_{1-6}alkyl, thienylC_{1-6}alkyl, pyridinylC_{1-6}alkyl, pyrimidinylC_{1-6}alkyl, pyridazinylC_{1-6}alkyl, azaindolylC_{1-}

$_{6}$alkyl, indolylC_{1-6}alkyl, quinolinylC_{1-6}alkyl, benzimidazolylC_{1-6}alkyl, benzofuranylC_{1-6}alkyl, dibenzofuranylC_{1-6}alkyl, benzothienylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyridinyl-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl.

In one aspect of the invention R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl.

In another aspect of the invention R^{19} is a group selected from methyl, ethyl, propyl, cyclopropyl, cyclobutyl, -CH_2CH_2OH, -$CH_2CH_2NMe_2$, -$C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl.

R^{18} and R^{19}

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more

substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In one aspect of the invention, R^{18} and R^{19} together with the nitrogen atom to which they are attached form a morpholine ring.

In one aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X-R**^{1} is $-C(CH_3)_2OH$ or $-CH_2OH$;

R^2 is selected from aryl and heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

each R^3, when present, is methyl;

R^4 and **R**^{5} are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ or $-NR^4S(O)_2-$, **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}

$_{6}$alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino,

sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X**-**R**^{1} is $-C(CH_3)_2OH$ or $-CH_2OH$;

R^2 is selected from aryl and heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

each R^3, when present, is methyl;

R^4 and **R**^{5} are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ or $-NR^4S(O)_2-$, **R**^{1} and **R**^{4} together with the atom or atoms to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and **R**^{7} are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0, 1 or 2;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NR^4-$ and $-NR^4C(O)-$;

$\mathbf{R}^1$ is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or $\mathbf{X}$-$\mathbf{R}^1$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R}^2$ is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

each $\mathbf{R}^3$, when present, is methyl;

$\mathbf{R}^4$ is hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CH_2-$ or $-NR^4C(O)-$, $\mathbf{R}^1$ and $\mathbf{R}^4$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R}^8$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0 or 1;

^{1}**Y** is CH and Y^2 is N;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl, furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

or $-\mathbf{XR^1}$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R^2}$ is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

$\mathbf{R^3}$, when present, is methyl;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 0 or 1;

$\mathbf{^1Y}$ is CH and $\mathbf{Y^2}$ is N;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

$\mathbf{R^1}$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$;

or –$\mathbf{XR^1}$ is –$C(CH_3)_2OH$ or –CH_2OH;

$\mathbf{R^2}$ is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

$\mathbf{R^3}$, when present, is methyl;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 1;

X is a linker group selected from -$S(O)_2CH_2$-, -$S(O)_2CH(CH_3)$- and -$S(O)_2C(CH_3)_2$-;

$^1\mathbf{Y}$ is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl,

furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -NMe_2, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$;

$\mathbf{R^2}$ is phenyl or pyridyl substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

$\mathbf{R^3}$ is methyl; and

$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

m is 1;

X is a linker group selected from -$S(O)_2CH_2$-, -$S(O)_2CH(CH_3)$- and -$S(O)_2C(CH_3)_2$-;

$^1\mathbf{Y}$ is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$;

$\mathbf{R^2}$ is phenyl or pyridyl substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, -$CONH_2$, –$CONHCH_3$ and -$CON(CH_3)_2$;

$\mathbf{R^3}$ is methyl; and

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

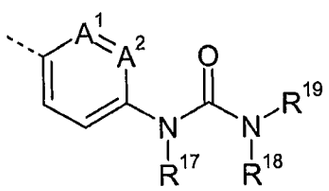
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}**Y** is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2NMe_2$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 3,5-difluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, oxetan-3-yl, 2-oxopyrolidin-3-yl, 1-methylimidazol-5-ylmethyl , 1-methylpyrrolidin-3-yl , thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

$\mathbf{R^2}$ is



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are selected from CH or N provided that at least one of A^1 or A^2 is CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen;

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, $-CH_2$(imidazol-2-yl), $-CH_2$(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyridinyl-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

and, R^3 is methyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

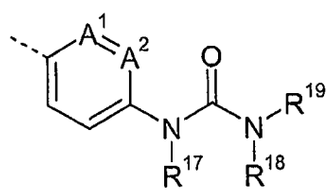
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^1Y is CH and Y^2 is N.

R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, , pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl,, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen;

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, $-CH_2$(imidazol-2-yl), $-CH_2$(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

and, R^3 is methyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

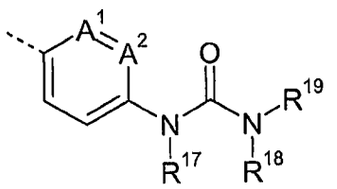
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^1Y is CH and Y^2 is N.

R^1 is methyl or cyclopropyl;

R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH;

R^{17} is hydrogen;

R^{18} is hydrogen;

R^{19} is methyl, ethyl, propyl, cyclopropyl, cyclobutyl, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl;

and, R^3 is methyl.

In a further particular class of compound of formula (I), or a pharmaceutically acceptable salt thereof;

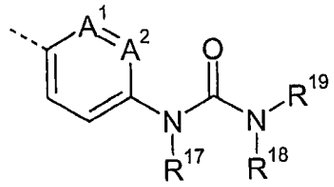
m is 1;

X is a $-S(O)_2C(CH_3)_2-$ linker group;

^{1}**Y** is CH and **Y**^{2} is N.

R^1 is ethyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, pyridin-4-yl or cyclopropyl;

R^2 is



wherein **A**^{1} and **A**^{2} are selected from CH or N provided that at least one of A^1 or A^2 is CH;

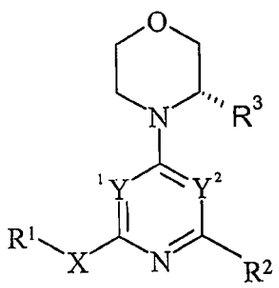
R^{17} is hydrogen;

R^{18} is hydrogen;

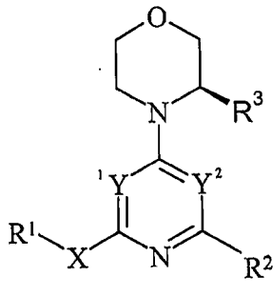
R^{19} is methyl, ethyl, propyl, cyclopropyl, cyclobutyl, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl;

and, **R**^{3} is methyl.

In one aspect of the invention there is provided a subset of compounds of formula (I) wherein the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

$\mathbf{R^1}$ is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and -NR^9COR^{10}; or $\mathbf{X}$-$\mathbf{R^1}$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R^2}$ is selected from aryl and heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ is methyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl;

or, when $\mathbf{X}$ is -$NR^4CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$-, -$NR^4C(O)$- or $-NR^4S(O)_2$-, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

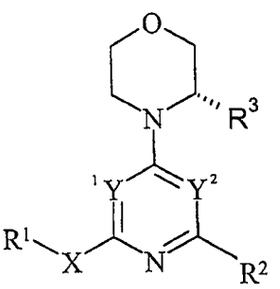
$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

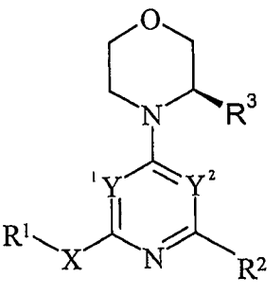
R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I) wherein the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^1Y and Y^2 are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$,

$-S(O)_2NR^4-$ and $-NR^4S(O)_2-$;

$\mathbf{R^1}$ is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or $\mathbf{X}$-$\mathbf{R^1}$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R^2}$ is selected from aryl and heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ is methyl;

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently hydrogen or C_{1-6}alkyl;

or, when $\mathbf{X}$ is $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ or $-NR^4S(O)_2-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

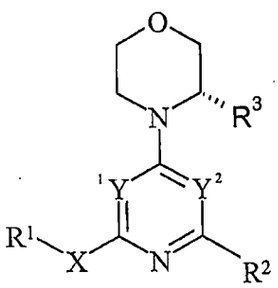
$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

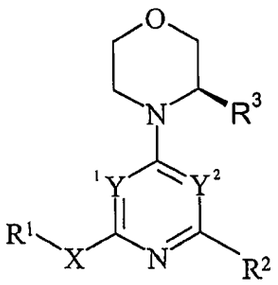
R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another aspect of the invention there is provided a subset of compounds of formula (I) wherein the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^1Y and Y^2 are independently N or CR^8 provided that one of ^1Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NR^4-$ and $-NR^4C(O)-$;

$\mathbf{R^1}$ is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or $\mathbf{X}$-$\mathbf{R^1}$ is $-C(CH_3)_2OH$ or $-CH_2OH$;

$\mathbf{R^2}$ is selected from 5 or 6 membered aryl and heteroaryl which group is substituted by $-NHCONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ is methyl;

$\mathbf{R^4}$ is hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CH_2-$ or $-NR^4C(O)-$, $\mathbf{R^1}$ and $\mathbf{R^4}$ together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^8}$ is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

$\mathbf{R^9}$ and $\mathbf{R^{10}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy,

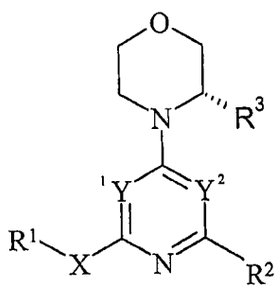
hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

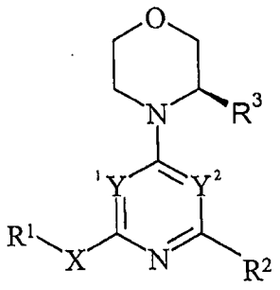
R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or R^{18} and R^{19} together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib),



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** is CH and **Y**^{2} is N;

X is a linker group selected from -S(O)$_2$CH$_2$-, -S(O)$_2$CH(CH$_3$)- and -S(O)$_2$C(CH$_3$)$_2$-;

R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl, furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -NMe$_2$, -NHCOCH$_3$, -CONH$_2$ and –CONHCH$_3$;

or –**XR**^{1} is –C(CH$_3$)$_2$OH or –CH$_2$OH;

R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by –NHCONHR^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} and –NR^{11}COR^{12};

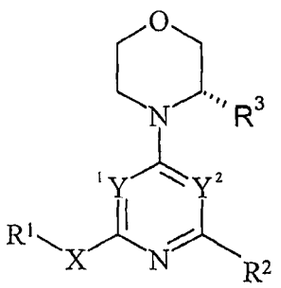
R^3 is methyl;

R^{11}, **R**^{12} and **R**^{18} are independently hydrogen or a group selected from C$_{1\text{-}6}$alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}6}$alkoxy, haloC$_{1\text{-}6}$alkyl, haloC$_{1\text{-}6}$alkoxy, hydroxyC$_{1\text{-}6}$alkyl, hydroxyC$_{1\text{-}6}$alkoxy, C$_{1\text{-}6}$alkoxyC$_{1\text{-}6}$alkyl, C$_{1\text{-}6}$alkoxyC$_{1\text{-}6}$alkoxy, amino, C$_{1\text{-}6}$alkylamino and bis(C$_{1\text{-}6}$alkyl)amino; and

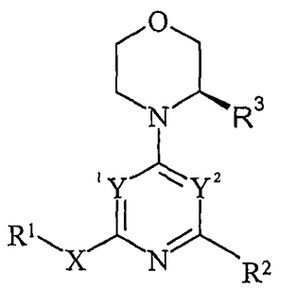
R^{19} is hydrogen or a group selected from C$_{1\text{-}6}$alkyl, C$_{3\text{-}6}$cycloakyl, aryl, heteroaryl, arylC$_{1\text{-}6}$alkyl and heteroarylC$_{1\text{-}6}$alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C$_{1\text{-}6}$alkyl, C$_{1\text{-}6}$alkoxy, haloC$_{1\text{-}6}$alkyl, haloC$_{1\text{-}6}$alkoxy, hydroxyC$_{1\text{-}6}$alkyl, hydroxyC$_{1\text{-}6}$alkoxy, C$_{1\text{-}6}$alkoxyC$_{1\text{-}6}$alkyl, C$_{1\text{-}6}$alkoxyC$_{1\text{-}6}$alkoxy, amino, C$_{1\text{-}6}$alkylamino, bis(C$_{1\text{-}6}$alkyl)amino, aminoC$_{1\text{-}6}$alkyl, (C$_{1\text{-}$

$_{6}$alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In another particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib),



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

^{1}**Y** is CH and **Y**^{2} is N;

X is a linker group selected from -$S(O)_2CH_2$-, -$S(O)_2CH(CH_3)$- and -$S(O)_2C(CH_3)_2$-;

R^{1} is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$;

or –**XR**^{1} is –$C(CH_3)_2OH$ or –CH_2OH;

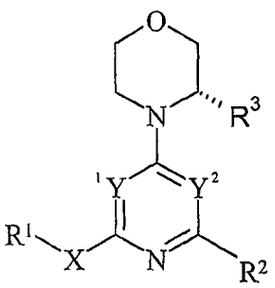
R^{2} is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl and thiazolyl which group is substituted by –$NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ and –$NR^{11}COR^{12}$;

R^{3} is methyl;

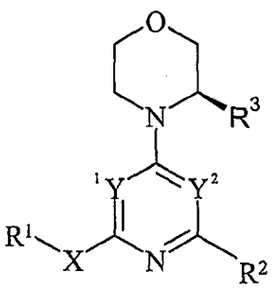
R^{11}, **R**^{12} and **R**^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino; and

R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}**Y** is CH and $\mathbf{Y}^2$ is N.

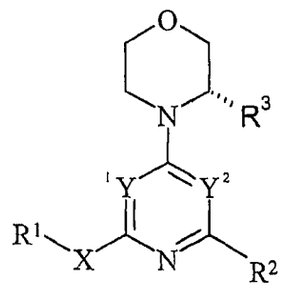
$\mathbf{R}^1$ is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl, furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

$\mathbf{R}^2$ is phenyl or pyridyl substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$;

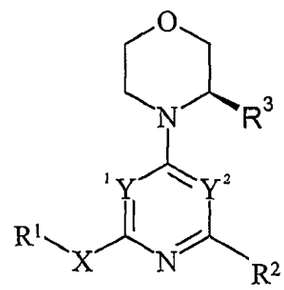
$\mathbf{R}^3$ is methyl; and

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}**Y** is CH and **Y**^{2} is N.

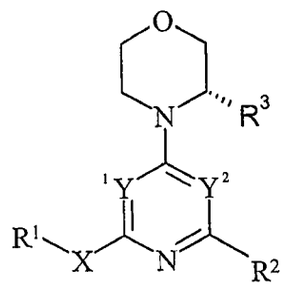
R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, $-NHCOCH_3$, $-CONH_2$ and $-CONHCH_3$;

R^2 is phenyl or pyridyl substituted by $-NHCONHR^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$;

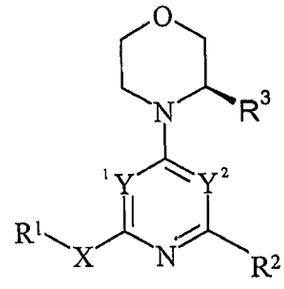
R^3 is methyl; and

R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

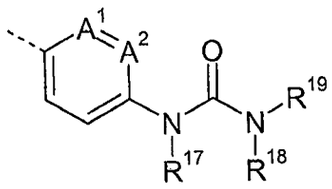
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}**Y** is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2NMe_2$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 3,5-difluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, oxetan-3-yl, 2-oxopyrolidin-3-yl, 1-methylimidazol-5-ylmethyl , 1-methylpyrrolidin-3-yl , thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

$\mathbf{R^2}$ is



wherein $\mathbf{A}^1$ and $\mathbf{A}^2$ are selected from CH or N provided that at least one of A^1 or A^2 is CH;

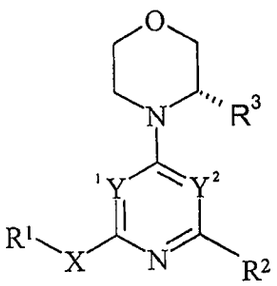
$\mathbf{R}^{17}$ is hydrogen;

$\mathbf{R}^{18}$ is hydrogen; and

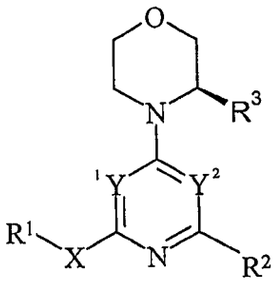
$\mathbf{R}^{19}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, $-CH_2$(imidazol-2-yl), $-CH_2$(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyridinyl-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

and, $\mathbf{R}^3$ is methyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

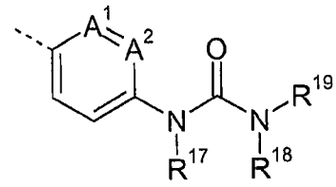
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}Y is CH and Y^2 is N.

R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl;

R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH;

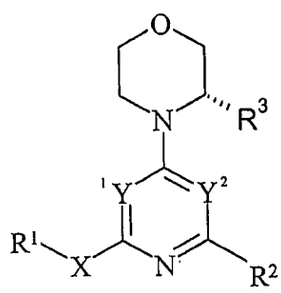
R^{17} is hydrogen;

R^{18} is hydrogen; and

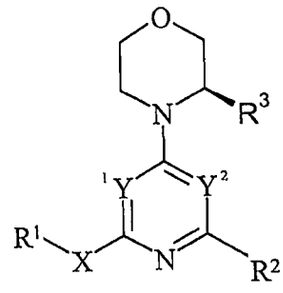
R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, $-CH_2$(imidazol-2-yl), $-CH_2$(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, $-CH_2$(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl;

and, R^3 is methyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

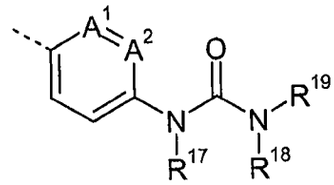
m is 1;

X is a linker group selected from $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ and $-S(O)_2C(CH_3)_2-$;

^{1}**Y** is CH and **Y**^{2} is N.

R^1 is methyl or cyclopropyl;

R^2 is



wherein **A**^{1} and **A**^{2} are selected from CH or N provided that at least one of A^1 or A^2 is CH;

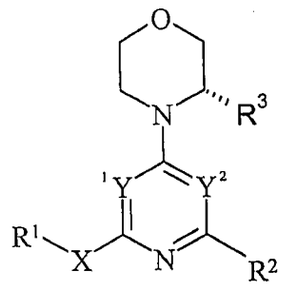
R^{17} is hydrogen;

R^{18} is hydrogen; and

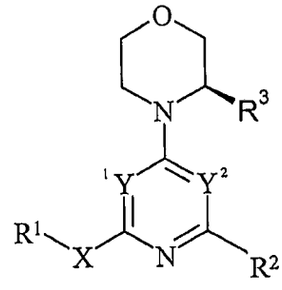
R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, cyclopropyl, cyclobutyl, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl;

and, **R**^{3} is methyl.

In a further particular class of compound of formula (I), the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

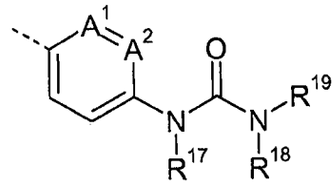
m is 1;

X is a $-S(O)_2C(CH_3)_2-$ linker group;

^{1}**Y** is CH and $\mathbf{Y^2}$ is N.

$\mathbf{R^1}$ is methyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, pyridin-4-yl or cyclopropyl;

$\mathbf{R^2}$ is



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are selected from CH or N provided that at least one of A^1 or A^2 is CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

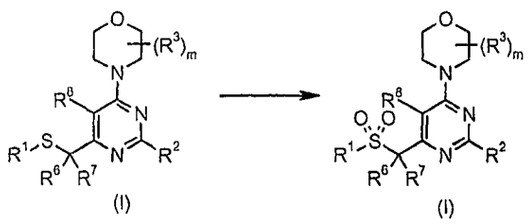
$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, cyclopropyl, cyclobutyl, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl;

and, $\mathbf{R^3}$ is methyl.

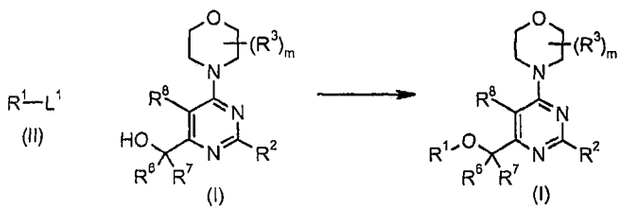
Another aspect of the invention provides a compound, or a combination of compounds, selected from any one of the Examples or a pharmaceutically acceptable salt thereof.

The invention also provides processes for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

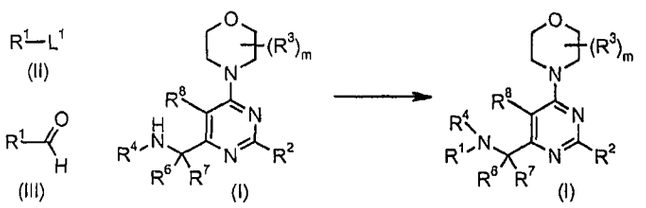
A compound of formula (I), wherein X = -S(O)$_2$CR^{6}R^7-, may be prepared by oxidising a compound of the formula (I), wherein X = SCR^{6}R^7-, for example by using Oxone® at room temperature in a mixed solvent system of water and ethanol



A compound of formula (I), wherein R^{1}X = R^{1}OCR^{6}R^7-, may be prepared by the reaction of a compound of formula (I), wherein R^{1}X = HOCR^{6}R^7-, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.

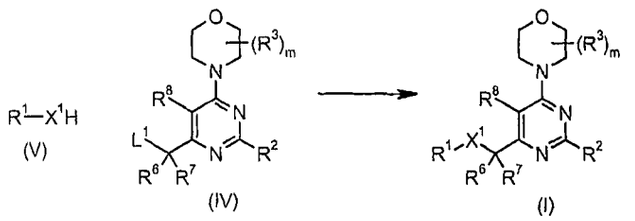


A compound of formula (I), wherein R^{1}X = R^{1}R^{4}NCR^{6}R^7-, may be prepared by the reaction of a compound of formula (I), wherein R^{1}X = HR^{4}NCR^{6}R^7-, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide; or by the reaction of a compound of formula (I), wherein R^{1}X = HR^{4}NCR^{6}R^7-, with a compound of formula (III) in the presence of a suitable reducing agent such as $NaCNBH_3$.

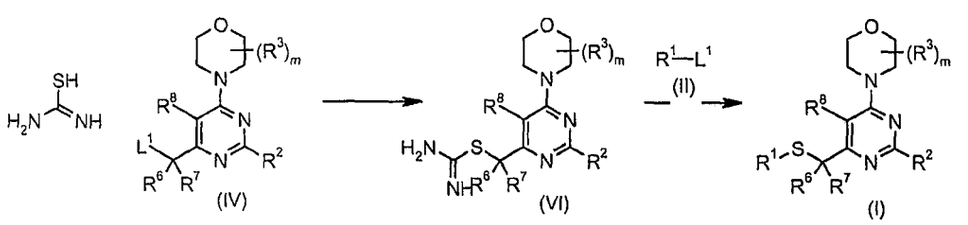


A compound of formula (I), wherein X^1 = -S(O)$_2$CR^{6}R^7-, -SCR^{6}R^7-, -OCR^{6}R^7-, -R^{4}NCR^{6}R^7-, -S(O)CR^{6}R^7-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula

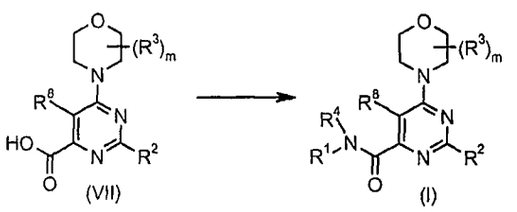
(V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



A compound of formula (I), wherein X = -SCR^6R^7-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (VI) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.

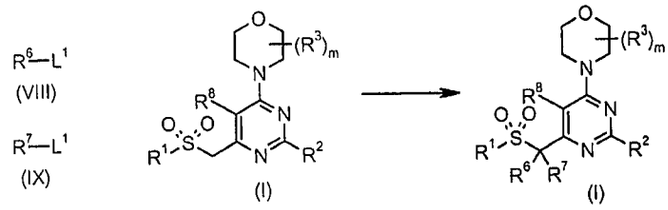


A compound of formula (I), wherein X = -$R^4NC(O)$-, may be prepared by the reaction of a compound of formula (VII) with an amine of formula R^1R^4NH following the suitable activation of the carboxylic acid by methods known in the literature such as the use of a coupling agent such as HATU or the conversion to an acyl chloride.

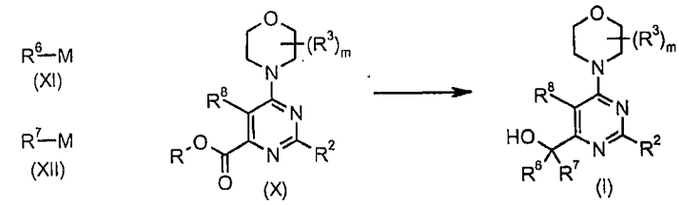


A compound of formula (I), wherein X = -$S(O)_2CR^6R^7$-, may be prepared by the sequential reaction of a compound of formula (I), wherein X = -$S(O)_2CH_2$-, with a compound of formula (VIII) followed by reaction with a compound of formula (IX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide.

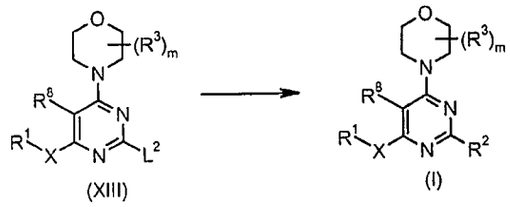
106



A compound of formula (I), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (X), with suitable organometallic reagents of fomula (XI) and formula (XII) such as the grignard reagent in a suitable solvent. Where R^6 and R^7 are different then it may be possible to use techniques known in the literature such the conversion of a compound of formula (X) to the Weinreb amide and reaction with an organometallic reagent of formula (XI) and then reaction with an organometallic reagent of formula (XII) in a subsequent step.

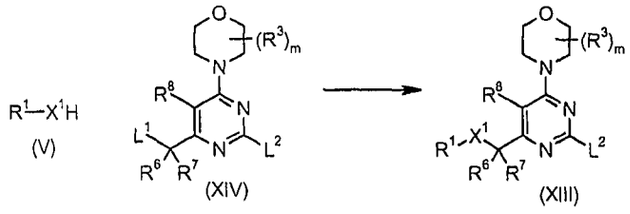


A compound of formula (I) may be prepared from a compound of formula (XIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (I) may be prepared from a compound of formula (XIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.

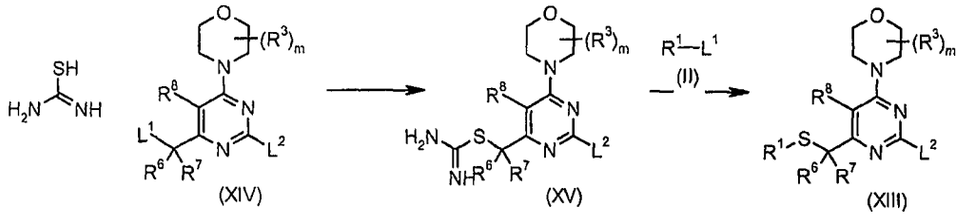


It will be appreciated that a compound of formula (XIII) may be transformed into another compound of formula (XIII) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

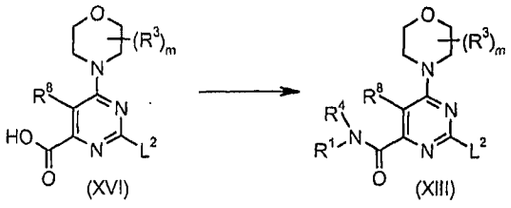
A compound of formula (XIII), wherein X^1 = $-S(O)_2CR^6R^7-$, $-SCR^6R^7-$, $-OCR^6R^7-$, $-R^4NCR^6R^7-$, $-S(O)CR^6R^7-$, may be prepared by the reaction of a compound of formula (XIV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



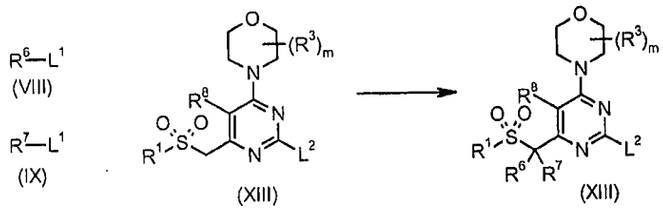
A compound of formula (XIII), wherein X = $-SCR^6R^7-$, may be prepared by the reaction of a compound of formula (XIV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XV) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.



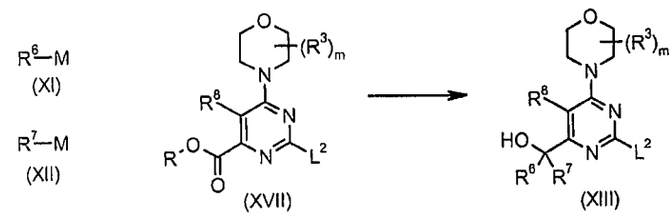
A compound of formula (XIII), wherein X = $-R^4NC(O)-$, may be prepared by the reaction of a compound of formula (XVI) with an amine of formula R^1R^4NH following the suitable activation of the carboxylic acid by methods known in the literature such as the use of a coupling agent such as HATU or the conversion to an acyl chloride.



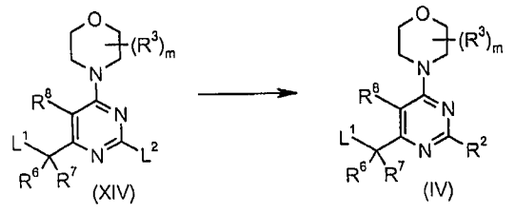
A compound of formula (XIII), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the sequential reaction of a compound of formula (XIII), wherein X = $-S(O)_2CH_2-$, with a compound of formula (VIII) followed by reaction with a compound of formula (IX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



A compound of formula (XIII), wherein $R^1X = HOCR^6R^7-$, may be prepared by the reaction of a compound of formula (XVII), with suitable organometallic reagents of fomula (XI) and formula (XII) such as the grignard reagent in a suitable solvent. Where R^6 and R^7 are different then it may be possible to use techniques known in the literature such the conversion of a compound of formula (XVII) to the Weinreb amide and reaction with an organometallic reagent of formula (XI) and then reaction with an organometallic reagent of formula (XII) in a subsequent step.

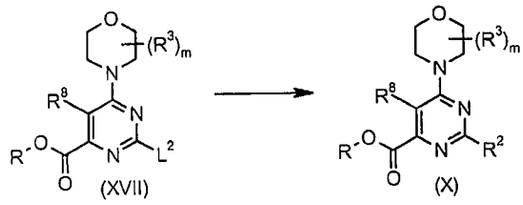


A compound of formula (IV) may be prepared from a compound of formula (XIV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (IV) may be prepared from a compound of formula (XIV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



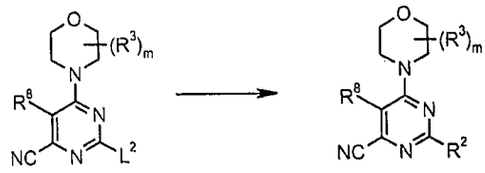
(XIV) (IV)

A compound of formula (X) may be prepared from a compound of formula (XVII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or C_{1-4} alkyl group, with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (X) may be prepared from a compound of formula (XVII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XVII) (X)

A compound of formula (XVIII) may be prepared from a compound of formula (XIX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XVIII) may be prepared from a compound of formula (XIX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



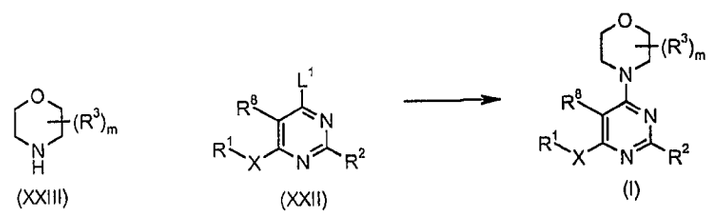
(XIX) (XVIII)

A compound of formula (XX) may be prepared from a compound of formula (XXI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XX) may be prepared from a compound of formula (XXI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XXI) (XX)

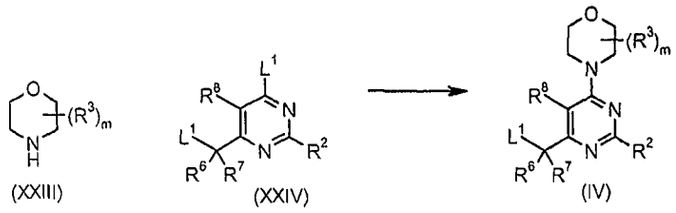
A compound of formula (I), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXII) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXIII) (XXII) (I)

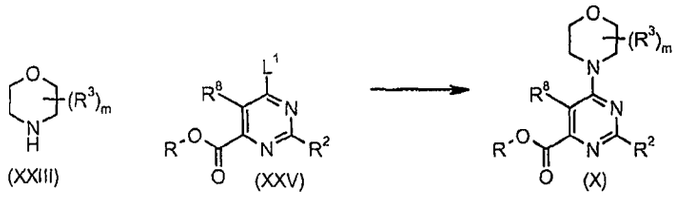
It will be appreciated that a compound of formula (XXII) may be transformed into another compound of formula (XXII) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

A compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXIV) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



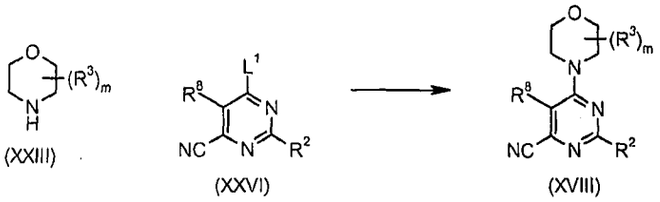
(XXIII) (XXIV) (IV)

A compound of formula (X), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXV) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



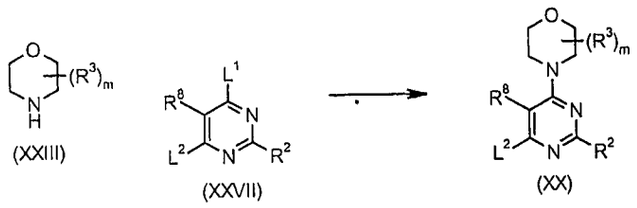
(XXIII) (XXV) (X)

A compound of formula (XVIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXVI) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



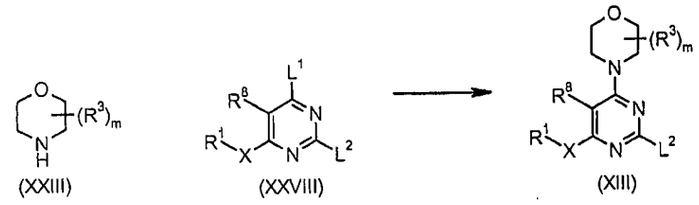
(XXIII) (XXVI) (XVIII)

A compound of formula (XX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXIII) (XXVII) (XX)

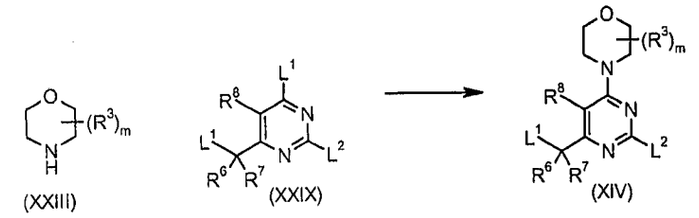
A compound of formula (XIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXVIII) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXIII) (XXVIII) (XIII)

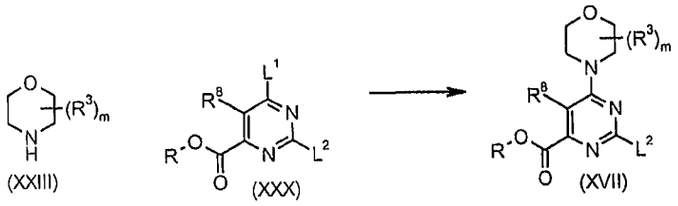
It will be appreciated that a compound of formula (XIII) may be transformed into another compound of formula (XIII) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

A compound of formula (XIV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXIX) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



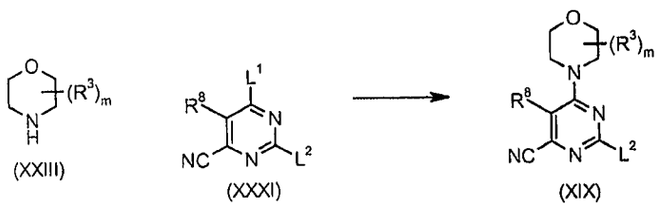
(XXIII) (XXIX) (XIV)

A compound of formula (XVII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXX) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



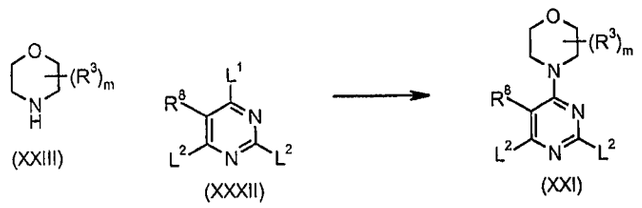
(XXIII) (XXX) (XVII)

A compound of formula (XIX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXI) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



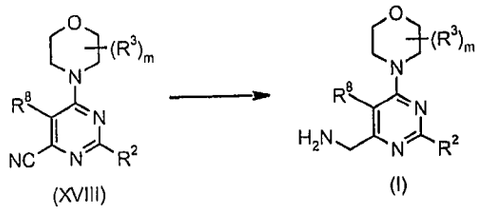
(XXIII) (XXXI) (XIX)

A compound of formula (XXI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXII) with a compound of formula (XXIII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



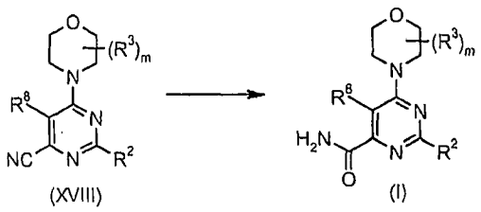
(XXIII) (XXXII) (XXI)

A compound of formula (I), wherein $R^1X = H_2NCH_2-$, may be prepared from a compound of formula (XVIII) by a reduction such as hydrogenation with hydrogen gas and a suitable catalyst such as Palladium on carbon in a suitable solvent such as ethanol.



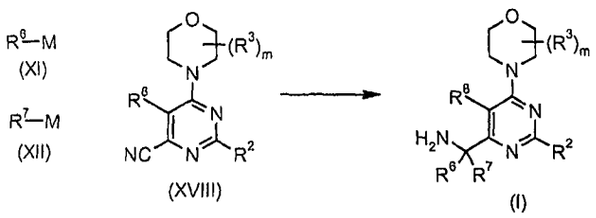
(XVIII) (I)

A compound of formula (I), wherein $R^1X = H_2NC(O)$-, may be prepared from a compound of formula (XVIII) by hydrolysis with, for example, sodium hydroxide in a suitable solvent such as a water ethanol mix.



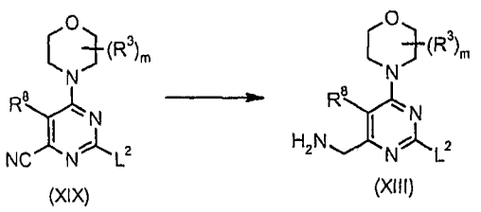
(XVIII) (I)

A compound of formula (I), wherein $R^1X = H_2NCR^6R^7$-, may be prepared from a compound of formula (XVIII) by reaction with organometallic reagents (XI) and (XII).



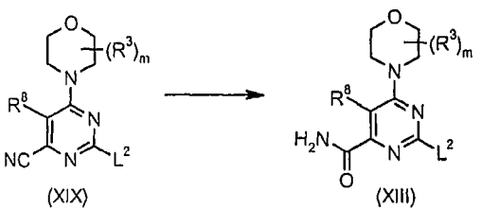
(XVIII) (I)

A compound of formula (XIII), wherein $R^1X = H_2NCH_2$-, may be prepared from a compound of formula (XIX) by a reduction such as hydrogenation with hydrogen gas and a suitable catalyst such as Palladium on carbon in a suitable solvent such as ethanol.



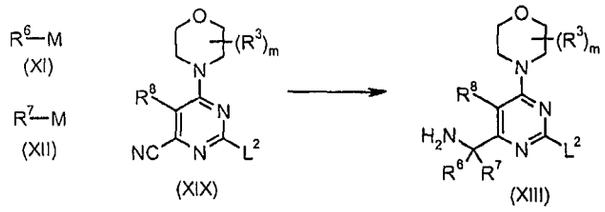
(XIX) (XIII)

A compound of formula (XIII), wherein $R^1X = H_2NC(O)$-, may be prepared from a compound of formula (XIX) by hydrolysis with, for example, sodium hydroxide in a suitable solvent such as a water ethanol mix.



(XIX) (XIII)

A compound of formula (XIII), wherein $R^1X = H_2NCR^6R^7$-, may be prepared from a compound of formula (XIX) by reaction with organometallic reagents (XI) and (XII).



It will be appreciated that the R^2 group may be introduced at any stage initially as a carbocyclic or heterocyclic amine (optionally with the nitrogen protected, such protecting groups include but are not limited to nitro, *tert*-butoxy carbamate etc.) which can be transformed at a subsequent stage in the synthesis (after appropriate deprotection) to a urea by either direct reaction with an isocyanate (or otherwise activated group such as a phenoxy carbamate, etc.) or by activation of the amine (such as with phosgene or the formation of a phenoxy carbamate, etc.) and subsequent reaction with an appropriate amine, or other methods of forming a urea known in the literature.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. For example compounds of formula (I) my be converted into further compounds of formula (I) by standard aromatic substitution reactions or by conventional functional group modifications. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis

with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as mTOR kinase inhibitors, as PI3 kinase inhibitors, as inhibitors *in vitro* of the activation of PI3 kinase signalling pathways and as inhibitors *in vitro* of the proliferation of MDA-MB-468 human breast adenocarcinoma cells.

(a) *In Vitro* mTOR Kinase 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 sulfate; 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 30 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) and 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)] was agitated at room temperature for 90 minutes.

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. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 10 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 (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left for about 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read 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.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(b) *In Vitro* PI3K 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 Type I PI3K enzymes of the lipid PI(4,5)P2.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, full length DNA of each of the p110α, p110β and p110δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110α, p110β and p110δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110γ isoform corresponding to amino acid residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag using standard purification techniques.

DNA corresponding to amino acids 263 to 380 of human general receptor for phosphoinositides (Grp1) PH domain was isolated from a cDNA library using standard molecular biology and PCR cloning techniques. The resultant DNA fragment was sub-cloned into a pGEX 4T1 *E. coli* expression vector containing a GST epitope tag (Amersham Pharmacia Biotech, Rainham, Essex, UK) as described by Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). The GST-tagged Grp1 PH domain was expressed and purified using standard 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, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng), DiC8-PI(4,5)P2 substrate (40 μM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μM) and a buffer solution [comprising Tris-HCl pH7.6 buffer (40 mM, 10 μl), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS; 0.04%), dithiothreitol (DTT; 2 mM) and magnesium chloride (10 mM)] was agitated at room temperature for 20 minutes.

120

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding wortmannin (6 μM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also agitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 μl of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidn acceptor beads. The enymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(c) *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.

(d) *In Vitro* MDA-MB-468 human breast adenocarcinoma Proliferation Assay

This assay determines the ability of test compounds to inhibit cell proliferation as assessed using Cellomics Arrayscan technology. A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Catalogue No. HTB-132) was routinely maintained as described in Biological Assay (b) herein.

For the proliferation assay, the cells were detached from the culture flask using Accutase and seeded into the inner 60 wells of a black Packard 96 well plate at a density of 8000 cells per well in 100 µl of complete growth media. The outer wells contained 100 µl of sterile PBS. 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 48 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 test concentrations. Aliquots (50 µl) of each compound dilution were placed in a well and the cells were incubated for 2 days at 37°C with 5% CO_2. Each plate contained control wells without test compound.

On day 4, BrdU labelling reagent (Sigma, Catalogue No. B9285) at a final dilution of 1:1000 was added and the cells were incubated for 2 hours at 37°C. The medium was removed and the cells in each well were fixed by treatment with 100 µl of a mixture of ethanol and glacial acetic acid (90% ethanol, 5% glacial acetic acid and 5% water) for 30 minutes at room temperature. The cells in each well were washed twice with PBS (100 µl). Aqueous hydrochloric acid (2M, 100 µl) was added to each well. After 20 minutes at room temperature, the cells were washed twice with PBS. Hydrogen peroxide (3%, 50 µl; Sigma,

Catalogue No. H1009) was added to each well. After 10 minutes at room temperature, the wells were washed again with PBS.

BrdU incorporation was detected by incubation for 1 hour at room temperature with mouse anti-BrdU antibody (50 µl; Caltag, Burlingame, CA, US; Catalogue No. MD5200) that was diluted 1:40 in PBS containing 1% BSA and 0.05% Tween-20. Unbound antibody was removed with two washes of PBS. For visualisation of incorporated BrdU, the cells were treated for 1 hour at room temperature with PBS (50 µl) and 0.05% Tween-20 buffer containing a 1:1000 dilution of Alexa fluor 488–labelled goat anti-mouse IgG. For visualisation of the cell nucleus, a 1:1000 dilution of Hoechst stain (Molecular Probes, Catalogue No. H3570) was added. Each plate was washed in turn with PBS. Subsequently, PBS (100 µl) was added to each well and the plates were analysed using a Cellomics array scan to assess total cell number and number of BrdU positive cells.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of MDA-MB-468 cell growth was expressed as an IC_{50} value.

Although the pharmacological properties of the compounds of formula (I) vary with structural change as expected, in general, it is believed that activity possessed by compounds of formula (I) may be demonstrated at the following concentrations or doses in one or more of the above tests (a) to (d) :-

Test (a):- IC_{50} versus mTOR kinase at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; for example 34b the IC50 was measured on two occasions, the values were 0.155 and 0.093µM.

Test (b):- IC_{50} versus p110γ Type Ib human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; and IC_{50} versus p110α Type Ia human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds;
for example 34b the IC50 was measured on two occasions, the values were 91.2 and 57.8 µM.

Test (c):- IC_{50} versus Serine 473 in Akt at less than 10 µM, in particular 0.1 - 20 µM for many compounds); for example 34b the IC50 was measured on two occasions, the values were 1.361 and 0.654µM.

Test (d):- IC_{50} at less than 20 µM;

The compounds of the present invention are advantageous in that they possess pharmacological activity. In particular, the compounds of the present invention modulate (in particular, inhibit) mTOR kinase and/or phosphatidylinositol-3-kinase (PI3K) enzymes, such as the Class Ia PI3K enzymes (*e.g.* PI3Kalpha, PI3Kbeta and PI3Kdelta) and the Class Ib PI3K enzyme (PI3Kgamma). More particularly compounds of the present invention modulate (in particular, inhibit) mTOR kinase. More particularly compounds of the present invention modulate (in particular, inhibit) one or more PI3K enzyme. The inhibitory properties of compounds of formula (I) may be demonstrated using the test procedures set out herein and in the experimental section. Accordingly, the compounds of formula (I) may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are mediated by mTOR kinase and/or one or more PI3K enzyme(s), and in particular by mTOR kinase.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent (more suitably from 1 to 250 mg, for example from 1 to 100 mg) compounded with an

appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of formula I will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 1 mg/kg to 100 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will be used. Typically, unit dosage forms will contain about 10 mg to 0.5 g of a compound of this invention.

As stated herein, it is known that mTOR kinase and the PI3K enzymes have roles in tumourigenesis as well as numerous other diseases. We have found that the compounds of formula (I) possess potent anti-tumour activity which it is believed is obtained by way of inhibition of mTOR kinase and/or one or more of the PI3K enzymes.

Accordingly, the compounds of the present invention are of value as anti-tumour agents. Particularly, the compounds of the present invention are of value as anti-proliferative, apoptotic and/or anti-invasive agents in the containment and/or treatment of solid and/or liquid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. The compounds may thus be used to produce an mTOR enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Certain compounds may be used to produce an PI3K enzyme inhibitory effect in a warm-blooded animal in need of such treatment.

As stated herein, inhibitors of mTOR kinase and/or one or more PI3K enzymes should be of therapeutic value for the treatment of proliferative disease such as cancer and in particular solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies and in particular 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 acute lymphoctic leukaemia (ALL) and chronic myelogenous leukaemia (CML)], multiple myeloma and lymphomas.

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

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

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

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

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

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

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

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an apoptotic 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 formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative 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), 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-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further aspect of the invention there is also provided a method for providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment 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.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment 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.

According to a further feature of the invention there is provided a method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating 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 in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

As stated herein, the *in vivo* effects of a compound of formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of formula (I).

The invention further relates to combination therapies wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently or sequentially or as a combined preparation with another treatment of use in the control of oncology disease.

In particular, the treatment defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy

or chemotherapy. Accordingly, the compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer.

Suitable agents to be used in combination include :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); 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 paclitaxel and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), 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 5α-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 and inhibitors of urokinase plasminogen activator receptor function);

(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™] and the anti-erbB1 antibody cetuximab [C225]); such inhibitors also include, for example, 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) and 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)) and inhibitors of cell signalling through MEK and/or Akt kinases;

(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), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 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 agent;

(viii) gene therapy approaches, including 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) immunotherapeutic approaches, including *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.

The invention will now be further explained by reference to the following illustrative examples.

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

In the examples ^{1}H NMR spectra were recorded on a Bruker DPX 300 (300 MHz), Bruker DRX 400 (400 MHz) instrument or a Bruker DRX 500 (500 MHz) instrument. The central peaks of chloroform-d (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or acetone-d_6 (δ_H 2.05 ppm) were used as internal references. The following abbreviations have been used: s, singlet; d, doublet;
t, triplet; q, quartet; m, multiplet; br, broad.

Column chromatography was carried out using silica gel (0.04-0.063 mm, Merck). In general, a Kromasil KR-100-5-C18 reversed-phase column (250 x 20 mm, Akzo Nobel) was used for preparative HPLC with mixtures of acetonitrile and water [containing 0.1% trifluoroacetic acid (TFA)] used as the eluent at a flow rate of 10 mL/min.
The following methods were used for liquid chromatography (LC) / mass spectral (MS) analysis :-

HPLC: Agilent 1100 or Waters Alliance HT (2790 & 2795)
Mass Spectrometer: Waters ZQ ESCi

HPLC Column

The standard HPLC column used is the Phemonenex Gemini C18 5µm, 50 x 2 mm.

Acidic HPLC Methods

The mobile phases used are:

Mobile phase A:	Water
Mobile Phase B:	Acetonitrile
Mobile Phase C:	1% Formic Acid in 50:50 Water:MeCN (v/v)

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

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Four generic HPLC methods are available:

5 Minute Monitor Acidic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Acidic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Mid Acidic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Acidic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
4.5	5	95	5	6	1.1

Basic HPLC methods

In some instances the standard acidic methods may be unsuitable for either the compound ionisation or the chromatography separation required. In such cases four comparable Basic HPLC methods are available.

The mobile phases used are: Mobile phase A: Water

Mobile Phase B: Acetonitrile

Mobile Phase D: 0.1% 880 Ammonia in acetonitrile

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

Minute Monitor Basic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Basic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

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Mid Basic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Basic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

The following method was used for liquid chromatography (LC) / mass spectral (MS) analysis :-

Instrument: Agilent 1100; Column: Waters 'Symmetry' 2.1 x 30 mm; Mass Spectral analysis using chemical ionisation (APCI); Flow rate: 0.7 mL/min; Absorption Wavelength: 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Solvent Gradient: 15-95% Solvent B for 2.7 minutes followed by 95% Solvent B for 0.3 minutes.

The following methods were used for LC analysis :-

Method A :- Instrument: Agilent 1100; Column: Kromasil C18 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.1% TFA/water, Solvent B: 0.08% TFA/acetonitrile; Flow Rate: 1 mL/min; Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelengths: 220, 254 and 280 nm. In general, the retention time of the product was noted.

Method B :- Instrument: Agilent 1100; Column: Waters 'Xterra' C8 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.015M ammonia in water, Solvent B:

acetonitrile; Flow Rate: 1 ml/min, Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelength: 220, 254 and 280 nm. In general, the retention time of the product was noted.

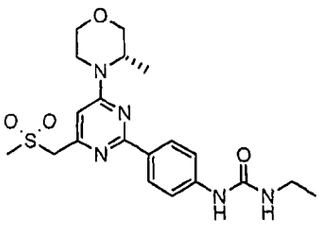
The following abbreviations are used herein or within the following illustrative examples :-

HPLC	High Performance Liquid Chromatography
HBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HOBT	1-hydroxybenzotriazole;
HOAT	1-hydroxy-7-azabenzotriazole;
NMP	*N*-methylpyrrolidin-2-one;
DMSO	dimethylsulfoxide;
DMF	*N*,*N*-dimethylformamide;
DMA	*N*,*N*-dimethylacetamide;
THF	tetrahydrofuran;
DME	1,2-dimethoxyethane;
DCCI	dicyclohexylcarbodiimide;
MeOH	methanol;
MeCN	acetonitrile;
DCM	dichloromethane;
DIPEA	*N*,*N*-diisopropylethylamine;
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
RT	room temperature (approximately 17 to 25°C);
tR	retention time;
m/z	mass/charge ratio.

The chemical names were generated by software which used the Lexichem Toolkit (v. 1.40) from OpenEye Scientific Software (www.eyesopen.com) to generate IUPAC conforming names.

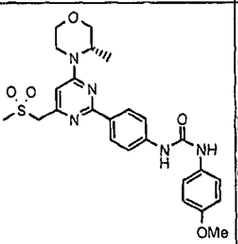
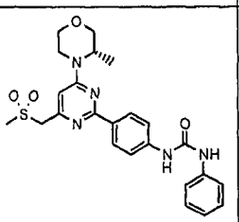
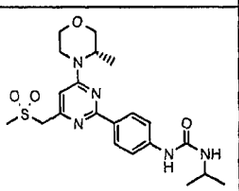
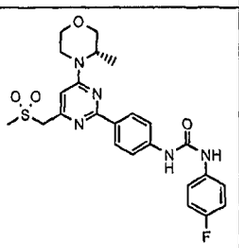
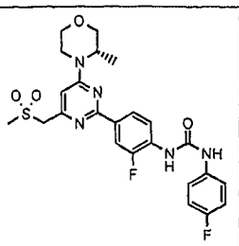
Example 1:

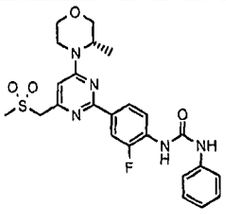
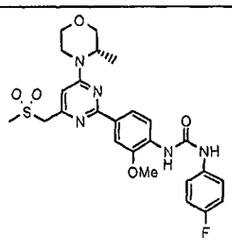
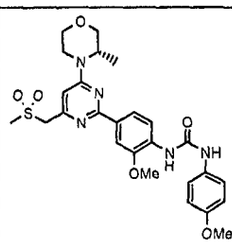
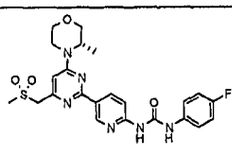
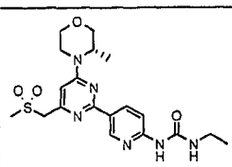
1-Ethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea



4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline (100 mg, 0.28 mmol) was dissolved in dioxane (4 mL). Ethylisocyanate (0.109 mL, 1.38 mmol) was added and the reaction heated at 70°C for 4 hours. Reaction was complete and was evaporated to dryness. The resultant oil was purified by chromatography, eluting with 10 – 50% ethyl acetate in isohexane, to give 3-ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea as a pale yellow oil (113 mg, 94%).
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.99 (t, 3H), 1.25 (d, 3H), 3.11 (q, 2H), 3.20 (s, 3H), 3.29 (m, 2H), 3.5 (m, 1H), 3.67 (m, 1H), 3.78 (m, 1H), 3.99 (m, 1H), 4.16 (m, 1H), 4.47 (s, 2H), 6.18 (t, 1H), 6.78 (s, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.68 (s, 1H)
LCMS Spectrum: MH+ 434, retention time 1.37 min, Method 5 Min Acid

The compounds shown in table were prepared in an analogous manner to 3-ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea by reacting the appropriate isocyanate with the appropriate aniline.

Example	Structure	NAME	LCMS MH+	Retention time (min)	Notes
1a		1-(4-methoxyphenyl)-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	512	2.19	Purified by ethyl acetate slurry then chromatography
1b		1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	482	2.26	Chromatography eluted with 0-8% MeOH/ DCM
1c		3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-propan-2-yl-urea	448	1.90	Chromatography eluted with 0-8% MeOH/ DCM
1e		3-(4-fluorophenyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	500	2.05	Triturated with ethyl acetate
1f		1-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(4-fluorophenyl)urea	518	2.38	Purified by reverse phase chromatography

Example	Structure	NAME	LCMS MH+	Retention time (min)	Notes
1g		1-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	500	2.36	Purified by reverse phase chromatography
1h		3-(4-fluorophenyl)-1-[2-methoxy-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	529	2.22	Crystallised from NMP/water then triturated with EtOAc
1i		3-[2-methoxy-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(4-methoxyphenyl)urea	542	2.06	Crystallised from NMP/water then triturated with EtOAc
1j		3-(4-fluorophenyl)-1-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-yl]urea	501	2.26	Crystallised from dimethylformamide/ water
1k		1-ethyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-yl]urea	435	1.51	Purified by reverse phase chromatography

Example 1a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.28 (d, 3H), 3.21 (s, 3H), 3.4 (m, 2H), 3.5 (m, 1H), 3.65 (m, 1H), 3.71 (s, 3H), 3.8 (d, 1H), 3.99 (m, 1H), 4.2 (m, 1H), 4.50 (s, 2H), 6.79 (s, 1H), 6.89 (d, 2H), 7.38 (d, 2H), 7.55 (d, 2H), 8.25 (d, 2H), 8.50 (s, 1H), 8.83 (s, 1H)

Example 1b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (d, 3H), 3.21 (s, 2H), 3.28-3.38 (m, 2H), 3.35 (t, 1H), 3.67 (d, 1H), 3.69 (d, 1H), 4.18-4.22 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.00 (m, 1H), 7.31 (m, 2H) 7.47 (d, 2H), 7.59 (d, 2H), 8.27 (d, 2H), 8.71 (s, 1H), 8.91 (s, 1H)

Example 1c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.10 (d, 6H), 1.24 (d, 3H), 3.29 (s, 3H), 3.49 (m, 1H), 3.64-3.66 (m, 1H), 3.77 (m, 2H), 4.18-4.21 (m, 1H), 4.49 (s, 3H), 6.08 (d, 1H), 6.79, (s, 1H), 7.48 (d, 2H), 8.22 (d, 2H), 8.51 (s, 1H)

Example 1d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 - 1.27 (m, 3H), 3.22 (s, 3H), 3.35 - 3.36 (m, 1H), 3.41 (s, 1H), 3.51 (d, 2H), 3.65 - 3.68 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.18 (s, 1H), 4.50 (s, 2H), 6.80 (s, 1H), 7.12 - 7.16 (m, 2H), 7.47 - 7.50 (m, 2H), 7.57 (d, 2H), 8.27 (d, 2H), 8.75 (s, 1H), 8.92 (s, 1H)

Example 1e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 - 1.27 (m, 3H), 3.21 (s, 3H), 3.25 (t, 1H), 3.48 - 3.54 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.19 (s, 1H), 4.50 (m, 1H), 4.51 (s, 2H), 6.84 (s, 1H), 7.16 (d, 2H), 7.47 - 7.51 (m, 2H), 8.08 - 8.12 (m, 1H), 8.13 - 8.15 (m, 1H), 8.31 (t, 1H), 8.77 (d, 1H), 9.17 (s, 1H)

Example 1f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.26 (d, 3H), 3.21 (s, 3H), 3.24-3.26 (m, 1H), 3.52 (t, 1H), 3.66 (t, 1H), 3.79 (d, 1H), 3.99 - 4.02 (m, 2H), 4.18 (m, 1H), 4.52 (s, 3H), 6.84 (s, 1H), 7.02 (t, 1H), 7.30 - 7.34 (m, 2H), 7.48 (d, 2H), 8.08 - 8.15 (m, 2H), 8.34 (t, 1H), 8.79 (d, 1H), 9.15 (s, 1H)

Example 1g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 - 1.27 (m, 3H), 3.24 (s, 3H), 3.30 (m, 1H), 3.49 - 3.53 (m, 1H), 3.65 - 3.69 (m, 1H), 3.80 (d, 1H), 3.98 (s, 3H), 4.00 (m, 1H), 4.02 (m, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 6.82 (s, 1H), 7.12 - 7.17 (m, 2H), 7.47 - 7.51 (m, 2H), 7.96 (s, 2H), 8.27 (s, 1H), 8.42 (s, 1H), 9.45 (d, 1H)

Example 1h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.26 (d, 3H), 3.24 (s, 3H), 3.30 (m, 1H), 3.49 - 3.55 (m, 1H), 3.65 - 3.69 (m, 1H), 3.74 (s, 3H), 3.80 (d, 1H), 3.97 (s, 3H), 4.00 (m, 1H), 4.02 (m, 1H), 4.18 - 4.22 (m, 1H), 4.47 - 4.49 (m, 1H), 4.52 (s, 2H), 6.81 (s, 1H), 6.88 - 6.91 (m, 2H, 7.36 - 7.40 (m, 2H), 7.95 (s, 2H), 8.28 (d, 1H), 8.36 (s, 1H), 9.23 (s, 1H)

Example 1i: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.27 (d, 3H), 3.21 (s, 3H), 3.25 (m, 1H), 3.48 - 3.55 (m, 1H), 3.65 - 3.69 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.20 (s, 1H), 4.52

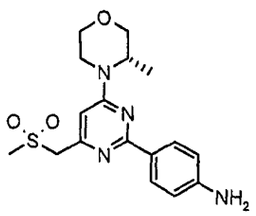
(s, 3H), 6.87 (s, 1H), 7.14 - 7.21 (m, 2H), 7.56 - 7.60 (m, 2H), 7.61 - 7.64 (m, 1H), 8.57 - 8.59 (m, 1H), 9.21 - 9.21 (m, 1H), 9.70 (s, 1H), 10.52 (s, 1H)

Example 1j: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.12 (t, 3H), 1.25 - 1.26 (m, 3H), 3.20 (s, 3H), 3.22 - 3.24 (m, 2H), 3.26 (m, 1H), 3.47 - 3.54 (m, 1H), 3.64 - 3.67 (m, 1H), 3.78 (d, 1H), 3.97 - 4.01 (m, 1H), 4.18 (s, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.48 (d, 1H), 8.10 (d, 1H), 8.48 - 8.51 (m, 1H), 9.11 (m, 1H), 9.41 (s, 1H)

Test (a): Example(1) 0.0062 μM; Example(1a) 0.062 μM; Example(1b) 0.013 μM; Example(1c) 0.078 μM; Example(1d) 0.042 μM; Example(1e) 0.32 μM; Example(1f) 0.36 μM; Eample(1g) 0.96 μM; Example(1h) 1.2 μM; Example(1i) 0.55 μM; Example(1j) 0.043 μM.

The preparation of the anilines 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline and 2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline are described below.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline

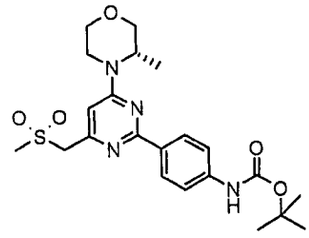


tert-Butyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (1.09 g, 2.35 mmol) was dissolved in methanol (5 mL) and 4M hydrogenchloride in dioxane (5 mL) was added. The solution was stirred at room temperature overnight, then the mixture evaporated to a dark brown oil and dissolved in ethyl acetate (10 mL). Water (5 mL) was added followed by the addition of sodium bicarbonate solution until neutral pH was achieved (~2 mL). The phases were separated and the organic phase washed with water (10 mL). The organic layer was dried over magnesium sulphate and evaporated to a pale yellow foam (805 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.31 (3H, s), 3.5 (1H, m), 3.64 (1H, m), 3.78 (1H, m), 4.13 (1H, m), 4.49 (2H, m), 5.57 (2H, s), 6.61 (2H, d), 6.68 (1H, s), 8.08 (1H, d)

LCMS Spectrum: MH+ 363, retention time 1.02 min, Method 5 Min Acid

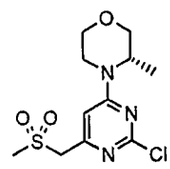
tert-Butyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.0 g, 3.27 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 DME:water:ethanol (7 mL). [4-[(2-Methylpropan-2-yl)oxycarbonylamino]phenyl]boronic acid (1.165 g, 4.91 mmol), 2M sodium carbonate solution (4 mL) and dichlorobis(triphenylphosphine) palladium catalyst (115 mg, 0.16 mmol) were then added to the solution and refluxed at 90°C for 5 hours under nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate and water. The organics were dried over magnesium sulphate, filtered and concentrated to dryness. The crude oil was dissolved in dichloromethane and filtered to remove insoluble material. A beige solid precipitated from the filtrates and the filtrates were filtered again. The solid was analysed and found to be the excess boronic acid and the filtrates contained the product and some impurities. The filtrates were purified by chromatography on silica, eluting with 0-40% ethyl acetate in isohexane, to give the desired compound as an orange oil (530 mg).

LCMS Spectrum: MH+ 463, retention time 2.23 min, Method 5 Min Acid

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine

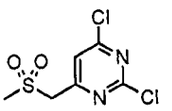


2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine (30 g, 0.13 mol) was dissolved in dichloromethane and stirred (under nitrogen) at -5°C. Triethylamine (17.4 mL, 0.13 mol) was added to give a clear brown solution. (3*S*)-3-Methylmorpholine was dissolved in dichloromethane and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the mixture stirred for 1 hour. The reaction mixture was heated at reflux for 2 hours, then the reaction mixture was washed with water, dried then evaporated. The crude material was purified by preparative HPLC to give the desired material as a solid (19.3 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 - 1.23 (m, 3H), 3.11 (s, 3H), 3.19 - 3.26 (m, 1H), 3.42 - 3.49 (m, 1H), 3.58 - 3.62 (1H, m), 3.73 (d, 1H), 3.92 - 3.96 (m, 2H), 4.27 - 4.31 (m, 1H), 4.45 (s, 2H), 6.92 (s, 1H)

LCMS Spectrum: MH+ 306, retention time 1.42 min, Method 5 Min Acid

2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine

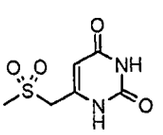


6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione (132 g, 0.65 mol) was added to phosphorus oxychloride (1.2 L) and the mixture heated to reflux for 16 hours, then cooled to room temperature. The excess phosphorus oxychloride was removed *in vacuo*, the residue azeotroped with toluene (2 x 500 mL) and dissolved in dichloromethane. This mixture was then poured slowly onto ice (4 L) and stirred for 20 minutes, then extracted with dichloromethane (3 x 1 L) (the insoluble black material was filtered off and discarded) and ethyl acetate (2 x 1 L). The extracts were combined, dried, then evaporated to leave the desired material as a dark brown solid (51 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: MH+ 239, retention time 1.21 min, Method 5 Min Acid

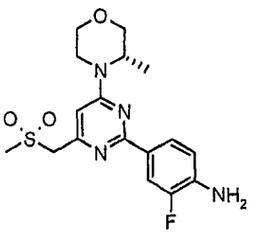
6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione



6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (175 g, 1.09 mol) was dissolved in DMF (2 L) and methanesulphinic acid sodium salt (133.5 g, 1.31 mol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water, filtered, then triturated with toluene. The solid was filtered then triturated with isohexane to leave the desired compound as a yellow solid (250 g). The material was used without further purification.

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline

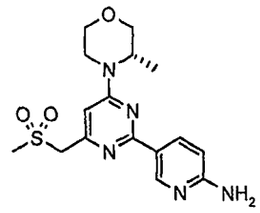


2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (860 mg) was dissolved in 18% DMF in 7:3:2 DME:water:ethanol (21 mL total solvent volume). 4-Pinacolato boron-2-fluoroaniline (1.005 g), 2M sodium carbonate (4 mL) and dichlorobis(triphenylposphine) palladium (99 mg) was then added to the solution and heated under reflux at 90°C for 5 hours under nitrogen atmosphere. The reaction was partitioned between DCM (50 mL) and water (50 mL). The organic extract was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The brown oil was dissolved in dichloromethane, filtered to remove fine material and loaded onto a Companion for purification using a 0-50% ethyl acetate in isohexane gradient over 20 minutes. The purified product was obtained as a pale yellow oil.

LCMS Spectrum: MH+ 381, retention time 1.32 min, Method 5 Min Acid

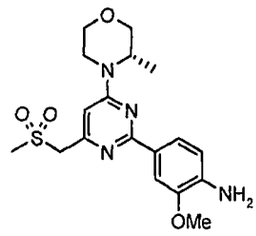
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5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-amine



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (363 mg, 1.19 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 DME:water:ethanol (7mL). 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (496 mg, 2.25 mmol), 2M sodium carbonate solution (2 mL) and dichlorobis(triphenylposphine) palladium (42 mg) were added to the solution and it was heated under reflux at 90°C for 90 minutes under nitrogen atmosphere. The reaction was partitioned between ethyl acetate (50 mL) and water (50 mL), the organics dried over magnesium sulphate, filtered and concentrated in *vacuo* to give the desired product as a yellow oil (410 mg) which was used without further purification.
LCMS Spectrum: MH+ 364, retention time 0.89 min, Method 5 Min Acid

2-Methoxy-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (700 mg, 2.29 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 DME:water:ethanol (7mL). (4-Amino-3-methoxy-phenyl)boronic acid (574 mg, 3.43 mmol), 2M sodium carbonate solution (4 mL) and dichlorobis(triphenylposphine) palladium (81 mg) was then added to the solution and refluxed at 90°C for 1 hour. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (50 mL) and water (50 mL), the

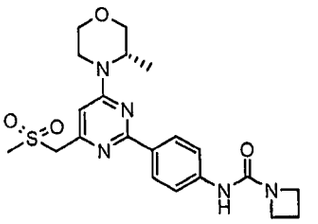
organics dried over magnesium sulphate, filtered and concentrated in *vacuo*. The residue was dissolved in dichloromethane and filtered to remove insoluble material. The filtrates were purified using a companion.

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.24 (d, 3H), 3.17 - 3.21 (m, 1H), 3.23 (s, 3H), 3.47 - 3.54 (m, 1H), 3.64 - 3.67 (m, 1H), 3.78 (d, 1H), 3.83 (s, 3H), 3.97 - 4.01 (m, 1H), 4.16 (d, 1H), 4.46 (s, 3H), 5.23 (s, 2H), 6.68 - 6.70 (m, 1H), 6.69 (s, 1H), 7.77 (m, 1H), 7.97 (s, 1H)

LCMS Spectrum: MH+ 393, retention time 1.17min, 5 min acid method

Example 2:

***N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]azetidine-1-carboxamide**

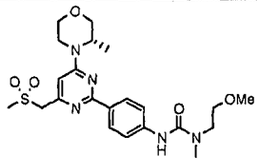
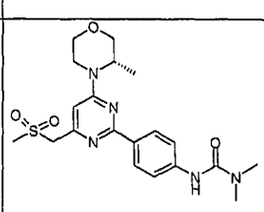
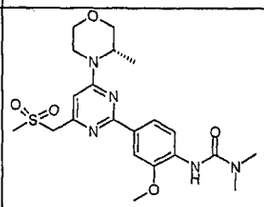
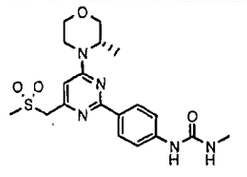
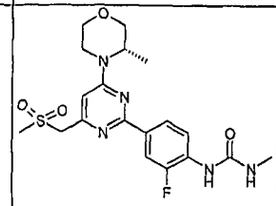


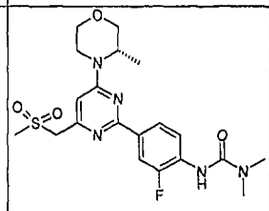
Phosgene 20% solution in toluene (0.245 ml, 0.50 mmol) was diluted with dichloromethane (0.5 mL). 4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline (150 mg, 0.41 mmol) was dissolved in dichloromethane (2 mL) and pyridine (0.5 mL). This was added to the phosgene solution dropwise over 2 minutes. The reaction was stirred at room temp for 1 hour. Then azetidine (0.034 mL, 0.50 mmol) was added and the mixture stirred at room temp for 1 hour. The reaction was partioned between water and ethyl acetate (25 mL of each). The organic layer was dried over magnesium sulphate and evaporated to dryness. The yellow oil was purified by chromatography, eluting with 10-70% ethyl acetate in isohexane, to give the desired material as a yellow foam (50 mg, 25%).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (d, 3H), 2.16 - 2.24 (m, 2H), 3.19 - 3.23 (m, 4H), 3.47 - 3.54 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.99 (t, 5H), 4.17 (s, 1H), 4.49 (s, 3H), 6.79 (s, 1H), 7.62 - 7.64 (m, 2H), 8.20 - 8.23 (m, 2H), 8.57 (s, 1H)

LCMS Spectrum: MH+ 446, retention time 1.37 min, Method 5 Min Acid

The following compounds were prepared in an analogous manner to *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]azetidine-1-carboxamide from 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)	Notes
2a		1-(2-methoxyethyl)-1-methyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	478	1.46	N/a
2b		1,1-dimethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	434	1.28	Purified by reverse phase chromatography
2c		3-[2-methoxy-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea	464	1.54	Purified by reverse phase chromatography
2d		1-methyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	420	1.19	Purified by reverse phase chromatography
2e		3-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-methyl-urea	438	1.44	Purified by reverse phase chromatography

Example	Structure	NAME	LCMS MH+	Retention time (min)	Notes
2f		3-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea	452	1.55	Purified by reverse phase chromatography

Example 2a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (d, 3H), 3.00 (s, 3H), 3.21 (s, 3H), 3.23 - 3.27 (m, 2H), 3.45 (m, 2H), 3.51 (s, 4H), 3.53 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.17 - 4.21 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.58 (s, 2H), 8.21 - 8.23 (m, 2H), 8.47 (s, 1H)

Example 2b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.24 - 1.26 (m, 3H), 2.96 (s, 6H), 3.21 (s, 3H), 3.25 (d, 1H), 3.48 - 3.54 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.19 (d, 1H), 4.49 (s, 3H), 6.79 (s, 1H), 7.58 - 7.62 (m, 2H), 8.20 - 8.23 (m, 2H), 8.50 (s, 1H)

Example 2c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 - 1.27 (m, 3H), 2.97 (s, 6H), 3.18 (m, 1H), 3.23 (s, 3H), 3.48 - 3.55 (m, 1H), 3.65 - 3.69 (m, 1H), 3.79 (d, 1H), 3.93 (s, 3H), 3.98 - 4.02 (m, 1H), 4.20 (d, 1H), 4.47 (s, 1H), 4.51 (s, 2H), 6.82 (s, 1H), 7.52 (s, 1H), 7.91 - 7.94 (m, 2H), 8.00 (s, 1H)

Example 2d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 (d, 3H), 2.66 - 2.67 (d, 3H), 3.21 (s, 3H), 3.23 (d, 1H), 3.47 - 3.54 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.97 - 4.01 (m, 1H), 4.18 (d, 1H), 4.48 (m, 1H), 4.49 (s, 2H), 6.08 (q, 1H), 6.78 (s, 1H), 7.49 - 7.53 (m, 2H), 8.20 - 8.22 (m, 2H), 8.76 (s, 1H)

Example 2e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.24 - 1.26 (m, 3H), 2.69 (d, 3H), 3.23 - 3.24 (m, 1H), 3.26 - 3.27 (m, 1H), 3.20 (s, 3H), 3.47 - 3.54 (m, 1H), 3.64 - 3.67 (m, 1H), 3.79 (d, 1H), 3.97 - 4.01 (m, 1H), 4.16 - 4.20 (m, 1H), 4.50 (s, 2H), 6.57 (q, 1H), 6.82 (s, 1H), 8.02 - 8.09 (m, 1H), 8.05 - 8.07 (m, 1H), 8.29 (m, 1H), 8.55 (d, 1H)

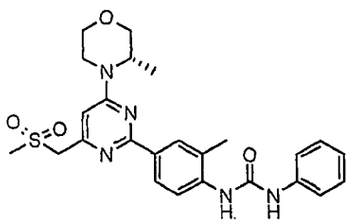
Example 2f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 - 1.27 (m, 3H), 2.96 (s, 6H), 3.20 (s, 3H), 3.48 - 3.55 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 3.98 - 4.02 (m, 1H), 4.21 (t, 1H), 4.40 (m, 1H), 4.51 (s, 2H), 6.85 (s, 1H), 7.68 (t, 1H), 8.02 - 8.11 (m, 2H), 8.15 (s, 1H)

Test (a): Example(2) 0.31 μM; Example(2a) 2.3 μM; Example(2b) 0.29 μM; Example(2c)

1.2 μM; Example(2d) 0.0068 μM; Example(2e) 0.038 μM; Example(2f) 1.7 μM.

Example 3:

1-[2-Methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea



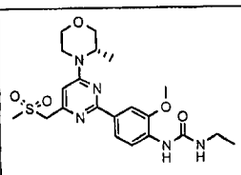
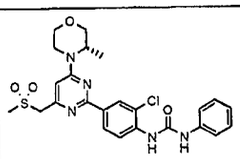
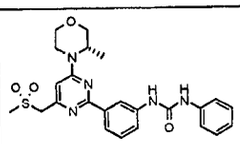
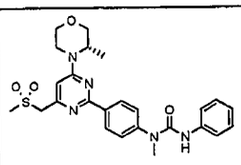
2-Methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline (130 mg, 0.34 mmol) was dissolved in 1,4-dioxane (4 mL). Phenylisocyanate (0.038 mL, 0.34 mmol) was added and the reaction heated at 75°C for 3 hours. The reaction mixture was evaporated to dryness and the resultant residue triturated with ethyl acetate to give the desired compound as a cream solid (42 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.25 (s, 3H), 2.34 (s, 3H), 3.21 (s, 3H), 3.23 - 3.26 (m, 1H), 3.48 - 3.55 (m, 1H), 3.64 - 3.68 (m, 1H), 3.79 (d, 1H), 4.00 (d, 1H), 4.20 (d, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 6.97 - 7.01 (m, 1H), 7.31 (d, 2H), 7.47 - 7.50 (m, 2H), 8.08 (s, 2H), 8.13 (d, 2H), 9.13 (s, 1H)

LCMS Spectrum: MH+ 496, retention time 2.08 minutes, Method 5 Min Acid

The following compound was prepared in an analogous fashion from the appropriate aniline and isocyanate.

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Example	Structure	NAME	LCMS MH+	Retention time (min)	Notes
3a		1-ethyl-3-[2-methoxy-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	464	1.54	Purified by reverse phase chromatography followed by normal phase chromatography
3b		1-[2-Chloro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	515	2.51	Purified on silica eluting with 0-4% methanol in DCM
3c		1-[3-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	481	2.30	Purified by recrystallisation from DMF/water (twice) followed by trituration with acetonitrile
3d		1-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	496	2.18	

Example 3a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.07 (t, 3H), 1.25 (d, 3H), 3.09 - 3.14 (m, 2H), 3.19-3.24 (m, 1H), 3.25 (s, 3H), 3.47 - 3.54 (m, 1H), 3.64 - 3.68 (m, 1H), 3.78 (d, 1H), 3.92 (s, 3H), 3.97 - 4.01 (m, H), 4.17 - 4.20 (m, 1H), 4.50 (s, 3H), 6.78 (s, 1H), 6.95 (t, 1H), 7.87 - 7.90 (m, 2H), 8.06 (s, 1H), 8.21 - 8.24 (m, 1H)

Example 3b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.26 (d, 3H), 3.20 (s, 3H), 3.25 (d, 1H), 3.48-3.54 (m, 1H), 3.64-3.68 (m, 1H), 3.79 (d, 1H), 3.98-4.02 (m, 1H), 4.20 (d, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 6.84 (s, 1H), 7.02 (t, 1H), 7.32 (d, 2H), 7.49 (d, 2H), 8.24-8.27 (m, 1H), 8.34 (d, 1H), 8.34-8.37 (m, 1H), 8.49 (s, 1H), 9.52 (s, 1H)

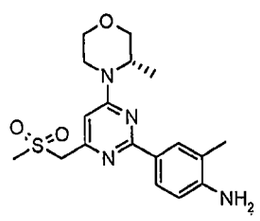
Example 3c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.27 (d, 3H), 3.23 (s, 3H), 3.26 (m, 1H), 3.49-3.56 (m, 1H), 3.65-3.69 (m, 1H), 3.80 (d, 1H), 3.99-4.03 (m, 1H), 4.20 (d, 1H), 4.53 (s, 3H), 6.87 (s, 1H), 6.98 (t, 1H), 7.29 (t, 2H), 7.40 (t, 1H), 7.47 (d, 2H), 7.71-7.74 (m, 1H), 7.95 (d, 1H), 8.31 (s, 1H), 8.65 (s, 1H), 8.82 (s, 1H)

Example 3d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.25 (d, 3H), 3.21 (s, 3H), 3.34 (s, 3H), 3.39 (m, 1H), 3.50 (d, 1H), 3.66 (d, 1H), 3.79 (d, 1H), 4.00 (d, 1H), 4.17 (d, 1H), 4.52 (s, 3H), 6.85 (s, 1H), 6.96 (t, 1H), 7.24 (t, 2H), 7.44 (m, 4H), 8.33 (s, 1H), 8.35 (s, 2H)

Test (a): Example(3) 1.5 μM; Example(3a) 0.1 μM; Example(3b) 0.44 μM; Example(3c) 3.3 μM; Example(3d) 2.9 μM.

The preparation of 2-methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline is described below.

2-Methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline



4-Bromo-2-methylaniline (1.00 g, 5.37 mmol), potassium acetate (1.59 g, 16.1 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.64 g, 6.45 mmol) were dissolved in 1,4-dioxane (20 mL) and the solution degassed for 5 minutes. Dichlorobis(triphenylphosphine)palladium (264 mg, 0.32 mmol) was added and the reaction stirred at 90°C for 4 hours. 2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.65 g, 5.37 mmol), ethanol (1.5 mL), 2M sodium carbonate aqueous solution (3 mL) and dichlorobis(triphenylphosphine)palladium (264 mg)

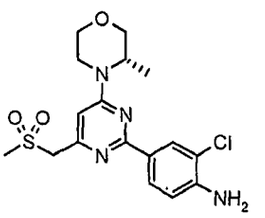
were added. The reaction was maintained at 90°C for 18 hours then allowed to cool to room temperature. Water (15 mL) and ethyl acetate (15 mL) were added and the mixture was filtered to remove the insoluble impurities. The phases were separated and the aqueous layer extracted with a second portion of ethyl acetate (15 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 0-3% methanol in DCM, to give the desired compound as a beige foam (290 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 - 1.24 (m, 3H), 3.16 - 3.19 (m, 1H), 3.20 (s, 3H), 3.46 - 3.52 (m, 1H), 3.62 - 3.66 (m, 1H), 3.77 (d, 1H), 3.90 (s, 1H), 3.96 - 4.00 (m, 1H), 4.14 - 4.18 (m, 1H), 4.43 (s, 2H), 4.45 (s, 1H), 5.32 (s, 2H), 6.63 (s, 1H), 6.66 (s, 1H), 7.91 - 7.94 (m, 2H)

LCMS Spectrum: MH+ 377, retention time 1.21 min, Method 5 Min Acid

The preparation of 2-chloro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline is described below.

2-Chloro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline



4-Bromo-2-chloroaniline (1.00 g, 4.84 mmol), potassium acetate (1.58 g, 14.5 mmol) and bis(pinacolato)diboron (1.64 g, 5.81 mmol) were dissolved in 1,4-dioxane (20 mL). The solution was degassed under nitrogen for 5min. [1,1'-Bis(diphenylphosphino)ferrocene] (213 mg, 0.29 mmol) was added. The reaction was stirred at 90°C for 4 hours. Ethanol (1.5 mL), 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.49 g, 4.84 mmol), 2M sodium carbonate solution (5.4 mL) and [1,1'-bis(diphenylphosphino)ferrocene] (213 mg) were added and heating was continued for 18 hours. The reaction was evaporated to dryness and the residue partitioned between water (15 mL) and ethyl acetate (15 mL). The mixture was filtered to remove the insoluble material, the phases were separated and the aqueous layer was washed with ethyl acetate (15 mL). The combined organics were dried

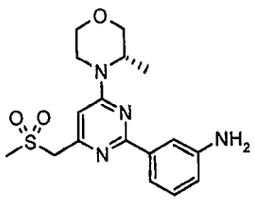
over magnesium sulfate and evaporated to a yellow oil. The crude product was purified by chromatography on silica, eluting with a 0-4% methanol in DCM, to give the desired material as a cream foam (1.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22-1.24 (m, 3H), 3.18 (s, 3H), 3.19-3.21 (m, 1H), 3.45-3.52 (m, 1H), 3.62-3.65 (m, 1H), 3.77 (d, 1H), 3.96-4.00 (m, 1H), 4.13-4.17 (m, 1H), 4.46 (s, 3H), 5.82 (s, 2H), 6.72 (s, 1H), 6.85 (d, 1H), 8.00-8.03 (m, 1H), 8.14 (d, 1H)

LCMS Spectrum: MH+397, retention time 1.64min, Method 5 Min Acid

The preparation of 3-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline is described below.

3-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline



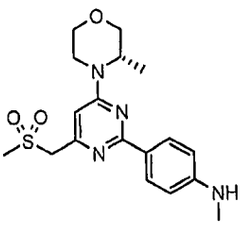
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.50 g, 4.91 mmol) was dissolved in 18% DMF in 7:3:2 dimethoxyethane:water:ethanol (15 mL). (3-Aminophenyl)boronic acid (1.01 g, 7.36 mmol), 2M sodium carbonate (5 mL) and dichlorobis(triphenylphosphine) palladium (173 mg, 0.25 mmol) were added to the solution. The reaction was refluxed at 90°C for 18 hours under a nitrogen atmosphere then the reaction allowed to cool and partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was dried over magnesium sulphate, filtered and vacuumed to dryness. The resultant brown oil was dissolved in DCM and filtered to remove insoluble material then the filtrate chromatographed on silica, eluting with 0-4% methanol in DCM, to give the desired product as a yellow oil (1.61 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24-1.26 (m, 3H), 2.90 (s, 3H), 3.19-3.26 (m, 1H), 3.47-3.54 (m, 1H), 3.64-3.68 (m, 1H), 3.77-3.80 (m, 1H), 3.99 (d, 1H), 4.17 (s, 1H), 4.49 (s, 3H), 6.67-6.70 (m, 1H), 6.81 (s, 1H), 7.11 (d, 1H), 7.50-7.52 (m, 1H), 7.57-7.58 (m, 1H), 7.96 (s, 1H)

LCMS Spectrum: MH+364, retention time 0.93min, Method 5 Min Acid

The preparation of *N*-methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline is described below

N-Methyl-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.01 g, 3.30 mmol) was dissolved in 18% DMF in 7:3:2 dimethoxy ethane:water:ethanol (7 mL). *N*-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.00 g, 4.29 mmol), 2M sodium carbonate solution (4 mL) and dichlorobis(triphenylphosphine) palladium (116 mg, 0.16 mmol) were added to the solution. The reaction was refluxed at 90°C for 3 hours under nitrogen atmosphere then the mixture allowed to cool and partitioned ethyl acetate (30 mL) and water (30 mL). The organic layer was dried over magnesium sulphate, filtered and evaporated to dryness. The brown oil was dissolved in DCM and filtered to remove insoluble material then the filtrate chromatographed on silica, eluting with 0-4% methanol in DCM, to give the desired product as a yellow foam (1.12 g, 90%)

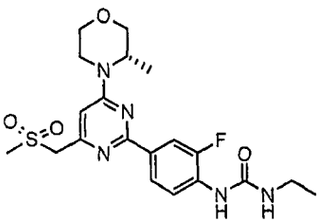
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.23 (d, 3H), 2.74 (d, 3H), 3.06-3.17 (m, 1H), 3.21 (s, 3H), 3.46-3.52 (m, 1H), 3.62-3.66 (m, 1H), 3.77 (d, 1H), 3.96-4.00 (m, 1H), 4.14 (d, 1H), 4.44 (s, 2H), 4.46 (s, 1H), 6.14 (q, 1H), 6.57-6.61 (m, 2H), 6.67 (s, 1H), 8.10-8.13 (m, 2H)

LCMS Spectrum: MH+377, retention time 1.33min, Method 5 Min Acid

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Example 4:

1-Ethyl-3-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea

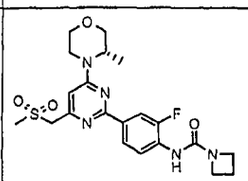


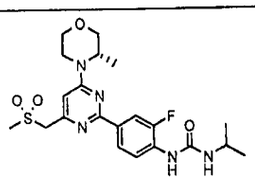
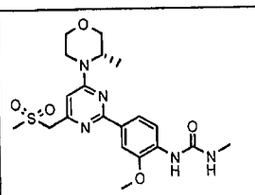
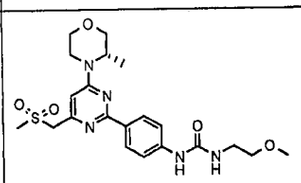
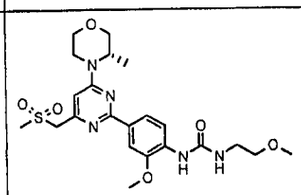
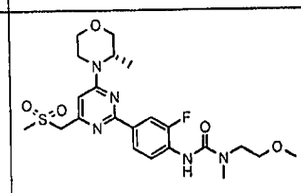
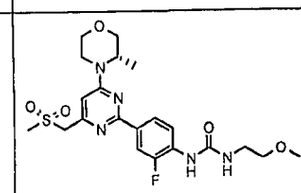
Bis(trichloromethyl) carbonate (44 mg, 0.16 mmol) was dissolved in DCM (0.25 mL) to give a colourless solution. 2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]aniline (140 mg, 0.39 mmol) was dissolved in DCM (2.0 mL) and pyridine (0.2 mL). The resultant solution was added dropwise to the bis(trichloromethyl) carbonate solution at 0°C and the mixture allowed to warm to room temperature then stirred for 10 minutes. Ethylamine (2M in THF, 0.5 mL, 1.0 mmol) was added and the mixture stirred at room temperature for 1 hour. Water (5 mL) was added and the aqueous layer ws extracted with DCM (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by prep HPLC to give the desired material as a white solid (149 mg, 84%).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.08 (t, 3H), 1.25 (d, 3H), 3.13 - 3.18 (m, 2H), 3.20 (s, 3H), 3.22 - 3.27 (m, 1H), 3.47 - 3.53 (m, 1H) 3.63 - 3.67 (m, 1H), 3.78 (d, 1H), 3.97 - 4.01 (m, 1H), 4.16 - 4.20 (m, 1H), 4.49 (m, 3H), 6.68 (t, 1H), 6.81 (s, 1H), 8.01 - 8.08 (m, 2H), 8.29 (t, 1H), 8.47 (d, 1H)

Mass Spectrum:

The following compounds were prepared in an analogous fashion using the appropriate aniline and amines.

Example	Structure	NAME	LCMS MH+	Retention time (min)
4a		*N*-[2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]azetidine-1-carboxamide	463	1.61

Example	Structure	NAME	LCMS MH+	Retention time (min)
4b		3-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-propan-2-yl-urea	465	1.83
4c		3-[2-methoxy-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-methyl-urea	450	1.36
4d*		1-(2-methoxyethyl)-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	464	1.32
4e*		1-(2-methoxyethyl)-3-[2-methoxy-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	440	1.47
4f*		3-[2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(2-methoxyethyl)-1-methyl-urea	495	1.74
4g*		3-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(2-methoxyethyl)urea	482	1.87

* Chromatographed on silica, eluting with 0 - 5% methanol in DCM

Example 4a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.25 (d, 3H), 2.16 - 2.24 (m, 2H), 3.20 (s, 3H), 3.23 - 3.26 (m, 1H), 3.47 - 3.54 (m, 1H), 3.63 - 3.67 (m, 1H), 3.78 (d, 1H), 4.00 (t, 5H), 4.19 (d, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.83 - 7.87 (m, 1H, 8.04 (d, 1H6), 8.08 - 8.10 (m, 1H), 8.18 (s, 1H)

Example 4b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.12 (d, 6H), 1.25 (d, 3H), 3.20 (s, 3H), 3.24 (d, 1H), 3.47 - 3.53 (m, 1H), 3.63 - 3.67 (m, 1H), 3.74 - 3.82 (m, 2H), 3.97 - 4.01 (m, 1H), 4.18 (d, 1H), 4.49 (s, 3H), 6.63 (d, 1H), 6.81 (s, 1H), 8.01 - 8.08 (m, 2H), 8.29 (t, 1H), 8.37 (d, 1H)

Example 4c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 - 1.26 (m, 3H), 2.66 - 2.67 (m, 3H), 3.18 (d, 1H), 3.23 (s, 3H), 3.48 - 3.55 (m, 1H), 3.65 - 3.68 (m, 1H), 3.79 (d, 1H), 3.92 (s, 3H), 3.98 - 4.02 (m, 1H) 4.19 (s, 1H), 4.50 (s, 2H), 6.79 (s, H.), 6.85 (d, 1H), 7.90 (s, 1H), 8.11 (s, 1H), 8.22 - 8.24 (m, 1H)

Example 4d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (d, 3H), 3.19 - 3.24 (m, 2H), 3.21 (s, 3H), 3.27 (s, 3H), 3.40 (t, 2H), 3.47 - 3.53 (m, 1H), 3.63 - 3.67 (m, 1H), 3.78 (d, 1H), 3.97 - 4.01 (m, 1H), 4.17 (s, 1H), 4.49 (s, 3H), 6.27 (t, 1H), 6.77 (s, 1H), 7.47 - 7.51 (m, 2H), 8.19 - 8.23 (m, 2H), 8.78 (s, 1H)

Example 4e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 - 1.26 (m, 3H), 3.23 (s, 3H), 3.27 (s, 1H), 3.28-3.21 (m, 2H), 3.38 - 3.40 (m, 2H), 3.51 (d, 1H), 3.66 (d, 1H), 3.77 (s, 1H), 3.92 (s, 3H), 4.00 (d, 1H), 4.17 - 4.21 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.12 (s, 1H), 7.88 - 7.90 (m, 2H), 8.22 - 8.24 (m, 1H), 8.26 (1s, H)

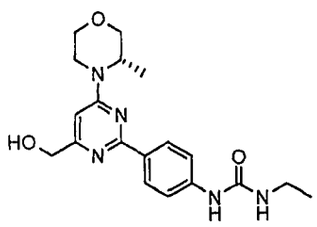
Example 4f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 - 1.26 (m, 3H.), 2.97 (s, 3H), 3.20 (s, 3H), 3.23 - 3.26 (m, 1H), 3.47 - 3.56 (m, 5H), 3.64 - 3.67 (m, 1H), 3.78 (d, 1H), 3.97 - 4.01 (m, 1H), 4.17 - 4.21 (m, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.82 (t, 1H), 8.02 - 8.10 (m, 2H), 8.41 (s, 1H)

Example 4g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 (d, 3H), 3.20 (s, 3H), 3.23 (m, 1H), 3.29 (m, 2H), 3.30 (s, 3H), 3.41 (t, 2H), 3.51 (d, 1H), 3.65 (d, 1H), 3.78 (d, 1H), 3.97 - 4.01 (m, 1H), 4.19 (d, 1H), 4.50 (s, 3H), 6.82 (s, 1H), 6.87 (t, 1H), 8.02 - 8.09 (m, 2H), 8.29 (t, 1H), 8.63 (d, 1H)

Test (a): Example (4) 0.031 μM; Example(4a) 1 μM; Example(4b) 0.14 μM; Example(4c) 0.8 μM; Example(4d) 0.17 μM; Example(4e) 0.6 μM; Example (4f) 0.68 μM; Example(4g) 0.83 μM.

Example 5:

1-Ethyl-3-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



1-[4-[4-[(Dimethyl-*tert*-butyl-silyl)oxymethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea (104 mg) was dissolved in THF (10 mL) and TBAF (1.0 M solution, 0.22 mL) was added. The reaction was allowed to stir for 1 hour at room temperature and then passed down a SCX-2 column. The column was washed with methanol and the desired material eluted with 7N ammonia in methanol. The fractions were concentrated *in vacuo* to give the desired compound (76 mg) as a white solid.

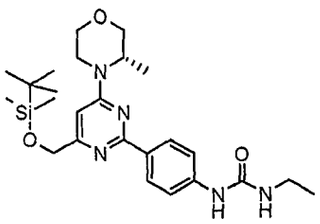
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.07 (3H, t), 1.23 (3H, d), 3.11 - 3.16 (2H, m), 3.19 - 3.23 (1H, m), 3.49 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.95 - 3.99 (1H, m), 4.16 (1H, d), 4.45 (2H, d), 4.48 (1H, s), 5.38 (1H, s), 6.14 (1H, t), 6.66 (1H, s), 7.46 (2H, d), 8.19 (2H, d), 8.62 (1H, s)

Mass Spectrum; $M+H^+$ 372.

Test (a): 0.063 μM.

The preparation of 1-[4-[4-[(dimethyl-*tert*-butyl-silyl)oxymethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea is described below.

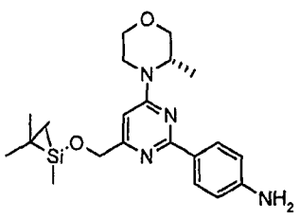
1-[4-[4-[(Dimethyl-*tert*-butyl-silyl)oxymethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea



4-[4-[(Dimethyl-*tert*-butyl-silyl)oxymethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (250 mg) was dissolved in 1,4-dioxane (4 mL) and ethyl isocyanate (0.144 mL) added. The reaction was heated to 120°C for 1 hour in a microwave reactor. The reaction was concentrated *in vacuo* then the residue chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired compound (106 mg) as a white solid.

Mass Spectrum; $M+H^+$ 486.

4-[4-[(Dimethyl-*tert*-butyl-silyl)oxymethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

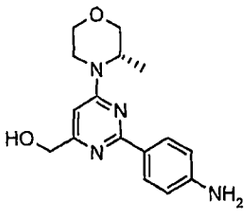


[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (1.54 g) was dissolved in DCM (60 mL) and *tert*-butyldiemethylsilylchloride (928 mg) and imidozole added. The mixture was stirred at room temperature for 0.5 hours before being filtered and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 1% methanol in DCM, to give the desired compound (1.61 g) as a white solid.

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.12 - 0.13 (6H, m), 0.94 - 0.95 (9H, m), 1.21 (3H, d), 3.13 - 3.20 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.13 (1H, d), 4.37 - 4.39 (1H, m), 4.60 (2H, s), 5.48 (2H, d), 6.50 (1H, s), 6.57 - 6.59 (2H, m), 8.02 - 8.04 (2H, m)

Mass Spectrum; $M+H^+$ 415.

[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol

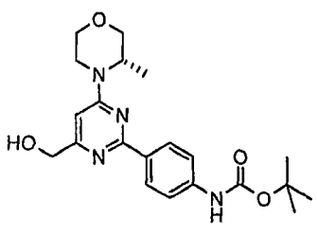


tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (1.20 g) was dissolved in 4M hydrogen chloride in dioxane (5 mL) and dioxane (5 mL). The reaction was stirred for 18 hour then DCM (10 mL) added to help solubilise material. The reaction was stirred at 40°C for a further 18 hours then evaporated to dryness. The solid was suspended in DCM (20 mL) and a mixture of a saturated aqueous solution of sodium hydrogen carbonate (6 mL) and water (4 mL) was added. The organics were separated, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (648 mg) as a pale yellow solid.

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.21 (3H, d), 3.16 (1H, d), 3.48 (1H, d), 3.61 - 3.65 (1H, m), 3.75 (1H, d), 3.95 (1H, d), 4.13 (1H, d), 4.41 (2H, d), 4.45 (1H, s), 5.32 (1H, t), 5.47 (2H, s), 6.57 - 6.59 (3H, m), 8.02 - 8.04 (2H, m)

Mass Spectrum; $M+H^+$ 301.

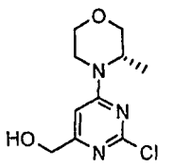
tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



A mixture of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (2.44 g), (4-Boc-aminophenyl)boronic acid (4.76 g), 2M solution of sodium carbonate (10 mL) and a solvent mixture (18% DMF in 7:3:2 DME: Water: Ethanol) (35 mL) was degassed. Dichlorobis(triphenylphosphine) palladium (300 mg) was added and the reaction heated at 80°C for 3 hour. The reaction was allowed to cool and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL), the organics washed with

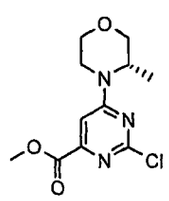
brine (100 mL) and dried ($MgSO_4$). The crude material was chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired compound (4.00 g) as a white solid.
Mass Spectrum; $M+H^+$ 401.

[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol



Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (3.15 g) was dissolved in dry THF (20 mL) and cooled to 0°C under nitrogen. To this is added dropwise a solution of lithium borohydride (2.0M in THF,6.09 mL). The solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched with water (20 mL) then evaporated to dryness. The residue was dissolved in ethyl acetate (150 mL) and washed with water (150 mL) followed by brine (50 mL). The organics were concentrated *in vacuo* to give to the desired compound (2.44 g) as white solid.
NMR Spectrum: ^1H NMR (399.9 MHz, DMSO-d_6) δ1.20 - 1.21 (3H, m), 3.18 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.56 - 3.60 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (1H, m), 3.98 (1H, d), 4.35 (3H, d), 5.51 (1H, t), 6.74 (1H, s)
Mass Spectrum; $M+H^+$ 244.

Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate



Methyl 2,6-dichloropyrimidine-4-carboxylate (5.00 g) was dissolved in DCM (120 mL). (3*S*)-3-Methylmorpholine (2.49 g) dissolved in triethylamine (3.70 mL) and DCM (10 mL) was added dropwise to the solution over 10 minutes. The reaction was left to stir at room temperature for 1 hour then the mixture concentrated *in vacuo* and dissolved in DCM (300 mL). The organics were washed with water (150 mL) and dried ($MgSO_4$). The crude material

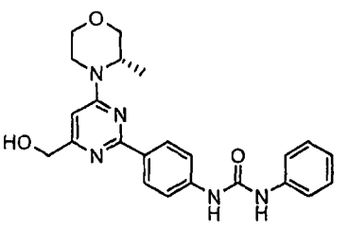
was chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired compound (3.15 g) as a white solid.

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.22 - 1.24 (3H, m), 3.25 (1H, d), 3.41 - 3.48 (1H, m), 3.57 - 3.61 (1H, m), 3.71 (1H, d), 3.87 (3H, s), 3.91 - 3.95 (1H, m), 4.25 (1H, s), 4.45 (1H, s), 7.29 (1H, s)

Mass Spectrum; M+H$^+$ 272.

Example 6:

1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-(4-Bromo-phenyl)-3-phenyl-urea (960 mg), potassium acetate (969 mg), bis(pinacolato)diboron (1.01 g) was dissolved in 1,4 dioxane (50 mL). The solution was degassed for 5 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct added (162 mg) and the reaction was heated to 80°C for 3 hours. Further 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct was added (162 mg) and the reaction stirred at 80°C for another 3 hours. [2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (803 mg), ethanol (3.75 mL), 2M sodium carbonate solution (6.9 mL) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (162 mg) were added and the heating was continued for 16 hours. More ethanol (5 mL) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (162 mg) were added and the reaction was allowed to stir for another 5 hours before being allowed to cool and neutralised with 2M hydrochloric acid. The reaction mixture was passed through three SCX-2 columns, each time loading the sample and washing with methanol, then removing the desired material with 7N ammonia in methanol. The solution was concentrated *in vacuo*, and the residue chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (398 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.24 (3H, d), 3.20 - 3.24 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.47 (2H, d), 4.50 (1H, s), 5.39 (1H, t), 6.68 (1H, s), 6.97 - 7.01 (1H, m), 7.28 - 7.31 (1H, m), 7.30 (1H, s), 7.46 - 7.48 (2H, m), 7.52 - 7.56 (2H, m), 8.25 - 8.27 (2H, m), 8.68 (1H, s), 8.87 (1H, s)

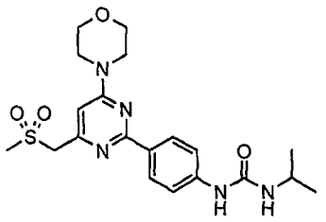
Mass Spectrum; $M+H^+$ 419.

Test (a): 0.56 μM.

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

Example 7:

3-[4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-propan-2-yl-urea

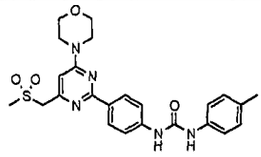
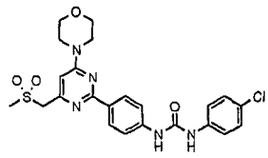
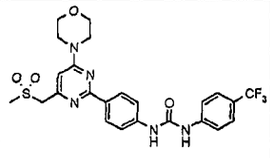
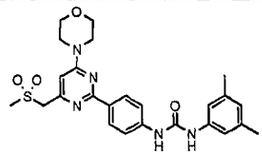
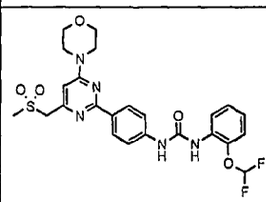
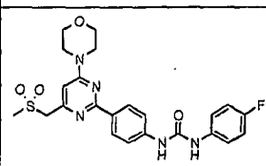


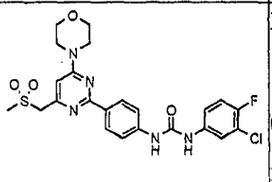
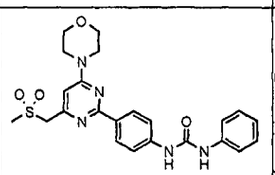
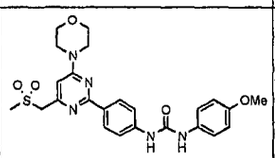
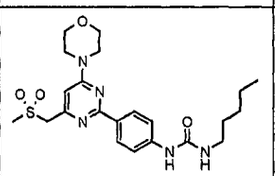
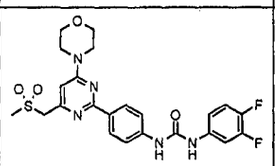
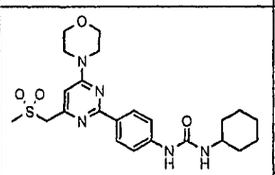
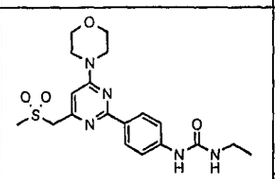
4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline (70 mg, 0.2 mmol) and isoproylisocyanate (0.1 mL, 1 mmol) were heated in dioxane (2 mL) at 70°C for 4 hours. The reaction mixture was evaporated and the residue triturated with ethyl acetate. The suspension was filtered and the white solid washed with ethyl acetate and diethyl ether then dried under vacuum at 60°C overnight to yield the title compound (38 mg).

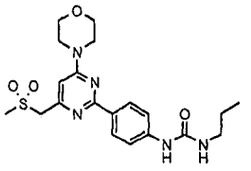
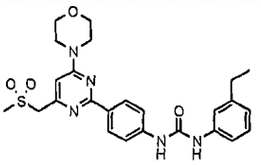
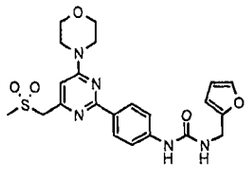
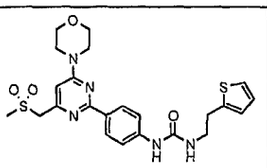
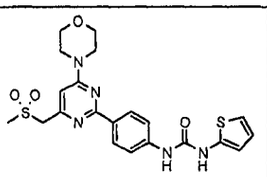
LCMS Spectrum: MH+ 434, Retention Time 1.66min, Method : Monitor Basic

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.11 (d, 6H), 3.2 (s, 3H), 3.7 (m, 8H), 3.76 (m, 1H), 4.48 (s, 2H), 6.05 (d, 1H), 6.8 (s, 1H), 7.48 (d, 2H), 8.2 (d, 2H), 8.54 (s, 1H)

The following compounds were prepared in an analogous fashion from XXX using the appropriate isocyanate.

Example	Structure	NAME	LCMS MH+	Retention Time (min)
7a		1-(4-methylphenyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	482.03	2.15
7b		3-(4-chlorophenyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	501.95	2.26
7c		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	536.00	2.39
7d		1-(3,5-dimethylphenyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	496.05	2.29
7e		3-[2-(difluoromethoxy)phenyl]-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	533.97	2.25
7f		3-(4-fluorophenyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	485.97	2.07

Example	Structure	NAME	LCMS MH+	Retention Time (min)
7g		3-(3-chloro-4-fluoro-phenyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	519.96	2.29
7h*		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-phenyl-urea	468.56	3.00
7i*		1-(4-methoxyphenyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	498.60	2.93
7j*		3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-pentyl-urea	462.64	3.02
7k*		3-(3,4-difluorophenyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	504.59	
7l*		3-cyclohexyl-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	474.63	3.02
7m*		1-ethyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	420.60	2.49

Example	Structure	NAME	LCMS MH+	Retention Time (min)
7n*		3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-propyl-urea	434.61	2.66
7o*		1-(3-ethylphenyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	496.62	3.29
7p*		3-(2-furylmethyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	472.58	2.76
7q*		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-(2-thiophen-2-ylethyl)urea	502.58	2.96
7r*		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-thiophen-2-yl-urea	474.54	2.92

* Compounds were further purified by prep HPLC

Example 7a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.25 (s, 3H), 3.21 (s, 3H), 3.71 (s, 8H), 4.49 (s, 2H), 6.83 (s, 1H), 7.09 (d, 2H), 7.34 (d, 2H), 7.56 (d, 2H), 8.26 (d, 2H), 8.6 (s, 1H), 8.88 (s, 1H)

Example 7b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.22 (s, 3H), 3.70 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (d, 2H), 7.50 (d, 2H), 7.56 (d, 2H), 8.28 (d, 2H), 8.84 (s, 1H), 8.95 (s, 1H)

Example 7c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.59 (d, 2H), 7.65 (m, 4H), 8.3 (d, 2H), 9.40 (s, 1H), 9.13 (s, 1H)

Example 7d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.23 (s, 6H), 3.21 (s, 3H), 3.72 (bs, 8H), 4.49 (s, 2H), 6.64 (s, 1H), 6.85 (s, 1H), 7.08 (s, 2H), 7.55 (d, 2H), 8.28 (d, 2H), 8.58 (s, 1H), 8.92 (s, 1H)

Example 7e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.05 (m, 1H), 7.22 (m, 2H), 7.59 (d, 2H), 8.24 (d, 1H), 8.3 (d, 2H), 8.38 (s, 1H), 9.60 (s, 1H)

Example 7f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.22 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.12 (m, 2H), 7.48 (m, 2H), 7.55 (d, 2H), 8.26 (d, 2H), 8.73 (s, 1H), 8.90 (s, 1H)

Example 7g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (m, 2H), 7.56 (m, 2H), 7.8 (m, 1H), 8.28 (m, 2H), 8.95 (s, 1H), 9.05 (s, 1H)

Example 7i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.22 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (d, 2H), 7.50 (d, 2H), 7.56 (d, 2H), 8.28 (d, 2H), 8.84 (s, 1H), 8.95 (s, 1H)

Example 7j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.88 (m, 3H), 1.39 (m, 4H), 1.43 (m, 2H), 3.08 (m, 2H), 3.21 (s, 3H), 3.70 (bs, 8H), 4.47 (s, 2H), 6.2 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.66 (s, 1H)

Example 7m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.05 (t, 3H), 3.12 (q, 2H), 3.21 (s, 3H), 3.7 (bs, 8H), 4.46 (s, 2H), 6.19 (t, 1H), 6.8 (s, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.69 (s, 1H)

Example 7n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.87 (m, 3H), 1.45 (m, 2H), 3.05 (m, 2H), 3.20 (s, 3H), 3.70 (bs, 8H), 4.45 (s, 2H), 6.14 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.69 (s, 1H)

Example 7o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.19 (t, 3H), 2.55 (q, 2H), 3.21 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.85 (m, 2H), 7.19 (t, 2H), 7.27 (d, 1H), 7.33 (s, 1H), 7.56 (d, 2H), 8.26 (d, 2H), 8.68 (s, 1H), 8.92 (s, 1H)

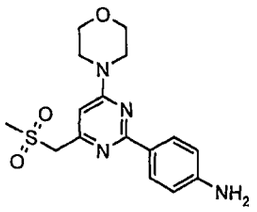
Example 7p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.20 (s, 3H), 3.70 (bs, 8H), 4.31 (d, 1H), 4.47 (s, 2H), 6.28 (d, 1h), 6.40 (d, 1H), 6.61 (t, 1H), 6.82 (s, 1H), 7.51 (d, 2H), 7.59 (s, 1H), 8.22 (d, 2H), 8.77 (s, 1H)

Example 7q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.98 (t, 2H), 3.21 (s, 3H), 3.38 (m, 2H), 3.70 (bs, 8H), 4.47 (s, 2H), 6.29 (t, 1H), 6.81 (s, 1H), 6.93 (d, 1H), 6.97 (m, 1H), 7.36 (m, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.80 (s, 1H)

Test(a): Example(7) 0.17 μM; Example(7a) 0.28 μM; Example(7b) 0.42 μM; Example(7c) 1.7 μM; Example(7d) 2.6 μM; Example(7e) 2.6 μM; Example(7f) 0.029 μM; Example(7g) 1.3 μM; Example(7h) 0.24 μM; Example(7i) 0.032 μM; Example(7j) 1.9 μM; Example(7k) 0.72 μM; Example(7l) 7 μM; Example(7m) 0.081 μM; Example(7n) 0.2 μM; Example(7o) 1.7 μM; Example(7p) 3.8 μM; Example(7q) 1.7 μM; Example(7r) 0.19 μM.

The preparation of 4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline is described below:

4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline

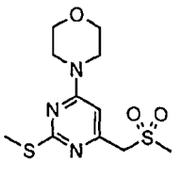


2-Methylsulfanyl-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (1.00g, 3.3 mmol), 4-aminophenylboronic acid (904 mg, 6.60 mmol), Copper(I)thiophene-2-carboxylate (1.64 g, 8.58 mmol), $Pd(PPh_3)_4$ (153 mg, 0.04 equiv., 0.13 mmol) were added to a microwave vessel and 1, 4-Dioxane (20 mL) added. The system was degassed with N_2, sealed and heated in a microwave reactor at 130° C for 1 hour. Upon cooling the reaction was poured into water and the resulting precipitate was collected by filtation and dried under vacuum to afford the title compound as an off-white solid. (988 mg)

LCMS Spectrum: MH+ 349.41, Retention Time 1.43 Method: Monitor Acid

NMR Spectrum: ^{1}H NMR (300.132 MHz, DMSO) δ3.20 (3H, s), 3.61 - 3.83 (8H, m), 4.43 (2H, s), 5.57 (1H, s), 6.60 (2H, d), 6.70 (1H, s), 8.04 (2H, d)

2-Methylsulfanyl-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine

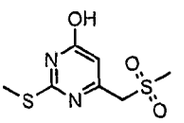


2-Methylsulfanyl-6-(methylsulfonylmethyl)pyrimidin-4-ol (15 g, 63.97 mmol) was heated at reflux in phosphorous oxychloride (100 ml) for approximately 1 hour. Phosphorous oxychloride was evaporated and the residue was neutralised with sodium hydroxide solution and extracted into ethyl acetate. The resultant mixture was then dried over magnesium sulfate, filtered and evaporated to dryness to afford the crude chloro product. This was then dissolved in DCM, morpholine (319 mmol, 28 ml) was added and the reaction stirred at room temperature. Upon completion the resulting precipitate was collected as a white solid. Concentration of the filtrate afforded more solid, giving a combined yield of 13.7g.

NMR Spectrum: ^{1}H NMR (300.132 MHz, DMSO) δ2.45 (s, 3H), 3.49 - 3.74 (m, 8H), 4.37 (s, 2H), 6.66 (s, 1H) ppm.

LCMS Spectrum: MH+ 304.50, Retention Time 1.49min, Method : Monitor Basic

2-Methylsulfanyl-6-(methylsulfonylmethyl)pyrimidin-4-ol

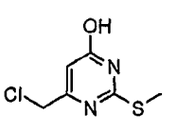


6-(Chloromethyl)-2-methylsulfanyl-pyrimidin-4-ol (19.07 g, 100 mmol) was suspended in acetonitrile (400 ml). To this stirring suspension was added methanesulphinic acid sodium salt (12.255g, 120 mmol) and DMF (100 ml). The reaction was then heated to 100° C to give a dark suspension and monitored by LCMS. Once complete, the solvents were removed and the resultant product added to 1:1 MeOH:DCM (200 ml) and acidified with acetic acid (10 ml). The resultant precipitate was collected, washed with water (200 ml) and MeOH (100 ml) and dried overnight *in vacuo* to afford the title compound as a white solid, 16.45g.

NMR Spectrum: ^{1}H NMR (300.132 MHz, DMSO) δ2.50 (s, 3H), 3.12 (s, 3H), 4.39 (s, 2H), 6.25 (s, 1H), 13.09 (s, 1H) ppm.

LCMS Spectrum: MH+ 235.2, Retention Time 0.5 minutes, Method: 5min Early Base

6-(Chloromethyl)-2-methylsulfanyl-pyrimidin-4-ol



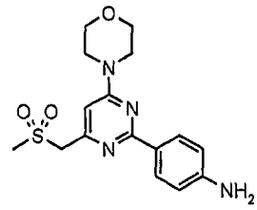
S-Methyl-2-thiopseudourea sulphate (20 g, 71.85 mmol), ethyl 4-chloroacetoacetate (10.755 ml, 79.04 mmol) and sodium carbonate (13.925 g, 107.78 mmol) were dissolved in water (100 ml) and stirred at room temperature overnight. The reaction was monitored by TLC, and once complete, the reaction precipitate was collected and the supernatant was neutralised with 6N hydrochloric acid to yield more reaction precipitate which was also collected. The accumulated precipitate was then washed with water (x3) and an off-white solid was obtained. This was dried *in vacuo* at 60° C for 48 hours to yield the desired compound as a pale yellow/white solid, 43.2g.

NMR Spectrum: ^{1}H NMR (300.132 MHz, $CDCl_3$) δ 2.59 (s, 3H), 4.35 (s, 2H), 6.41 (s, 1H), 12.70 (s, 1H) ppm

Mass Spectrum: M^+ 190

4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline can also be prepared from 2,4-dichloro-6-(methylsulfonylmethyl)pyrimidine as described below

4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline

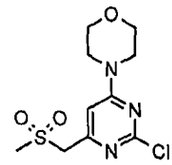


2-Chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (5 g, 17.1 mmol), was dissolved in a mixture of DMF:DME:water:ethanol (16.5 mL:41 mL:18 mL:12 mL). 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (5.62 g, 25.6 mmol), a 2M aqueous solution of sodium carbonate (25 mL), and dichlorobis(triphenylposphine) palladium (600 mg) were added and the mixture refluxed for 5 hours under a nitrogen atmosphere. The mixture was cooled, diluted with water and extracted into DCM. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude material was dissolved in minimum of hot DCM then hexane added and the precipitate filtered to give the desired material (1.6 g).

LCMS Spectrum: MH+349, Retention time 1.48min, Method : Monitor Base

NMR Spectrum ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.20 (3H, s), 3.67 - 3.72 (8H, m), 4.43 (2H, s), 5.55 - 5.56 (2H, m), 6.59 (2H, d), 6.70 (1H, s), 8.03 (2H, d)

2-Chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine



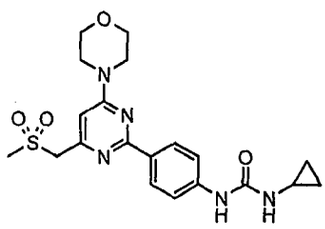
A suspension of 2,4-dichloro-6-(methylsulfonylmethyl)pyrimidine (10.56 g) in DCM (230 mL) was stirred magnetically (under nitrogen) and cooled to -5°C. Triethylamine (6.78 mL) was added followed by the dropwise addition of a solution of morpholine (3.85 mL) in DCM (30 mL) maintaining the reaction temperature below -5°C. The reaction was stirred at room temperature for 1 hour and then the organic mixture washed with water (300 mL). The organic phase was dried (MgSO4), filtered and evaporated to a brown solid which was chromatographed on silica, eluting with 50% ethyl acetate in DCM, to give the desired material (6.81g) as a white solid.

NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ3.12 (3H, s), 3.63 (4H, s), 3.68 - 3.70 (4H, m), 4.45 (2H, s), 6.96 (1H, s)

Mass Spectrum: MH+ 292.

Example 8:

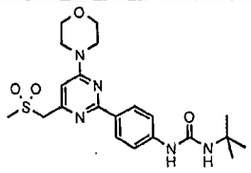
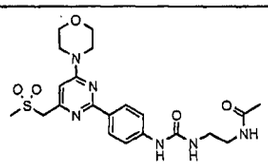
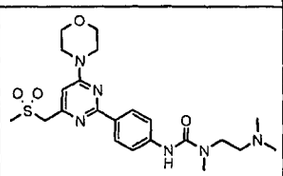
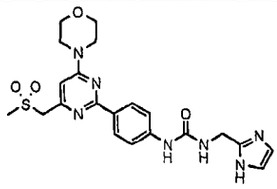
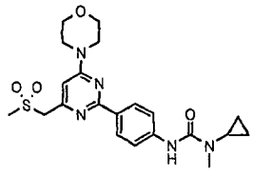
3-Cyclopropyl-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea

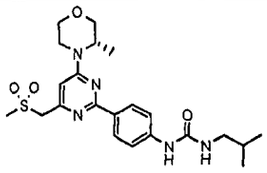
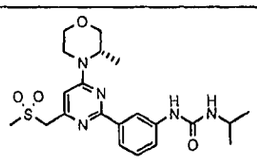
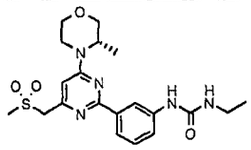
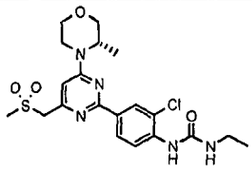
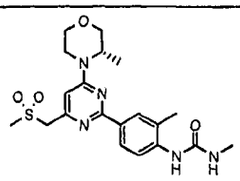


A mixture of phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate (94 mg,0.2 mmol) , cyclopropylamine (0.069 mL, 1 mmol), and triethylamine (0.090 mL, 0.65 mmol), in NMP (1 – 2 mL) was heated at 50-70°C for 2 hours.The mixture was then purified directly using prep HPLC (monitor basic method) to give the desired material.

LCMS Spectrum : MH+432, Retention time 2.42 min, Method Basic

The following compounds were prepared in an analogous fashion from the required phenyl carbamate and the appropriate amine, using either NMP or DMF as the solvent.

Example	Structure	NAME	LCMS MH+	Retention Time (min)	Notes
8a		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-tert-butyl-urea	448	2.82	
8b		N-[2-[[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamoylamino]ethyl]acetamide	478	2.24	
8c		1-(2-dimethylaminoethyl)-1-methyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	478	2.6	
8d		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	472	2.11	
8e		1-cyclopropyl-1-methyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	446	2.45	

Example	Structure	NAME	LCMS MH+	Retention Time (min)	Notes
8f		1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	462	2.84	
8g		1-[3-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	448	1.71	Purified by trituration with methanol
8h		3-Ethyl-1-[3-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	434	1.71	Purified by recrystallisation from methanol
8i		1-[2-Chloro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-ethyl-urea	468	1.78	
8j		3-Methyl-1-[2-methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	434	1.28	

Example 8g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.11 (d, 6H), 1.26 (d, 3H), 3.23 (s, 3H), 3.25 (d, 1H), 3.48-3.55 (m, 1H), 3.65-3.68 (m, 1H), 3.76 (d, 1H), 3.80 (t, 1H), 3.98-4.02 (m, 1H), 4.18 (d, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 5.98 (d, 1H), 6.85 (s, 1H), 7.32 (t, 1H), 7.65-7.68 (m, 1H), 7.86-7.88 (m, 1H), 8.20 (t, 1H), 8.43 (s, 1H)

Example 8h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (t, 3H), 1.26 (d, 3H), 3.09-3.14 (m, 2H), 3.22 (s, 3H), 3.24 (m, 1H), 3.48-3.55 (m, 1H), 3.65-3.68 (m, 1H), 3.79 (d, 1H), 3.98-4.02 (m, 1H), 4.18 (s, 1H), 4.51 (s, 3H), 6.08 (t, 1H), 6.85 (s, 1H), 7.32 (t, 1H), 7.64-7.67 (m, 1H), 7.86-7.88 (m, 1H), 8.23 (t, 1H), 8.55 (s, 1H)

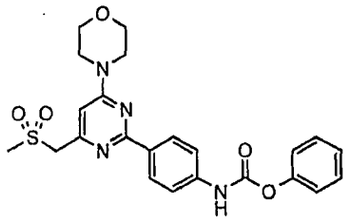
Example 8i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.09 (t, 3H), 1.25 (d, 3H), 3.15 (m, 2H), 3.19 (s, 3H), 3.20-3.26 (m, 1H), 3.47-3.53 (m, 1H), 3.63-3.67 (m, 1H), 3.78 (d, 1H), 3.97-4.01 (m, 1H), 4.18 (d, 1H), 4.46 (s, 1H), 4.50 (s, 2H), 6.82 (s, 1H), 7.13 (t, 1H), 8.14 (s, 1H), 8.17-8.20 (m, 1H), 8.28 (d, 1H), 8.33 (d, 1H)

Example 8j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (d, 3H), 2.26 (s, 3H), 2.68 (d, 3H), 3.20 (s, 3H), 3.22-3.26 (m, 1H), 3.47-3.54 (m, 1H), 3.63-3.67 (m, 1H), 3.78 (d, 1H), 3.97-4.01 (m, 1H), 4.19 (d, 1H), 4.49 (s, 3H), 6.56 (q, 1H), 6.77 (s, 1H), 7.79 (s, 1H), 8.02 (s, 1H), 8.06-8.09 (m, 2H)

Test(a): Example(8) 0.031 μM; Example(8a) 0.47 μM; Example(8b) 0.42 μM; Example(8c) 2.2 μM; Example(8d) 0.57 μM; Example(8e) 0.28 μM; Example(8f) 0.3 μM; Example(8g) 0.96 μM; Example(8h) 0.92 μM; Example(8i) 1.4 μM; Example(8j) 0.16 μM.

The preparation of phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate

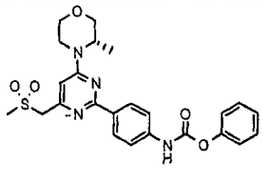
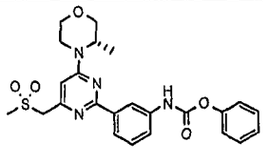
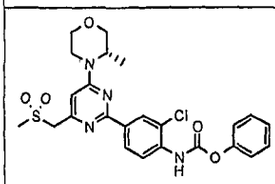


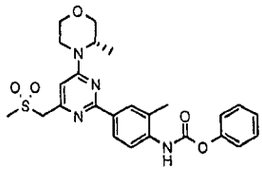
Phenyl chloroformate (1.33 mL, 10.6 mmol) was added at 0-5°C to a mixture of sodium hydrogencarbonate (1.34 g, 15.9 mmol) and 4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]aniline (3.7 g, 10.6 mmol) in dioxane (150 mL). The reaction was stirred at RT for 3 hours, evaporated then dissolved in DCM. The organic mixture was washed with water, dried over Na_2SO_4, filtered and evaporated to a pale yellow foam which was triturated with hexane/ether then filtered yielding the desired material as a white solid (5.4 g).

LCMS Spectrum MH+470 , Retention time 2.18 Method: Monitor base

NMR Spectrum ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.22 (3H, s), 3.58 (4H, s), 3.73 (4H, s), 4.50 (2H, s),6.88(1H,s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.30 (2H, d), 10.45(1H,s).

The following phenyl carbamates were prepared in an analogous fashion from the appropriate aniline.

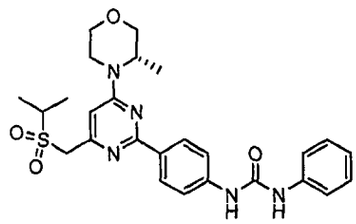
Structure	NAME	LCMS MH+	Retention Time (min)	NMR ^{1}H NMR (400.13 MHz, DMSO-d_6)
	Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate	483	2.37	
	Phenyl *N*-[3-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate	482	2.36	δ1.26 (d, 3H), 3.23 (s, 3H), 3.21-3.29 (m, 1H), 3.49-3.54 (m, 1H), 3.58 (s, 1H), 3.64-3.68 (m, 1H), 3.79 (d, 1H), 3.98-4.06 (m, 1H), 4.19 (d, 1H), 4.53 (s, 2H), 6.87 (s, 1H), 7.23-7.31 (m, 2H), 7.42 (d, 1H), 7.44-7.47 (m, 2H), 7.61-7.66 (m, 1H), 7.71 (d, 1H), 8.02-8.05 (m, 1H), 8.50 (t, 1H), 10.36 (s, 1H)
	Phenyl *N*-[2-chloro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate	517	2.40	δ1.26 (s, 3H), 3.20 (s, 3H), 3.24-3.25 (m, 1H), 3.48-3.54 (m, 1H), 3.64-3.68 (m, 1H), 3.79 (d, 1H), 3.98-4.02 (m, 1H), 4.18-4.23 (m, 1H), 4.51 (m, 1H), 4.55 (s, 2H), 6.90 (s, 1H), 7.14-7.18 (m, 1H), 7.24-7.28 (m, 2H), 7.42-7.45 (m, 2H), 7.84 (d, 1H), 8.29-8.31 (m,1H), 8.39 (d, 1H), 9.83 (s, 1H)

Structure	NAME	LCMS MH+	Retention Time (min)	NMR ^{1}H NMR (400.13 MHz, DMSO-d_6)
	Phenyl *N*-[2-methyl-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate	496	1.61	

The preparations of anilines required above were described earlier.

Example 9:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea



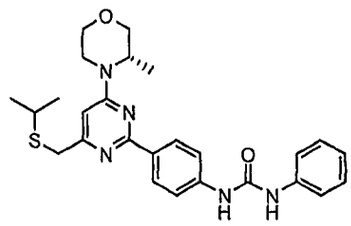
1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (78 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperoxybenzoic acid (75%) (34 mg) added followed immediately by sodium permanganate (40 mg). The reaction was allowed to stir at room temperature for 2 hours. The reaction was loaded onto a SCX-2 column, the column washed with methanol and the desired material eluted with 7N ammonia in methanol. The fractions were concentrated *in vacuo* to give the desired compound as a pale yellow solid (77 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.25 (3H, d), 1.31 - 1.38 (6H, m), 3.18 - 3.24 (1H, m), 3.48 - 3.58 (2H, m), 3.64 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.01 (1H, m), 4.18 (1H, d), 4.48 (3H, s), 6.79 (1H, s), 6.97 - 7.01 (1H, m), 7.28 - 7.31 (1H, m), 7.31 (1H, d), 7.46 - 7.49 (2H, m), 7.56 - 7.58 (2H, m), 8.25 (2H, d), 8.73 (1H, s), 8.92 (1H, s)

Mass Spectrum; $M+H^+$ 510.

Test(a): 0.59 μM.

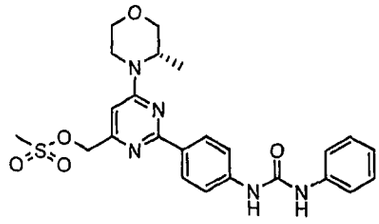
1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea



Isopropyl mercaptan (0.075 mL) was dissolved in acetonitrile (5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.12 mL). The reaction was allowed to stir at room temperature for 15 minutes then 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (228 mg) in acetonitrile (5 mL) added.The reaction was stirred for 30 minutes then concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired compound (78 mg) as a gum.

Mass Spectrum; $M+H^+$ 478.

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea

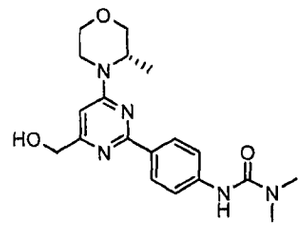


1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea (388 mg) was dissolved in DCM (15 mL) and triethylamine (0.194 mL) and the solution was cooled to 0°C. Methanesulfonyl chloride (0.108 mL) was added and the reaction stirred for 90mins at 0°C. The reaction mixture was concentrated *in vacuo* and partitioned between DCM (20 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (273 mg) as a solid.

The preparation of 1-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 10:

3-[4-[4-(Hydroxymethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea



3-(4-Bromophenyl)-1,1-dimethyl-urea (825 mg), potassium acetate (998 mg), and bis(pinacolato)diboron (1.03 g) were dissolved in 1,4 dioxane (45 mL). The solution was degassed for 5 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct was added (167 mg) and the reaction was heated to 85°C for 3 hours. [2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (828 mg), ethanol (3.75 mL), 2M sodium carbonate solution (8.53 mL) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (167 mg) were added and the heating was continued for 16 hours. The reaction was cooled and evaporated to dryness and the residue partitioned between ethyl acetate (125 mL) and water (100 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (737 mg) as a white solid.

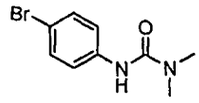
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.22 - 1.24 (3H, m), 2.95 (6H, s), 3.16 - 3.23 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.45 - 4.50 (3H, m), 5.38 (1H, t), 6.66 (1H, s), 7.55 - 7.59 (2H, m), 8.18 - 8.22 (2H, m), 8.45 (1H, s)

Mass Spectrum; $M+H^+$ 372.

Test(a): 19 μM.

The preparation of 3-(4-bromophenyl)-1,1-dimethyl-urea is described below.

3-(4-Bromophenyl)-1,1-dimethyl-urea



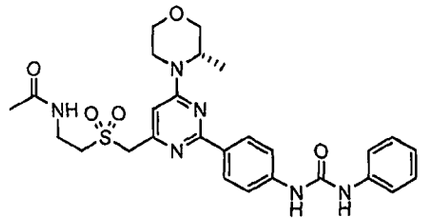
4-Bromophenyl isocyante (1.00 g) was dissolved in THF (30 mL). Dimethylamine (2.0M in THF, 2.78 mL) was added to the solution and the reaction stirred at RT for 2 hours. The reaction was filtered, concentrated *in vacuo* and the residue chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (830 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ2.90(6H, s), 7.37 - 7.40 (2H, m), 7.45 - 7.47 (2H, m), 8.37 (1H, s)

Mass Spectrum; M+H$^+$ 244.

Example 11:

***N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenylcarbamoylamino)phenyl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide**



N-[2-[[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-(phenylcarbamoylamino)phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide (100 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (40 mg) added followed immediately by sodium permanganate (47 mg). The reaction was allowed to stir at RT for 2 hours. Further 3-chloroperbenzoic acid (4 mg) and sodium permanganate (4 mg) were added and the reaction stirred for an extra hour. The reaction was loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material was isolated as a white solid (102 mg).

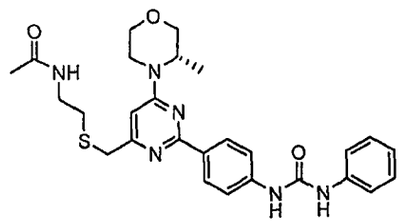
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 1.84 (3H, s), 3.18 - 3.24 (1H, m), 3.48 - 3.54 (2H, m), 3.52 (1H, s), 3.58 (2H, q), 3.64 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.01 (1H, m), 4.18 (1H, d), 4.49 (1H, s), 4.53 (2H, s), 6.80 (1H, s), 6.99 (1H, t), 7.31 (2H, d), 7.46 - 7.49 (2H, m), 7.57 (2H, d), 8.16 (1H, t), 8.27 (2H, d), 8.70 (1H, s), 8.92 (1H, s)

Mass Spectrum; M+H$^+$ 553.

Test(a): 0.14 μM.

The preparation of *N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenylcarbamoylamino)phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide is decribed below.

N-[2-[[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-(phenylcarbamoylamino)phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide



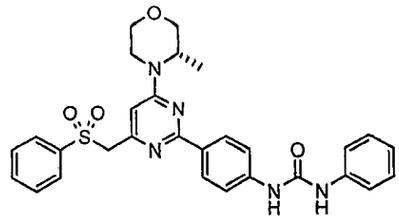
N- Acetylcysteamine (0.086mL) was dissolved in acetonitrile (5 mL). DBU (0.120 mL) was then added to the solution and was allowed to stir at RT for 15minutes. 1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (228 mg) in acetonitrile (5 mL) was added to the reaction and stirred for 30 minutes. The reaction was concentrated *in vacuo* and the crude residue purified on silica, eluting with 5% methanol in DCM, to give the desired compound (100 mg) as a white solid.

Mass Spectrum; M+H$^+$ 521.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 12:

1-[4-[4-(Benzenesulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (62 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (26 mg) was added followed immediately by sodium permanganate (30 mg). The reaction was allowed to stir at RT for 2 hours then further 3-chloroperbenzoic acid (4 mg) and sodium permanganate (4 mg) were added. The reaction was stirred for an extra 1 hour then the reaction was loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material was isolated as a pale yellow solid (64 mg),

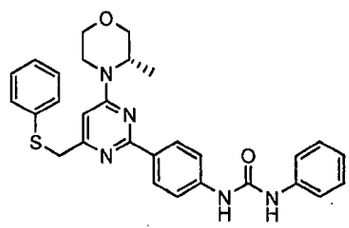
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.20 (3H, d), 3.14 - 3.21 (1H, m), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.10 (1H, d), 4.38 (1H, s), 4.71 (2H, s), 6.63 (1H, s), 6.99 (1H, m), 7.31 (2H, d), 7.46 (4H, t), 7.63 (2H, t), 7.73 - 7.78 (1H, m), 7.82 (1H, d), 7.82 - 7.84 (1H, m), 7.87 (2H, d), 8.69 (1H, s), 8.87 (1H, s).

Mass Spectrum; M+H$^+$ 544.

Test(a): 0.23 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea is described below.

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea

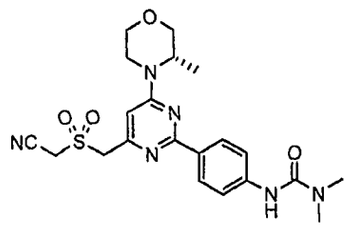


Thiophenol (0.029 mL) was dissolved in Acetonitrile (3 mL). DBU (0.043 mL) was then added to the solution and was allowed to stir at RT for 15 minutes. 1-[4-[4-[(3*S*)-3-

Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (80 mg) was added to the reaction and stirred for 30 minutes. The reaction was concentrated in vacuo and the residue chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (62 mg) as a white solid, Mass Spectrum; $M+H^+$ 512.

Example 13:

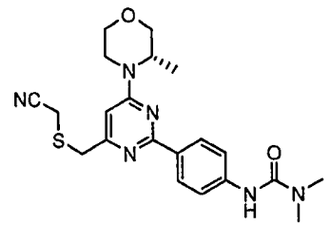
3-[4-[4-(Cyanomethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea



3-[4-[4-(Cyanomethylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea (162 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (79 mg) was added followed immediately by sodium permanganate (92 mg). The reaction was allowed to stir at RT for 2 hours. Further 3-chloroperbenzoic acid (40 mg) and sodium permanganate (45 mg) were added and the reaction stirred for 1 hour then further 3-chloroperbenzoic acid (40 mg) and sodium permanganate (45 mg) added and the reaction stirred for 1 hour. The reaction was loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material was isolated as a white solid (17 mg).
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 2.96 (6H, s), 3.18 (1H, d), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.79 (1H, d), 3.98 - 4.01 (1H, m), 4.17 (1H, s), 4.46 (1H, d), 4.74 (2H, s), 5.10 (2H, d), 6.82 (1H, s), 7.59 - 7.61 (2H, m), 8.21 - 8.23 (2H, m), 8.49 (1H, s)
Mass Spectrum; $M+H^+$ 459.
Test(a): 2.1 μM.

The preparation of 3-[4-[4-(cyanomethylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea is described below.

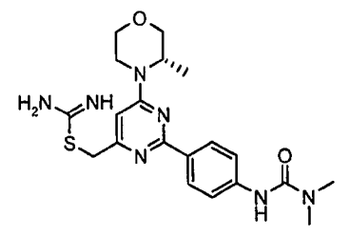
3-[4-[4-(Cyanomethylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea



3-[4-[4-(Carbamimidoylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea (0.38 mmol) was dissolved in DMF (2 mL). This was treated with bromoacetonitrile (0.030 mL) and then the sodium hydroxide (61 mg) in water (1 mL) and stirred at RT for 15 minutes. The reaction mixture was concentrated *in vacuo* and the residue loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material was isolated and used without further chromatography.

Mass Spectrum; $M+H^+$ 427.

3-[4-[4-(Carbamimidoylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea

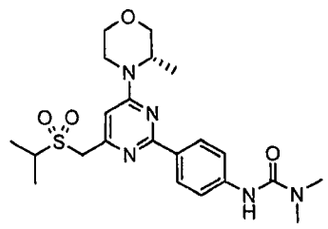


3-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea (140 mg) was dissolved in DCM (5 mL) and triethylamine (0.079 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.044 mL) and the reaction was stirred for 15 minutes at RT. The solvent was removed under reduced pressure and replaced with ethanol (5 mL) then thiourea (32 mg) added. The reaction was then heated to 70°C for 30 minutes then allowed to cool and concentrated *in vacuo* to give the desired material which was used without further purification.

Mass Spectrum; $M+H^+$ 430.

Example 14:

1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea



1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea (163 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (79 mg) was added followed immediately by sodium permanganate (92 mg). The reaction was allowed to stir at RT for 2 hours then further 3-chloroperbenzoic acid (20 mg) and sodium permanganate (25 mg) were added. The reaction was allowed to stir for 1 hour then loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material (90 mg) was isolated as a white solid.

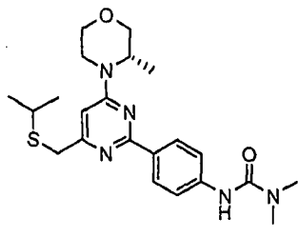
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 1.35 - 1.37 (6H, m), 2.95 (6H, s), 3.21 - 3.26 (2H, m), 3.47 - 3.54 (2H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.24 (1H, m) 4.45 - 4.47 (2H, m), 6.78 (1H, s), 7.58 - 7.61 (2H, m), 8.17 - 8.20 (2H, m), 8.48 (1H, s)

Mass Spectrum; M+H$^+$ 462.

Test(a): 0.42 μM.

The preparation of 1,1-dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea is described below.

1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea

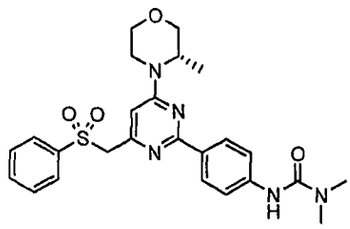


3-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea (140 mg) was dissolved in DCM (5 mL) and triethylamine (0.079 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.044 mL) and the reaction was stirred for 15 minutes at RT before being concentrated *in vacuo* to give the mesylate which was used without further purification. Isopropyl mercaptan (0.062 mL) was dissolved in acetonitrile (5 mL). DBU (0.099 mL) was then added to the solution and was allowed to stir at RT for 5 minutes. The crude mesylate from above was suspended in acetonitrile (5 mL) and added to the thiol solution. The reaction was left to stir at RT for 1 hour then further DBU (0.099 mL) added and the reaction stirred at RT for 30 minutes. The reaction mixture was concentrated *in vacuo* to give the desired material which was used without further purification.

Mass Spectrum; $M+H^+$ 430.

Example 15:

3-[4-[4-(Benzenesulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea



1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea (158 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (89 mg) was added followed immediately by sodium permanganate (96 mg). The reaction was allowed to stir at RT for 16 hours then further 3-chloroperbenzoic acid (20 mg) and sodium permanganate (25 mg) were added. The reaction was allowed to stir for 1 hour then loaded onto a SCX-2 column, washed

with methanol and the desired material removed with 7N ammonia in methanol. The desired material was isolated as a white solid (90 mg).

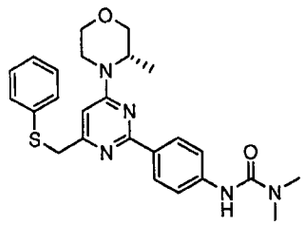
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.20 (3H, d), 2.95 (6H, s), 3.13 - 3.20 (1H, m), 3.44 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.07 (1H, t), 4.36 (1H, s), 4.70 (2H, s), 6.62 (1H, s), 7.47 - 7.49 (2H, m), 7.62 (2H, t), 7.72 - 7.75 (1H, m), 7.79 - 7.84 (4H, m), 8.43 (1H, s)

Mass Spectrum; M+H$^+$ 496.

Test(a): 1 μM.

The preparation of 1,1-dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea is described below.

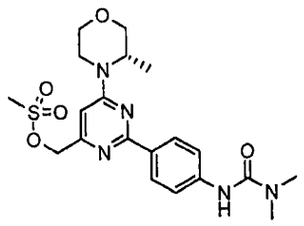
1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea



Thiophenol (0.062 mL) was dissolved in acetonitrile (5 mL). DBU (0.141 mL) was then added to the solution and was allowed to stir at RT for 5 minutes. 1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (154 mg) was suspended in acetonitrile (5 mL) and added to the thiol. The reaction was left to stir at RT of 1 hour then concentrated *in vacuo* to give the desired material which was used without further purification.

Mass Spectrum; M+H$^+$ 464.

1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea

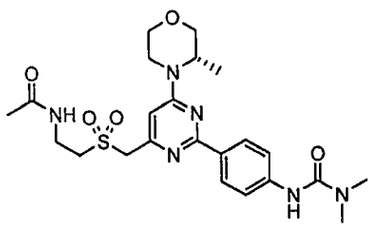


3-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1,1-dimethyl-urea (384 mg) was dissolved in DCM (12 mL) and triethylamine (0.216 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.121 mL) and the reaction was stirred for 15 minutes at RT before being concentrated *in vacuo* to give the desired material.

Mass Spectrum; $M+H^+$ 450.

Example 16:

***N*-[2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide**



N-[2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide (158 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (116 mg) was added followed immediately by sodium permanganate (134 mg). The reaction was allowed to stir at RT for 1 hour then loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material (84 mg) was isolated as a white solid.

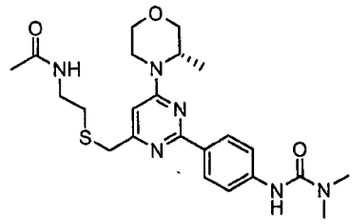
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 1.83 (3H, s), 2.96 (6H, s), 3.20 - 3.25 (1H, m), 3.47 - 3.50 (1H, m), 3.52 (2H, d), 3.57 (2H, q), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.51 (3H, m), 6.78 (1H, s), 7.58 - 7.61 (2H, m), 8.16 - 8.19 (1H, m), 8.19 - 8.22 (2H, m), 8.49 (1H, s)

Mass Spectrum; $M+H^+$ 505.

Test(a): 4 μM.

The preparation of *N*-[2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide is described below.

N-[2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide

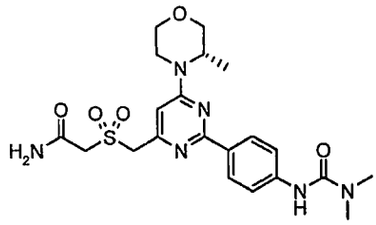


N-Acetylcysteamine (0.064 mL) was dissolved in acetonitrile (5 mL). DBU (0.141 mL) was then added to the solution and was allowed to stir at RT for 5 minutes. 1,1-Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (154 mg) was suspended in acetonitrile (5 mL) and added to the thiol. The reaction was left to stir at RT of 1 hour then concentrated in vacuo to give the desired material.

Mass Spectrum; $M+H^+$ 473.

Example 17:

2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]acetamide



2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide (158 mg) was dissolved in 1,4-dioxane (6 mL) and water (1 mL). The solution was cooled to 0°C and 3-chloroperbenzoic acid (75%) (123 mg) was added followed immediately by sodium permanganate (143 mg). The reaction was allowed to stir at RT for 1 hour then loaded onto a SCX-2 column, washed with methanol and the desired

material removed with 7N ammonia in methanol. The desired material (55 mg) was isolated as a white solid.

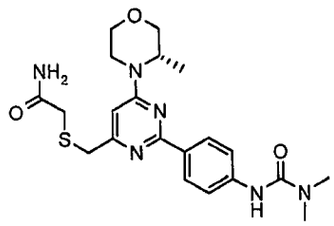
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 2.96 (6H, s), 3.22 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.27 (2H, s), 4.47 (1H, s), 4.67 (2H, s), 6.77 (1H, s), 7.53 (1H, s), 7.58 - 7.61 (2H, m), 7.79 (1H, s), 8.17 - 8.21 (2H, m), 8.49 (1H, s)

Mass Spectrum; M+H$^+$ 477.

Test(a): 1.1 μM.

The preparation of 2-[[2-[4-(dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide is described below.

2-[[2-[4-(Dimethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide

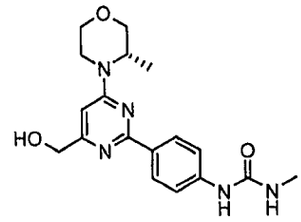


Dimethyl-3-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (154 mg) was dissolved in ethanol (5 mL) and thiourea (29 mg) was added. The reaction was then heated to 70°C for 30 minutes before being concentrated *in vacuo*. The residue was dissolved in DMF (2 mL) and treated with 2-bromoacetamide (52 mg) followed by sodium hydroxide (55 mg) in water (1 mL) and stirred at RT for 30 minutes. The reaction mixture was concentrated *in vacuo* then loaded onto a SCX-2 column, washed with methanol and the desired material removed with 7N ammonia in methanol. The desired material was used without further purification.

Mass Spectrum; M+H$^+$ 445.

Example 18:

1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



1-(4-Bromophenyl)-3-methyl-urea (2.50 g), potassium acetate (3.21 g), and bis(pinacolato)diboron (3.33 g) were dissolved in 1,4 dioxane (120 mL). The solution was degassed for 5 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct was added (535 mg) and the reaction was heated to 90°C for 3 hours. Further 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (250 mg) was added and heating continued for 1 hour. Further 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (250 mg) was added and heating continued for a further 1 hour. [2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (2.66 mg), ethanol (9.5 mL), 2M sodium carbonate solution (27.3 mL) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) dichloromethane adduct (535 mg) were added and the heating was continued for 16 hours. The reaction was cooled and evaporated to dryness then the residue partitioned between ethyl acetate (250 mL) and water (100 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (1.25 g) as a brown solid.

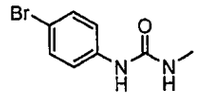
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.23 (3H, d), 2.66 (3H, d), 3.18 - 3.23 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.96 - 3.99 (1H, m), 4.16 (1H, d), 4.45 (2H, d), 4.49 (1H, d), 5.38 (1H, t), 6.05 (1H, q), 6.66 (1H, s), 7.46 - 7.48 (2H, m), 8.18 - 8.21 (2H, m), 8.69 (1H, s)

Mass Spectrum; $M+H^+$ 358.

Test(a): 0.12 μM.

The preparation of 1-(4-bromophenyl)-3-methyl-urea is described below.

1-(4-Bromophenyl)-3-methyl-urea



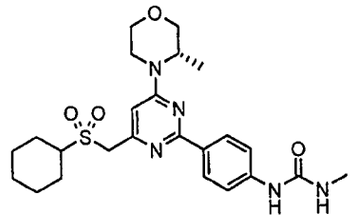
4-Bromophenyl isocyante (2.50 g) was dissolved in THF (75 mL). Methylamine (2.0M in THF, 75 mL) was added to the solution and stirred at RT for 1 hour. The reaction was filtered and vacuumed to dryness. The crude material was chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (2.65 g) as a white solid.

NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ2.64 (3H, d), 6.03 (1H, d), 7.37 (4H, s), 8.61 (1H, s)

Mass Spectrum; M+H$^+$ 229.

Example 19:

1-[4-[4-(Cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



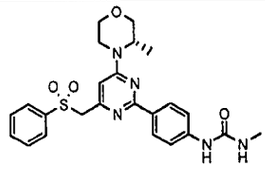
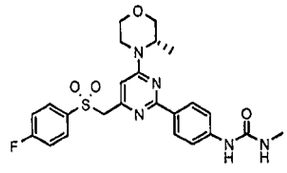
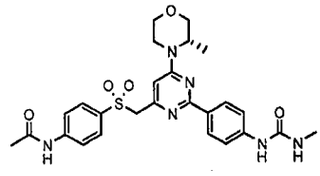
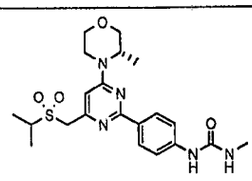
1-[4-[4-(Cyclohexylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea (0.35 mmol) was dissolved in 1,4-dioxane (5 mL) and water (1 mL). 3-chloroperbenzoic acid (75%) (121 mg) was added to the solution followed immediately by sodium permanganate (140 mg) and the reactions stirred at RT for 1 hour. Further 3-chloroperbenzoic acid (75%) (121 mg) and sodium permanganate (140 mg) were added and the reactions allowed to stir at RT for 1 hour. Further 3-chloroperbenzoic acid (75%) (121 mg) and sodium permanganate (140 mg) were added and the reactions allowed to stir at RT for another 1 hour then loaded onto a SCX-3 column. The column was washed with methanol and the desired material removed with 7N ammonia in methanol. The crude material was purified by prep-HPLC (basic) to give the desired material (74 mg) as a white solid.

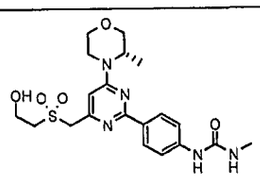
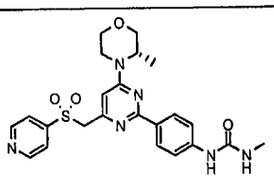
NMR Spectrum: ^{1}H NMR (DMSO-d_6) δ1.18 - 1.32 (7H, m), 1.42 (1H, d), 1.48 (1H, d), 1.68 (1H, d), 1.89 (2H, d), 2.25 (3H, d), 2.32 - 2.34 (1H, m), 2.66 (3H, d), 3.46 - 3.53 (1H, m),

3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.43 (3H, s), 6.08 (1H, t), 6.77 (1H, s), 7.50 - 7.52 (2H, m), 8.19 - 8.21 (2H, m)

Mass Spectrum; $M+H^+$ 488.

The following compounds were prepared in an analogous fashion from the appropriate sulfides.

Example	Structure	NAME	LCMS MH+
19a		1-[4-[4-(benzenesulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	482
19b		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	500
19c		*N*-[4-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]phenyl]acetamide	539
19d		3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	448

Example	Structure	NAME	LCMS MH+
19e		1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	450
19f		3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	483

Example 19a: ^{1}H NMR (DMSO-d_6) δ1.18 (3H, d), 2.66 (3H, q), 3.11 - 3.19 (1H, m), 3.43 - 3.50 (1H, m), 3.60 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.08 (1H, d), 4.35 (1H, s), 4.69 (2H, s), 6.04 (1H, q), 6.59 (1H, s), 7.36 - 7.38 (2H, m), 7.61 (2H, t), 7.71 - 7.75 (1H, m), 7.79 - 7.81 (3H, m), 7.82 (1H, s), 8.69 (1H, s)

Example 19b: ^{1}H NMR (DMSO-d_6) δ1.20 (3H, d), 2.66 (3H, d), 3.14 - 3.21 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.11 (1H, d), 4.37 (1H, s), 4.71 (2H, s), 6.04 (1H, q), 6.64 (1H, s), 7.37 - 7.41 (2H, m), 7.43 - 7.48 (2H, m), 7.77 - 7.80 (2H, m), 7.85 - 7.89 (2H, m), 8.71 (1H, s)

Example 19c: ^{1}H NMR (DMSO-d_6) δ1.18 (3H, d), 2.13 (3H, s), 2.60 - 2.61 (3H, m), 2.67 (3H, q), 2.68 (1H, s), 3.44 - 3.49 (1H, m), 4.08 (1H, d), 4.35 (1H, s), 4.60 (2H, s), 6.05 (1H, q), 6.54 (1H, s), 7.37 - 7.39 (2H, m), 7.70 (2H, d), 7.77 (2H, d), 7.82 (2H, d), 8.68 (1H, s), 10.37 (1H, s)

Example 19d: ^{1}H NMR (DMSO-d_6) δ1.24 (3H, d), 1.35 - 1.37 (7H, m), 2.66 - 2.69 (3H, m), 3.21 - 3.25 (1H, m), 3.47 - 3.54 (2H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.46 (3H, s), 6.08 (1H, q), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 8.17 - 8.19 (2H, m), 8.73 (1H, s)

Example 19e: ^{1}H NMR (DMSO-d_6) δ1.24 (3H, d), 2.66 (2H, s), 2.68 (2H, q), 3.21 - 3.26 (1H, m), 3.51 (3H, t), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.89 - 3.94 (2H, m), 3.97 - 4.01 (1H, m),

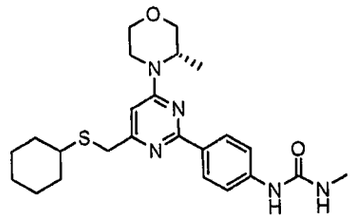
4.50 (3H, s), 5.18 (1H, t), 6.07 (1H, d), 6.76 (1H, s), 7.49 - 7.51 (2H, m), 8.20 - 8.22 (2H, m), 8.74 (1H, s)

Example 19f: ^{1}H NMR (DMSO-d_6) δ1.20 - 1.25 (3H, m), 2.66 (3H, t), 3.15 - 3.21 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, t), 3.95 - 3.99 (1H, m), 4.11 (1H, d), 4.39 (1H, s), 4.87 (2H, s), 6.05 (1H, q), 6.71 (1H, s), 7.35 - 7.37 (2H, m), 7.64 - 7.66 (2H, m), 7.81 - 7.82 (2H, m), 8.70 (1H, d), 8.90 (1H, d), 8.91 (1H, s)

Test(a): Example(19) 0.25 μM; Example(19a) 0.0047 μM; Example(19b) 0.033 μM; Example(19c) 0.022 μM; Example(19d) 0.066 μM; Example(19e) 0.011 μM; Example(19f) 0.027 μM.

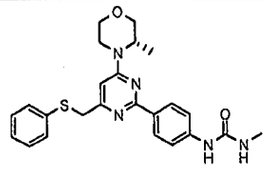
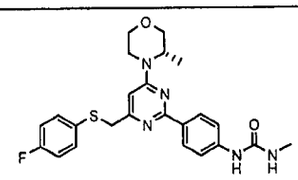
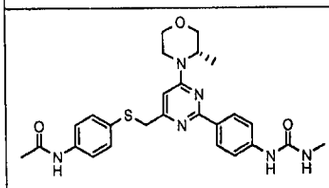
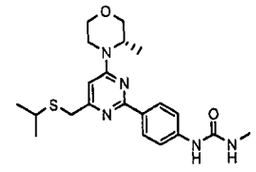
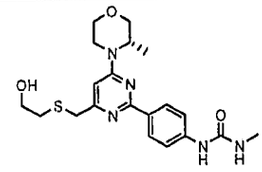
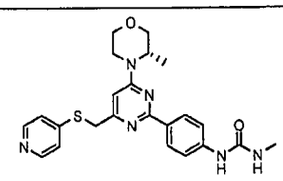
The preparation of 1-[4-[4-(cyclohexylsulfanylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea is described below.

1-[4-[4-(Cyclohexylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



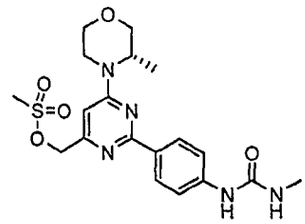
Cyclohexanethiol (0.61 mmol) was dissolved in acetonitrile (4 mL). DBU (0.050 mL) was then added and the solution allowed to stir at RT for 5 minutes. 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (151 mg) dissolved in acetonitrile (2 mL) and DBU (0.054 mL) was added and the reactions stirred at RT for 2 hours. The reaction mixture was concentrated *in vacuo* to give the desired material which was used without further purification.

The following sulfides were made in an analogous manner from 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea and the appropriate thiol.

Structure	NAME
	3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(phenylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea
	1-[4-[4-[(4-fluorophenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea
	*N*-[4-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]phenyl]acetamide
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea
	1-[4-[4-(2-hydroxyethylsulfanylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea

The preparation of 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea is described below.

3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea

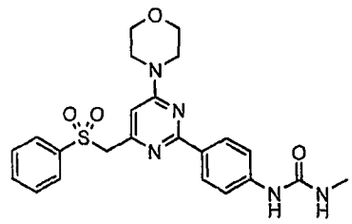


1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea (1.24 g) was partially dissolved in DCM (30 mL) and triethylamine (0.724 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.405 mL) and the reaction was stirred for 15 minutes at RT then concentrated *in vacuo* to give the desired material.

Mass Spectrum; $M+H^+$ 436.

Example 20:

3-[4-[4-(Benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-methyl-urea



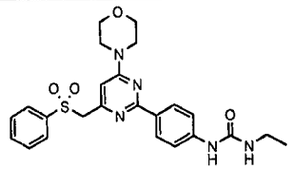
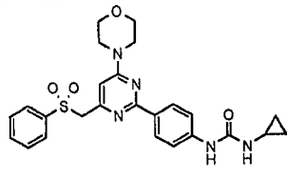
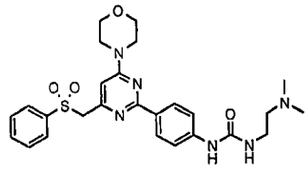
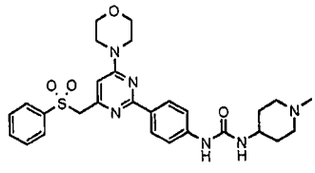
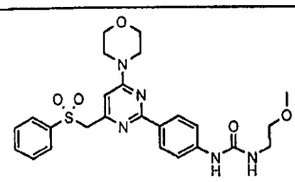
Phenyl (4-{4-morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate (250 mg, 0.45 mmol) was dissolved in DMF (5 mL). Triethylamine (0.188 mL, 1.35 mmol) was added followed by methylamine (2M in THF, 1.1 mL) and the solution heated at 50°C for 1 hour. The reaction was cooled to room temperature and concentrated *in vacuo.* The resultant oil was purified by chromatography on silica, eluting with 0-5% methanol in DCM to give the desired material as a white solid (120 mg).

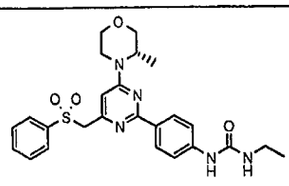
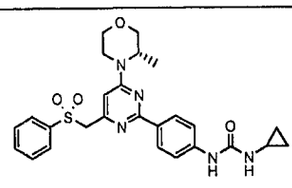
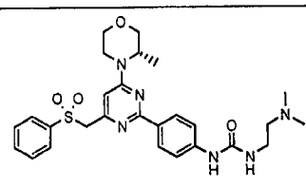
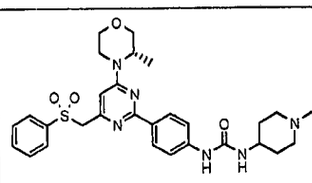
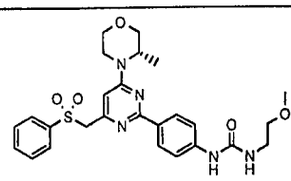
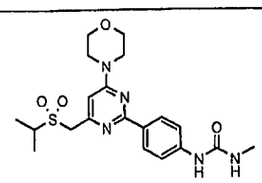
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.66 (d, 3H), 3.63 (m, 4H), 3.70 (m, 4H), 4.69 (s, 2H), 6.05 (m, 1H), 6.65 (s, 1H), 7.38 (d, 2H), 7.63 (t, 2H), 7.74 (d, 1H), 7.80 (m, 3H), 8.69 (s, 1H)

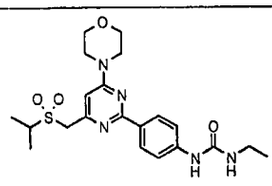
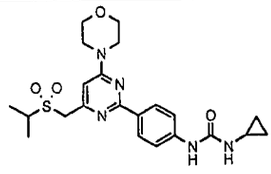
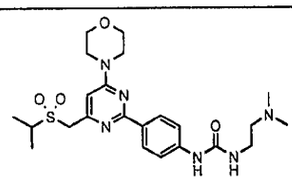
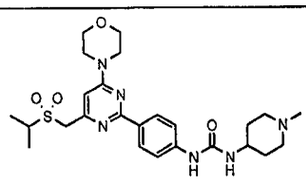
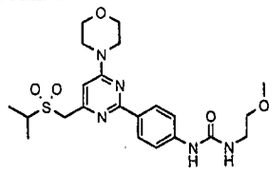
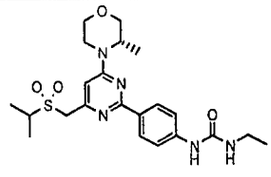
LCMS Spectrum: MH+ 468, retention time 1.76 min, Method 5 Min Base

The compounds shown in table were prepared in an analogous manner *N*'-(4-{4-morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)urea by reacting the appropriate amine

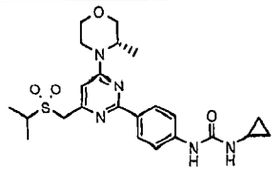
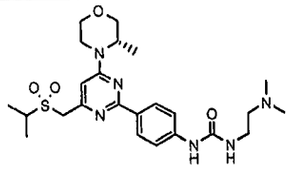
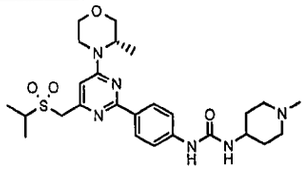
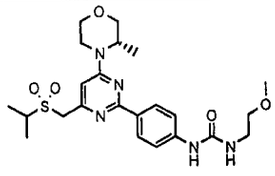
with the appropriate carbamate and purification by either chromatography on silica or by preparative HPLC.

Example	Structure	NAME	LCMS MH+	Retention time (min)
20a		3-[4-[4-(benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-ethyl-urea	482	1.98
20b		1-[4-[4-(benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea	494	1.92
20c		3-[4-[4-(benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-(2-dimethylaminoethyl)urea	525	1.98
20d		3-[4-[4-(benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-(1-methyl-4-piperidyl)urea	551	1.93
20e		3-[4-[4-(benzenesulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-1-(2-methoxyethyl)urea	512	1.77

Example	Structure	NAME	LCMS MH+	Retention time (min)
20f		3-[4-[4-(benzenesulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	496	2.06
20g		1-[4-[4-(benzenesulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea	508	2.08
20h		1-[4-[4-(benzenesulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	539	1.94
20i		1-[4-[4-(benzenesulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methyl-4-piperidyl)urea	565	1.94
20j		1-[4-[4-(benzenesulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methoxyethyl)urea	526	1.98
20k		3-methyl-1-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	434	1.47

Example	Structure	NAME	LCMS MH+	Retention time (min)
20l		1-ethyl-3-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	448	1.61
20m		3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	460	1.63
20n		3-(2-dimethylaminoethyl)-1-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	491	1.59
20o		3-(1-methyl-4-piperidyl)-1-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	517	1.61
20p		3-(2-methoxyethyl)-1-[4-[4-morpholin-4-yl-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	478	1.53
20q		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	462	1.75

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Example	Structure	NAME	LCMS MH+	Retention time (min)
20r		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	474	1.77
20s		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	505	1.76
20t		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(1-methyl-4-piperidyl)urea	531	1.77
20u		3-(2-methoxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	492	1.67

Example 20a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.00 (t, 3H), 3.05 (m, 2H), 3.56 (s, 4H), 3.63 (m, 4H), 4.62 (s, 2H), 6.07 (t, 1H), 6.59 (s, 1H), 7.30 (d, 2H), 7.55 (t, 2H), 7.71 (m, 5H), 8.54 (s, 1H)

Example 20b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 2.55 (m, 1H), 3.64 (m, 4H), 3.71 (m, 4H), 4.69 (s, 2H), 6.41 (d, 1H), 6.66 (s, 1H), 7.38 (d, 2H), 7.63 (t, 2H), 7.75 (m, 1H), 7.81 (m, 4H), 8.49 (s, 1H)

Example 20c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.20 (s, 6H), 2.38 (t, 2H), 3.20 (m, 2H), 3.63 (s, 4H), 3.70 (s, 4H), 4.69 (s, 2H), 6.17 (s, 1H), 6.65 (s, 1H), 7.37 (d, 2H), 7.62 (t, 2H), 7.75 (t, 1H), 7.81 (t, 4H), 8.87 (s, 1H)

Example 20d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.49 (m, 2H), 1.86 (m, 2H), 2.32 (s, 3H), 2.84 (m, 2H), 3.54 (m, 2H), 3.63 (s, 4H), 3.70 (m, 4H), 4.69 (s, 2H), 6.46 (d, 1H), 6.65 (s, 1H), 7.35 (d, 2H), 7.63 (t, 2H), 7.74 (t, 2H), 7.81 (m, 3H), 8.76 (s, 1H)

Example 20e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.27 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.63 (s, 4H), 3.71 (m, 4H), 4.69 (s, 2H), 6.25 (t, 1H), 6.66 (s, 1H), 7.35 (d, 2H), 7.62 (t, 1H), 7.75 (m, 2H), 7.81 (m, 4H), 8.73 (s, 1H)

Example 20f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.15 (t, 3H), 1.25 (d, 3H), 3.12 (m, 3H), 3.47 (t, 1H), 3.62 (d, 1H), 3.76 (d, 1H), 3.96 (d, 1H), 4.08 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.14 (t, 1H), 6.60 (s, 1H), 7.38 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.81 (m, 4H), 8.62 (s, 1H)

Example 20g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.20 (d, 3H), 2.55 (m, 1H), 3.16 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.97 (m, 1H), 4.09 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.42 (d, 1H), 6.60 (s, 1H), 7.39 (d, 2H), 7.63 (t, 2H), 7.75 (t, 1H), 7.82 (m, 4H), 8.49 (s, 1H)

Example 20h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.19 (d, 3H), 2.23 (s, 6H), 2.40 (t, 2H), 3.21 (m, 3H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.96 (m, 1H), 4.08 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.21 (t, 1H), 6.60 (s, 1H), 7.40 (d, 2H), 7.62 (t, 2H), 7.75 (t, 1H), 7.82 (m, 3H), 7.96 (s, 1H), 8.90 (s, 1H)

Example 20i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.19 (d, 3H), 1.40 (m, 2H), 1.79 (m, 2H), 2.02 (t, 2H), 2.16 (s, 3H), 2.64 (m, 2H), 3.16 (m, 1H), 3.47 (m, 2H), 3.62 (m, 1H), 3.75 (d, 1H), 3.96 (m, 1H), 4.08 (d, 1H), 4.35 (s, 1H), 4.69 (s, 2H), 6.16 (d, 1H), 6.60 (s, 1H), 7.35 (d, 2H), 7.65 (t, 2H), 7.74 (t, 1H), 7.81 (m, 4H), 8.52 (s, 1H)

Example 20j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.20 (d, 3H), 3.15 (t, 1H), 3.29 (m, 5H), 3.40 (t, 2H), 3.47 (t, 1H), 3.62 (d, 1H), 3.75 (d, 1H), 3.96 (d, 1H), 4.08 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.25 (t, 1H), 6.60 (s, 1H), 7.37 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 4H), 8.73 (s, 1H)

Example 20k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.36 (d, 6H), 2.66 (s, 3H), 3.51 (m, 1H), 3.72 (s, 8H), 4.47 (s, 2H), 6.09 (s, 1H), 6.83 (s, 1H), 7.51 (d, 2H), 8.18 (d, 2H), 8.76 (s, 1H)

Example 20l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.07 (t, 3H), 1.35 (d, 6H), 3.12 (m, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.47 (s, 2H), 6.18 (s, 1H), 6.83 (s, 1H), 7.51 (d, 2H), 8.18 (d, 2H), 8.68 (s, 1H)

Example 20m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.38 (d, 6H), 2.56 (m, 1H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.45 (s, 1H), 6.82 (s, 1H), 7.51 (d, 2H), 8.19 (d, 2H), 8.55 (s, 1H)

Example 20n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.36 (d, 6H), 2.85 (d, 6H), 3.20 (m, 2H), 3.46 (m, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.56 (t, 1H), 6.83 (s, 1H), 7.55 (d, 2H), 8.21 (d, 2H), 9.10 (s, 1H)

Example 20o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.36 (d, 6H), 1.57 (m, 2H), 1.97 (d, 2H), 2.59 (s, 1H), 2.78 (s, 2H), 3.16 (d, 2H), 3.29 (s, 3H), 3.50 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.44 (d, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.65 (s, 1H)

Example 20p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.38 (d, 6H), 3.28 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.28 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.77 (s, 1H)

Example 20q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.07 (t, 3H), 1.24 (d, 3H), 1.36 (m, 6H), 3.13 (m, 2H), 3.23 (m, 1H), 3.51 (m, 2H), 3.65 (m, 1H), 3.72 (d, 1H), 3.99 (m, 1H), 4.17 (d, 1H), 4.46 (s, 3H), 6.17 (t, 1H), 6.77 (s, 1H), 7.50 (d, 2H), 8.18 (d, 2H), 8.65 (s, 1H)

Example 20r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.25 (d, 3H), 1.37 (d, 6H), 2.57 (m, 2H), 3.23 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.44 (d, 1H), 6.77 (s, 1H), 7.51 (d, 2H), 8.19 (d, 2H), 8.53 (s, 1H)

Example 20s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 1.36 (m, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.21 (m, 2H), 3.50 (m, 2H), 3.65 (m, 1H), 3.76 (d, 1H), 3.99 (m, 1H), 4.06 (q, 2H), 4.17 (d, 1H), 4.46 (s, 2H), 6.17 (t, 1H), 6.77 (s, 1H), 7.49 (d, 2H), 8.18 (d, 2H), 8.89 (s, 1H)

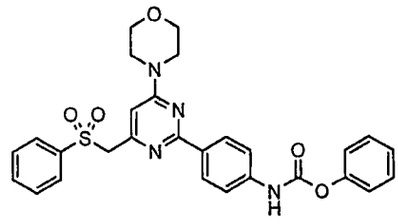
Example 20t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 1.36 (m, 6H), 1.42 (m, 2H), 1.80 (m, 2H), 2.03 (t, 2H), 2.17 (s, 3H), 2.65 (d, 2H), 3.18 (d, 1H), 3.23 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.76 (d, 1H), 3.98 (m, 1H), 4.06 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.19 (d, 1H), 6.77 (s, 1H), 7.48 (d, 2H), 8.18 (d, 2H), 8.56 (s, 1H)

Example 20u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (d, 4H), 1.36 (m, 6H), 3.18 (d, 3H), 3.24 (m, 2H), 3.40 (t, 2H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.06 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.28 (t, 1H), 6.77 (s, 1H), 7.49 (d, 2H), 8.19 (d, 2H), 8.77 (s, 1H)

Test(a): Example(20) 0.043 μM; Example(20a) 0.15 μM; Example(20b) 0.17 μM; Example(20c) 1 μM; Example(20d) 1.6 μM; Example(20e) 2.1 μM; Example(20f) 0.035 μM; Example(20g) 0.039 μM; Example(20h) 0.44 μM; Example(20i) 0.7 μM; Example(20j) 0.75 μM; Example(20k) 0.036 μM; Example(20l) 0.074 μM; Example(20m) 0.081 μM; Example(20n) 0.86 μM; Example(20o) 1.3 μM; Example(20p) 0.91 μM; Example(20q) 0.039 μM; Example(20r) 0.094 μM; Example(20s) 0.62 μM; Example(20t) 0.6 μM; Example(20u) 0.27 μM.

The preparations of the carbamates phenyl (4-{4-morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate, phenyl (4-{4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate, phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate, phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate are described below.

Phenyl (4-{4-morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate



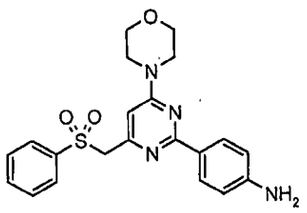
(4-{4-Morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)amine (1 g, 2.44 mmol) was dissolved in dioxane(10 mL). Sodium bicarbonate (307 mg, 3.65 mmol) was added, followed by phenyl chloroformate (0.307 mL, 2.44 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 10mL DCM and 10mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was

chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (790 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.64 (s, 4H), 3.70 (m, 4H), 4.71 (s, 2H), 6.70 (s, 1H), 7.27 (m, 3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (m, 1H), 7.85 (m, 4H), 10.38 (s, 1H)

LCMS Spectrum: MH+ 531, retention time 2.61 min, Method 5 Min Base

(4-{4-Morpholin-4-yl-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)amine

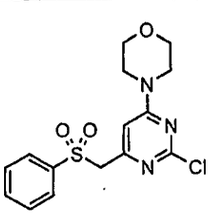


4-{2-Chloro-6-[(phenylsulfonyl)methyl]pyrimidin-4-yl}morpholine (3.3 g, 9.33 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (36 mL). [4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (3.07 g, 13.99 mmol), 2M sodium carbonate solution (12 mL) and dichlorobis(triphenylphosphine) palladium catalyst (328 mg, 0.47 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water (20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude oil was dissolved in DCM and filtered to remove insoluble material. A beige solid precipitated from the filtrates and the filtrates were filtered again. The solid was analysed and found to be the desired material (2.2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.60 (m, 4H), 3.69 (m, 4H), 4.64 (s, 2H), 5.50 (s, 2H), 6.48 (d, 2H), 6.54 (s, 1H), 7.63 (m, 4H), 7.74 (t, 1H), 7.82 (m, 2H)

LCMS Spectrum: MH+ 411, retention time 1.70 min, Method 5 Min Base

4-{2-Chloro-6-[(phenylsulfonyl)methyl]pyrimidin-4-yl}morpholine

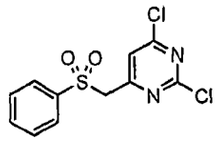


2,4-dichloro-6-[(phenylsulfonyl)methyl]pyrimidine (6 g, 19.8 mmol) was dissolved in DCM (50 mL) and stirred (under nitrogen) at -5°C. Triethylamine (3.06 mL, 21.8 mmol) was added to give a clear brown solution. Morpholine (1.65 mL, 19.8 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (4 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.53 (s, 4H), 3.65 (t, 4H), 4.61 (s, 2H), 6.71 (s, 1H), 7.64 (t, 2H), 7.77 (m, 3H)

LCMS Spectrum: MH+ 354, retention time 1.50 min, Method 5 Min Base

2,4-dichloro-6-[(phenylsulfonyl)methyl]pyrimidine

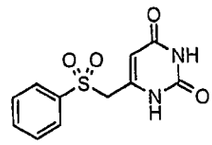


6-[(Phenylsulfonyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (13.3 g, 49 mmol) was added to phosphorus oxychloride (100 mL) and the mixture heated to reflux for 16 hours. The reaction was then cooled to room temperature and the excess phosphorus oxychloride was removed *in vacuo*. The residue was azeotroped with toluene (2 x 100 mL) and dissolved in DCM. This mixture was then poured slowly onto ice (1 L) and stirred for 20 minutes, then extracted with DCM (3 x 500 mL) The extracts were combined, dried over magnesium sulphate, then concentrated *in vacuo* to give the desired material as a brown solid (12 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ4.97 (s, 2H), 7.65 (t, 2H), 7.72 (s, 1H), 7.79 (m, 3H)

LCMS Spectrum: M-H 301, retention time 2.08 min, Method 5 Min Basic

6-[(Phenylsulfonyl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione

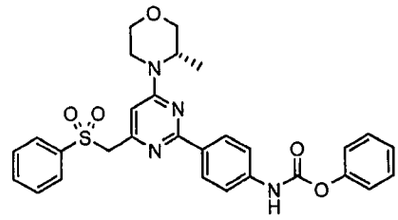


6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (8 g, 50 mmol) was dissolved in DMF (200 mL) and benzenesulphinic acid sodium salt (9.8 g, 60 mmol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water (100 mL), filtered, then triturated with acetonitrileto give the desired material as a cream solid (13.2 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ4.46 (s, 2H), 7.69 (t, 2H), 7.81 (m, 1H), 7.87 (m, 3H), 10.85 (s, 1H), 11.11 (s, 1H)

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

Phenyl (4-{4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate



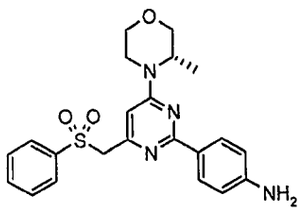
(4-{4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)amine (2 g, 4.71 mmol) was dissolved in dioxane(20 mL). Sodium bicarbonate (594 mg, 7.07 mmol) was added, followed by phenyl chloroformate (0.593 mL, 4.71 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 20 mL DCM and 20 mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (1.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.20 (d, 3H), 3.17 (m, 1H), 3.48 (m, 1H), 3.63 (m, 1H), 3.76 (d, 1H), 3.97 (m ,1H), 4.11 (d, 1H), 4.37 (s, 1H), 4.72 (s, 2H), 6.65 (s,

1H), 7.27 (m ,3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 2H), 7.90 (d, 2H), 10.38 (s, 1H)

LCMS Spectrum: MH+ 545, retention time 2.7 min, Method 5 Min Base

(4-{4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)amine

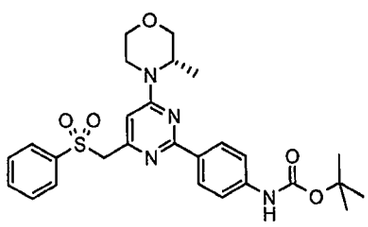


Tert-butyl (4-{4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate (3.1 g, 5.91 mmol) was dissolved in DCM (20 mL) and trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 hours then diluted with DCM (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). Organic phase collected, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the desired material as a beige solid (2.5 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 3.24 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.78 (d, 1H), 3.98 (m, 1H), 4.14 (s, 1H), 4.37 (s, 1H), 4.75 (s, 2H), 6.56 (s, 1H), 6.67 (d, 3H), 7.65 (m, 2H), 7.78 (m, 3H), 7.84 (m, 3H)

LCMS Spectrum: MH+ 425, retention time 2.03 min, Method 5 Min Base

Tert-butyl (4-{4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(phenylsulfonyl)methyl]pyrimidin-2-yl}phenyl)carbamate



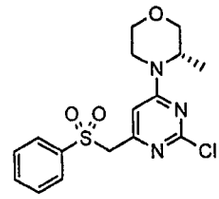
(3*S*)-4-{2-Chloro-6-[(phenylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine (3.2 g, 8.70 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (36 mL). *Tert*-butyl [4-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)phenyl]carbamate (4.16 g, 13.05 mmol), 2M sodium carbonate solution (8 mL) and dichlorobis(triphenylphosphine) palladium catalyst (306 mg, 0.43 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water (20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-30% ethyl acetate in DCM to give the desired material as a beige solid (3.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.19 (d, 3H), 1.49 (s, 9H), 3.16 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.97 (m, 1H), 4.10 (d, 1H), 4.35 (s, 1H), 4.70 (s, 2H), 6.62 (s, 1H), 7.44 (d, 2H), 7.63 (d, 2H), 7.74 (m, 1H), 7.82 (m, 4H), 9.49 (s, 1H)

LCMS Spectrum: MH+ 525, retention time 2.80 min, Method 5 Min Base

(3*S*)-4-{2-chloro-6-[(phenylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine

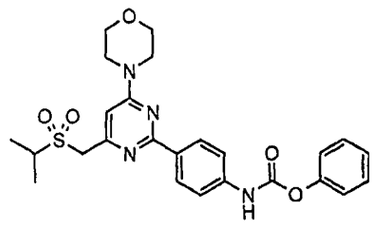


2,4-dichloro-6-[(phenylsulfonyl)methyl]pyrimidine (2.8 g, 9.24 mmol) was dissolved in DCM (20 mL) and stirred (under nitrogen) at -5°C. Triethylamine (1.42 mL, 10.17 mmol) was added to give a clear brown solution. (3*S*)-3-methylmorpholine (935 mg, 9.24 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (2.6 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.15 (d, 3H), 3.15 (m, 1H), 3.42 (m, 1H), 3.56 (m, 1H), 3.72 (d, 1H), 3.92 (m, 2H), 4.15 (s, 1H), 4.62 (s, 2H), 6.66 (s, 1H), 7.74 (t, 1H), 7.76 (t, 1H), 7.78 (d, 1H), 7.80 (m, 2H)

LCMS Spectrum: MH+ 368, retention time 1.95 min, Method 5 Min Base

Phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate

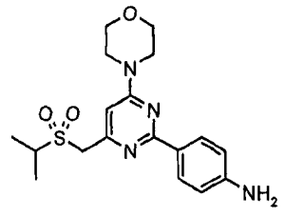


(4-{4-[(Isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)amine (1.5 g, 3.98 mmol) was dissolved in dioxane(10 mL). Sodium bicarbonate (503 mg, 5.98 mmol) was added, followed by phenyl chloroformate (0.502 mL, 3.98 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 10 mL DCM and 10 mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.30 (d, 6H), 3.45 (m, 1H), 3.65 (s, 8H), 4.40 (s, 2H), 6.78 (s, 1H), 7.20 (m, 3H), 7.38 (t, 2H), 7.56 (d, 2H), 8.22 (d, 2H), 10.37 (s, 1H)

LCMS Spectrum: MH+ 497, retention time 2.54 min, Method 5 Min Base

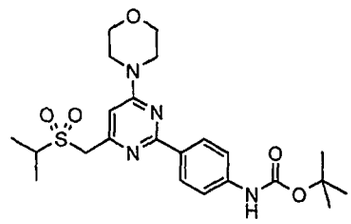
(4-{4-[(Isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)amine



Tert-butyl (4-{4-[(isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate (2.7 g, 5.67 mmol) was dissolved in DCM (20 mL) and trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 hours then diluted with DCM (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). Organic phase collected, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the desired material as a cream solid (2.1 g).

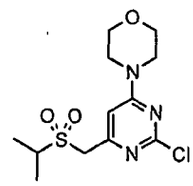
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.35 (d, 6H), 3.50 (m, 1H), 3.67 (m, 4H), 3.72 (m, 4H), 4.41 (s, 2H), 5.57 (s, 2H), 6.60 (d, 2H), 6.70 (s, 1H), 8.03 (d, 2H)
LCMS Spectrum: MH+ 377, retention time 1.61 min, Method 5 Min Base

Tert-butyl (4-{4-[(isopropylsulfonyl)methyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate



4-{2-Chloro-6-[(isopropylsulfonyl)methyl]pyrimidin-4-yl}morpholine (1.5 g, 4.69 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (36 mL). {4-[(*Tert*-butoxycarbonyl)amino]phenyl}boronic acid (1.67 g, 7.04 mmol), 2M sodium carbonate solution (12 mL) and dichlorobis(triphenylphosphine) palladium catalyst (165 mg, 0.23 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water (20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude oil was dissolved in DCM and filtered to remove insoluble material. A brown solid precipitated from the filtrates and the filtrates were filtered again. The solid was analysed and found to be the desired material (1.9 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.36 (d, 6H), 1.50 (s, 9H), 3.52 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.83 (s, 1H), 7.57 (d, 2H), 8.22 (d, 2H), 9.56 (s, 1H)
LCMS Spectrum: MH+ 477, retention time 2.50 min, Method 5 Min Base

4-{2-Chloro-6-[(phenylsulfonyl)methyl]pyrimidin-4-yl}morpholine



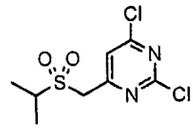
2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine (2.65 g, 9.85 mmol) was dissolved in DCM (50 mL) and stirred (under nitrogen) at -5°C. Triethylamine (1.5 mL, 10.84 mmol) was

added to give a clear brown solution. Morpholine (0.86 mL, 9.85 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material (2.5 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.30 (d, 6H), 3.42 (m, 1H), 3.62 (s, 4H), 3.68 (m, 4H), 4.42 (s, 2H), 6.95 (s, 1H)

LCMS Spectrum: MH+ 320, retention time 1.51 min, Method 5 Min Base

2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine

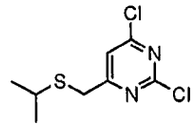


2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine (6.2 g, 26.16 mmol) was dissolved in DCM (100 mL) and 3,5-dichlorobenzenecarboperoxoic acid (13.5 g, 78.4 mmol) was added portionwise over 10 minutes. The reaction was stirred at room temperature for 4 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a cream solid. Purification by normal phase chromatography, eluting with 0-50% ethyl acetate in iso-hexane gave the desired material as a cream solid (5.3 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.25 (d, 6H), 3.43 (m, 1H), 4.77 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: M-H 267, retention time 1.64 min, Method 5 Min Basic

2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine



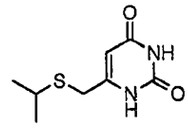
6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (8 g, 40 mmol) was added to phosphorus oxychloride (100 mL) and the mixture heated to reflux for 16 hours. The reaction

was then cooled to room temperature and the excess phosphorus oxychloride was removed *in vacuo*,. The residue was azeotroped with toluene (2 x 100 mL) and dissolved in DCM. This mixture was then poured slowly onto ice (1 L) and stirred for 20 minutes, then extracted with DCM (3 x 500 mL) The extracts were combined, dried over magnesium sulphate, then concentrated *in vacuo* to give the desired material as a brown oil (6.5 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 (d, 6H), 2.96 (m, 1H), 3.85 (s, 2H), 7.82 (s, 1H)

LCMS Spectrum: Retention time 2.51 min, Method 5 Min Basic

6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione



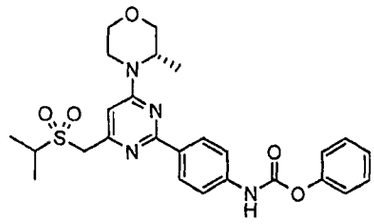
6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (8 g, 50 mmol) was dissolved in acetonitrile (200 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (13 mL, 87.19 mmol) was added and the reaction stirred at room temperature for 15 minutes. Isopropyl mercaptan (8.1 mL, 87.19 mmol) was then added and the reaction stirred at room temperature for a further 2 hours. Solvent removed *in vacuo* and the resulting brown oil was dissolved in DCM and washed with water. Organic phase dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resulting oil was chromatographed on silica, eluting with 0-10% methanol in DCM to give the desired material as a white solid (8 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 (d, 6H), 2.90 (m, 1H), 3.42 (s, 2H), 5.49 (s, 1H), 10.82 (s, 1H), 10.94 (s, 1H)

LCMS Spectrum: M-H 199, retention time 0.63 min, Method 5 Min Basic

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

Phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate

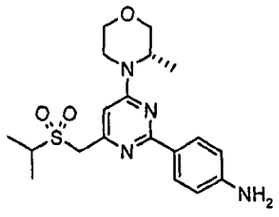


(4-{4-[(Isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)amine (1.5g, 3.84 mmol) was dissolved in dioxane(10 mL). Sodium bicarbonate (485 mg, 5.76 mmol) was added, followed by phenyl chloroformate (0.484 mL, 3.84 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 10mL DCM and 10mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (1.8 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.18 (d, 3H), 1.30 (m, 6H), 3.17 (m, 2H), 3.44 (m, 2H), 3.58 (m, 1H), 3.70 (d, 1H), 3.92 (m, 1H), 4.12 (d, 1H), 4.41 (s, 2H), 6.74 (s, 1H), 7.20 (m, 3H), 7.38 (t, 2H), 7.56 (d, 2H), 8.22 (d, 2H), 10.37 (s, 1H)

LCMS Spectrum: MH+ 511, retention time 2.67 min, Method 5 Min Base

(4-{4-[(Isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)amine



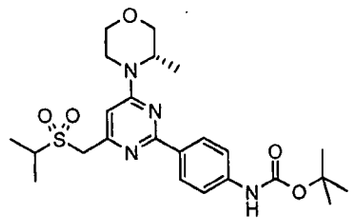
Tert-butyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate (3.2 g, 6.52 mmol) was dissolved in DCM (20 mL) and trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 hours then diluted with DCM (20 mL) and washed with saturated aqueous sodium bicarbonate (20

mL). Organic phase collected, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the desired material as a cream solid (2.4 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 1.35 (m, 6H), 3.19 (m, 1H), 3.49 (m, 2H), 3.64 (m, 1H), 3.77 (d, 1H), 3.97 (m, 1H), 4.14 (d, 1H), 4.41 (s, 2H), 4.45 (m, 1H), 5.56 (s, 2H), 6.60 (d, 2H), 6.66 (s, 1H), 8.02 (d, 2H)

LCMS Spectrum: MH+ 391, retention time 1.84 min, Method 5 Min Base

Tert-butyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate

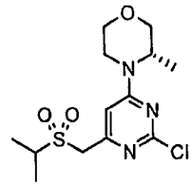


(3*S*)-4-{2-Chloro-6-[(isopropylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine (2.0 g, 5.99 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (16 mL). {4-[(T*ert*-butoxycarbonyl)amino]phenyl}boronic acid (2.13 g, 8.99 mmol), 2M sodium carbonate solution (8 mL) and dichlorobis(triphenylphosphine) palladium catalyst (211 mg, 0.30 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water (20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a brown solid (3.2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.36 (m, 6H), 1.50 (s, 9H), 3.24 (m, 4H), 3.51 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.18 (d, 1H), 4.47 (s, 2H), 6.79 (s, 1H), 7.57 (d, 2H), 8.21 (d, 2H), 9.55 (s, 1H)

LCMS Spectrum: MH+ 491, retention time 2.67 min, Method 5 Min Base

(3*S*)-4-{2-Chloro-6-[(isopropylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine



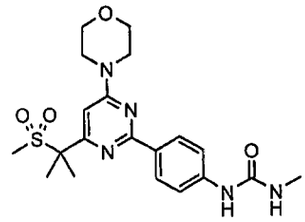
2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine (2.65 g, 9.85 mmol) was dissolved in DCM (50 mL) and stirred (under nitrogen) at -5°C. Triethylamine (1.5 mL, 10.84 mmol) was added to give a clear brown solution. 3S-3-Methyl morpholine (997 mg, 9.85 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 1.31 (d, 6H), 3.22 (m, 1H), 3.43 (m, 2H), 3.60 (m, 1H), 3.74 (d, 1H), 3.98 (m, 1H), 4.30 (s, 1H), 4.43 (s, 2H), 6.91 (s, 1H)

LCMS Spectrum: MH+ 332, retention time 1.70 min, Method 5 Min Base

Example 21:

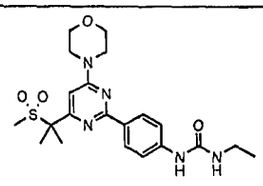
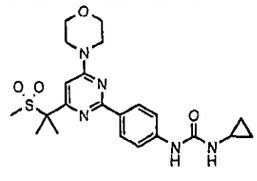
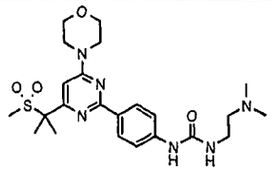
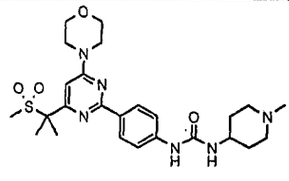
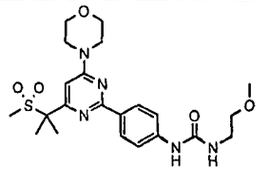
3-Methyl-1-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea

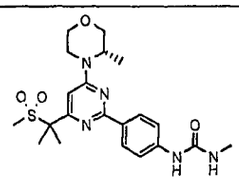
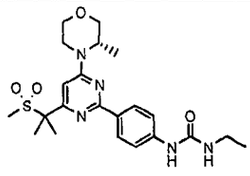
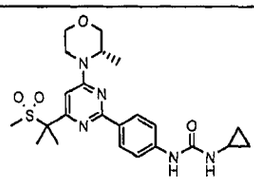
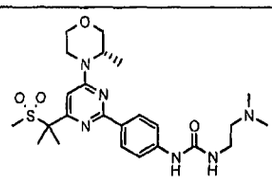
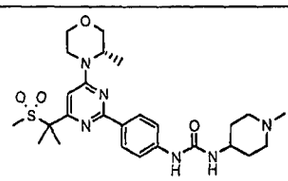
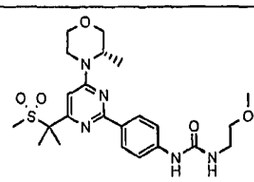


Phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate (116 mg, 0.22 mmol) was dissolved in DMF (3 mL). Triethylamine (0.098 mL, 0.7 mmol) was added followed by methylamine (2M in THF, 0.6 mL, 1.17 mmol). The mixture was stirred at 50°C for 1 hour. The reaction was concentrated and purified by preparative HPLC to give the desired material as a white solid (54 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.77 (s, 6H), 2.66 (d, 3H), 3.04 (s, 3H), 3.73 (s, 8H), 6.06 (m, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.74 (s, 1H)
LCMS Spectrum: MH+ 434, retention time 1.64 min, Method 5 Min Base

The following compounds were prepared in analogous fashion from either phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate or phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
21a		1-ethyl-3-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	448	1.78
21b		3-cyclopropyl-1-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	460	1.91
21c		3-(2-dimethylaminoethyl)-1-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	491	1.71
21d		3-(1-methyl-4-piperidyl)-1-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	517	1.75
21e		3-(2-methoxyethyl)-1-[4-[4-(2-methylsulfonylpropan-2-yl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	478	1.72

Example	Structure	NAME	LCMS MH+	Retention time (min)
21f		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	448	1.76
21g		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	462	1.92
21h		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	474	1.93
21i		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	505	1.83
21j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1-methyl-4-piperidyl)urea	531	1.86
21k		3-(2-methoxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-l)pyrimidin-2-yl]phenyl]urea	492	1.84

Example 21a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.07 (t, 3H), 1.77 (s, 6H), 3.04 (s, 3H), 3.13 (m, 2H), 3.73 (s, 8H), 6.15 (t, 1H), 6.79 (s, 1H), 7.50 (d, 2H), 8.24 (d, 2H), 8.66 (s, 1H)

Example 21b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.77 (s, 6H), 2.57 (m, 1H), 3.04 (s, 3H), 3.73 (s, 8H), 6.43 (d, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.54 (s, 1H)

Example 21c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.77 (s, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.04 (s, 3H), 3.19 (m, 2H), 3.73 (s, 8H), 6.15 (t, 1H), 6.79 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.90 (s, 1H)

Example 21d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.40 (m, 2H), 1.77 (s, 6H), 2.03 (m, 2H), 2.17 (s, 3H), 2.45 (m, 2H), 2.67 (m, 2H), 3.04 (s, 3H), 3.47 (m, 1H), 3.73 (s, 8H), 6.18 (d, 1H), 6.79 (s, 1H), 7.48 (d, 2H), 8.24 (d, 2H), 8.57 (s, 1H)

Example 21e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.77 (s, 6H), 3.04 (s, 3H), 3.27 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.73 (s, 8H), 6.26 (t, 1H), 6.79 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.79 (s, 1H)

Example 21f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.16 (d, 3H), 1.70 (s, 6H), 2.59 (d, 3H), 2.96 (s, 3H), 3.16 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.70 (d, 1H), 3.91 (m, 1H), 4.16 (d, 1H), 4.53 (s, 1H), 5.99 (m, 1H), 6.66 (s, 1H), 7.44 (d, 2H), 8.16 (d, 2H), 8.67 (s, 1H)

Example 21g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.00 (t, 3H), 1.16 (d, 3H), 1.70 (d, 6H), 2.96 (s, 3H), 3.06 (m, 2H), 3.16 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.70 (d, 1H), 3.91 (m, 1H), 4.16 (d, 1H), 4.52 (s, 1H), 6.09 (t, 1H), 6.67 (s, 1H), 7.43 (d, 2H), 8.16 (d, 2H), 8.59 (s, 1H)

Example 21h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.23 (d, 3H), 1.78 (d, 6H), 2.56 (m, 1H), 3.03 (s, 3H), 3.23 (m, 1H), 3.50 (m, 1H), 3.65 (m, 1H), 3.78 (d, 1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.60 (s, 1H), 6.43 (d, 1H), 6.74 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.54 (s, 1H)

Example 21i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.23 (d, 3H), 1.77 (d, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.03 (s, 3H), 3.19 (m, 3H), 3.49 (m, 1H), 3.65 (m, 1H), 3.77 (d, 1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.59 (s, 1H), 6.16 (t, 1H), 6.73 (s, 1H), 7.49 (d, 2H), 8.23 (d, 2H), 8.90 (s, 1H)

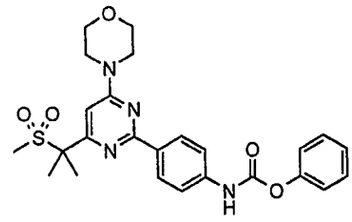
Example 21j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (s, 3H), 1.41 (m, 2H), 1.78 (d, 6H), 1.81 (m, 2H), 2.02 (t, 2H), 2.16 (s, 3H), 2.64 (m, 2H), 3.03 (s, 3H), 3.22 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.61 (s, 1H), 6.18 (d, 1H), 6.74 (s, 1H), 7.48 (d, 2H), 8.23 (d, 2H), 8.57 (s, 1H)

Example 21k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.23 (d, 3H), 1.77 (d, 6H), 3.03 (s, 3H), 3.21 (m, 2H), 3.27 (m, 1H), 3.40 (t, 2H), 3.48 (m, 2H), 3.65 (m, 1H), 3.72 (d, 1H), 3.97 (m, 1H), 4.23 (d, 1H), 4.60 (s, 1H), 6.26 (t, 1H), 6.74 (s, 1H), 6.86 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.78 (s, 1H)

Test(a): Example(21) 0.05 μM; Example(21a) 0.73 μM; Example(21b) 0.36 μM; Example(21c) 0.48 μM; Example(21d) 0.27 μM; Example(21e) 1 μM; Example(21f) 0.017 μM; Example(21g) 0.02 μM; Example(21h) 0.028 μM; Example(21i) 0.076 μM; Example(21j) 0.51 μM; Example(21k) 0.31 μM.

The preparations of phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate and phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate are described below.

Phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate

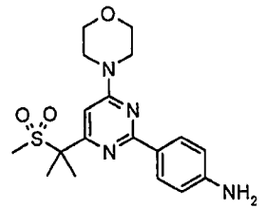


(4-{4-[1-Methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)amine (1.5 g, 3.98 mmol) was dissolved in dioxane (15 mL). Sodium bicarbonate (503 mg, 5.98 mmol) was added, followed by phenyl chloroformate (0.502 mL, 3.98 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 20mL DCM and 20mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (700 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.20 (d, 3H), 3.17 (m, 1H), 3.48 (m, 1H), 3.63 (m, 1H), 3.76 (d, 1H), 3.97 (m ,1H), 4.11 (d, 1H), 4.37 (s, 1H), 4.72 (s, 2H), 6.65 (s, 1H), 7.27 (m ,3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 2H), 7.90 (d, 2H), 10.38 (s, 1H)

LCMS Spectrum: MH+ 545, retention time 2.7 min, Method 5 Min Base

(4-{4-[1-Methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)amine

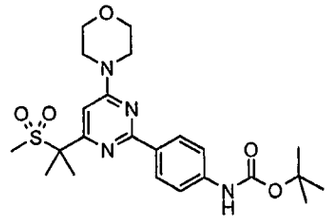


Tert-butyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate (2.6 g, 5.46 mmol) was dissolved in DCM (20 mL) and trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred at room temperature for 2 hours then diluted with DCM (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). Organic phase collected, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the desired material as a cream solid (2.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.75 (s, 6H), 3.03 (s, 3H), 3.71 (s, 8H), 5.56 (s, 2H), 6.61 (d, 2H), 6.69 (s, 1H), 8.07 (d, 2H)

LCMS Spectrum: MH+ 377, retention time 1.84 min, Method 5 Min Base

Tert-butyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-morpholin-4-ylpyrimidin-2-yl}phenyl)carbamate



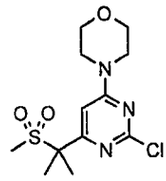
(3*S*)-4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine (1.75 g, 5.47 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (18 mL). *Tert*-butyl [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (2.62 g, 8.2 mmol), 2M sodium carbonate solution (8 mL) and dichlorobis(triphenylphosphine) palladium catalyst (192 mg, 0.27 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water

(20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-30% ethyl acetate in DCM to give the desired material as a white solid (2.6 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.50 (s, 9H), 1.77 (s, 6H), 3.04 (s, 3H), 3.73 (s, 8H), 6.80 (s, 1H), 7.57 (d, 2H), 8.26 (d, 2H), 9.54 (s, 1H)

LCMS Spectrum: MH+ 477, retention time 2.66 min, Method 5 Min Base

4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}morpholine

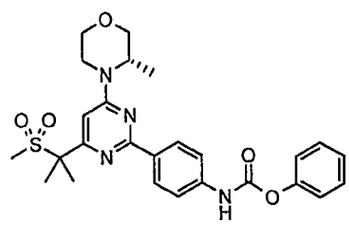


4-{2-Chloro-6-[(methylsulfonyl)methyl]pyrimidin-4-yl}morpholine (2.9 g, 9.94 mmol) was dissolved in DMF (20 mL) and the reaction cooled to -5°C. Sodium t-butoxide (956 mg, 9.94 mmol) was added to the reaction, followed by iodomethane (0.6 mL, 9.94 mmol), maintaining the temperature at -5°C. A second equivalent of sodium t-butoxide (956 mg, 9.94 mmol) and iodomethane (0.6 mL, 9.94 mmol) were then added and the reaction stirred at -5°C for 1 hour, then at room temperature for 4 hours. DCM (20 mL) was added and the reaction washed with 2M aqueous HCl (20 mL). The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (1.7 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.68 (s, 6H), 2.99 (s, 3H), 3.67 (s, 8H), 6.91 (s, 1H)

LCMS Spectrum: MH+ 320, retention time 1.67 min, Method 5 Min Base

Phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate

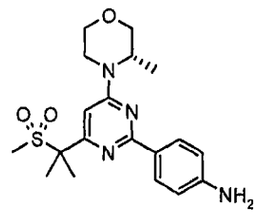


(4-{4-[1-Methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)amine (3.6 g, 8.77 mmol) was dissolved in dioxane (20 mL). Sodium bicarbonate (1.1 g, 13.15 mmol) was added, followed by phenyl chloroformate (1.1 mL, 8.77 mmol) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*, and the resultant oil partitioned between 20 mL DCM and 20 mL water. The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo.* The cream solid obtained was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material as a white solid (2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (d, 3H), 1.78 (d, 6H), 3.04 (s, 3H), 3.24 (m, 1H), 3.51 (m, 1H), 3.65 (m, 1H), 3.78 (d, 1H), 3.96 (m, 1H), 4.25 (d, 1H), 4.61 (s, 1H), 6.77 (s, 1H), 7.27 (m, 3H), 7.45 (m, 2H), 7.64 (d, 2H), 8.34 (d, 2H), 10.43 (s, 1H)

LCMS Spectrum: MH+ 511, retention time 2.7 min, Method 5 Min Base

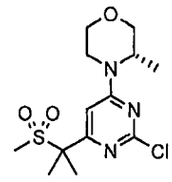
(4-{4-[1-Methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)amine



(3*S*)-4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine (2.2 g, 6.59 mmol) was dissolved in a solution of 18% DMF in a mixture of 7:3:2 dimethoxyethane:water:ethanol (18 mL). [4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (2.17 g, 9.89 mmol), 2M sodium carbonate solution (8 mL) and dichlorobis(triphenylphosphine) palladium catalyst (232 mg, 0.33 mmol) were then added and the reaction refluxed at 90°C for 2 hours under a nitrogen atmosphere. The reaction was allowed to cool to room temp then partitioned between ethyl acetate (20 mL) and water (20 mL). The organics were dried over magnesium sulphate, filtered and concentrated *in vacuo.* The crude solid was chromatographed on silica, eluting with 0-10% methanol in DCM to give the desired material as a brown oil (3.6 g).

LCMS Spectrum: MH+ 389, retention time 1.00 min, Method 5 Min Base

(3*S*)-4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine



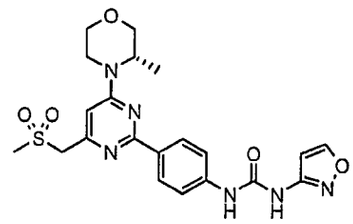
(3*S*)-4-{2-Chloro-6-[(methylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine (2.1 g, 6.87 mmol) was dissolved in DMF (20 mL) and the reaction cooled to -5°C. Sodium t-butoxide (650 mg, 6.87 mmol) was added to the reaction, followed by iodomethane (0.4 mL, 6.87 mmol), maintaining the temperature at -5°C. A second equivalent of sodium t-butoxide (650 mg, 6.87 mmol) and iodomethane (0.4 mL, 6.87 mmol) were then added and the reaction stirred at -5°C for 1 hour, then at room temperature for 4 hours. DCM (20 mL) was added and the reaction washed with 2M aqueous hydrochloric acid (20 mL). The organic phase was dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material (2.2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 (d, 3H), 1.68 (s, 6H), 2.74 (s, 3H), 3.21 (m, 1H), 3.45 (m, 1H), 3.59 (m, 1H), 3.73 (d, 1H), 3.94 (m, 1H), 4.07 (d, 1H), 4.45 (s, 1H), 6.86 (s, 1H)

LCMS Spectrum: MH+ 334, retention time 1.85 min, Method 5 Min Base

Example 22:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea



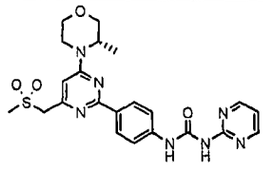
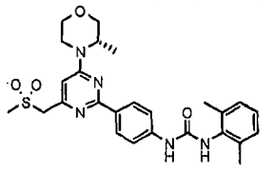
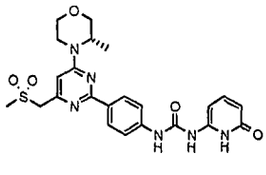
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (170 mg, 0.35 mmol) was dissolved in DMF (1.5 mL). Triethylamine (0.147 mL, 1.06 mmol) was added. 1,2-oxazol-3-amine (198 mg, 2.35 mmol) was added and

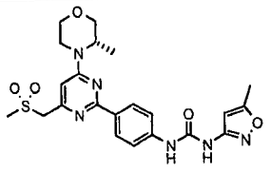
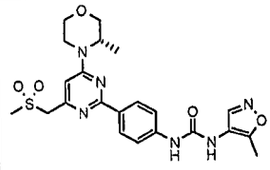
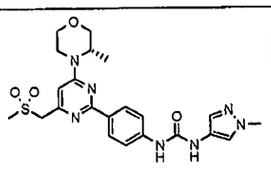
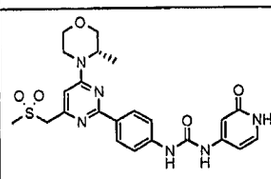
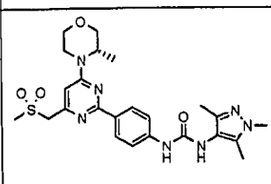
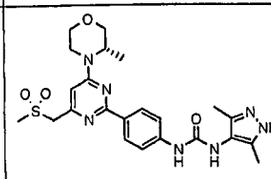
the reaction stirred at 60°C for 2 hours. The reaction was evaporated to dryness and purified by reverse phase chromatography to give the desired material as a white solid (81 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 - 1.26 (3H, m), 3.21 (3H, s), 3.23 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.01 (1H, m), 4.17 - 4.20 (1H, m), 4.50 (3H, s), 6.81 (1H, s), 6.87 (1H, d), 7.58 (2H, d), 8.29 (2H, d), 8.75 (1H, d), 9.07 (1H, s), 9.62 (1H, s)

LCMS Spectrum: MH+ 473, Retention Time 1.63min, Method Monitor Acid

The following compounds were prepared in an analogous manner from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention Time (min)
22a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-pyrimidin-2-yl-urea	484	1.60
22b		1-(2,6-dimethylphenyl)-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	510	1.98
22c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(6-oxo-1H-pyridin-2-yl)urea	499	1.35

Example	Structure	NAME	LCMS MH+	Retention Time (min)
22d		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea	487	1.72
22e		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-4-yl)urea	487	1.46
22f		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	486	1.27
22g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(2-oxo-1H-pyridin-4-yl)urea	499	1.21
22h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-(1,3,5-trimethylpyrazol-4-yl)urea	514	1.29
22i		1-(3,5-dimethyl-1H-pyrazol-4-yl)-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	500	1.21

Example 22a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.22 (3H, s), 3.24 - 3.26 (1H, m), 3.48 - 3.55 (1H, m), 3.65 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.02 (1H, m), 4.20 (1H, d), 4.51 (3H, s), 6.82 (1H, s), 7.16 (1H, t), 7.71 - 7.73 (2H, m), 8.30 - 8.33 (2H, m), 8.70 (2H, d), 10.21 (1H, s), 11.63 (1H, s)

Example 22b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 - 1.26 (3H, m), 2.23 (6H, s), 3.21 (3H, s), 3.23 (1H, d), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 - 4.20 (1H, m), 4.49 (3H, s), 6.79 (1H, s), 7.08 (3H, d), 7.55 - 7.59 (2H, m), 7.78 (1H, s), 8.23 - 8.27 (2H, m), 9.00 (1H, s)

Example 22c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.22 (3H, s), 3.24 (1H, d), 3.48 - 3.55 (1H, m), 3.64 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.02 (1H, m), 4.19 (1H, d), 4.51 (3H, s), 6.24 (1H, d), 6.81 (1H, s), 7.56 (1H, t), 7.70 (2H, d), 8.28 - 8.30 (2H, m), 9.28 (1H, s)

Example 22d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.38 (3H, d), 3.21 (3H, s), 3.23 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.79 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.50 (3H, s), 6.57 (1H, d), 6.81 (1H, s), 7.56 (2H, d), 8.27 - 8.29 (2H, m), 9.05 (1H, d), 9.46 (1H, s)

Example 22e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.37 (3H, s), 3.21 (3H, s), 3.22 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, s), 4.49 (3H, s), 6.80 (1H, s), 7.55 - 7.58 (2H, m), 8.18 (1H, s), 8.25 - 8.27 (2H, m), 8.67 (1H, d), 8.99 (1H, s)

Example 22f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 3.21 (3H, s), 3.22 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.77-3.30 (1H, m) 3.79 (3H, s), 3.97 - 4.01 (1H, m), 4.18 (1H, s), 4.49 (3H, s), 6.79 (1H, s), 7.38 (1H, d), 7.53 - 7.57 (2H, m), 7.76 (1H, s), 8.23 - 8.26 (2H, m), 8.39 (1H, s), 8.84 (1H, s)

Example 22g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 3.21 (3H, s), 3.23 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.50 (3H, s), 6.25 - 6.27 (1H, m), 6.46 (1H, d), 6.81 (1H, s), 7.25 (1H, d), 7.55 - 7.57 (2H, m), 8.27 - 8.29 (2H, m), 8.92 (1H, s), 9.05 (1H, s), 11.04 (1H, s)

Example 22h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.01 (3H, s), 2.10 (3H, s), 3.21 (3H, s), 3.25 (1H, d), 3.47 - 3.54 (1H, m), 3.64 (3H, s), 3.66 - 3.70 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.48 (1H, s), 7.53 - 7.57 (2H, m), 8.22 - 8.24 (2H, m), 8.80 (1H, s)

Example 22i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.03 (3H, s), 2.09 (3H, s), 3.21 (3H, s), 3.25 (1H, d), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.44 (1H, s), 7.55 (2H, d), 8.23 (2H, d), 8.81 (1H, s), 12.04 (1H, s)

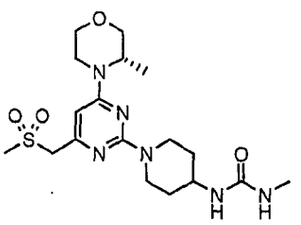
Test(a): Example(22a) 0.06 μM; Example(22b) 1.6 μM; Example(22d) 0.0048 μM; Example(22e) 0.56 μM; Example(22f) 0.091 μM; Example(22g) 0.0045 μM; Example(22h) 1.5 μM; Example(22i) 4.3 μM.

Test(c): Example(22c) 0.21 μM.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate was described earlier

Example 23:

3-Methyl-1-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]urea

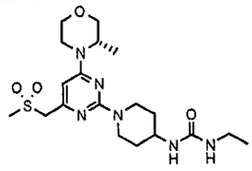


Phenyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate (220 mg, 0.45 mmol) was dissolved in DMF (3 mL). Triethylamine (0.188 mL, 1.35mmol) was added, followed by 2M methylamine in THF (1.2 mL, 2.25 mmol). The mixture was stirred at 50°C for 3 hours. The reaction mixture was evaporated to dryness and purified by normal phase chromatography using a 0-6% methanol in DCM gradient to give an oil which upon trituration with diethyl ether gave the desired material as a white solid (153 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.20 - 1.27 (2H, m), 1.77 (2H, d), 2.54 (3H, d), 2.99 (2H, d), 3.08 (1H, d), 3.12 (3H, s), 3.37 - 3.40 (1H, m), 3.43 (1H, d), 3.57 (1H, d), 3.71 (1H, d), 3.91 (1H, d), 3.94 (1H, d), 4.23 (2H, s), 4.26 (1H, d), 4.42 (2H, d), 5.57 (1H, q), 5.83 (1H, d), 6.14 (1H, s)

LCMS Spectrum: MH+ 427, Retention Time 0.85min, Method 5 Minute Acid

The following compound was prepared in an analogous from phenyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate and the appropriate amine.

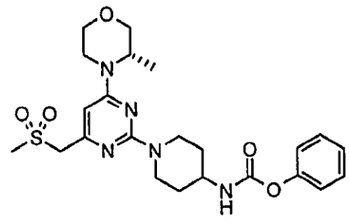
Example	Structure	NAME	LCMS MH+	Retention Time (min)	Notes
23a		1-ethyl-3-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl) pyrimidin-2-yl]-4-piperidyl]urea	441	1.03	Purified by reverse phase chromatography

Example 23a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.98 (3H, t), 1.13 - 1.18 (3H, m), 1.20 - 1.26 (2H, m), 1.77 (2H, d), 2.97 - 3.03 (4H, m), 3.05 - 3.10 (1H, m), 3.12 (3H, s), 3.38 - 3.45 (1H, m), 3.55 - 3.59 (1H, m), 3.63 (1H, t), 3.71 (1H, d), 3.92 (1H, d), 3.92 (1H, d), 4.23 (2H, s), 4.27 (1H, m), 4.41 (2H, d), 5.64 (1H, t), 5.77 (1H, d), 6.14 (1H, s)

Test(a): Example(23) 5.6 μM; Example(23a) 3.7 μM.

The preparation of phenyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate is described below.

Phenyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate



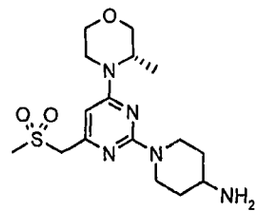
230

1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]piperidin-4-amine (500 mg, 1.35 mmol) was dissolved in dioxane (10 mL). Sodium bicarbonate (171 mg, 1.50 mmol) was added. Then phenyl chloroformate (0.171 mL, 1.35 mmol) was added dropwise over 2 minutes. The slurry was stirred at RT for 3 hours. Phenyl chloroformate (0.021 mL, 0.27 mmol) and sodium bicarbonate (21 mg, 0.12 mmol) were added. Stirring at room temp was continued for 1 hour and the reaction mixture evaporated to dryness and partitioned between water (10 mL) and ethyl acetate (10 mL). The water was extracted with a second portion of ethyl acetate (10 mL). The combined organics were dried over magnesium sulfate and evaporated to give the desired material as a foam (701 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.34 - 1.44 (2H, m), 1.86 (2H, d), 2.99 (2H, d), 3.11 (1H, d), 3.13 (3H, s), 3.40 - 3.46 (1H, m), 3.60 (2H, d), 3.72 (2H, d), 3.91 - 3.96 (2H, m), 4.25 (2H, s), 4.28 (1H, m), 4.52 (2H, d), 6.16 (1H, s), 7.10 (2H, d), 7.20 (1H, t), 7.38 (2H, t), 7.76 (1H, d)

LCMS Spectrum: MH+ 490, Retention Time 1.58min, Method Monitor Acid

1-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]piperidin-4-amine



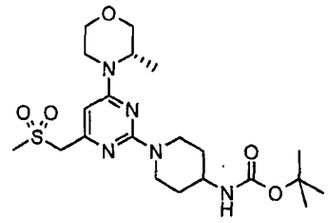
tert-Butyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate (1.30 g, 2.77 mmol) was dissolved in methanol (10 mL). 4M Hydrochloric acid in dioxane (10 mL) was added. The reaction was stirred at RT for 3 hours. Saturated aqueous sodium bicarbonate was added until pH7 was reached and the organic solvents were removed *in vacuo*. Water (20 mL) was added and the product was extracted into ethyl acetate (50 mL). The aqueous layer was extracted with a second portion of ethyl acetate (25 mL). The combined organics were evaporated to give the desired material as a yellow foam (1.05 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.69 - 1.73 (2H, m), 2.75 - 2.80 (1H, m), 2.87 - 2.94 (2H, m), 3.07 (1H, d), 3.11 (1H,m), 3.12 (3H, s), 3.39 - 3.45 (1H,

m), 3.55 - 3.62 (1H, m), 3.69 - 3.73 (1H, m), 3.90 - 3.94 (2H, m), 4.22 (2H, s), 4.26 (1H, s), 4.43 (1H, s), 4.46 (1H, d), 6.12 (1H, s)

LCMS Spectrum: MH+ 370, Retention Time 0.48min, Method Monitor Acid

tert-Butyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.00 g, 3.27 mmol), potassium carbonate (498 mg, 3.60 mmol) and tert-butyl N-(4-piperidyl)carbamate (721 mg, 3.60 mmol). Acetonitrile (10 mL) was added and the mixture was heated under reflux for 4 hours. The acetonitrile was evaporated off to leave a white solid which was partitioned between water (40 mL) and ethyl acetate (60 mL). The phases were separated and the aqueous layer was extracted with a second portion of ethyl acetate (40 mL). The combined organics were evaporated to dryness to give the desired material as a cream solid (1.32 g).

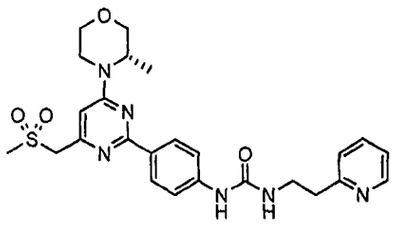
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.16 - 1.18 (3H, m), 1.23 - 1.31 (2H, m), 1.39 (9H, s), 1.74 (2H, d), 2.91 (2H, t), 3.06 - 3.09 (1H, m), 3.11 (3H, s), 3.39 - 3.44 (1H, m), 3.49 (1H, s), 3.55 - 3.59 (1H, m), 3.71 (1H, d), 3.90 (1H, d), 3.94 (1H, d), 4.23 (2H, s), 4.26 (1H, d), 4.50 (2H, d), 6.14 (1H, s), 6.78 (1H, d)

LCMS Spectrum: MH+ 470, Retention Time 1.39min, Method Monitor Acid

The preparation of 2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

Example 24:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(2-pyridin-2-ylethyl)urea

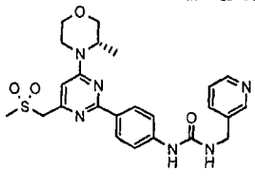


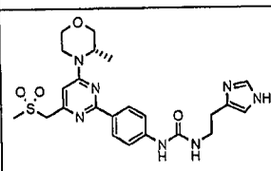
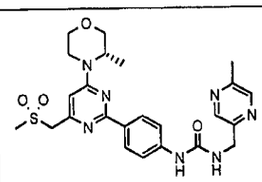
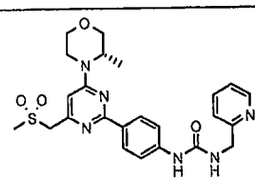
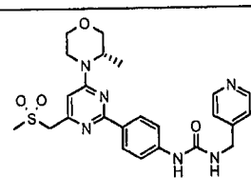
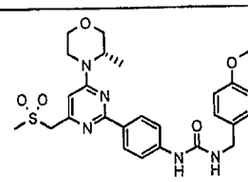
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (242mg, 0.50mmol) was dissolved in DMF (1.5 mL). Triethylamine (0.209 mL, 1.50mmol) was added. 2-Pyridin-2-ylethanamine (306 mg, 2.50 mmol) was added. The reaction was stirred at 40°C for 2 hours. The reaction mixture was purified by reverse phase chromatography to give the desired material as a white solid (239 mg).

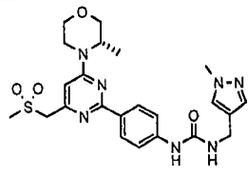
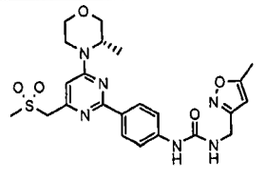
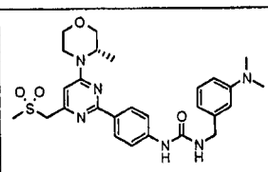
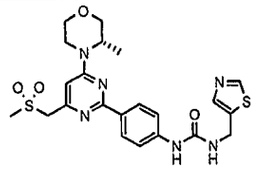
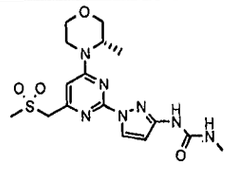
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.94 (2H, t), 3.21 (3H, s), 3.22 - 3.26 (1H, m), 3.48 (1H, d), 3.50 - 3.54 (2H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.26 (1H, t), 6.77 (1H, s), 7.22 - 7.26 (1H, m), 7.30 (1H, d), 7.47 - 7.51 (2H, m), 7.71 - 7.75 (1H, m), 8.19 - 8.22 (2H, m), 8.52 - 8.54 (1H, m), 8.77 (1H, s)

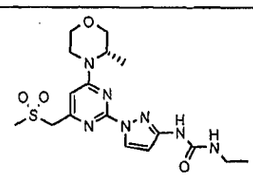
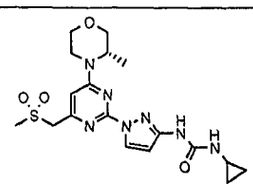
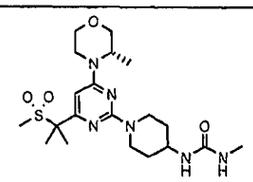
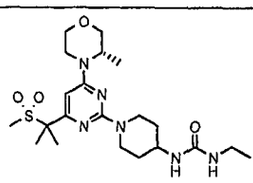
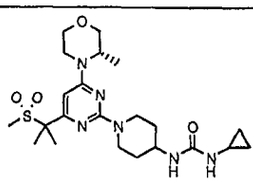
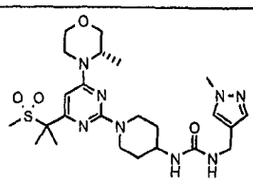
LCMS Spectrum: MH+ 511, Retention Time 1.67min, Method 5 Minute Basic

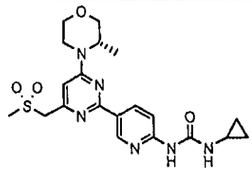
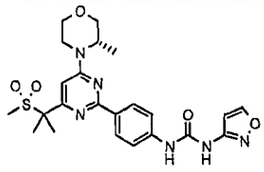
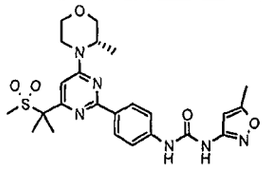
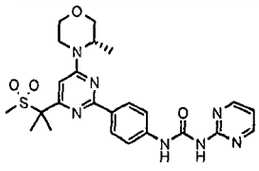
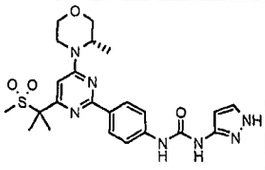
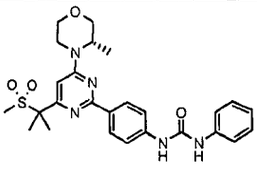
The following compounds were prepared in an analogous manner from the appropriate carbamate and the appropriate amine.

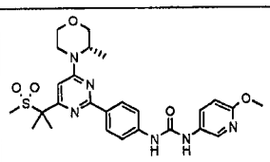
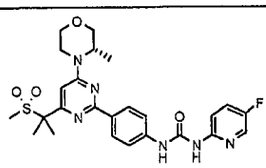
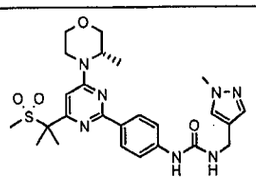
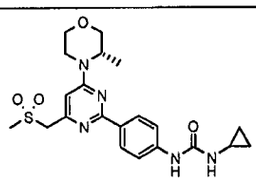
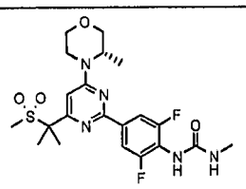
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(pyridin-3-ylmethyl)urea	497	1.56

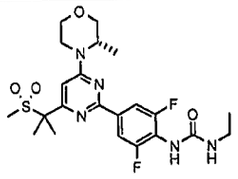
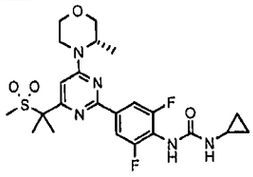
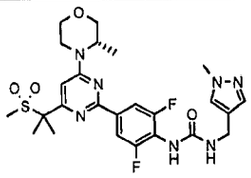
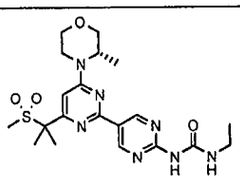
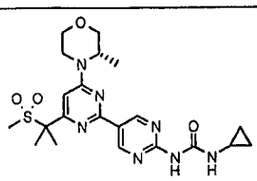
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24b		3-[2-(1H-imidazol-4-yl)ethyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	500	1.42
24c		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-[(5-methylpyrazin-2-yl)methyl]urea	512	1.52
24d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(pyridin-2-ylmethyl)urea	497	1.62
24e		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(pyridin-4-ylmethyl)urea	497	1.55
24f		3-[(4-methoxyphenyl)methyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	526	2.04

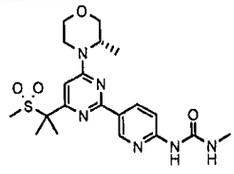
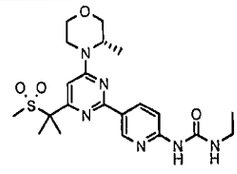
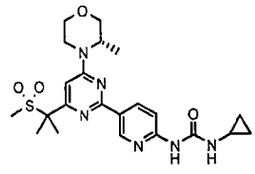
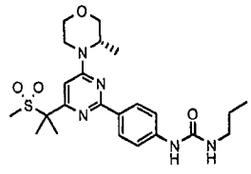
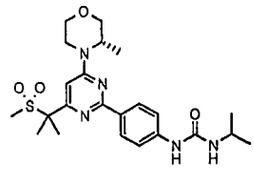
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	500	1.50
24h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-[(5-methyl-1,2-oxazol-3-yl)methyl]urea	501	1.73
24i		3-[(3-dimethylaminophenyl)methyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	539	2.15
24j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-5-ylmethyl)urea	503	1.58
24k		3-methyl-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]urea	410	2.18

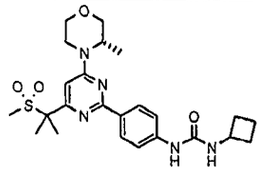
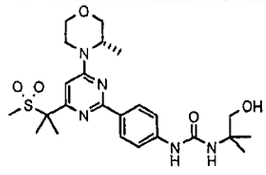
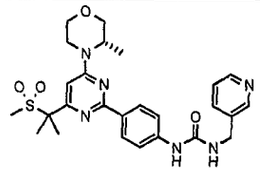
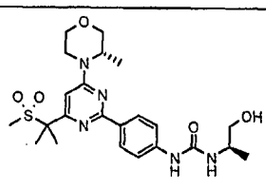
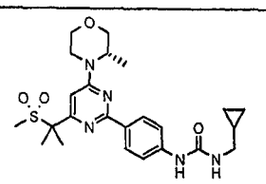
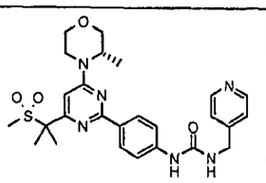
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24l		1-ethyl-3-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]urea	424	2.29
24m		3-cyclopropyl-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]urea	436	2.30
24n		3-methyl-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]urea	455	1.63
24o		1-ethyl-3-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]urea	469	1.76
24p		3-cyclopropyl-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]urea	481	1.80
24q		1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	535	1.69

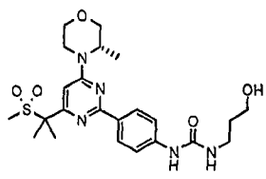
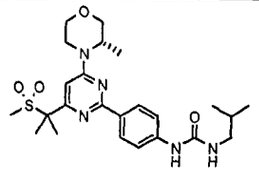
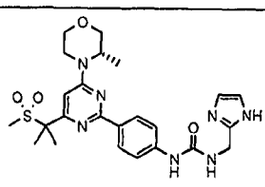
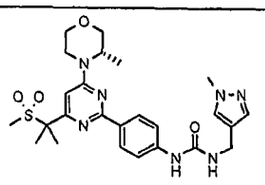
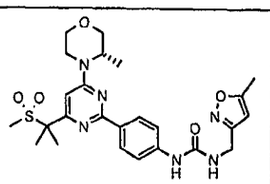
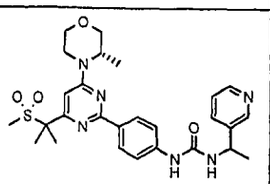
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24r		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-yl]urea	446	1.56
24s		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	501	1.64
24t		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea	515	2.22
24u		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-pyrimidin-2-yl-urea	512	2.10
24v		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1H-pyrazol-3-yl)urea	500	2.05
24w		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	510	2.40

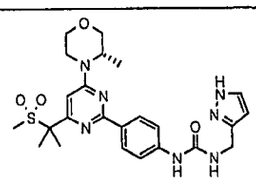
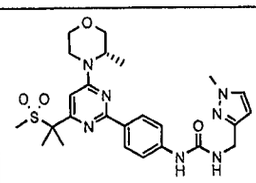
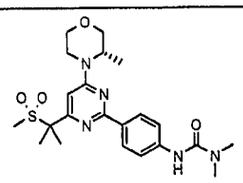
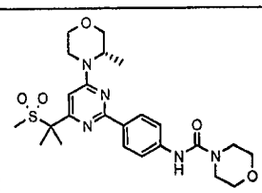
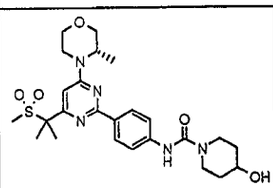
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24x		3-(6-methoxypyridin-3-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	541	2.14
24y		3-(5-fluoropyridin-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	529	2.39
24z		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-yl]-3-[(1-methylpyrazol-4-yl)methyl]urea	530	1.68
24aa		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	446	1.38
24ab		1-[2,6-difluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-methyl-urea	484	2.44

Example	Structure	NAME	LCMS MH+	Retention Time (min)
24ac		3-[2,6-difluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-1-ethyl-urea	498	2.56
24ad		3-cyclopropyl-1-[2,6-difluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	510	2.58
24ae		1-[2,6-difluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	564	2.46
24af		1-ethyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-yl]urea	464	1.86
24ag		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-yl]urea	476	1.88

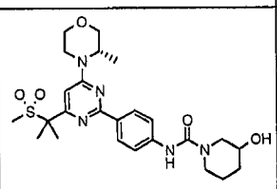
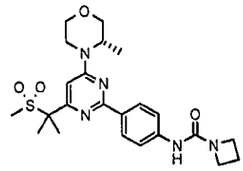
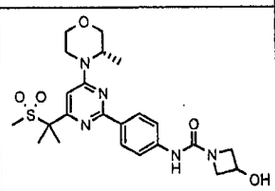
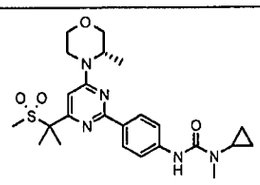
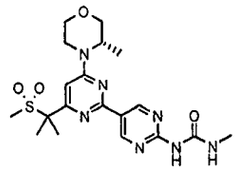
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24ah		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-yl]urea	449	1.77
24ai		1-ethyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-yl]urea	463	1.92
24aj		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-yl]urea	475	1.95
24ak		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-1-propyl-urea	476	1.92
24al		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	476	2.08

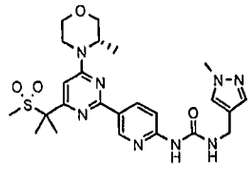
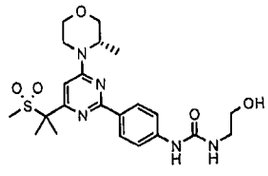
Example	Structure	NAME	LCMS MH+	Retention Time (min)
24am		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	488	2.15
24an		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	506	1.88
24ao		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(pyridin-3-ylmethyl)urea	525	1.83
24ap		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	492	1.71
24aq		3-(cyclopropylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	488	2.14
24ar		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(pyridin-4-ylmethyl)urea	525	1.81

Example	Structure	NAME	LCMS MH+	Retention Time (min)
24as		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	492	1.66
24at		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	490	2.24
24au		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	514	1.76
24av		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	528	1.93
24aw		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-1-[(5-methyl-1,2-oxazol-3-yl)methyl]urea	529	2.01
24ax		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1-pyridin-3-ylethyl)urea	539	1.91

Example	Structure	NAME	LCMS MH+	Retention Time (min)
24ay		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1H-pyrazol-3-ylmethyl)urea	514	1.75
24az		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-3-yl)methyl]urea	528	1.84
24ba		1,1-dimethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	462	1.87
24bb		N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]morpholine-4-carboxamide	504	1.84
24bc		4-hydroxy-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	518	1.68

1

Example	Structure	NAME	LCMS MH+	Retention Time (min)
24bd		3-hydroxy-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	518	1.75
24be		N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]azetidine-1-carboxamide	474	1.91
24bf		3-hydroxy-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]azetidine-1-carboxamide	490	1.62
24bg		1-cyclopropyl-1-methyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	488	2.18
24bh		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-yl]urea	450	1.70

Example	Structure	NAME	LCMS MH+	Retention Time (min)
24bi		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-yl]-3-[(1-methylpyrazol-4-yl)methyl]urea	529	1.75
24bj		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	478	1.61

Example 24a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.22 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.35 (2H, d), 4.48 (3H, s), 6.77 (1H,t), 6.78 (1H, s), 7.35 - 7.38 (1H, m), 7.52 (2H, d), 7.71 - 7.74 (1H, m), 8.22 (2H, d), 8.46 - 8.47 (1H, m), 8.55 (1H, d), 8.88 (1H, s)

Example 24b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.67 (2H, t), 3.21 (3H, s), 3.24 (1H, d), 3.34 - 3.39 (2H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.23 (1H, t), 6.77 (1H, s), 6.83 (1H, s), 7.49 - 7.51 (2H, m), 7.55 (1H, d), 8.21 (2H, s), 8.79 (1H, s), 11.81 (1H, s)

Example 24c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.48 (3H, s), 3.21 (3H, s), 3.22 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.45 (2H, d), 4.49 (3H, s), 6.78 (1H, s), 6.85 (1H, t), 7.50 - 7.53 (2H, m), 8.21 - 8.23 (2H, m), 8.49 - 8.51 (2H, m), 9.01 (1H, s)

Example 24d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.25 (1H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.44 (2H, d), 4.49 (3H, s), 6.78 (1H, s), 6.84 (1H, t), 7.27 - 7.30 (1H, m), 7.37 (1H, d), 7.51 - 7.55 (2H, m), 7.76 - 7.80 (1H, m), 8.22 (2H, d), 8.53 - 8.55 (1H, m), 9.04 (1H, s)

Example 24e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.23 - 3.26 (1H, m), 3.50 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 (1H, d), 4.00 - 4.19 (1H, m), 4.36 (2H, d), 4.48 (2H, s), 4.49 (1H, s), 6.78 (1H, s), 6.81 (1H, t), 7.30 - 7.31 (2H, m), 7.51 - 7.55 (2H, m), 8.21 - 8.24 (2H, m), 8.51 - 8.52 (2H, m), 8.96 (1H, s)

Example 24f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.24 (1H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.74 (3H, s), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.25 (2H, d), 4.48 - 4.48 (2H, m), 6.59 (1H, t), 6.78 (1H, s), 6.89 - 6.92 (2H, m), 7.23 - 7.26 (2H, m), 7.50 - 7.52 (2H, m), 8.20 - 8.23 (2H, m), 8.76 (1H, s)

Example 24g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.24 (1H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 - 4.01 (1H, m), 4.13 (2H, d), 4.19 (1H, s), 4.48 (2H, s), 4.49 (1H, s), 6.42 (1H, t), 6.77 (1H, s), 7.35 (1H, s), 7.49 - 7.51 (2H, m), 7.59 (1H, s), 8.20 - 8.22 (2H, m), 8.69 (1H, s)

Example 24h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.38 (3H, s), 3.25 (1H, d), 3.48 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.32 (2H, d), 4.48 (2H, s), 4.49 (1H, s), 6.16 (1H, d), 6.71 (1H, t), 6.78 (1H, s), 7.50 - 7.53 (2H, m), 8.21 - 8.24 (2H, m), 8.91 (1H, s)

Example 24i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.88 (6H, s), 3.21 (3H, s), 3.25 (1H, d), 3.50 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.25 (2H, d), 4.48 (1H, d), 4.49 (2H, s), 6.59 (2H, t), 6.63 (1H, d), 6.68 (1H, d), 6.78 (1H, s), 7.14 (1H, t), 7.51 (2H, d), 8.22 (2H, d), 8.77 (1H, s)

Example 24j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.21 (3H, d), 3.23 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, s), 4.49 (1H, d), 4.49 (2H, s), 4.54 (2H, d), 6.78 (1H, s), 6.80 (1H, t), 7.50 - 7.54 (2H, m), 7.79 (1H, d), 8.21 - 8.24 (2H, m), 8.87 (1H, s), 8.97 (1H, d)

Example 24k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.69 (3H, d), 3.19 (1H, d), 3.25 (3H, s), 3.48 (1H, d), 3.63 (1H, d), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.12 (1H, s), 4.44 (1H, m), 4.48 (2H, s), 6.49 (1H, d), 6.72 (1H, s), 6.78 (1H, s), 8.44 (1H, d), 9.30 (1H, s)

Example 24l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.08 (3H, t), 1.25 (3H, d), 3.12 - 3.19 (2H, m), 3.23 (3H, s), 3.24 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.12 (1H, s), 4.45 (1H, m), 4.48 (2H, s), 6.46 (1H, d), 6.78 (1H, s), 6.89 (1H, s), 8.44 (1H, d), 9.22 (1H, s)

Example 24m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.64 - 0.69 (2H, m), 1.25 (3H, d), 2.56 - 2.60 (1H, m), 3.22 (3H, s), 3.25 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.95 - 3.99 (1H, m), 4.12 (1H, s), 4.45 (1H, s), 4.48 (2H, s), 6.47 (1H, d), 6.78 (1H, s), 7.09 (1H, s), 8.44 (1H, d), 9.16 (1H, s)

Example 24n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.18 - 1.24 (2H, m), 1.64 (6H, s), 1.77 (2H, d), 2.54 (3H, d), 2.98 (3H, s), 3.02 (2H, t), 3.08 - 3.12 (1H, m), 3.39 - 3.45 (1H, m), 3.55 - 3.60 (1H, m), 3.62 - 3.66 (1H, m), 3.69 - 3.74 (1H, m), 3.90 - 3.93 (1H, m), 3.98 (1H, d), 4.36 (1H, d), 4.42 (2H, d), 5.57 (1H, q), 5.82 (1H, s), 6.14 (1H, s)

Example 24o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.98 (3H, t), 1.15 (3H, t), 1.20 - 1.27 (2H, m), 1.64 (6H, s), 1.77 (2H, d), 2.98 (4H, s), 3.00 - 3.02 (2H, m), 3.05 (1H, d), 3.08 - 3.12 (1H, m), 3.39 - 3.45 (1H, m), 3.55 - 3.60 (1H, m), 3.64 (1H, d), 3.71 (1H, d), 3.90 - 3.93 (1H, m), 3.99 (1H, d), 4.36 (1H, d), 4.42 (2H, d), 5.64 (1H, t), 5.76 (1H, d), 6.14 (1H, s)

Example 24p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.29 - 0.33 (2H, m), 0.53 - 0.57 (2H, m), 1.16 (3H, d), 1.31 (2H, m), 1.64 (6H, s), 1.76 (2H, d), 2.09 (3H, s), 2.37 - 2.43 (1H, m), 2.75 (1H, s), 2.98 (3H, s), 2.96 - 3.01 (1H, m), 3.05 - 3.12 (1H, m), 3.39 - 3.45 (1H, m), 3.55 - 3.59 (1H, m), 3.66 (1H, t), 3.71 (1H, d), 3.90 - 3.93 (1H, m), 3.99 (1H, d), 4.36 (1H, d), 4.44 (2H, d), 5.72 (1H, d), 5.97 (1H, d), 6.14 (1H, s)

Example 24q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.18 - 1.27 (2H, m), 1.64 (6H, s), 1.78 (2H, d), 2.98 (3H, s), 3.00 (1H, s), 3.03 (1H, d), 3.08 - 3.12 (1H, m), 3.39 - 3.45 (1H, m), 3.58 (1H, d), 3.65 (1H, t), 3.71 (1H, t), 3.78 (3H, s), 3.89 - 3.93 (1H, m), 4.00 (3H, d), 4.35 (1H, s), 4.41 (2H, d), 5.82 (1H, d), 5.89 (1H, t), 6.14 (1H, s), 7.28 (1H, s), 7.51 (1H, s)

Example 24r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.47 - 0.50 (2H, m), 0.66 - 0.71 (2H, m), 1.25 (3H, d), 2.61 - 2.67 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.49 (3H, d), 6.83 (1H, s), 7.54 (1H, d), 8.10 (1H, s), 8.48 - 8.51 (1H, m), 9.09 (1H, d), 9.32 (1H, s)

Example 24s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.78 (6H, s), 3.04 (3H, s), 3.19 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.25 (1H, d), 4.61 (1H, s), 6.77 (1H, s), 6.87 (1H, d), 7.58 (2H, d), 8.31 (2H, d), 8.75 (1H, d), 9.07 (1H, s), 9.61 (1H, s)

Example 24t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.78 (6H, d), 2.38 (3H, d), 3.04 (3H, s), 3.19 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 -

4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, d), 6.57 (1H, d), 6.77 (1H, s), 7.55 - 7.58 (2H, m), 8.31 (2H, d), 9.05 (1H, s), 9.46 (1H, s)

Example 24u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 - 3.25 (1H, m), 3.47 - 3.53 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.83 (3H, s), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.80 (1H, d), 7.57 (2H, d), 7.83 - 7.86 (1H, m), 8.21 (1H, d), 8.29 (2H, d), 8.62 (1H, s), 8.97 (1H, s)

Example 24v: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.79 (6H, d), 3.04 (3H, s), 3.19 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.25 (1H, d), 4.63 (1H, s), 5.42 (1H, s), 5.90 (1H, d), 6.78 (1H, s), 7.84 (2H, d), 8.06 (1H, d), 8.34 (2H, d), 9.84 (1H, s)

Example 24w: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.20 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.99 (1H, t), 7.30 (2H, d), 7.47 (2H, d), 7.57 (2H, d), 8.30 (2H, d), 8.71 (1H, s), 8.91 (1H, s)

Example 24x: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.20 - 3.25 (1H, m), 3.27 (3H, s),
3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.99 (1H, t), 7.30 (2H, d), 7.47 (2H, d), 7.57 (2H, d), 8.30 (2H, d), 8.71 (1H, s), 8.91 (1H, s)

Example 24y: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 - 3.26 (1H, m), 3.48 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.25 (1H, d), 4.62 (1H, s), 6.77 (1H, s), 7.61 (2H, d), 7.71 - 7.76 (1H, m), 7.78 - 7.82 (1H, m), 8.29 (1H, d), 8.32 (2H, d), 9.38 (1H, s), 9.87 (1H, s)

Example 24z: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.77 (6H, s), 3.00 (3H, s), 3.02 - 3.23 (1H, m), 3.46 - 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.80 (3H, s), 3.95 - 3.98 (1H, m), 4.28 (1H, m), 4.29 (2H, d), 4.63 (1H, s), 6.83 (1H, s), 7.39 (1H, s), 7.63 (1H, s), 9.25 (1H, t), 9.36 (2H, s), 10.09 (1H, s)

Example 24aa: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.41 - 0.45 (2H, m), 0.63 - 0.68 (2H, m), 1.25 (3H, d), 2.53 - 2.59 (1H, m), 3.21 (3H, s), 3.25 (1H, d), 3.47 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.44 (1H, d), 6.78 (1H, s), 7.52 (2H, d), 8.22 (2H, d), 8.55 (1H, s)

Example 24ab: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.79 (6H, d), 2.66 (3H, d), 3.02 (3H, s), 3.20 - 3.27 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.27 (1H, q), 6.86 (1H, s), 7.95 - 8.01 (2H, m), 8.14 (1H, s)

Example 24ac: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.25 (3H, d), 1.79 (6H, d), 3.01 (3H, s), 3.09 - 3.15 (2H, m), 3.20 - 3.27 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.36 (1H, t), 6.85 (1H, s), 7.95 - 8.01 (2H, m), 8.05 (1H, s)

Example 24ad: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.43 - 0.47 (2H, m), 0.63 - 0.67 (2H, m), 1.25 (3H, d), 1.79 (6H, d), 2.53 - 2.58 (1H, m), 3.02 (3H, s), 3.20 - 3.27 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.66 (1H, d), 6.86 (1H, s), 7.97 (2H, d), 8.00 (1H, s)

Example 24ae: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.79 (6H, d), 3.02 (3H, s), 3.20 - 3.27 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.81 (3H, s), 3.97 - 4.01 (1H, m), 4.12 (2H, d), 4.27 (1H, d), 4.63 (1H, s), 6.63 (1H, t), 6.86 (1H, s), 7.35 (1H, d), 7.58 (1H, s), 7.97 - 8.01 (2H, m), 8.09 (1H, s)

Example 24af: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (3H, t), 1.25 (3H, d), 1.78 (6H, d), 3.02 (3H, s), 3.20 - 3.24 (1H, m), 3.27-3.29 (2H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.28 (1H, d), 4.64 (1H, s), 6.84 (1H, s), 9.06 (1H, t), 9.39 (2H, s), 10.01 (1H, s)

Example 24ag: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.54 - 0.57 (2H, m), 0.70 - 0.74 (2H, m), 1.25 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.68 - 2.73 (1H, m), 3.02 (3H, s), 3.19 - 3.27 (1H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.28 (1H, d), 4.63 (1H, s), 6.84 (1H, s), 9.13 (1H, d), 9.38 (2H, s), 10.07 (1H, s)

Example 24ah: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.76 (3H, d), 3.03 (3H, s), 3.20 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.25 (1H, d), 4.62 (1H, s), 6.80 (1H, s), 7.42 - 7.45 (1H, m), 8.15 (1H, d), 8.52 - 8.55 (1H, m), 9.14 (1H, d), 9.48 (1H, s)

Example 24ai ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.12 (3H, t), 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 3.02 (3H, s), 3.19 - 3.23 (2H, m), 3.24 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.25 (1H, d), 4.61 (1H, s), 6.80 (1H, s), 7.46 - 7.49 (1H, m), 8.17 (1H, t), 8.52 - 8.55 (1H, m), 9.14 (1H, d), 9.40 (1H, s)

Example 24aj ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.47 - 0.51 (2H, m), 0.67 - 0.71 (2H, m), 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.61 - 2.67 (1H, m), 3.02 (3H, s), 3.19 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.26 (1H, d), 4.62 (1H, s), 6.80 (1H, s), 7.53 (1H, d), 8.16 (1H, s), 8.53 - 8.56 (1H, m), 9.13 (1H, d), 9.33 (1H, s)

Example 24ak: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (3H, t), 1.24 (3H, d), 1.42 - 1.49 (2H, m), 1.78 (6H, d), 3.04 (3H, s), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.61 (1H, d), 6.21 (1H, t), 6.74 (1H, s), 7.49 - 7.52 (2H, m), 8.23 - 8.25 (2H, m), 8.66 (1H, s))

Example 24al: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.12 (6H, d), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.04 (3H, s), 3.21 - 3.24 (1H, m), 3.48 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.76 - 3.81 (2H, m), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, d), 6.07 (1H, d), 6.74 (1H, s), 7.47 - 7.51 (2H, m), 8.23 (2H, d), 8.55 (1H, s)

Example 24am: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.59 - 1.66 (2H, m), 1.78 (6H, d), 1.84 - 1.89 (2H, m), 2.19 - 2.25 (2H, m), 3.04 (3H, s), 3.21 - 3.25 (1H, m), 3.48 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.15 (1H, q), 4.23 (1H, d), 4.60 (1H, d), 6.47 (1H, d), 6.74 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.58 (1H, s)

Example 24an: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.25 - 1.25 (5H, m), 1.78 (6H, s), 3.04 (3H, s), 3.19 - 3.24 (1H, m), 3.40 (2H, d), 3.50 (1H, d), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.24 (1H, d), 4.59 (1H, s), 4.96 (1H, t), 6.01 (1H, s), 6.74 (1H, s), 7.46 (2H, d), 8.23 (2H, d), 8.74 (1H, s)

Example 24ao: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.36 (2H, d), 4.60 (1H, d), 6.75 (1H, s), 6.78 (1H, t), 7.36 - 7.39 (1H, m), 7.53 (2H, d), 7.72 - 7.75 (1H, m), 8.25 (2H, d), 8.46 - 8.48 (1H, m), 8.55 (1H, d), 8.88 (1H, s)

Example 24ap: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.04 (3H, s), 3.19 - 3.25 (1H, m), 3.34 - 3.42 (2H, m), 3.47 - 3.54 (1H, m), 3.65 (1H, d), 3.70 - 3.74 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 4.79 (1H, t), 6.10 (1H, d), 6.74 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.73 (1H, s)

Example 24aq: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.18 - 0.22 (2H, m), 0.42 - 0.47 (2H, m), 0.94 - 0.98 (1H, m), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.00 (2H, t), 3.04 (3H, s), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 6.27 (1H, t), 6.74 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.70 (1H, s)

Example 24ar: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.20 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.24 (1H, d), 4.36 (2H, d), 4.60 (1H, s), 6.74 (1H, s), 6.83 (1H, t), 7.30 - 7.31 (2H, m), 7.51 - 7.55 (2H, m), 8.23 - 8.26 (2H, m), 8.51 - 8.52 (2H, m), 9.01 (1H, s)

Example 24as: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.56 - 1.62 (2H, m), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.14 - 3.19 (2H, m), 3.20 - 3.24 (1H, m), 3.44 - 3.47 (2H, m), 3.49 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, s), 4.52 (1H, t), 4.59 (1H, s), 6.22 (1H, t), 6.74 (1H, s), 7.48 - 7.51 (2H, m), 8.23 (2H, d), 8.75 (1H, s)

Example 24at: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.22 (3H, t), 1.66 - 1.73 (1H, m), 1.74 - 1.76 (3H, m), 1.77 (3H, s), 2.94 (2H, t), 3.04 (3H, s), 3.20 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, s), 4.60 (1H, s), 6.26 (1H, t), 6.74 (1H, s), 7.48 - 7.51 (2H, m), 8.23 (2H, d), 8.68 (1H, s)

Example 24au: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.24 (1H, d), 4.32 (2H, d), 4.60 (1H, s), 6.64 (1H, t), 6.74 (1H, s), 6.83 (1H, s), 7.04 (1H, s), 7.50 - 7.53 (2H, m), 8.22 - 8.26 (2H, m), 8.96 (1H, s), 11.87 (1H, s)

Example 24av: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.96 - 4.00 (1H, m), 4.12 (2H, d), 4.23 (1H, s), 4.60 (1H, s), 6.44 (1H, t), 6.74 (1H, s), 7.35 (1H, s), 7.50 (2H, d), 7.60 (1H, s), 8.24 (2H, d), 8.74 (1H, s)

Example 24aw: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 2.38 (3H, d), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77

(1H, d), 3.96 - 4.00 (1H, m), 4.24 (1H, d), 4.32 (2H, d), 4.60 (1H, s), 6.16 (1H, d), 6.71 (1H, s), 6.74 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.96 (1H, s)

Example 24ax: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.44 (3H, d), 1.76 (3H, s), 1.76 (3H, s), 3.03 (3H, s), 3.19 - 3.24 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.95 - 3.99 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 4.88 (1H, t), 6.74 (1H, s), 6.81 (1H, d), 7.36 - 7.39 (1H, m), 7.48 (2H, d), 7.75 - 7.78 (1H, m), 8.23 (2H, d), 8.45 - 8.47 (1H, m), 8.59 (1H, d), 8.71 (1H, s)

Example 24ay: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22-4.33 (1H, m), 4.28 (2H, d), 4.60 (1H, s), 6.18 (1H, s), 6.52 (1H, s), 6.74 (1H, s), 7.51 (2H, d), 7.67 (1H, s), 8.25 (2H, d), 8.84 (1H, s), 12.64 (1H, s)

Example 24az: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 - 1.76 (5H, m), 1.77 (3H, s), 3.20 (1H, d), 3.47 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.76 - 3.80 (4H, m), 3.96 - 4.00 (1H, m), 4.23 (2H, d), 4.25 (1H, s), 4.60 (1H, s), 6.14 (1H, d), 6.52 (1H, t), 6.74 (1H, s), 7.51 (2H, d), 7.61 (1H, d), 8.24 (2H, d), 8.84 (1H, s)

Example 24ba: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 2.95 (6H, s), 3.04 (3H, s), 3.20 - 3.24 (1H, m), 3.49 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, s), 4.60 (1H, s), 6.75 (1H, s), 7.59 (2H, d), 8.23 (2H, d), 8.52 (1H, s)

Example 24bb: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.45 (4H, t), 3.49 - 3.52 (1H, m), 3.61 - 3.63 (4H, m), 3.65 (1H, s), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.25 (1H, d), 4.60 (1H, s), 6.75 (1H, s), 7.59 (2H, d), 8.25 (2H, d), 8.77 (1H, s)

Example 24bc: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.29 - 1.38 (2H, m), 1.75-1.77 (2H, m), 1.77 (3H, s), 1.77 (3H, s), 3.04 (4H, s), 3.07 - 3.11 (2H, m), 3.16 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.67 - 3.70 (1H, m), 3.77 (1H, d), 3.85 (2H, q), 3.96 - 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 4.74 (1H, d), 6.74 (1H, s), 7.58 (2H, d), 8.23 (2H, d), 8.72 (1H, s)

Example 24bd: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 - 1.41 (2H, m), 1.69 - 1.73 (1H, m), 1.77 (3H, s), 1.77 (3H, s), 1.85 - 1.88 (1H, m), 2.74 - 2.79 (1H, m), 2.91 - 2.97 (1H, m), 3.04 (3H, s), 3.17 - 3.24 (1H, m), 3.45 - 3.53 (2H, m), 3.62 - 3.66 (1H, m), 3.76 (1H,

s), 3.79 (1H, t), 3.93 - 4.00 (2H, m), 4.24 (1H, d), 4.60 (1H, s), 4.88 (1H, d), 6.74 (1H, s), 7.57 - 7.59 (2H, m), 8.21 - 8.24 (2H, m), 8.69 (1H, s)

Example 24be: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, t), 1.76 (3H, s), 1.77 (3H, s), 2.15 - 2.23 (2H, m), 3.04 (3H, s), 3.18 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.98 (5H, t), 4.22 (1H, s), 4.60 (1H, s), 6.74 (1H, s), 7.62 (2H, d), 8.22 - 8.25 (2H, m), 8.59 (1H, s)

Example 24bf: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.16 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.71 - 3.75 (2H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.14 - 4.18 (2H, m), 4.24 (1H, d), 4.41 - 4.46 (1H, m), 4.60 (1H, s), 5.66 (1H, d), 6.74 (1H, s), 7.62 (2H, d), 8.22 - 8.25 (2H, m), 8.64 (1H, s)

Example 24bg: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.68 - 0.72 (2H, m), 0.90 (2H, d), 1.23 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 2.70 - 2.74 (1H, m), 2.87 (3H, s), 3.04 (3H, d), 3.17 - 3.24 (1H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.25 (1H, d), 4.59 (1H, s), 6.75 (1H, s), 7.63 - 7.66 (2H, m), 8.24 (2H, d), 8.43 (1H, s)

Example 24bh: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 2.80 (3H, d), 3.02 (3H, s), 3.18 - 3.26 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.95 - 3.99 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.84 (1H, s), 8.98 (1H, d), 9.37 (2H, s), 10.11 (1H, s)

Example 24bi: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.24 (3H, d), 1.78 (6H, d), 3.02 (3H, s), 3.18 - 3.26 (1H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.80 (3H, s), 3.96 - 4.00 (1H, m), 4.24 (2H, d), 4.27 (1H, m), 4.61 (1H, s), 6.79 (1H, s), 7.38 (1H, s), 7.49 - 7.52 (1H, m), 7.62 (1H, s), 8.36 (1H, s), 8.53 - 8.56 (1H, m), 9.12 (1H, d), 9.45 (1H, s).

Example 24bj: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.23 (3H, d), 1.77 (6H, d), 3.03 (3H, s), 3.17 (2H, q), 3.23 (1H, d), 3.46 (2H, q), 3.49 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.60 (1H, d), 4.73 (1H, t), 6.25 (1H, t), 6.74 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.81 (1H, s)

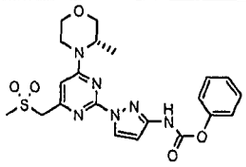
Test(a): Example(24) 0.34 μM; Example(24a) 0.082 μM; Example(24b) 0.038 μM; Example(24c) 0.56 μM; Example(24d) 4.4 μM; Example(24e) 0.81 μM; Example(24f) 4.5 μM; Example(24g) 0.31 μM; Example(24h) 4.4 μM; Example(24i) 0.33 μM; Example(24j) 0.22 μM; Example(24k) 0.18 μM; Example(24l) 0.84 μM; Example(24m) 0.65 μM; Example(24n) 3.2 μM; Example(24o) 3.4 μM; Example(24p) 0.89 μM; Example(24q) 5.8 μM; Example(24r) 0.34 μM; Example(24s) 0.0047 μM; Example(24t) 0.012 μM;

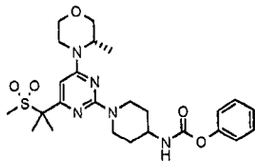
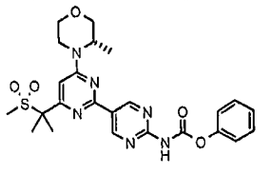
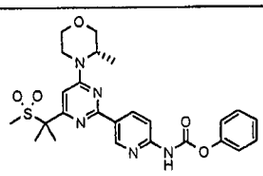
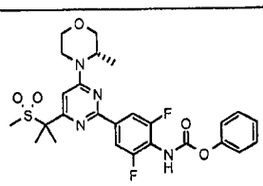
Example(24u) 0.12 μM; Example(24v) 0.055 μM; Example(24w) 0.034 μM; Example(24x) 0.1 μM; Example(24y) 2.2 μM; Example(24z) 0.37 μM; Example(24aa) 0.11 μM; Example(24ab) 0.042 μM; Example(24ac) 0.048 μM; Example(24ad) 0.51 μM; Example(24ae) 0.24 μM; Example(24bh) 0.012 μM; Example(24bi) 0.43 μM; Example(24bj) 0.051 μM.

Test(c): Example(24af) 1.4 μM; Example(24ag) 0.32 μM; Example(24ah) 0.51 μM; Example(24ai) 0.26 μM; Example(24aj) 0.45 μM; Example(24ak) 0.21 μM; Example(24al) 0.038 μM; Example(24am) 0.21 μM; Example(24an) 1.8 μM; Example(24ao) 0.24 μM; Example(24ap) 0.077 μM; Example(24aq) 2 μM; Example(24ar) 0.049 μM; Example(24as) 0.22 μM; Example(24at) 0.089 μM; Example(24au) 2.4 μM; Example(24av) 4.9 μM; Example(24aw) 3.4 μM; Example(24ax) 0.64 μM; Example(24ay) 7.9 μM; Example(24az) 5.6 μM; Example(24ba) 5.1 μM; Example(24bb) 7.8 μM; Example(24bc) 0.69 μM; Example(24bd) 3.2 μM; Example(24be) 4.9 μM; Example(24bf) 6.7 μM; Example(24bg) 2.4 μM.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate and phenyl (4-{4-[1-methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate is described earlier.

The following carbamates were prepared from the appropriate amine or aniline in an analogous fashion to phenyl *N*-[1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-4-piperidyl]carbamate, described earlier.

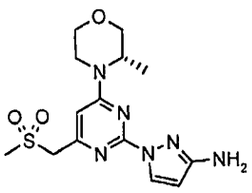
Structure	NAME	LCMS MH+	Retention Time (min)	Notes
	phenyl N-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]carbamate	495	2.09	Purified by chromatography using 0-55% ethyl acetate in isohexane

Structure	NAME	LCMS MH+	Retention Time (min)	Notes
	phenyl N-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]carbamate	518	2.34	
	phenyl N-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate	513	2.21	Purified by chromatography using 0-3% methanol in DCM
	phenyl N-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-yl]carbamate	512	2.60	Purified by chromatography using 0-3% methanol in DCM
	(S)-phenyl 2,6-difluoro-4-(4-(3-methylmorpholino)-6-(2-(methylsulfonyl)propan-2-yl)pyrimidin-2-yl)phenylcarbamate	547	2.67	

(S)-Phenyl 2,6-difluoro-4-(4-(3-methylmorpholino)-6-(2-(methylsulfonyl)propan-2-yl)pyrimidin-2-yl)phenylcarbamate: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.25 (3H, d), 1.79 (6H, d), 3.00 (3H, s), 3.20-3.27 (1H, m), 3.47 - 3.55 (1H, m), 3.58 (15H, s), 3.65 (1H, d), 3.75 (1H, d), 3.97 - 4.01 (1H, m), 4.28 (1H, d), 4.63 (1H, s), 6.88 (1H, s), 7.21 (2H, d), 7.27 (1H, t), 7.44 (2H, t), 8.08 (2H, d), 9.96 (1H, s)

The preparation of 1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-amine is described below.

1-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-amine

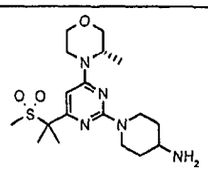
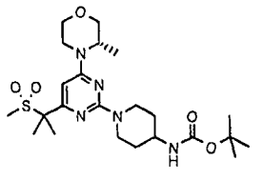


2-Chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.00 g), 1H-pyrazol-3-amine (300 mg) and potassium carbonate (498 mg) were dissolved in butyronitrile (20 mL). The mixture was heated at reflux for 24 hours. The reaction was diluted with ethyl acetate (20 mL) and washed with water (20 mL). The water was extracted with ethyl acetate (20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by chromatography on silica, eluting with 0-5% methanol in DCM to give the desired material (635 mg).

NMR Spectrum: 1H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.20 (3H, s), 3.24 (1H, m), 3.43 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.06 - 4.12 (1H, m), 4.43 (1H, s), 4.43 (2H, s), 5.25 (2H, s), 5.75 (1H, s), 5.80 (1H, d), 6.66 (1H, s), 8.26 (1H, d)

LCMS Spectrum: MH+ 490, Retention Time 1.58min, Method Monitor Acid

1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]piperidin-4-amine was prepared from (3*S*)-4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine and *tert*-butyl *N*-(4-piperidyl)carbamate in an analogous two step procedure to 1-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]piperidin-4-amine.

Structure	NAME	LCMS MH+	Retention Time (min)
	1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]piperidin-4-amine	398	0.94
	tert-butyl N-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]carbamate	498	2.43

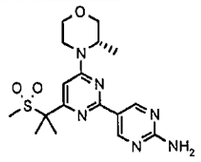
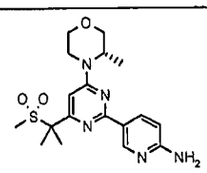
1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]piperidin-4-amine: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.27 (3H, d), 1.75 (6H, s), 1.83 - 1.87 (2H, m), 2.88 (1H, d), 2.91 (5H, s), 2.94 (1H, d), 3.17 - 3.25 (1H, m), 3.50 - 3.57 (1H, m), 3.68 (1H, d), 3.70 (2H, s), 3.75 - 3.77 (1H, m), 3.92 (1H, s), 3.95 - 3.99 (2H, m), 4.30 (1H, d), 4.61 (2H, d), 6.06 (1H, s)

tert-butyl N-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-4-piperidyl]carbamate: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.25 (5H, d), 1.27 (2H, d), 1.30 - 1.35 (2H, m), 1.45 (9H, s), 1.54 (6H, s), 1.98 (2H, d), 2.04 (4H, s), 2.90 (3H, s), 2.95 - 3.01 (2H, m), 3.17 - 3.24 (1H, m), 3.50 - 3.57 (1H, m), 3.66 - 3.70 (2H, m), 3.76 (1H, d), 3.95 - 3.99 (2H, m), 4.29 (1H, d), 4.56 (2H, d), 6.07 (1H, s)

The preparation of (3*S*)-4-{2-chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine was described earlier.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-amine and 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-amine were prepared from (3*S*)-4-{2-chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine in an analogous fashion to (4-{4-

[1-Methyl-1-(methylsulfonyl)ethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)amine, described earlier.

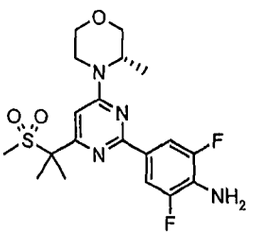
Structure	NAME	LCMS MH+	Retention Time (min)
	5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-amine	393	1.57
	5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-amine	392	1.16

5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyrimidin-2-amine: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.23 (3H, d), 1.75 - 1.76 (6H, m), 3.00 (3H, s), 3.16 - 3.23 (1H, m), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 6.74 (1H, s), 7.11 (2H, s), 9.09 (2H, s)

5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]pyridin-2-amine: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.86 (6H, s), 2.93 (3H, s), 3.31 - 3.35 (1H, m), 3.56 - 3.62 (1H, m), 3.72 - 3.75 (1H, m), 3.82 (1H, d), 4.02 - 4.05 (1H, m), 4.12 (1H, d), 4.48 - 4.50 (1H, m), 4.83 (2H, s), 6.52 - 6.55 (1H, m), 6.59 (1H, s), 8.35 - 8.38 (1H, m), 9.08 - 9.09 (1H, m)

The preparation of 2,6-difluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline is described below.

2,6-Difluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline

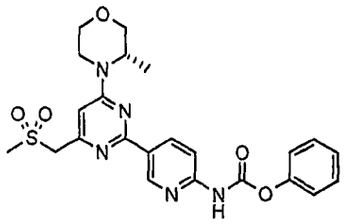


4-Bromo-2,6-difluoro-aniline (400 mg, 1.92 mmol), potassium acetate (566 mg, 5.77 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (587 mg, 2.31 mmol) were dissolved in 1,4 dioxane (5 mL). The solution was degassed for 10 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium was added (95 mg, 0.12 mmol) and the reaction was stirred at 90°C for 3 hours. (3*S*)-4-{2-Chloro-6-[1-methyl-1-(methylsulfonyl)ethyl]pyrimidin-4-yl}-3-methylmorpholine (450 mg, 1.35 mmol), ethanol (1 mL), 2M sodium carbonate (1 mL) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (95 mg, 0.12 mmol) were added and the heating was continued for 18 hours. The reaction was allowed to cool to RT then water (50 mL) added, followed by ethyl acetate (50 mL). The undissolved solid was removed by filtration. The phases were separated and the aqueous phase was extracted with a second portion of ethyl acetate (30 mL). The combined organics were dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was dissolved in DCM (25 mL), filtered to remove the insoluble material and the filtrate purified by chromatography on silica, eluting with 0-35% ethyl acetate in isohexane, to give the desired material as an off-white solid (402 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.76 (6H, d), 3.00 (3H, s), 3.17 - 3.24 (1H, m), 3.45 - 3.51 (1H, m), 3.62 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 5.70 (2H, d), 6.73 (1H, s), 7.83 - 7.85 (2H, m)
LCMS Spectrum: MH+ 427, Retention Time 2.35min, Method Monitor Acid

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-yl]carbamate



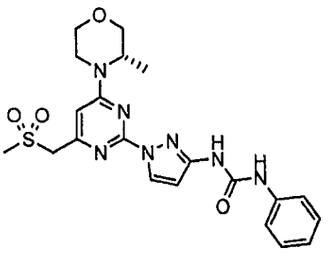
5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-amine (770 mg, 2.12 mmol) was dissolved in dioxane (10 mL) and sodium bicarbonate (267 mg, 3.18 mmol) was added to give a thin yellow slurry. Phenyl chloroformate (0.267 mL, 2.12 mmol) was added dropwise over 10 minutes, controlling the exotherm using a water bath and the mixture was stirred at RT for 16 hours. Further sodium bicarbonate (267 mg, 3.18 mmol) and phenyl chloroformate (0.267 mL, 2.12 mmol) were added and the mixture was stirred at RT for 2 hours. Again phenyl chloroformate (0.267 mL, 2.12mmol) was added and the mixture was stirred at RT for 1 hour then heated to 35°C for 16 hours. The reaction was evaporated to dryness and the residue was partitioned between water (15 mL) and ethyl acetate (20 mL). The white solid was filtered off and washed with water (5 mL), DCM (5 mL) and methanol (5 mL). The solid was dried under vacuum at 40°C for 5 hours to give the product as a white solid (117 mg).

LCMS Spectrum: MH+ 484, retention time 2.32 min, Method Monitor Acid

The preparation of 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyridin-2-amine was described earlier.

Example 25:

1-[1-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]-3-phenyl-urea

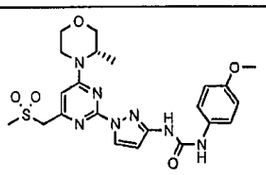
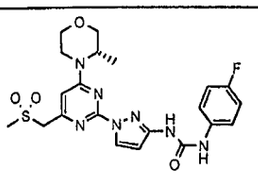


1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-amine (90 mg, 0.26 mmol) was dissolved in dioxane (4 mL). Phenyl isocyanate (0.024 mL, 0.22 mmol) was added to the resultant solution. The mixture was heated at 80°C for 2 hours. The solid was filtered off and washed with diethyl ether (5 mL) to give the desired material as a white solid (66 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.23 (3H, s), 3.40 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.98 (1H, d), 4.14 (1H, s), 4.47 (1H, m), 4.51 (2H, d), 6.60 (1H, d), 6.81 (1H, s), 7.01 (1H, t), 7.29 - 7.33 (2H, m), 7.47 (2H, d), 8.51 (1H, d), 9.18 (1H, s), 9.50 (1H, s)

LCMS Spectrum: MH+ 472, Retention Time 1.86min, Method 5 Minute Acid

The following compounds were prepared in an analogous manner from 1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-amine and the appropriate isocyanate.

Example	Structure	NAME	LCMS MH+	Retention Time (min)
25a		3-(4-methoxyphenyl)-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]urea	502	1.98
25b		3-(4-fluorophenyl)-1-[1-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]pyrazol-3-yl]urea	512	2.06

261

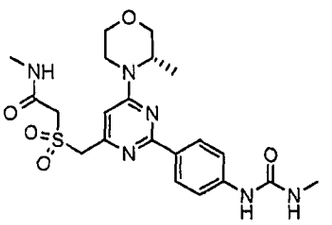
Example 25a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.47 - 3.53 (1H, m), 3.56 (1H, d), 3.63 - 3.67 (1H, m), 3.73 (3H, s), 3.78 (1H, d), 3.96 - 4.00 (1H, m), 4.14 (1H, s), 4.47 (1H, m), 4.50 (2H, s), 6.57 (1H, d), 6.81 (1H, s), 6.87 - 6.91 (2H, m), 7.35 - 7.39 (2H, m), 8.50 (1H, d), 9.04 (1H, s), 9.42 (1H, s)

Example 25b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.26 (1H, m), 3.46 - 3.53 (1H, m), 3.58 (3H, s), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.96 - 4.00 (1H, m), 4.14 (1H, s), 4.46 (1H, m), 4.50 (2H, s), 6.59 (1H, d), 6.81 (1H, s), 7.13 - 7.18 (2H, m), 7.45 - 7.50 (2H, m), 8.51 (1H, d), 9.17 (1H, s), 9.51 (1H, s)

Test(a): Example(25) 1.9 μM; Example(25a) 4.4 μM; Example(25b) 4.4 μM.

Example 26:

***N*-Methyl-2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]acetamide**

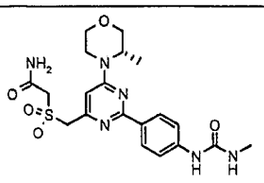
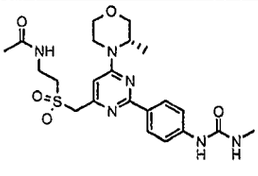


N-Methyl-2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide (0.35 mmol) was dissolved in 1,4-Dioxane (5 mL) and water (1 mL). m-CPBA (75%) (121 mg) followed immediately by sodium permanganate (140 mg) were added to the solution and the reaction stirred at RT for 1 h. Further m-CPBA (75%) (121 mg) followed immediately by sodium permanganate (140 mg) were added to the solution and stirred at RT for 1 h. Again further m-CPBA (75%) (121 mg) followed immediately by sodium permanganate (140 mg) were added and the reaction stirred at RT for 1 h. The reaction was loaded onto a SCX-3 (10 g) column, which was washed with methanol and the product eluted with 7N ammonia in methanol. The material was further purified by prep-HPLC (basic) to give the desired material (30 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 - 1.25 (3H, m), 2.66 - 2.70 (3H, m), 2.68 (1H, d), 3.21 - 3.26 (1H, m), 3.46 - 3.53 (3H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.29 (2H, s), 4.47 (1H, s), 4.67 (2H, s), 6.07 (1H, q), 6.76 (1H, s), 7.48 - 7.52 (2H, m), 8.17 - 8.20 (2H, m), 8.31 (1H, t), 8.74 (1H, s)

Mass Spectrum; $M+H^+$ 477.

The following compounds were prepared in an analogous fashion from the appropriate sulphides.

Example	Structure	NAME	LCMS MH+
26a		2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]acetamide	463
26b		N-[2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide	491

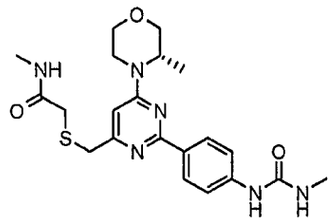
Example 26a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.66 (3H, d), 3.18 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.27 (2H, s), 4.48 (1H, s), 4.66 (2H, s), 6.07 (1H, q), 6.76 (1H, s), 7.48 - 7.52 (3H, m), 7.79 (1H, s), 8.17 - 8.21 (2H, m), 8.74 (1H, s)

Example 26b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.83 (3H, s), 2.66 (2H, s), 2.68 (2H, q), 3.21 - 3.26 (1H, m), 3.47 - 3.53 (2H, m), 3.52 (1H, s), 3.57 (2H, q), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.51 (2H, s), 6.06 (1H, q), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.14 - 8.21 (3H, m), 8.74 (1H, s)

Test(a): Example(26) 0.029 μM; Example(26a) 0.037 μM; Example(26b) 0.041 μM.

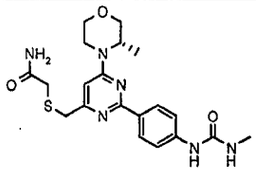
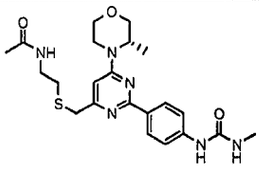
The preparation of *N*-methyl-2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide is described below.

N-Methyl-2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide



N-Methyl-2-sulfanyl-acetamide (0.61 mmol) was dissolved in Acetonitrile (4 mL). DBU (0.050 mL) was then added to the solution and stirred at RT for 5min. A solution of 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (151 mg) in acetonitrile (2 mL) and DBU (0.054 mL) were added and the reaction stirred at RT for 2 h before being concentrated *in vacuo* and used immediately in the subsequent step.

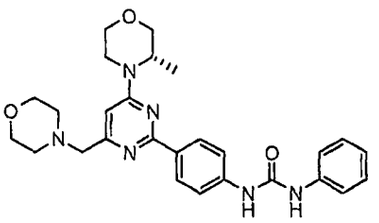
The following sulphides were made in an analogous fashion.

Structure	NAME
	2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]acetamide
	N-[2-[[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide

The preparation of 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 27:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(morpholin-4-ylmethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea (90 mg) was dissolved in DCM (5 mL) and triethylamine (0.045 mL) and the solution cooled to 0°C. Methane sulfonyl chloride (0.026 mL) was added and the reaction stirred for 1 h at RT. Morpholine (0.2 mL) was added and the reaction was left at RT for 72 hours before being concentrated *in vacuo* and purified by prep-HPLC (basic) to give the desired compound (64 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 3.17 (4H, t), 3.46 - 3.52 (4H, m), 3.63 (4H, d), 3.65 (1H, s), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.14 (1H, d), 4.49 (1H, s), 6.64 (1H, s), 6.97 (1H, t), 7.29 (2H, d), 7.45 (2H, d), 7.53 (2H, d), 8.25 (2H, d), 8.68 (1H, s), 8.87 (1H, s).

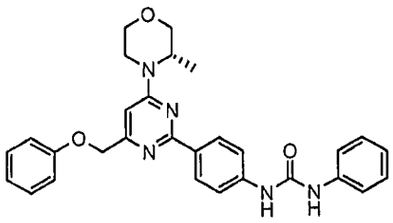
Mass Spectrum; $M+H^+$ 489.

Test(a): 0.19 μM.

The preparation of 1-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 28:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(phenoxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was dissolved in DCM (5 mL), phenol (41 mg) added and the reaction left to stir at RT for 1 h. DBU (0.2 mL) was added and the mixture left to stir for 18 hours before being concentrated *in vacuo* and purified by prep-HPLC (basic) to give the desired material (26 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 - 1.21 (3H, m), 3.18 (1H, s), 3.47 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.16 (1H, s), 4.51 (1H, s), 5.08 (2H, s), 6.72 (1H, s), 6.96 - 7.01 (2H, m), 7.07 - 7.10 (2H, m), 7.28 - 7.35 (4H, m), 7.48 (2H, d), 7.57 (2H, d), 8.28 (2H, d), 8.75 (1H, s), 8.95 (1H, s)

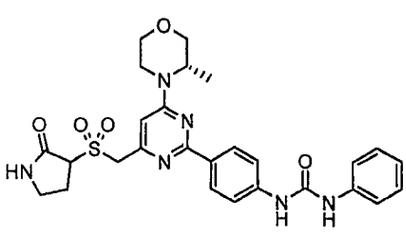
Mass Spectrum; M+H$^+$ 496.

Test(a): 4.7 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 29:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(2-oxopyrrolidin-3-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(2-oxopyrrolidin-3-yl)sulfanylmethyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea (0.26 mmol) was dissolved in 1,4-Dioxane (5 mL) and water (1 mL). m-CPBA (75%) (113 mg) followed immediately by sodium permanganate (125 mg) was added to the solution and left to stir at RT for 1 h. The reaction was loaded onto a SCX-2 (10 g) column, which was washed with methanol and the product eluted with 7N ammonia in methanol. The material was further purified by prep-HPLC (basic) to give the desired material (18 mg) as a white solid.

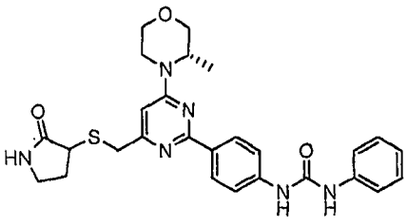
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.32 - 2.34 (1H, m), 2.47 (1H, d), 3.24 (2H, t), 3.34 (2H, d), 3.51 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.49 (1H, s), 4.58 - 4.63 (2H, m), 5.01 (1H, d), 6.79 (1H, s), 6.97 - 7.01 (1H, m), 7.28 - 7.32 (1H, m), 7.30 (1H, s), 7.46 - 7.48 (2H, m), 7.56 - 7.58 (2H, m), 8.24 - 8.27 (2H, m), 8.38 (1H, s), 8.72 (1H, s), 8.92 (1H, s)

Mass Spectrum; M+H$^+$ 551.

Test(a): 0.56 μM.

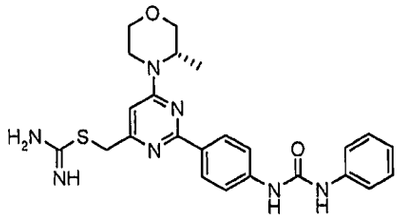
The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-oxopyrrolidin-3-yl)sulfanylmethyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea is described below.

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(2-oxopyrrolidin-3-yl)sulfanylmethyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-(Carbamimidoylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea (125 mg) was dissolved in DMF (3 mL). The solution was then treated with 3-bromo-pyrrolidin-2-one (48 mg) followed by sodium hydroxide (42 mg) in water (1 mL), heated to 40°C and left to stir for 24 h. The reaction was diluted in a little methanol and loaded onto a SCX-2 column (20 g), which was washed with methanol and the desired product eluted with 7N ammonia in methanol to give the desired material which was used without further characterisation.

1-[4-[4-(Carbamimidoylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea

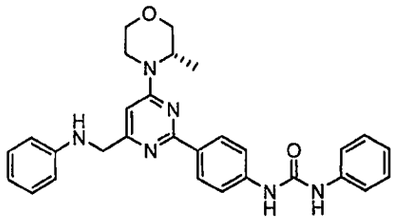


1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (865 mg) was dissolved in ethanol (30 mL) and thiourea (146 mg) added. The reaction was then heated to 70°C for 30min then allowed to cool and concentrated *in vacuo* to give the desired material which was used without further characterisation.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 30:

1-[4-[4-(Anilinomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



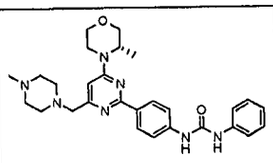
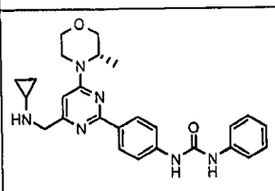
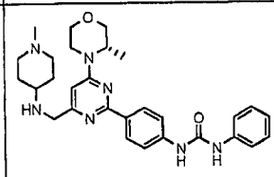
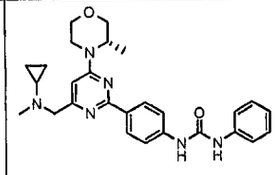
1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (105 mg, 0.21 mmol) dissolved in a solution of DCM (5 mL) was added to aniline (0.097 mL, 1.06 mmol) and stirred at RT for 18 h. The mixture was vacuumed to dryness and purified by prep-HPLC (basic) to give the desired material (41 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.15 (3H, d), 3.12 - 3.18 (1H, m), 3.43 - 3.50 (1H, m), 3.59 - 3.63 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, d), 4.24 (2H, d), 4.39 (1H, s), 6.20 (1H, t), 6.55 (1H, d), 6.60 (1H, s), 6.63 (1H, d), 6.65 (1H, s), 6.97 - 7.01

(1H, m), 7.06 - 7.10 (2H, m), 7.28 - 7.32 (1H, m), 7.30 (1H, s), 7.46 - 7.49 (2H, m), 7.55 - 7.57 (2H, m), 8.29 - 8.31 (2H, m), 8.69 (1H, s), 8.88 (1H, s).

Mass Spectrum; $M+H^+$ 495.

The following compounds were prepared in an analogous fashion.

Example	Structure	NAME	LCMS MH+
30a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea	502
30b		1-[4-[4-[(cyclopropylamino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea	459
30c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[(1-methyl-4-piperidyl)amino]methyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea	516
30d		1-[4-[4-[(cyclopropyl-methyl-amino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea	473

Example 30a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 2.22 (3H, s), 2.44 (2H, d), 2.53 (2H, d), 2.56 (2H, s), 2.60 - 2.61 (1H, m), 2.67 - 2.69 (1H, m), 3.15 - 3.23 (1H, m), 3.46 - 3.54 (3H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.15 (1H, d), 4.47 - 4.49 (1H, m), 6.63 (1H, s), 6.97 - 7.01 (1H, m), 7.28 - 7.32 (1H, m), 7.30 (1H, s), 7.46 - 7.48 (2H, m), 7.53 - 7.56 (2H, m), 8.25 - 8.27 (2H, m), 8.69 (1H, s), 8.88 (1H, s)

Example 30b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.30 - 0.31 (2H, m), 0.37 - 0.40 (2H, m), 1.23 (3H, d), 2.14 - 2.19 (1H, m), 3.15 - 3.23 (1H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H,

m), 3.72 (2H, s), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 (1H, d), 4.51 (1H, d), 6.67 (1H, s), 6.99 - 7.01 (1H, m), 7.28 - 7.32 (2H, m), 7.46 - 7.48 (2H, m), 7.53 - 7.56 (2H, m), 8.28 (2H, d), 8.69 (1H, s), 8.87 (1H, s)

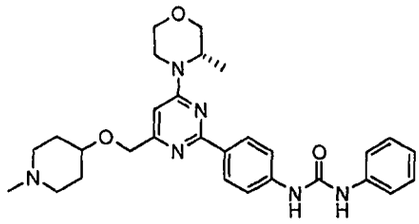
Example 30d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40- 0.41 (2H, t), 0.45 - 0.49 (2H, m), 1.21 (3H, d), 1.90 - 1.95 (1H, m), 2.34 (3H, s), 3.14 - 3.21 (1H, m), 3.46 - 3.53 (1H, m), 3.63 (3H, t), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.49 (1H, s), 6.54 (1H, s), 6.97 - 7.01 (1H, m), 7.28 - 7.32 (1H, m), 7.30 (1H, s), 7.46 - 7.48 (2H, m), 7.54 - 7.56 (2H, m), 8.26 - 8.28 (2H, m), 8.69 (1H, s), 8.87 (1H, s)

Test(a): Example(30) 0.9 μM; Example(30a) 0.12 μM; Example(30b) 0.18 μM; Example(30c) 1.1 μM; Example(30d) 0.28 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 31:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(1-methyl-4-piperidyl)oxymethyl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (105 mg) dissolved in a solution of DCM (5 mL) and triethylamine (0.045 mL) was added to 4-hydroxy-1-methylpiperidine (5 equivalents). DBU (0.158 mL) was added and stirred at RT for 18 h. The mixture was vacuumed to dryness and purified by prep-HPLC (basic) to give the desired material (64 mg) as a white solid.

Mass Spectrum; $M+H^+$ 517.

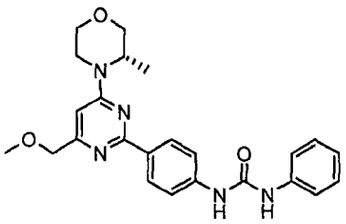
Test(a): 0.35 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

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Example 32:

1-[4-[4-(Methoxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-phenyl-urea



1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea (90 mg) dissolved in a solution of DCM (5 mL) and triethylamine (0.045 mL). Sodium methoxide (33% in methanol) (0.073 mL) was added to the reaction and the mixture stirred at RT for 18 h before being quenched with water and partitioned. The organic phase was dried over magnesium sulphate and evaporated to give a gum which was purified by prep-HPLC (basic) to give the desired compound (32 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.34 (1H, d), 3.43 (3H, s), 3.49 (1H, t), 3.63 - 3.66 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.41 (2H, s), 4.51 (1H, d), 6.59 (1H, s), 6.99 (1H, t), 7.30 (2H, t), 7.46 - 7.48 (2H, m), 7.55 (2H, d), 8.26 (2H, d), 8.69 (1H, s), 8.88 (1H, s)

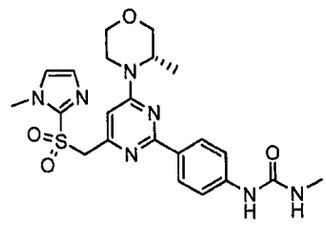
Mass Spectrum; $M+H^+$ 434.

Test(a): 0.0062 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea was described earlier.

Example 33:

3-Methyl-1-[4-[4-[(1-methylimidazol-2-yl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

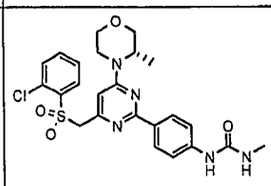


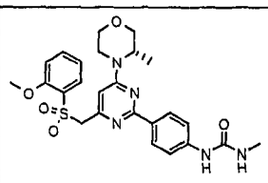
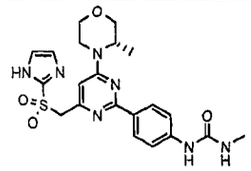
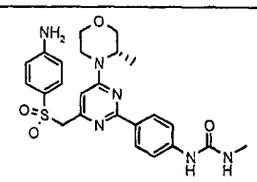
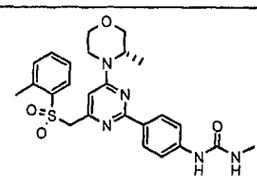
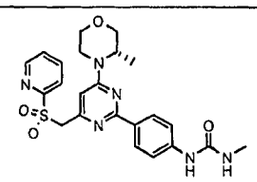
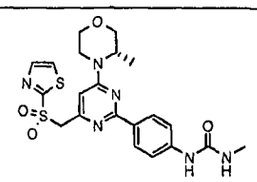
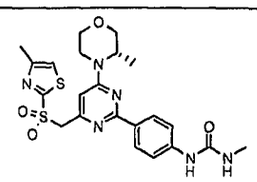
3-Methyl-1-[4-[4-[(1-methylimidazol-2-yl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea (0.23 mmol) was dissolved in 1,4-Dioxane (4 mL) and water (1 mL). m-CPBA (75%) (80 mg), followed immediately by sodium permanganate (92 mg), was added to the solution. The reaction was allowed to stir at RT for 18 h then loaded onto a SCX-2 (10 g) column, which was washed with methanol and the product eluted with 7N ammonia in methanol. The reaction was vacuumed to dryness and purified by prep-HPLC (basic) to give the desired material (37 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17 - 1.22 (3H, m), 2.66 (3H, d), 2.68 (1H, t), 3.14 - 3.22 (1H, m), 3.45 - 3.49 (1H, m), 3.62 (3H, s), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.09 - 4.12 (1H, m), 4.41 (1H, s), 4.75 (2H, s), 6.07 (1H, q), 6.61 (1H, s), 7.20 (1H, d), 7.43 - 7.47 (2H, m), 7.43 - 7.49 (1H, m), 7.95 - 7.97 (2H, m), 8.72 (1H, s)

Mass Spectrum; M+H$^+$ 486.

The following compounds were prepared in an analogous fashion from the appropriate sulphides.

Example	Structure	NAME	LCMS MH+
33a		1-[4-[4-[(2-chlorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	516

Example	Structure	NAME	LCMS MH+
33b		1-[4-[4-[(2-methoxyphenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	512
33c		1-[4-[4-(1H-imidazol-2-ylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	472
33d		1-[4-[4-[(4-aminophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	497
33e		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	496
33f		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	483
33g		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	489
33h		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	503

Example 33a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, q), 2.65 - 2.68 (3H, m), 2.68 (1H, d), 3.17 (1H, d), 3.44 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.09 (1H, t), 4.88 (2H, s), 6.05 (1H, q), 6.71 (1H, s), 7.33 - 7.35 (2H, m), 7.44 - 7.48 (1H, m), 7.65 - 7.69 (1H, m), 7.67 (1H, s), 7.71 - 7.77 (2H, m), 7.83 - 7.85 (1H, m), 8.68 (1H, s).

Example 33b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 2.66 - 2.69 (3H, m), 3.12 - 3.21 (1H, m), 3.43 - 3.50 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.05 (4H, m), 4.37 (1H, s), 4.70 - 4.77 (2H, m), 6.04 (1H, q), 6.61 (1H, s), 7.01 - 7.05 (1H, m), 7.34 - 7.36 (2H, m), 7.39 (1H, d), 7.54 - 7.57 (1H, m), 7.67 - 7.74 (3H, m), 8.67 (1H, s).

Example 33c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.66 (3H, d), 3.12 - 3.20 (1H, m), 3.43 - 3.50 (1H, m), 3.60 - 3.63 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.08 (1H, d), 4.36 (1H, s), 4.71 (2H, s), 6.06 (1H, q), 6.47 (1H, s), 7.34 (2H, s), 7.42 - 7.44 (2H, m), 7.95 - 7.97 (2H, m), 8.70 (1H, s), 13.52 (1H, s)

Example 33d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d),2.66 - 2.69 (3H, m), 3.12 - 3.21 (1H, m), 3.44 - 3.48 (1H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.05 (1H, t), 4.33 (1H, s), 4.44 (2H, s), 6.06 (1H, t), 6.12 (2H, d), 6.41 (1H, s), 6.58 - 6.62 (2H, m), 7.34 - 7.38 (2H, m), 7.42 - 7.46 (2H, m), 7.99 - 8.01 (2H, m), 8.70 (1H, s)

Example 33e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.67 (6H, m), 3.14 - 3.18 (1H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.94 - 3.98 (1H, m), 4.06 (1H, q), 4.37 (1H, s), 4.66 (2H, s), 6.05 (1H, d), 6.60 (1H, s), 7.34 (1H, d), 7.36 - 7.38 (2H, m), 7.47 (1H, d), 7.56 - 7.60 (1H, m), 7.66 - 7.68 (1H, m), 7.77 - 7.80 (2H, m), 8.69 (1H, s)

Example 33f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.65 - 2.68 (3H, m), 3.16 - 3.21 (1H, m), 3.44 - 3.51 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.11 (1H, d), 4.38 (1H, s), 4.80 - 4.88 (2H, m), 6.04 (1H, q), 6.68 (1H, s), 7.34 - 7.36 (2H, m), 7.64 - 7.67 (2H, m), 7.78 - 7.81 (1H, m), 7.88 - 7.90 (1H, m), 8.07 - 8.12 (1H, m), 8.69 (1H, s), 8.92 - 8.94 (1H, m)

Example 33g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.67 (3H, q), 3.16 - 3.21 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.40 (2H, s), 4.91 (2H, d), 6.06 (1H, d), 6.70 (1H, s), 7.40 - 7.42 (2H, m), 7.84 (2H, d), 8.27 - 8.29 (2H, m), 8.71 (1H, s).

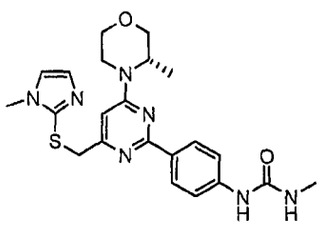
Example 33h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 - 1.27 (3H, m), 2.52 - 2.61 (3H, m), 2.66 - 2.69 (3H, m), 3.15 - 3.22 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H,

d), 3.96 - 4.00 (1H, m), 4.13 (1H, d), 4.40 (1H, s), 4.87 (2H, d), 6.05 (1H, q), 6.70 (1H, s), 7.41 - 7.43 (2H, m), 7.82 (1H, S)

Test(a): Example(33) 0.84 μM; Example(33a) 0.06 μM; Example(33b) 0.066 μM; Example(33c)0.0014 μM; Example(33d) 0.00031 μM; Example(33e) 0.088 μM; Example(33f) 0.27 μM; Example(33g) 0.021 μM; Example(33h) 0.048 μM.

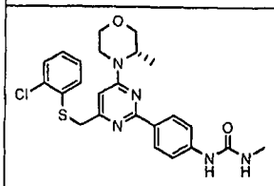
The preparation of 3-methyl-1-[4-[4-[(1-methylimidazol-2-yl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea is described below.

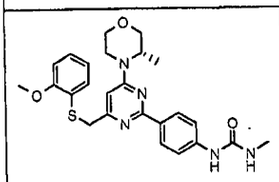
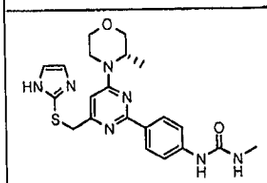
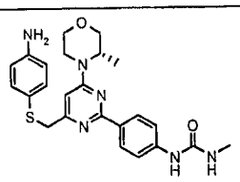
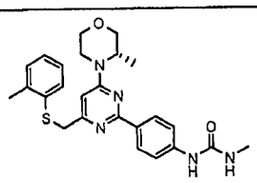
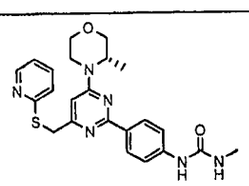
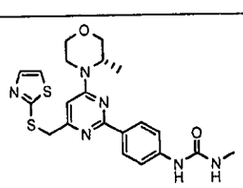
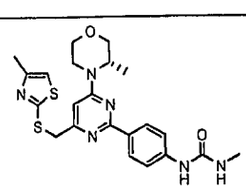
3-Methyl-1-[4-[4-[(1-methylimidazol-2-yl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



1-Methylimidazole-2-thiol (0.23 mmol) was dissolved in acetonitrile (2 mL), DBU (0.035 mL) added and the reaction allowed to stir at RT for 5 min. A solution of 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (100 mg) in acetonitrile (2 mL) and DBU (0.034 mL) were added and the mixture left to stir at RT of 18 h, before being concentrated *in vacuo* to give the desired material. The material was used without further purification.

The following sulphides were prepared in an analogous fashion.

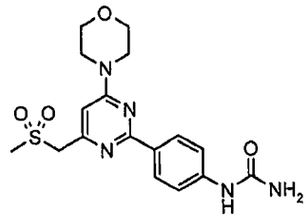
Structure	NAME
	1-[4-[4-[(2-chlorophenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea

Structure	NAME
	1-[4-[4-[(2-methoxyphenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea
	1-[4-[4-(1H-imidazol-2-ylsulfanylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea
	1-[4-[4-[(4-aminophenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfanylmethyl]pyrimidin-2-yl]phenyl]urea
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]urea
	3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidin-2-yl]phenyl]urea

The preparation of 3-methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 34:

[4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea

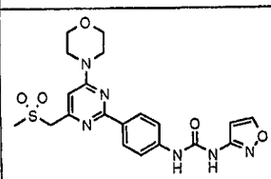
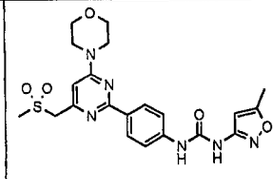
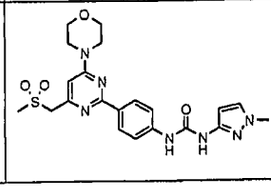


Phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate (110 mg) was dissolved in DMF (2 mL) and triethylamine (0.098 mL) added. 2-Aminopyrimidine (108 mg) was added and the reaction stirred at 40°C for 2 hours. The crude mixture was purified by prep-HPLC (basic), however, only [4-[4-(Methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea was isolated from the mixture (8 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.21 (3H, s), 3.71 - 3.72 (8H, m), 4.48 (2H, s), 5.91 (2H, s), 6.81 (1H, s), 7.49 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.76 (1H, s)

Mass Spectrum; M+H$^+$ 392.

The following compounds were prepared in an analogous procedure.

Example	Structure	NAME	LCMS MH+
34a		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	458
34b		1-(5-methyl-1,2-oxazol-3-yl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	472
34c		1-(1-methylpyrazol-3-yl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	471

Example 34a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.21 (3H, s), 3.73 (8H, s), 4.50 (2H, s), 6.85 - 6.87 (2H, m), 7.56 - 7.59 (2H, m), 8.28 - 8.31 (2H, m), 8.75 (1H, d), 9.07 (1H, s), 9.62 (1H, s)

Example 34b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.15 - 3.25 (3H, s), 3.21 - 3.26 (3H, S), 3.73 (8H, s), 4.49 (2H, s), 6.56 (1H, s), 6.85 (1H, s), 7.55 - 7.57 (2H, m), 8.28 - 8.30 (2H, m), 9.05(1H, s), 9.47 (1H, s)

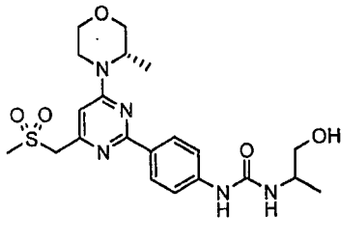
Example 34c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.21 (3H, s), 3.72 (3H, s), 3.74 (8H, s), 4.49 (2H, s), 6.25 (1H, d), 6.84 (1H, s), 7.54 - 7.56 (2H, m), 7.57 (1H, d), 8.26 - 8.28 (2H, m), 8.93 (1H, s), 9.18 (1H, s).

Test(a): Example(34) 0.21 μM; Example(34a) 0.042 μM; Example(34b) 0.12 μM; Example(34c) 0.72 μM.

The preparation of phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 35:

3-(1-Hydroxypropan-2-yl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea

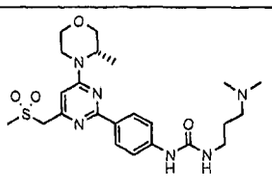
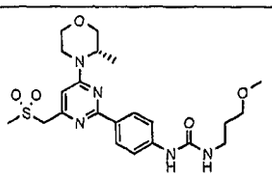
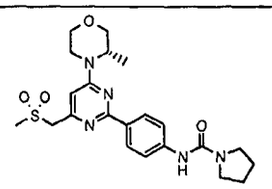
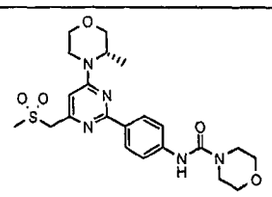
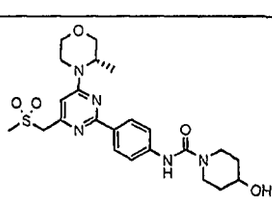
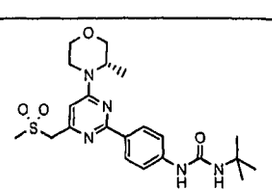


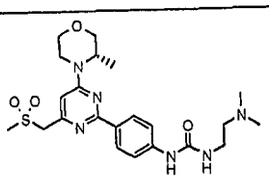
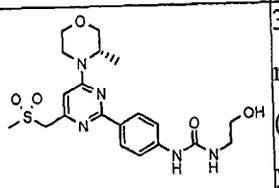
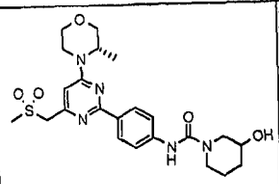
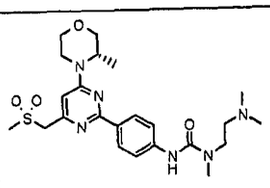
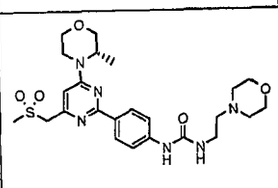
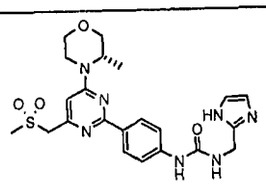
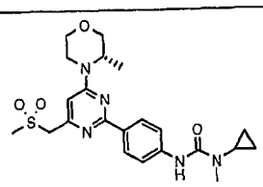
A solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (110 mg, 0.23 mmol) and triethylamine (0.079 mL, 0.68 mmol) in DMF (2 mL) was added to 2-aminopropan-1-ol (1.14 mmol). The reaction was stirred at 40°C for 2 hours then purified by prep-HPLC (basic) to give the desired material as a solid (22 mg).

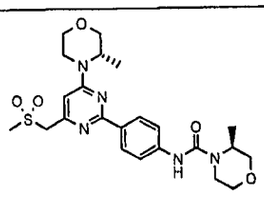
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.24 (3H, d), 3.21 (3H, s), 3.37 - 3.43 (2H, m), 3.47 - 3.53 (2H, m), 3.63 - 3.67 (1H, m), 3.72 (1H, d), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.15 - 4.19 (1H, m), 4.48 (3H, s), 4.78 (1H, t), 6.09 - 6.11 (1H, m), 6.77 (1H, s), 7.47 - 7.49 (2H, m), 8.20 - 8.22 (2H, m), 8.71 (1H, s)

Mass Spectrum; $M+H^+$ 463.

The following compounds were prepared in an analogous fashion

Example	Structure	NAME	LCMS MH+
35a		3-(3-dimethylaminopropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	491
35b		3-(3-methoxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	478
35c		N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide	460
35d		N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]morpholine-4-carboxamide	476
35e		4-hydroxy-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	490
35f		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-tert-butyl-urea	462

Example	Structure	NAME	LCMS MH+
35g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	477
35h		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	450
35i		3-hydroxy-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	490
35j		1-(2-dimethylaminoethyl)-1-methyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	491
35k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(2-morpholin-4-ylethyl)urea	486
35l		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	460
35m		1-cyclopropyl-1-methyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	460

Example	Structure	NAME	LCMS MH+
35n		(3S)-3-methyl-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]morpholine-4-carboxamide	490

Example 35a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.62 (2H, m), 2.10 - 2.14 (6H, s), 2.23 (2H, d), 2.32 - 2.34 (1H, m), 2.44 - 2.47 (1H, m), 3.07 - 3.15 (2H, m), 3.21 (3H, s), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.32 (1H, t), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.19 - 8.21 (2H, m), 8.79 (1H, s)

Example 35b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.68 (2H, t), 3.15 (2H, d), 3.21 (3H, s), 3.25 (4H, s), 3.38 (2H, t), 3.50 (1H, d), 3.67 (1H, d), 3.76 - 3.79 (1H, m), 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.21 (1H, s), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.70 (1H, s)

Example 35c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.85 - 1.88 (4H, m), 3.21 (3H, s), 3.40 (5H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.48 (3H, s), 6.78 (1H, s), 7.63 - 7.66 (2H, m), 8.19 - 8.22 (2H, m), 8.31 (1H, s)

Example 35d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ δ 1.25 (3H, d), 3.21 (3H, s), 3.33 - 3.34 (1H, m), 3.46 (5H, t), 3.61 - 3.63 (4H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.19 (1H, d), 4.49 (3H, s), 6.79 (1H, s), 7.57 - 7.61 (2H, m), 8.21 - 8.23 (2H, m), 8.74 (1H, s)

Example 35e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 - 1.30 (4H, m), 1.31 - 1.39 (1H, m), 1.67 (2H, d), 1.71 - 1.72 (1H, m), 1.74 - 1.78 (2H, m), 3.09 - 3.12 (1H, m), 3.22 (3H, d), 3.48 (1H, d), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.84 (1H, d), 3.83 - 3.88 (1H, m), 3.97 - 4.01 (1H, m), 4.19 (1H, d), 4.48 - 4.51 (3H, m), 4.69 (1H, s), 6.76 (1H, t), 7.57 - 7.59 (2H, m), 8.19 - 8.22 (2H, m), 8.69 (1H, s)

Example 35f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.31 (9, s), 3.20 (3H, s), 3.22 (1H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.06 (1H, s), 6.77 (1H, s), 7.43 - 7.47 (2H, m), 8.19 - 8.21 (2H, m), 8.48 (1H, s)

Example 35g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.18 (6H, s), 2.34 (2 h t), 3.17 - 3.25 (5H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.16 (1H, t), 6.77 (1H, s), 7.47 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.89 (1H, s)

Example 35h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H d), 3.21 (5H, t), 3.46 (3H, t), 3.52 (1H, d), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.15 - 4.19 (1H, m), 4.48 (3H, s), 4.73 (1H, s), 6.26 (1H, t), 6.77 (1H, s), 7.48 - 7.50 (2H, m), 8.21 (2H, d), 8.82 (1H, s)

Example 35i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.38 (2H, d), 1.70 (1H, d), 1.89 (1H, s), 2.74 - 2.78 (1H, m), 2.96 (1H, s), 3.20 (3H, s), 3.47 - 3.50 (1H, m), 3.51 (1H, s), 3.66 - 3.67 (1H, m), 3.77 - 3.80 (2H, m), 3.98 (2H, d), 4.17 (1H, d), 4.48 (3H, s), 4.83 (1H, d), 6.78 (1H, s), 7.57 - 7.59 (2H, m), 8.19 - 8.21 (2H, m), 8.66 (1H, s)

Example 35j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 2.26 (6H, s), 2.67 - 2.69 (2H, m), 2.95 (3H, s), 3.21 (3H, s), 3.40 (3H, t), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.50 - 7.53 (2H, m), 8.20 - 8.23 (2H, m), 9.51 (1H, s)

Example 35k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.39 (2H, d), 2.41 (4H, d), 3.21 (3H, s), 3.24 (2H, t), 3.47 - 3.53 (1H, m), 3.58 - 3.63 (5H, m), 3.67 (1H, d), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.17 (1H, t), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 8.21 (2H, d), 8.88 (1H, s)

Example 35l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 3.19 - 3.23 (3H, m), 3.26 (1H, s), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.16 - 4.19 (1H, m), 4.32 (2H, d), 4.48 (3H, s), 6.63 (1H, t), 6.78 (1H, s), 6.93 (2H, s), 7.51 - 7.53 (2H, m), 8.22 (2H, d), 8.93 (1H, s), 11.84 (1H, s)

Example 35m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.69 - 0.73 (2H, m), 0.88 - 0.93 (2H, m), 1.25 (3H, d), 2.70 - 2.76 (1H, m), 2.88 (3H, s), 3.21 (3H, s), 3.22 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.19 (1H, d), 4.49 (3H, s), 6.79 (1H, s), 7.62 - 7.65 (2H, m), 8.21 - 8.23 (2H, m), 8.39 (1H, s)

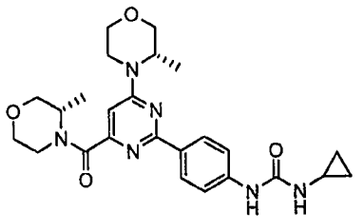
Example 35n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.25 (3H, d), 3.15 - 3.23 (1H, m), 3.20 (3H, s), 3.36 - 3.42 (2H, m), 3.50 (1H, d), 3.53 - 3.57 (1H, m), 3.64 - 3.68 (2H, m), 3.75 (1H, s), 3.78 (2H, d), 3.85 - 3.88 (1H, m), 3.97 - 4.01 (1H, m), 4.20 (2H, d), 4.49 (3H, s), 6.79 (1H, s), 7.58 - 7.61 (2H, m), 8.21 - 8.23 (2H, m), 8.65 (1H, s).

Test(a): Example(35) 0.064 μM; Example(35a) 6.4 μM; Example(35b) 0.42 μM; Example(35c) 3.4 μM; Example(35d) 3.2 μM; Example(35e) 2.5 μM; Example(35f) 0.82 μM; Example(35g) 0.66 μM; Example(35h) 0.024 μM; Example(35i) 0.77 μM; Example(35j) 3.6 μM; Example(35k) 1.2 μM; Example(35l) 0.47 μM; Example(35m) 2 μM; Example(35n)1.1 μM.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate was described earlier

Example 36:

3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholine-4-carbonyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

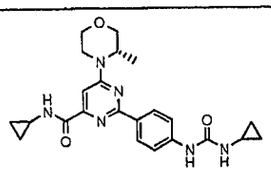
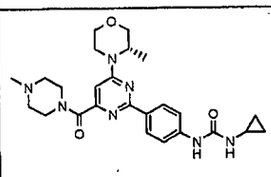


2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid (95 mg) was dissolved in DMF (3 mL) and (3*S*)-3-methylmorpholineadded. DIPEA (0.125 mL) and HATU (137 mg) were added and the reactions stirred at RT for 3 h before being concentrated *in vacuo* and partitioned between DCM (25 mL) and water (25 mL). The organic layer was dried over magnesium sulphate, filtered and evaporated to dryness to give the desired material as a solid (88 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (6H, m), 2.52 - 2.61 (1H, m), 3.23-3.29 (2H, m) 3.41 - 3.42 (1H, m), 3.46 - 3.47 (1H, m), 3.50 - 3.55 (2H, m), 3.60 (2H, d), 3.70 - 3.81 (2H, m), 3.97 (2H, d), 4.17 (1H, s), 4.53 (1H, s), 6.43 (1H, s), 6.74 (1H, d), 7.51 (2H, d), 8.20 (2H, t), 8.54 (1H, s)

Mass Spectrum; $M+H^+$ 480.

The following samples were prepared in an analogous fashion

Example	Structure	NAME	LCMS MH+
36a		N-cyclopropyl-2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	436
36b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylpiperazine-1-carbonyl)pyrimidin-2-yl]phenyl]urea	479

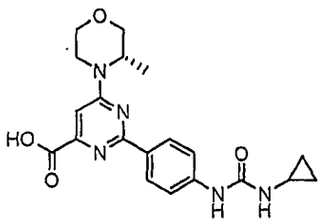
Example 36a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.56 - 0.61 (2H, m), 0.65 - 0.68 (2H, m), 0.74 - 0.76 (2H, m), 1.24 (3H, d), 2.52 - 2.59 (1H, m), 2.53 - 2.61 (1H, m), 3.25 (1H, s), 3.50 (1H, d), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.25 (1H, s), 4.53 (1H, s),6.42 - 6.43 (1H, m), 7.12 (1H, d), 7.51 (2H, d), 8.38 - 8.41 (2H, m), 8.56 (1H, s), 8.69 (1H, d).

Example 36b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (3H, d), 2.25 - 2.26 (3H, m), 2.40 - 2.48 (2H, m), 2.43 - 2.48 (2H, m), 2.52 - 2.61 (1H, m), 3.18 - 3.25 (1H, m), 3.46 - 3.52 (3H, m), 3.62 - 3.66 (3H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.22 (1H, d), 4.55 (1H, s), 6.44 (1H, d), 6.73 (1H, s), 7.50 - 7.52 (2H, m), 8.18 - 8.20 (2H, m), 8.54 (1H, s).

Test(a): Example(36) 0.062 μM; Example(36a) 2.9 μM; Example(36b) 0.18 μM.

The preparation of 2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid is described below.

2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid

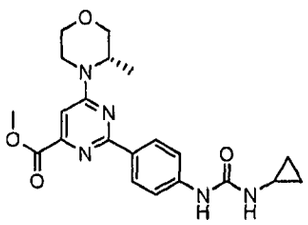


Methyl 2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (350 mg) was dissolved in water (15 mL) containing sodium hydroxide (67 mg) and the reaction was allowed to stir at RT for 1 h. A further 2 equivalents of sodium hydroxide were added along with THF (3 mL). The reaction was stirred for another 1 h then the THF removed under reduced pressure and the aqueous solution partitioned with ethyl acetate (15 mL). The aqueous layer was acidified with concentrated hydrochloric acid and the precipitate was filtered and dried in a vac-oven at 50°C for 18 h to give the desired material (350 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.60 - 0.64 (2H, m), 1.22 (3H, d), 2.52 - 2.58 (1H, m), 3.17 - 3.21 (1H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.75 (1H, d), 3.95 - 3.99 (1H, m), 4.14 - 4.17 (1H, m), 4.48 (1H, d), 6.92 (1H, s), 7.28 (1H, s), 7.56 (2H, d), 8.22 (2H, d), 9.41 (1H, s)

Mass Spectrum; M+H$^+$ 398.

Methyl 2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate



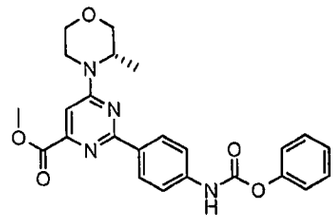
Methyl 6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidine-4-carboxylate (547 mg) was dissolved in DMF (8 mL) and triethylamine (0.59 mL) followed by cyclopropylamine (0.491 mL) added. The reaction was stirred at 40°C for 2 hours then the mixture was vacuumed to dryness and partitioned between DCM (50 mL) and water (50 mL). The organic layer was dried over magnesium sulphate and vacuumed to dryness then

chromatographed on silica, eluting with 5% methanol in DCM, to give the desired material (351 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.25 (3H, d), 2.52 - 2.58 (1H, m), 2.67 - 2.69 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.76 (1H, d), 3.91 (3H, s), 3.96 - 4.00 (1H, m), 4.23 - 4.27 (1H, m), 4.58 (1H, s), 6.43 (1H, d), 7.14 (1H, s), 7.51 - 7.53 (2H, m), 8.22 - 8.25 (2H, m), 8.56 (1H, s)

Mass Spectrum; M+H$^+$ 412.

Methyl 6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidine-4-carboxylate

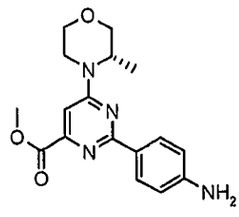


Methyl 2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (400 mg) was dissolved in dioxane (10 mL) and sodium bicarbonate (154 mg) and phenylchloroformate (0.154 mL) added dropwise. The mixture was stirred at RT for 16 hours then the dioxane removed under reduced pressure and the residue partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was dried over magnesium sulphate, filtered and evaporated to give the desired material as a brown foam (624 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.11 (1H, s), 3.47 - 3.54 (1H, m), 3.58 (1H, s), 3.63 - 3.67 (1H, m), 3.73 (1H, d), 3.91 (3H, s), 3.96 - 4.00 (1H, m), 4.27 (1H, s), 6.73 - 6.78 (1H, m), 7.14 - 7.20 (1H, m), 7.24 - 7.30 (2H, m), 7.43 - 7.48 (2H, m), 7.64 - 7.66 (2H, m), 8.32 - 8.34 (2H, m), 10.46 (1H, s)

Mass Spectrum; M+H$^+$ 449.

Methyl 2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate

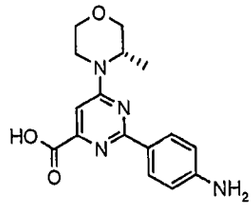


2-(4-Aminophenyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid (1.15 g) was dissolved in methanol (15 mL), sulfuric acid (0.01 mL) was added and the reaction was heated at 80°C for 24 h. A small quantity of activated molecular sieve 4A was added to the reaction and stirred for 2 h. The reaction was filtered, vacuumed to dryness then suspended in ethyl acetate (250 mL) and washed once with a saturated solution of sodium bicarbonate (250 mL). The organic layer was filtered, dried over magnesium sulphate and vacuumed to dryness to give the desired material as a brown solid (405 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.08 (1H, s), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.75 (1H, d), 3.89 (3H, s), 3.97 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 5.59 (2H, d), 6.59 - 6.63 (2H, m), 7.04 (1H, s), 8.06 - 8.08 (2H, m)

Mass Spectrum; M+H$^+$ 329.

2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid



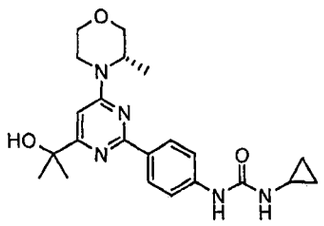
Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (1.00 g) was dissolved in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (10 mL). (4-Aminophenyl)boronic acid pinacol ester (1.21 g) and 2M sodium carbonate (5 mL) was then added and the solution and degassed for 5 min. Dichlorobis(triphenylphosphine) palladium catalyst (130 mg) was added and the reaction refluxed at 90°C for 18 h under nitrogen atmosphere. The reaction was allowed to cool, concentrated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was filtered and the volume reduced in vacuo. The resultant solution was acidified with concentrated hydrochloric acid and vacuumed to dryness give the desired material.

Mass Spectrum; M+H$^+$ 315.

The preparation of methyl 2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate was described earlier.

Example 37:

3-Cyclopropyl-1-[4-[4-(2-hydroxypropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



2-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol (70 mg) was dissolved in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (4 mL) and 4-(3-cyclopropylureido)phenylboronic acid (98 mg) and 2M sodium carbonate (1 mL) added. Dichlorobis(triphenylphosphine) palladium catalyst (10 mg) was added and the solution heated in a microwave reactor at 100°C for 0.5 h. The mixture was acidified with concentrated hydrochloric acid and loaded directly onto a SCX-2 column (10 g), column washed with methanol then product eluted with 7N ammonia in methanol, to give the desired material (55 mg) as a white solid.

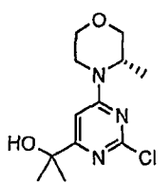
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.23 (3H, d), 1.45 (6H, s), 2.54 (1H, t), 3.19 - 3.23 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 (1H, d), 4.14 - 4.17 (1H, m), 4.50 (1H, s), 5.17 (1H, s), 6.41 (1H, d), 6.80 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.50 (1H, s)

Mass Spectrum; M+H$^+$ 412.

Test(a): 0.051 μM.

The preparation of 2-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol is described below.

2-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol



Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (300 mg) was dissolved in dry THF and cooled to –78°C. Methylmagnesium bromide (3.0M in diethyl ether, 0.74 mL) was added dropwise over 2 min then the reaction allowed to stir at –78°C for 20 min before allowing to warm to RT. The reaction was stirred for a further 20 min and then quenched with water (2 mL). The reaction was reduced to dryness and partitioned between ethyl acetate (50 mL) and water (50 mL) and the organic layer dried over magnesium sulphate and vacuumed to dryness to the desired material as a white solid (291 mg).

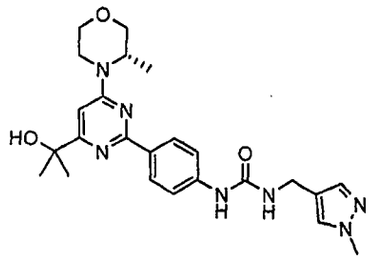
NMR Spectrum: (400.13 MHz, DMSO-d_6) δ 1.16 - 1.23 (3H, m), 1.36 (6H, s), 3.15 - 3.23 (1H, m), 3.40 - 3.47 (1H, m), 3.56 - 3.60 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (2H, m), 4.34 (1H, s), 5.28 (1H, s), 6.87 (1H, s).

Mass Spectrum; $M+H^+$ 272.

The preparation of methyl 2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate was described earlier.

Example 38:

1-[4-[4-(2-Hydroxypropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea



2-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol (70 mg) was dissolved in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (4 mL). 3-[(1-Methylpyrazol-4-yl)methyl]-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (115 mg) and 2M sodium carbonate (1 mL) were added. Dichlorobis(triphenylphosphine) palladium catalyst (10 mg) was added and the solution heated in a microwave reactor at 100°C for 0.5 h. The mixture was acidified with concentrated hydrochloric acid and loaded directly onto a SCX-2 column (10 g), column washed with methanol then product eluted with 7N ammonia in methanol, to give the desired material (55 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.45 (6H, s), 3.16 - 3.23 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.78 - 3.80 (1H, m), 3.75 - 3.81 (3H, s), 3.96 - 3.99 (1H, m), 4.13 (3H, d), 4.49 - 4.52 (1H, m), 5.17 (1H, s), 6.39 (1H, t), 6.80 (1H, s), 7.35 (1H, s), 7.47 - 7.49 (2H, m), 7.59 (1H, s), 8.22 - 8.24 (2H, m), 8.65 (1H, s)

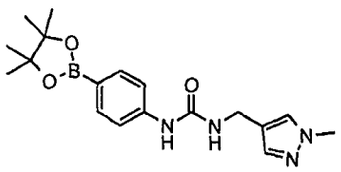
Mass Spectrum; M+H$^+$ 466.

Test (a): 1.3 μM.

The preparation of 2-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol was described earlier.

The preparation of 3-[(1-methylpyrazol-4-yl)methyl]-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea is described below.

3-[(1-Methylpyrazol-4-yl)methyl]-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea



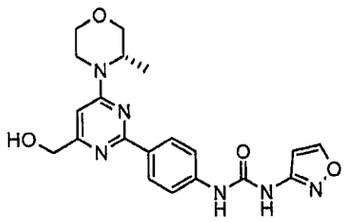
(4-Aminophenyl)boronic acid pinacol ester (200 mg) was dissolved in dry THF (5 mL) and sodium bicarbonate (116 mg) added followed by the dropwise addition of phenylchloroformate (0.115 mL). The mixture was stirred at RT for 1 hour. (1-Methylpyrazol-4-yl)methanamine (102 mg) was added and the reaction left to stir at RT for 2 h before being heated to 40°C for 16 h. The mixture was concentrated *in vacuo* and the residue partitioned between DCM (25 mL) and water (25 mL). The organics were dried over magnesium sulphate, filtered and vacuumed to dryness. The material was chromatographed on silica, eluting with ethyl acetate, to give the desired material (232 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.28 (12 H, s), 3.79 (3H, s), 4.11 (2H, d), 6.39 (1H, t), 7.34 (1H, s), 7.39 - 7.41 (2H, m), 7.52 - 7.54 (2H, m), 7.59 (1H, s), 8.56 (1H, s)

Mass Spectrum; M+H$^+$ 357.

Example 39:

1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea



[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (500 mg) was dissolved in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (10 mL). 3-(1,2-Oxazol-3-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (811 mg) and 2M aqueous sodium carbonate solution (4 mL) were then added to the solution and the resultant mixture degassed for 5 min. Dichlorobis(triphenylphosphine) palladium catalyst (73 mg) was added and the solution refluxed at 90°C for 7 h under nitrogen atmosphere. The reaction was allowed to cool then neutralised with concentrated hydrochloric acid and loaded directly onto a SCX-2 column (50 g), the column was washed with methanol and the product eluted with 7N ammonia in methanol. The material was further purified by chromatography on silica, eluting with 5% methanol in DCM, to give the desired material (318 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.20 - 3.24 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.16 - 4.19 (1H, m), 4.47 (2H, d), 4.50 (1H, s), 5.40 (1H, t), 6.69 (1H, s), 6.87 (1H, d), 7.53 - 7.56 (2H, m), 8.27 - 8.29 (2H, m), 8.75 - 8.75 (1H, m), 9.03 (1H, d), 9.60 (1H, s)

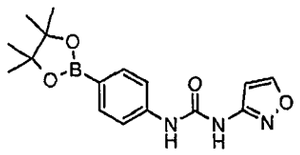
Mass Spectrum; $M+H^+$ 411.

Test(a): 0.075 μM.

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol has been described earlier.

The preparation of 3-(1,2-oxazol-3-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea is described below.

3-(1,2-Oxazol-3-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea



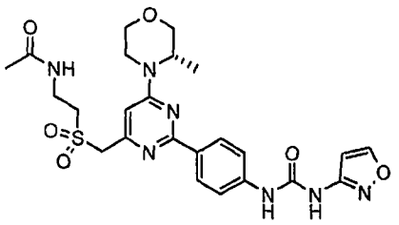
(4-Aminophenyl)boronic acid pinacol ester (1 g) was dissolved in dry THF (30 mL), sodium bicarbonate (576 mg) added followed by the dropwise addition of phenylchloroformate (0.575 mL). The mixture was stirred at RT for 1 hour then . 3-aminoisoxazole (0.506 mL) added and the reaction left to stir at 40°C for 16 h. More 3-aminoisoxazole (0.506 mL) and sodium bicarbonate (576 mg) were added and the reaction heated to 75°C for 8 h. before the mixture was concentrated *in vacuo* and partitioned between DCM (50 mL) and water (50 mL). The organic layer was dried over magnesium sulphate, filtered and vacuumed to dryness. The residue was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (1.05 g) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.29 (12 h, s), 5.89 (1H, d), 6.86 (1H, d), 7.47 - 7.49 (2H, m), 7.61 - 7.63 (2H, m), 8.32 (1H, t), 8.75 (1H, d)

Mass Spectrum; M+H$^+$ 330.

Example 40:

***N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(1,2-oxazol-3-ylcarbamoylamino)phenyl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide**



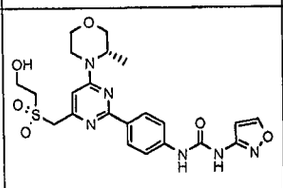
1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea (89 mg, 0.18 mmol) was partially dissolved in acetonitrile (4 mL) and *N*-(2-sulfanylethyl)acetamide (0.034 mL, 0.32 mmol) added. DBU (0.055 mL, 0.36 mmol) was added and the reaction stirred at RT for 6 h before being vacuumed to dryness. The material was dissolved in 1,4-Dioxane (2 mL) and a solution of m-CPBA (75%) (158 mg) in 1,4 Dioxane (2 mL), followed immediately by a solution of sodium permanganate (175 mg) in

water (1 mL), added. The reaction was allowed to stir at RT for 1 h then loaded onto a SCX-2 (10 g) column, the column was washed with methanol and the product eluted with 7N ammonia in methanol. The material was further purified by prep-HPLC (basic) to give the desired material as a solid (13 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.84 (3H, s), 3.24 (1H, d), 3.52 (2H, t), 3.54 (1H, s), 3.58 (2H, t), 3.65 - 3.68 (1H, m), 3.79 (1H, d), 3.98 - 4.02 (1H, m), 4.20 (1H, s), 4.54 (3H, m), 6.82 (1H, s), 6.88 (1H, d), 7.56 - 7.59 (2H, m), 8.16 - 8.17 (1H, m), 8.28 - 8.31 (2H, m), 8.76 - 8.77 (1H, m), 9.09 (1H, d), 9.62 (1H, s)

Mass Spectrum; M+H$^+$ 544.

The following compounds was prepared in an analogous fashion from 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea and the appropriate thiol.

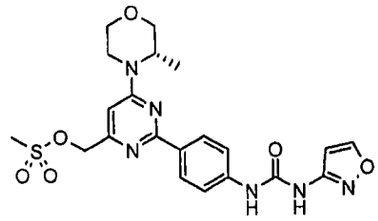
Example	Structure	NAME	LCMS MH+
40a		1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	503

Example 40a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.24 (1H, d), 3.53 (3H, t), 3.65 - 3.68 (1H, m), 3.79 (1H, d), 3.93 (2H, q), 3.98 - 4.02 (1H, m), 4.20 (1H, s), 4.51 (3H, d), 5.20 (1H, t), 6.80 (1H, s), 6.88 - 6.88 (1H, m), 7.58 (2H, d), 8.29 - 8.31 (2H, m), 8.76 (1H, s), 9.09 (1H, d), 9.64 (1H, s).

Test(c): Example(40) 0.1 μM; Example(40a) 0.055 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea is described below.

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea

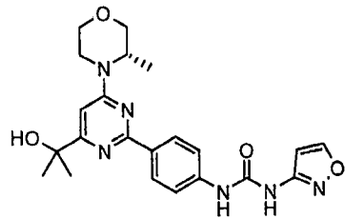


1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea (300 mg) was partially dissolved in DCM (10 mL) and triethylamine (0.153 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.086 mL) and the reaction was stirred for 45 mins at RT. The reaction was then washed with water (2 mL) and dried over magnesium sulphate. The solution was vacuumed to dryness to give the desired material as a yellow solid.

Mass Spectrum; $M+H^+$ 489.

Example 41:

1-[4-[4-(2-Hydroxypropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea



2-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol (160 mg, 0.59 mmol) was added to 3-(1,2-oxazol-3-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (242 mg) and Dichlorobis(triphenylphosphine) palladium catalyst (21 mg) in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (6 mL). The reaction was heated to 100°C for 30 minutes in the microwave reactor and cooled to RT. The reaction mixture was acidified with 2M hydrochloric acid and the crude material loaded onto a SCX (10 g) column, the desired material was eluted with 7N ammonia in methanol. The material was further purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material (52 mg) as a white solid.

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.47 (6H, s), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.16 - 4.19 (1H, m), 4.51 - 4.53 (1H, m), 5.20 (1H, s), 6.84 (1H, s), 6.88 (1H, d), 7.55 - 7.57 (2H, m), 8.30 - 8.32 (2H, m), 8.76 (1H, d), 9.06 (1H, s), 9.61 (1H, s)

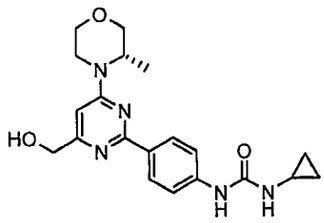
Mass Spectrum: $M+H^+$ 439.4

Test(c): 0.047 μM.

The preparation of both 2-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]propan-2-ol and 3-(1,2-oxazol-3-yl)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea were described earlier.

Example 42:

3-Cyclopropyl-1-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (3.30 g) was dissolved in an 18% DMF in a mixture of 7:3:2 DME:water:ethanol (50 mL). 4-(3-cyclopropylureido)phenylboronic acid (4.92 g) and 2M sodium carbonate (5 mL) were then added and the solution degassed for 5 min. Dichlorobis(triphenylphosphine) palladium catalyst (476 mg) was then added to the solution and refluxed at 90°C for 7h under a nitrogen atmosphere. The reaction was allowed to cool, evaporated, and the residue partitioned between DCM (200 mL) and water (200 mL). The organic layer was dried over magnesium sulphate, evaporated, and purified by chromatography on silica, eluting with 5% methanol in DCM, to give the desired material (4.33 g) as a yellow solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.23 (3H, d), 2.54 - 2.58 (1H, m), 3.17 - 3.22 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.45 (2H, d), 4.49 (1H, d), 5.38 (1H, t), 6.41 (1H, d), 6.66 (1H, s), 7.46 - 7.50 (2H, m), 8.18 - 8.22 (2H, m), 8.49 (1H, s),

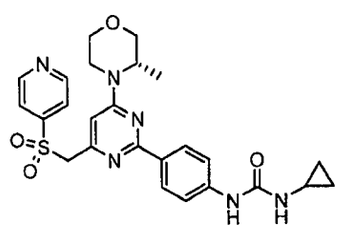
Mass Spectrum; M+H$^+$ 384.

Test(a): 0.19 μM.

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol has been described earlier.

Example 43:

3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea



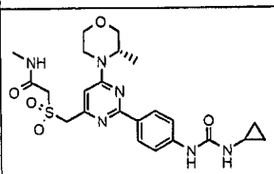
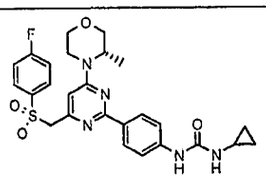
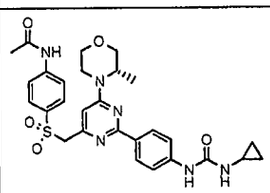
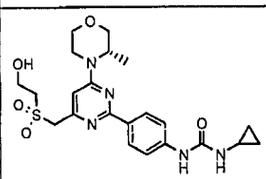
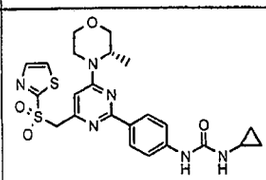
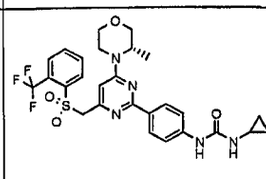
3-Cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (100 mg, 0.24 mmol) was partially dissolved in acetonitrile (4 mL) and pyridine-4-thiol (0.38 mmol) added. The reaction was stirred for 1 h at RT then DBU (0.065 mL, 0.43 mmol) added and the reaction stirred at RT for 18 h. The reaction was evaporated to dryness and dissolved in 1,4-Dioxane (2 mL). A solution of m-CPBA (75%) (94 mg) in 1,4 Dioxane (2 mL), followed immediately by a solution of sodium permanganate (104 mg) in water (1 mL), was added to the reaction and allowed to stir at RT for 1 h. A further solution of m-CPBA (75%) (94 mg) in 1,4 Dioxane (1 mL), followed immediately by a solution of sodium permanganate (104 mg) in water (0.5 mL), was added and reaction stirred at RT for 1 h. The reaction mixture was loaded onto a SCX-2 (10 g) column, the column was washed with methanol and the product eluted with 7N ammonia in methanol. The material was further purified by prep-HPLC (basic) to give the desired material as a solid (10 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.21 (3H, d), 2.58 - 2.61 (1H, m), 3.15 - 3.25 (1H, m), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.10 - 4.14 (1H, m), 4.38 (1H, s), 4.86 (2H, t), 6.41 - 6.42 (1H, m), 6.71 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.81 - 7.82 (2H, m), 8.50 (1H, s), 8.90 - 8.91 (2H, m)

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17 337/09

Mass Spectrum; $M+H^+$ 509.

The following compounds were prepared in an analogous fashion using the appropriate thiol.

Example	Structure	NAME	LCMS MH+
43a		2-[[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-N-methyl-acetamide	503
43b		3-cyclopropyl-1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	526
43c		N-[4-[[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]phenyl]acetamide	565
43d		3-cyclopropyl-1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	476
43e		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	515
43f		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	576

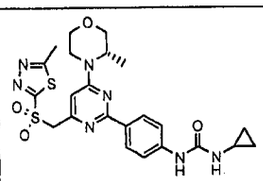
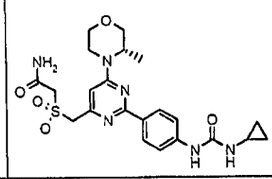
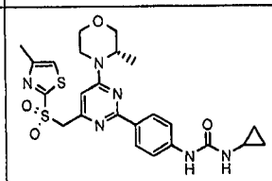
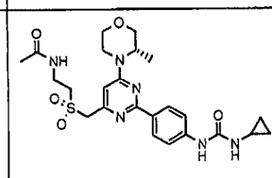
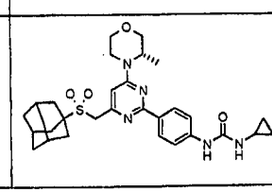
Organizacion y
Digitalizacion CSA Ltda

Patente de Invención

DKA

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3/5

Example	Structure	NAME	LCMS MH+
43g		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	530
43h		2-[[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]acetamide	489
43i		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	529
43j		N-[2-[[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide	517
43k		1-[4-[4-(1-adamantylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea	598

Example 43a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.23 - 1.25 (3H, m), 2.57 - 2.60 (1H, m), 2.67 - 2.70 (3H, m), 3.19 - 3.25 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.15 - 4.19 (1H, m), 4.29 (2H, s), 4.48 (1H, s), 4.67 (2H, s), 6.43 - 6.44 (1H, m), 6.77 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.31 (1H, t), 8.54 (1H, s)

Example 43b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.20 (3H, d), 2.52 - 2.60 (1H, m), 3.15 - 3.20 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H,

m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.10 - 4.13 (1H, m), 4.38 (1H, s), 4.71 (2H, s), 6.40 (1H, d), 6.65 (1H, s), 7.38 - 7.41 (2H, m), 7.43 - 7.48 (2H, m), 7.79 (2H, d), 7.85 - 7.89 (2H, m), 8.51 (1H, s)

Example 43c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.19 (3H, d), 2.13 (3H, s), 2.53 - 2.61 (1H, m), 3.15 - 3.20 (1H, m), 3.43 - 3.50 (1H, m), 3.60 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.09 (1H, s), 4.34 (1H, s), 4.60 (2H, s), 6.41 - 6.42 (1H, m), 6.55 (1H, s), 7.39 (2H, d), 7.70 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.48 (1H, s), 10.37 (1H, s)

Example 43d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (3H, d), 2.59 - 2.61 (1H, m), 3.15 - 3.20 (1H, m), 3.51 (3H, t), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.92 (2H, q), 3.97 - 4.01 (1H, m), 4.16 - 4.19 (1H, m), 4.50 (3H, s), 5.18 (1H, t), 6.44 (1H, d), 6.76 (1H, s), 7.50 - 7.52 (2H, m), 8.21 - 8.23 (2H, m), 8.54 (1H, s)

Example 43e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.20 (3H, d), 2.52 - 2.61 (1H, m), 3.15 - 3.20 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.12 (1H, d), 4.40 (2H, s), 4.90 - 4.91 (1H, m), 6.42 (1H, d), 6.71 (1H, s), 7.40 - 7.43 (2H, m), 7.84 (2H, d), 8.27 - 8.29 (2H, m), 8.50 (1H, s)

Example 43f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.20 - 1.22 (3H, m), 2.53 (1H, m), 3.17 (1H, d), 3.49 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.95 - 3.99 (1H, m), 4.12 (1H, d), 4.40 (1H, s), 4.74 - 4.75 (2H, m), 6.42 - 6.42 (1H, m), 6.70 (1H, s), 7.37 (2H, d), 7.72 (2H, d), 7.80 (1H, d), 7.90 (2H, t), 8.08 (1H, d), 8.48 (1H, s)

Example 43g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.42 (2H, d), 0.63 - 0.67 (2H, m), 1.23 (3H, d), 2.53 (1H, d), 2.80 (3H, s), 3.20 (1H, d), 3.48 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 4.12 (1H, d), 4.40 (2H, s), 5.04 (2H, t), 6.44 (1H, s), 6.80 (1H, s), 7.43 (2H, d), 7.79 (2H, d), 8.53 (1H, s)

Example 43i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.21 (3H, d), 2.60 - 2.61 (1H, m), 3.20 (1H, d), 3.34 - 3.39 (3H, s), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.12 (1H, d), 4.41 (1H, s), 4.86 - 4.87 (2H, m), 6.41 - 6.42 (1H, m), 6.71 (1H, s), 7.41 - 7.44 (2H, m), 7.82 (1H, d), 7.87 (2H, d), 8.51 (1H, s)

Example 43j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (3H, t), 1.83 (3H, s), 2.52 - 2.60 (1H, m), 3.19 - 3.25 (1H, m), 3.47 - 3.50 (2H, m), 3.52 (2H, d), 3.56 (2H, d), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.12 (1H, d),

4.50 (2H, d), 6.43 (1H, d), 6.78 (1H, s), 7.50 (2H, d), 8.19 - 8.22 (2H, m), 8.54 (1H, s), 9.00 (1H, s)

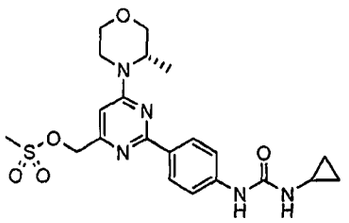
Example 43k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (3H, d), 1.67 (6H, d), 2.03 (6H, s), 2.12 (3H, s), 2.53 - 2.60 (1H, m), 3.20 - 3.24 (1H, m), 3.47 - 3.51 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.12 (1H, d), 4.39 - 4.45 (3H, m), 6.43 (1H, d), 6.73 (1H, s), 7.49 - 7.51 (2H, m), 8.22 (2H, d), 8.53 (1H, s)

Test(a): Example(43) 0.076 μM; Example(43a) 0.087 μM; Example(43b) 0.15 μM; Example(43c) 0.013 μM; Example(43d) 0.011 μM; Example(43e) 0.13 μM; Example(43f) 0.11 μM; Example(43h) 0.0071 μM; Example(43i) 0.058 μM; Example(43j) 1.8 μM.

Test(c): Example(43g) 1.9 μM; Example(43k) 2.9 μM

The preparation of 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea is described below.

3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea

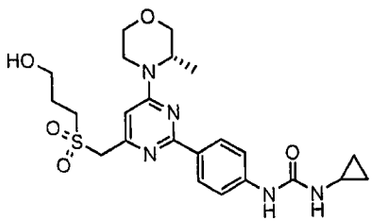


3-Cyclopropyl-1-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea (1.83 g) was partially dissolved in DCM (50 mL) and triethylamine (1 mL) and the solution was cooled to 0°C. Methane sulfonyl chloride was added (0.56 mL) and the reaction was stirred for 45mins at RT. The reaction was then washed with water (10 mL) and the organics dried over magnesium sulphate. The solution was vacuumed to dryness to give the desired material as a yellow solid.

Mass Spectrum; $M+H^+$ 462.

Example 44:

3-Cyclopropyl-1-[4-[4-(3-hydroxypropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



Sodium permanganate monohydrate (38 mg, 0.24 mmol) was added to m-CPBA (33.2 mg, 0.19 mmol) and 3-cyclopropyl-1-[4-[4-(3-hydroxypropylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea (44 mg, 0.10 mmol) in Dioxane (2 mL) and Water (1 mL) at 20°C. The resulting solution was stirred at 20 °C for 45 minutes and the mixture loaded onto a SCX-3 (5 g) column, the desired product was eluted from the column using 7M ammonia in methanol. The material was further purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material (19 mg) as a white solid.

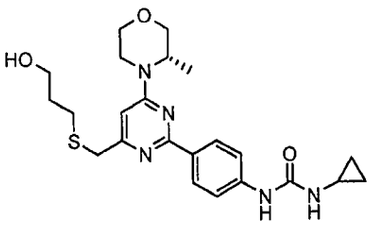
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.24 (3H, d), 1.92 - 1.99 (2H, m), 2.53 - 2.60 (1H, m), 3.18 - 3.26 (1H, m), 3.39 (2H, q), 3.47 - 3.50 (1H, m), 3.55 (2H, q), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.16 - 4.19 (1H, m), 4.46 (3H, s), 4.72 (1H, t), 6.43 (1H, d), 6.78 (1H, s), 7.49 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.53 (1H, s)

Mass Spectrum; $M+H^+$ 490

Test(a): 1.8 μM.

The preparation of 3-cyclopropyl-1-[4-[4-(3-hydroxypropylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea is described below.

3-Cyclopropyl-1-[4-[4-(3-hydroxypropylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



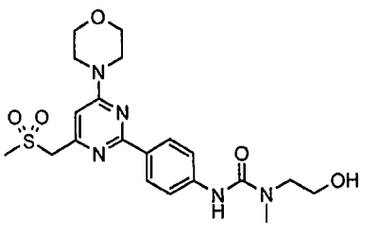
3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (100 mg) was partially dissolved in acetonitrile (4 mL) and added to 3-sulfanylpropan-1-ol (0.38 mmol). The reactions was stirred for 1 h at RT. DBU (0.065uL) was added to the reaction and the mixture left to stir at RT for 18 h. The mixture was concentrated *in vacuo* and purified by prep-HPLC (basic) to give the desired material (44 mg) as a white solid.

Mass Spectrum; $M+H^+$ 458.

The preparation of 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 45:

1-(2-Hydroxyethyl)-1-methyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea

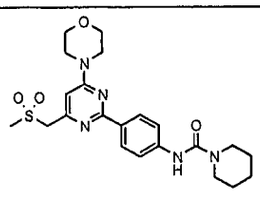
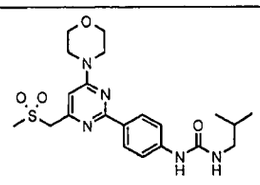
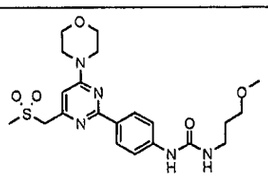
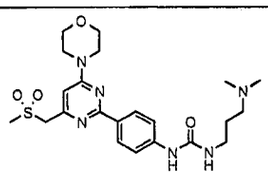
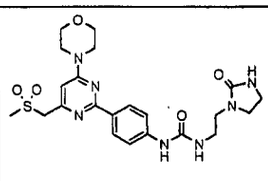


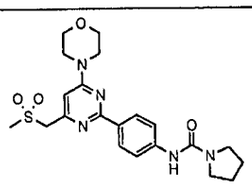
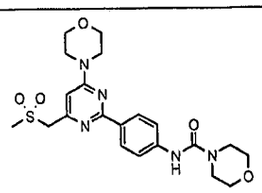
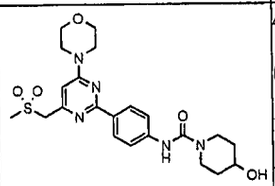
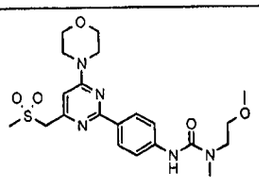
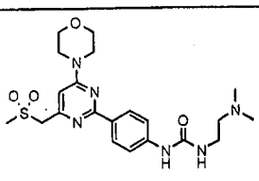
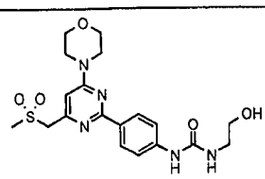
A solution of phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate (94 mg, 2 mmol) and triethylamine (0.09 mL,9.2 mmol) in NMP (1 mL) was added to 2-methylaminoethanol (10 mmol) . The mixture was heated at 70°C for 2 hours and the reaction purified by prep HPLC, to give the desired compound.

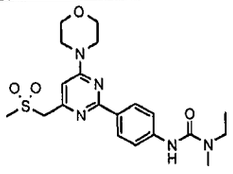
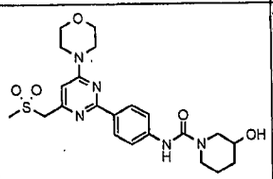
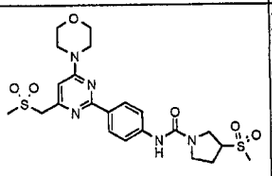
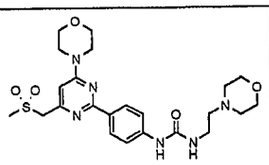
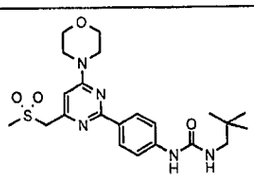
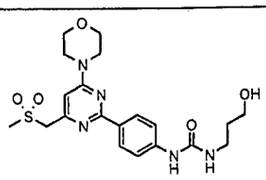
LCMS Spectrum: MH+ 450, Retention Time 2.07 min.

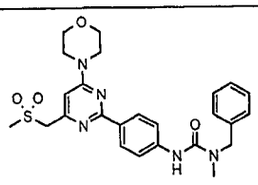
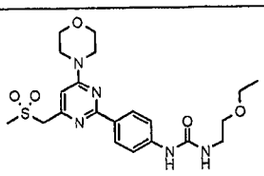
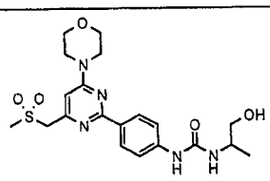
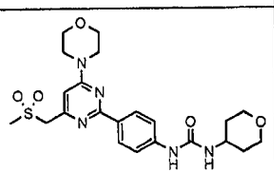
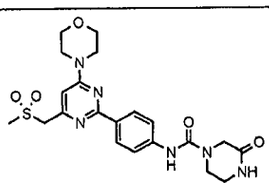
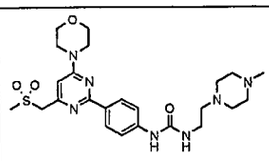
The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-

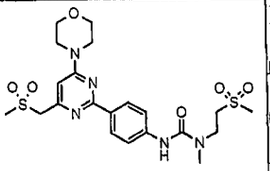
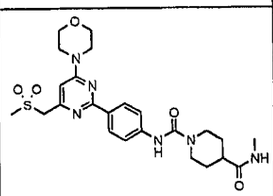
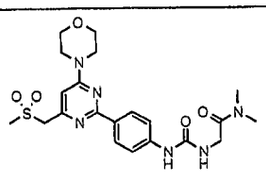
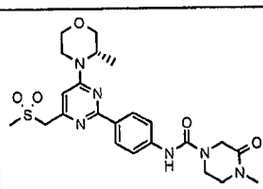
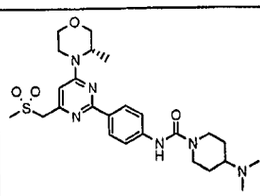
[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention Time (min)
45a		N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	460	2.74
45b		1-(2-methylpropyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	448	2.76
45c		1-(3-methoxypropyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	464	2.46
45d		1-(4-dimethylaminobutyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	491	2.8
45e		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-[2-(2-oxoimidazolidin-1-yl)ethyl]urea	504	2.27

Example	Structure	NAME	LCMS MH+	Retention Time (min)
45f		N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide	446	2.56
45g		N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]morpholine-4-carboxamide	462	2.4
45h		4-hydroxy-N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	476	2.28
45i		1-(1-methoxypropan-2-yl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	464	2.51
45j		1-(2-dimethylaminoethyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	463	2.52
45k		3-(2-hydroxyethyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	436	2.21

Example	Structure	NAME	LCMS MH+	Retention Time (min)
45l		1-ethyl-1-methyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	434	2.54
45m		3-hydroxy-N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	476	2.35
45n		3-methylsulfonyl-N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide	524	2.34
45o		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-(2-morpholin-4-ylethyl)urea	505	2.14
45p		1-(2,2-dimethylpropyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	462	2.68
45q		3-(3-hydroxypropyl)-1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	450	2.05

Example	Structure	NAME	LCMS MH+	Retention Time (min)
45r		1-benzyl-1-methyl-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	496	2.74
45s		1-(2-ethoxyethyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	464	2.29
45t		1-(1-hydroxypropan-2-yl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	450	2.09
45u		1-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-(oxan-4-yl)urea	476	2.21
45v		N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]-3-oxo-piperazine-1-carboxamide	475	2.00
45w		1-[2-(4-methylpiperazin-1-yl)ethyl]-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	518	2.11

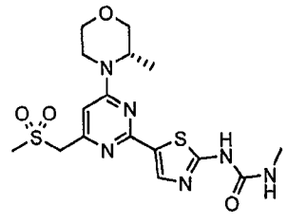
Example	Structure	NAME	LCMS MH+	Retention Time (min)
45x		1-methyl-1-(2-methylsulfonylethyl)-3-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]urea	512	2.14
45y		N'-methyl-N-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]piperidine-1,4-dicarboxamide	516	2.07
45z		N,N-dimethyl-2-[[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamoylamino]acetamide	477	2.11
45aa		4-methyl-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-oxo-piperazine-1-carboxamide	489	1.23
45ab		4-dimethylamino-N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]piperidine-1-carboxamide	518	1.6

Test(a): Example(45) 0.66 μM; Example(45a) 0.63 μM; Example(45b) 0.12 μM; Example(45c) 0.082 μM; Example(45d) 0.56 μM; Example(45e) 0.56 μM; Example(45f) 1.6 μM; Example(45g) 0.041 μM; Example(45h) 0.14 μM; Example(45i) 3 μM; Example(45j) 0.72 μM; Example(45k) 0.049 μM; Example(45l) 1.1 μM; Example(45m) 0.17 μM; Example(45n) 0.63 μM; Example(45o) 0.9 μM; Example(45p) 0.92 μM; Example(45q) 0.032 μM; Example(45r) 0.41 μM; Example(45s) 0.3 μM; Example(45t) 0.082 μM; Example(45u) 0.42 μM; Example(45v) 1.2 μM; Example(45w) 0.74 μM; Example(45x) 1.1 μM; Example(45y) 1.2 μM; Example(45z) 1 μM; Example(45aa) 0.83 μM; Example(45ab) 0.39 μM.

The preparation of phenyl *N*-[4-[4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidin-2-yl]phenyl]carbamate and phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate were described earlier.

Example 46:

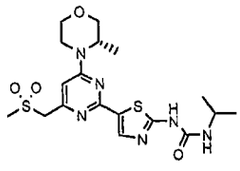
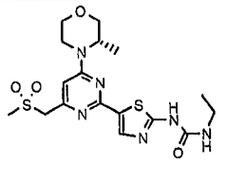
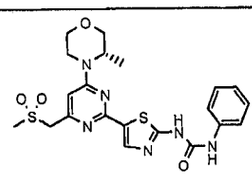
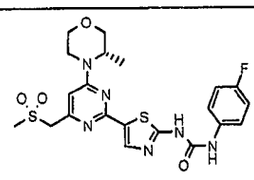
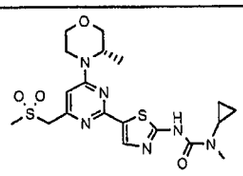
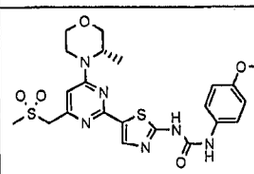
3-Methyl-1-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea

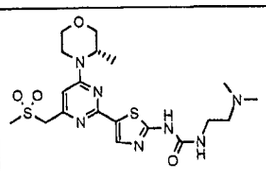
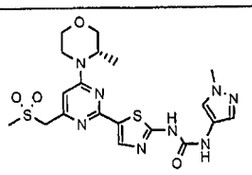
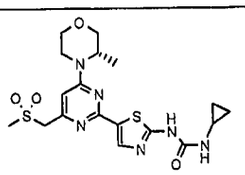


A mixture of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate (100 mg, 0.2 mmol), methylamine (1 mmol), and triethylamine (0.085 mL, 0.6 mmol) in NMP (2 mL), was heated at 70°C for 2 hours. The material was purified by prep HPLC to give the desired material as a white solid (27 mg).

LCMS Spectrum: MH+ 427, Retention Time 1.44 min

The following compounds were prepared in an analogous fashion.

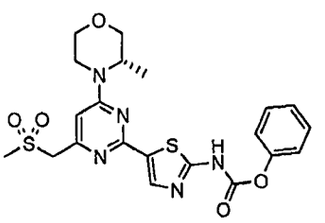
Example	Structure	NAME	LCMS MH+	Retention Time (min)
46a		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-3-propan-2-yl-urea	455	1.84
46b		1-ethyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	441	1.48
46c		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-3-phenyl-urea	489	1.86
46d		3-(4-fluorophenyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	507	1.88
46e		1-cyclopropyl-1-methyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	467	1.69
46f		3-(4-methoxyphenyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	519	1.82

Example	Structure	NAME	LCMS MH+	Retention Time (min)
46g		3-(2-dimethylaminoethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	484	1.39
46h		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-3-(1-methylpyrazol-4-yl)urea	493	1.25
46i		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	453	1.59

Test(a): Example(46) 0.14 μM; Example(46a) 0.35 μM; Example(46b) 0.0061 μM; Example(46c) 0.45 μM; Example(46d) 0.85 μM; Example(46e) 0.71 μM; Example(46f) 1.2 μM; Example(46g) 0.73 μM; Example(46h) 0.063 μM; Example(46i) 0.097 μM.

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate is described below.

Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate

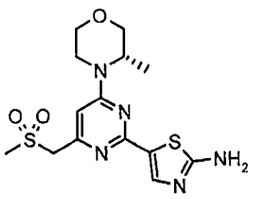


A solution of 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-amine (1 g, 2.71 mmol), sodium hydrogen carbonate (342 mg), and phenyl

chloroformate (0.511 mL) in dioxane was stirred at RT for 2 hours then concentrated *in vacuo*. The residue was partitioned between DCM and water and the organic layer dried over sodium sulphate and evaporated to give a foam. The foam was triturated with a mixture of hexane and diethyl ether to give the desired material as a white solid (1.1 g).

LCMS Spectrum MH+490, retention time 2.17, method monitor acid.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-amine

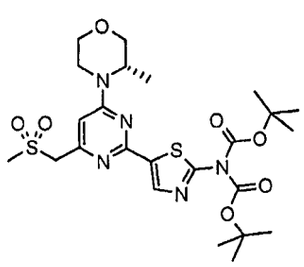


A solution of *tert*-butyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-*N*-[(2-methylpropan-2-yl)oxycarbonyl]carbamate (1.7 g, 2.9 mmol) and TFA (8 mL) in DCM (15 mL) was stirred at RT for 16 hours. The solvent was removed under reduced pressure and the residue made basic with aqueous ammonia solution. The product was extracted with ethyl acetate, the organics dried over sodium sulphate, filtered and evaporated to give the desired material as a white solid (1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.16 - 1.22 (3H, m), 3.13 - 3.18 (1H, m), 3.19 (3H, s), 3.43 - 3.50 (1H, m), 3.60 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, dd), 4.04 (1H, d), 4.37 (1H, s), 4.40 (2H, s), 5.75 (1H, s), 6.64 (1H, s), 7.40 (2H, s), 7.73 (1H, s)

LCMS Spectrum: MH+ 370, retention time 1.38 mins, method monitor base.

tert-Butyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-*N*-[(2-methylpropan-2-yl)oxycarbonyl]carbamate

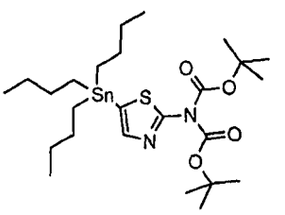


A mixture of *tert*-butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(5-tributylstannyl-1,3-thiazol-2-yl)carbamate (3 g, 5.1 mmol), 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1 g, 3.2 mmol) and palladium tetrakis (triphenylphosphine) (50 mg), in toluene (10 mL) was heated at 105°C for 2 hours under nitrogen. The mixture was chromatographed on silica to give the desired material (1.7 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.53 (9H, s), 3.18 (3H, s), 3.55 (1H, t), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, d), 4.10 (1H, s), 3.90 (1H, s), 3.98 (2H, s), 6.80 (1H, s), 8.18 (1H, s)

LCMS Spectrum: MH+ 570, retention time 2.89mins, method monitor base.

tert-Butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(5-tributylstannyl-1,3-thiazol-2-yl)carbamate

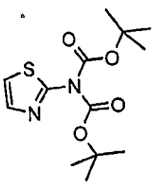


n-Butyl lithium (1.6M in hexanes, 30 mL, 0.48 mol), was added to diisopropylamine (6.7 mL, 0.48mol) in THF (480 mL) at 0°C. The mixture was stirred at 0°C for 30 mins then cooled to –78°C. *tert*-Butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(1,3-thiazol-2-yl)carbamate (12 g, 0.05 mol) was added and solution stirred for 30 minutes. Tributyltin chloride (16.3 mL) was added and solution stirred for 30minutes before allowing to warm to RT. The reaction was quenched with a saturated aqueous solution of ammonium chloride (20 mL) and the product extracted with ethyl acetate. The organics were dried over sodium sulphate, concentrated *in vacuo* and chromatographed on silica, eluting with 5-15% ethyl acetate in hexane, to give the desired material as a clear oil (9 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 (18H, s), 7.50 (1H, d), 7.55 (1H, d)

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tert-Butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(1,3-thiazol-2-yl)carbamate



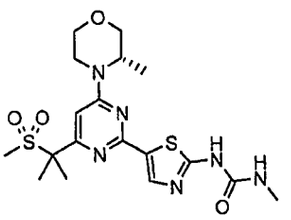
A solution of 2-aminothiazole (5 g, 0.05 mol), (2-methylpropan-2-yl)oxycarbonyl tert-butyl carbonate (27.8 g, 0.15 mol) and DMAP (100 mg) in THF (100 mL) was stirred at reflux overnight. The mixture was allowed to cool and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 8% ethyl acetate in hexane, to give the desired material as a white solid (12 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 (18H, s), 7.50 (1H, d), 7.55 (1H, d)

LCMS Spectrum MH- 299, retention time 2.6 mins, method monitor base

Example 47:

3-Methyl-1-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea

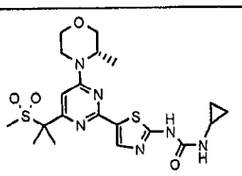
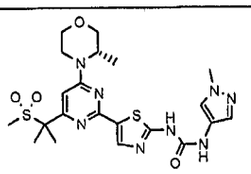
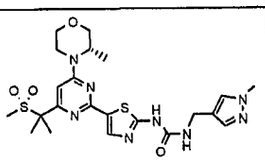
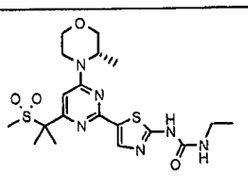


A solution of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate (200 mg, 0.39 mmol), methyl amine (1.5 mmol) and triethylamine (0.163 mL, 1.16 mmol) in NMP (3 mL) was heated at 70°C for 2 hours. The mixture was chromatographed on silica, eluting with 0-5% methanol in ethyl acetate to give the desired material.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.70 (6H, s), 3.19 (3H, s), 3.20 (1H, dd), 3.45 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.52 (1H, s), 6.40 (1H, s), 6.65 (1H, s), 8.09 (1H, s), 10.70 (1H, s)

LCMS Spectrum: MH+ 455, retention time 1.78 mins.

The following compounds were prepared in an analogous fashion.

Example	Structure	NAME	LCMS MH+	Retention Time (min)
47a		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	481	1.94
47b		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-3-(1-methylpyrazol-4-yl)urea	521	1.62
47c		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]-3-[(1-methylpyrazol-4-yl)methyl]urea	535	1.81
47d		1-ethyl-3-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]urea	469	1.95

Example 47a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.45 (2H, q), 0.68 (2H, q), 1.20 (3H, d), 1.70 (6H, s), 3.05 (3H, s), 3.20 (1H, dd), 3.48 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, dd), 4.18 (1H, d), 4.55 (1H, s), 6.68 (1H, s), 6.75 (1H, s), 8.05 (1H, s), 11.0 (1H, s).

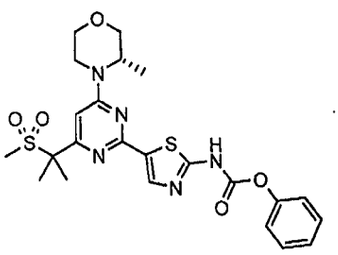
Example 47b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.70 (6H, s), 3.03 (3H, s), 3.20 (1H, dd), 3.48 (1H, dd), 3.65 (1H, d), 3.70-3.80 (4H, m), 3.99 (1H, dd), 4.15 (1H, d), 4.53 (1H, s), 6.70 (1H, s), 7.42 (1H, s), 7.82 (1H, s), 8.10 (1H, s), 8.72 (1H, s), 10.75 (1H, s)

Example 47c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.70 (6H, s), 2.68 (3H, s), 3.05 (3H, s), 3.18 (1H, dd), 3.48 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, d), 4.05 (1H, q), 4.18 (2H, s), 4.51 (1H, s), 6.68 (1H, s), 6.78 (1H, s), 7.35 (1H, s), 7.62 (1H, s), 8.09 (1H, s), 10.60 (1H, s).

Test(a): Example(47) 0.26 μM; Example(47a) 1.2 μM; Example(47b) 0.41 μM; Example(47c) 1.4 μM; Example(47d) 0.97 μM.

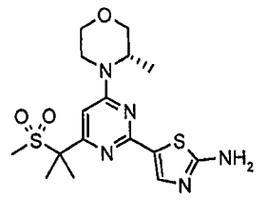
The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate is described below.

Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-yl]carbamate



A mixture of 5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-amine (1.05 g, 2.6 mmol), phenyl chloroformate (618 mg, 3.9 mmol) and sodium hydrogen carbonate (311 mg, 3.9 mmol) in dioxane (10 mL) was stirred at RT for 2 hours then diluted with ethyl actetate and washed with water (150 mL) and brine (100 mL). The organics were dried over magnesium sulphate and concentrated *in vacuo*. The residue was recrystallised from diethyl ether and hexane to give the desired product as a beige solid (1 g).

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidin-2-yl]-1,3-thiazol-2-amine



A mixture of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidine (1.2 g, 3.6 mmol), *tert*-butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(5-tributylstannyl-1,3-thiazol-2-yl)carbamate (3.1 g, 5.2 mmol), and palladium tetrakis (triphenylphosphine) (200 mg) in toluene (30 mL) was heated at 110°C under a nitrogen atmosphere overnight. The mixture was diluted with ethyl acetate and washed with water. The organics were dried over magnesium sulphate, filtered and evaporated. The residue was dissolved in DCM (50 mL) and trifluroacetic acid (15 mL) added. After allowing to stir for 2 hours the mixture was evaporated and water added. The mixture was made basic with aqueous ammonia solution and extracted with ethyl acetate. The organics were dried over magnesium sulphate, filtered and evaporated to a solid. The residue was triturated with a mixture of diethyl ether and hexane to give the desired material (1.05 g).

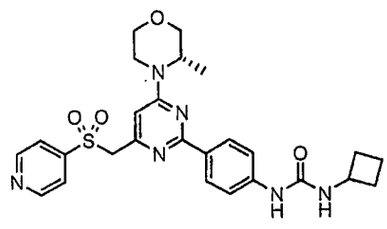
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.65 (6H, s), 3.0 (3H, s), 3.15 (3H, dd), 3.45 (1H, dd), 3.60 (1H, dd), 3.71 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.50 (1H, S), 6.60 (1H, s), 7.35 (2H, s), 7.75 (1H, s).

LCMS Spectrum: MH+ 398 retention time 1.76 mins, method monitor base

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(2-methylsulfonylpropan-2-yl)pyrimidine and *tert*-butyl *N*-[(2-methylpropan-2-yl)oxycarbonyl]-*N*-(5-tributylstannyl-1,3-thiazol-2-yl)carbamate was described earlier.

Example 48:

3-Cyclobutyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea



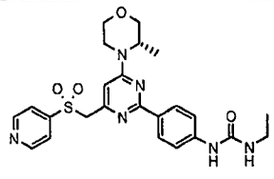
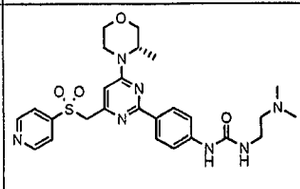
316

Cyclobutylamine (0.074 mL, 0.87 mmol) was added to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (0.095 g, 0.17 mmol) and triethylamine (0.073 mL, 0.52 mmol) in DMF (3 mL) then warmed to 50°C under nitrogen. The resulting solution was stirred at 50 °C for 2 hours. The solvent was removed *in vacuo* and the crude product purified by prep HPLC to give the desired material as a white solid (0.089 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20-1.22(3H, d), 1.59-1.66(2H, m), 1.82-1.92(2H, m), 2.18-2.25(2H, m), 3.15-3.22(1H, td), 3.45-3.52(1H, td), 3.62-3.65(1H, td), 3.75-3.78(1H, d), 3.96-3.99(1H, dd), 4.09-4.17(2H, m), 4.39(1H, bs), 4.87(2H, s), 6.52-6.54(1H, d), 6.71(1H, s), 7.33-7.35(2H, d), 7.64-7.67(2H, d), 7.80-7.82(2H, q), 8.61(1H, s), 8.90-8.91(2H, q).

LCMS Spectrum: MH+ 523 retention time 1.96 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
48a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	497	1.74
48b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	540	1.83

Example 48a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.05-1.09(3H, t), 1.20-1.22(3H, d), 3.09-3.16(2H, m), 3.16-3.22(1H, td), 3.45-3.52(1H, td), 3.62-3.65(1H, dd), 3.75-3.78(1H, d), 3.96-

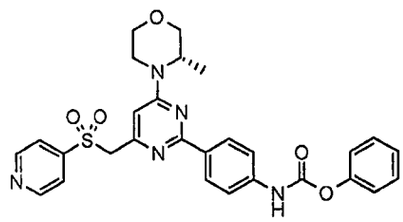
3.99(1H, dd), 4.10-4.14(1H, d), 4.39(1H, bs), 4.88(2H, s), 6.14-6.17(1H, t), 6.71(1H, s), 7.35-7.37(2H, d), 7.65-7.67(2H, d), 7.81-7.82(2H, d), 8.64(1H, s), 8.90-8.91(2H, d).

Example 48b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20-1.21(3H, d), 2.41(2H, bs), 2.74(3H, s), 2.90(3H, s), 3.15-3.23(1H, td), 3.2-3.4(2H, m), 3.45-3.51(1H, td), 3.61-3.65(1H, dd), 3.75-3.78(1H, d), 3.96-3.99(1H, dd), 4.10-4.13(1H, d), 4.39(1H, bs), 4.87(2H, s), 6.25(1H, t), 6.72(1H, s), 7.35-7.37(2H, d), 7.65-7.67(2H, d), 7.81-7.82(2H, q), 7.96(1H, s), 8.89-8.91(2H, d).

Test(c): Example(48) 0.038 μM; Example(48a) 0.25 μM.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate

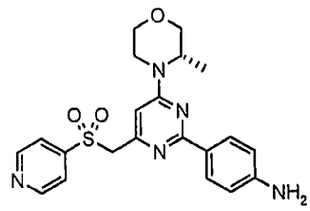


Phenyl chloroformate (0.029 mL, 0.23 mmol) was added to a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]aniline (0.097 g, 0.23 mmol) and sodium bicarbonate (0.029 g, 0.34 mmol) in dioxane at RT. The resulting slurry was stirred at RT for 2 hours. Additional phenyl chloroformate (2 x 0.005mL) was added to drive the reaction to completion. Water was then added to the reaction and the solid filtered, and dried in a vacuum oven to give the desired material as an off-white solid (0.098 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21-1.23(3H, d), 3.16-3.24(1H, td), 3.46-3.52(1H, td), 3.62-3.66(1H, dd), 3.76-3.79(1H, d), 3.96-4.00(1H, dd), 4.13-4.16(1H, bd), 4.41(1H, bs), 4.90(2H, s), 6.76(s, 1H), 7.23-7.31(3H, m), 7.43-7.51(4H, m), 7.74-7.77(2H, m), 7.81-7.83(2H, dd), 8.90-8.92(2H, dd), 10.39(1H, s).

LCMS Spectrum: MH+ 546 retention time 2.35 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]aniline

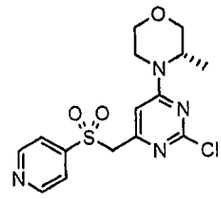


trans-Dichlorobis(triphenylphosphine)palladium (II) (0.039 g, 0.06 mmol) was added to a mixture of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (0.411 g, 1.11 mmol), 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.366 g, 1.67 mmol) and sodium carbonate (0.233 mL, 5.56 mmol) in 18% DMF in a mixture of 7:3:2 DME:water:ethanol (100mL) at RT under nitrogen. The resulting solution was stirred at 90 °C for 5 hours. The reaction was cooled and diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate and the combined organics dried ($MgSO_4$), filtered and evaporated. The crude product was chromatographed on silica, eluting with 0 - 5% methanol in DCM, to give the desired material as a white solid (0.453 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19-1.20(3H, d), 3.12-3.19(1H, td), 3.44-3.50(1H, td), 3.61-3.64(1H, dd), 3.74-3.77(1H, d), 3.95-3.98(1H, dd), 4.07-4.11(1H, d), 4.37(1H, bs), 4.83(2H, s), 5.50-5.52(2H, d), 6.45-6.47(2H, d), 6.60(1H, s), 7.48-7.50(2H, d), 7.80-7.81(2H, q), 8.89-8.90(2H, q).

LCMS Spectrum: MH+ 426 retention time 1.80 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine



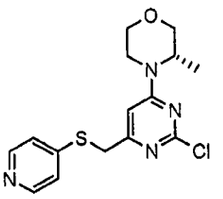
A solution of hydrogen peroxide (1.799 mL, 58.19 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine (0.980 g, 2.91 mmol), sodium tungstate dihydrate (0.005 mL, 0.06 mmol) and 2N sulfuric acid (0.075 mL) in dioxane (200 mL) at 55°C, over a period of 5 minutes under air. The resulting solution was stirred at 55 °C for 3 hours. Water (200mL) was

added and the reaction was cooled, the solids filtered, washed with water and dried in the vacuum oven at 50°C overnight to give the desired material as a white solid (0.580 g). Additional material was obtained by extracting the aqueous layer with DCM. The extracts were dried ($MgSO_4$), filtered, evaporated and chromatographed on silica, eluting with 0 - 3% methanol in DCM, to give a further portion of the desired material (0.144 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17-1.19(3H, d), 3.14-3.22(1H, td), 3.40-3.47(1H, td), 3.56-3.60(1H, dd), 3.71-3.74(1H, d), 3.90(1H, bs), 3.91-3.95(1H, dd), 4.20(1H, bs), 4.79(2H, s), 6.79(1H, s), 7.77-7.79(2H, q), 8.92-8.93(2H, q).

LCMS Spectrum: MH+ 369 retention time 1.39 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine

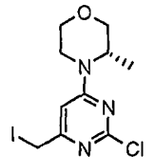


4-Mercaptopyridine (0.752 g, 6.77 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.596 g, 4.51 mmol) in acetonitrile (100 mL) at RT under air. DBU (0.3 mL, 2.01 mmol) was then added and the resulting solution was stirred at RT for 2 minutes. The solvent was removed and DCM was added. The reaction mixture was washed sequentially with water, the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was chromatographed on silica, eluting with 0 - 2% methanol in DCM. Impure fractions were further chromatographed on silica, eluting with 0 – 4.5% methanol in DCM and combined with the initial pure fractions to give the desired material as a yellow gum (0.980 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14-1.16(3H, d), 3.11-3.18(1H, td), 3.37-3.44(1H, td), 3.53-3.57(1H, dd), 3.64-3.67(1H, d), 3.86-3.90(2H, dd), 4.01(2H, s), 4.14(1H, bs), 6.43(1H, s), 7.04-7.06(2H, d), 8.29-8.30(2H, d).

LCMS Spectrum: MH+ 337 retention time 1.62 min.

2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

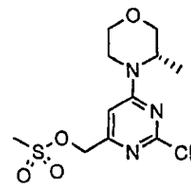


Sodium iodide (1.006 ml, 24.61 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidine (1.584 g, 4.92 mmol) in DCM at RT. The resulting solution was refluxed at 40°C for 18 hours. The reaction mixture was diluted with DCM and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired product (1.596 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.27-1.28(3H, d), 3.20-3.27(1H, td), 3.46-3.53(1H, td), 3.62-3.65(1H, dd), 3.72-3.75(1H, d), 3.93-3.97(2H, dd), 4.17(2H, s), 4.26(1H, bs), 6.41(1H, s).

LCMS Spectrum: MH+ 354 retention time 1.85 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidine



Methanesulfonyl chloride (0.488 mL, 6.31 mmol) was added dropwise to [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (1.025 g, 4.21 mmol), and triethylamine (0.880 mL, 6.31 mmol) in DCM at 0°C over a period of 2 minutes. The resulting solution was allowed to gradually warm up to RT over a period of 2 hours. The reaction mixture was diluted with DCM (50 mL), and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.584 g) which was used without further purification.

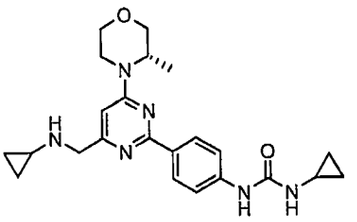
LCMS Spectrum: MH+ 322 retention time 1.60 min.

The preparartion of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

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Example 49:

3-Cyclopropyl-1-[4-[4-[(cyclopropylamino)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

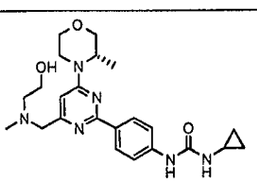


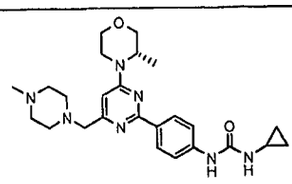
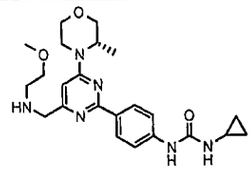
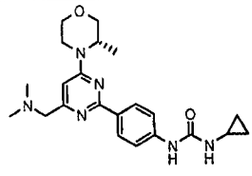
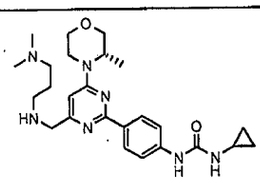
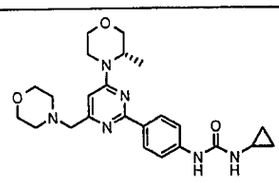
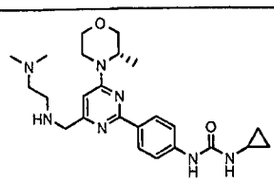
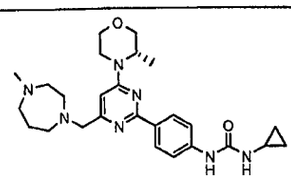
3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (107 mg, 0.23 mmol) was dissolved in DCM (5 mL) and added to cyclopropylamine (1.16 mmol). Triethylamine (0.162 mL, 1.16 mmol) was added to the solution and stirred at RT for 18 hours. The reaction was evaporated to dryness and purified by prep-HPLC (basic) to give the desired material as a white solid (27 mg).

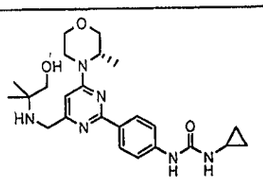
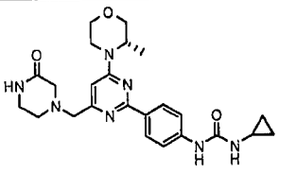
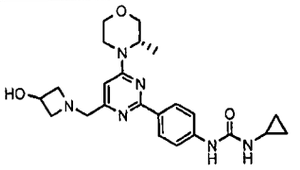
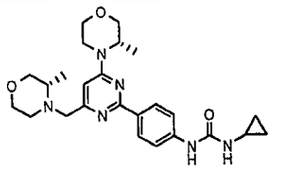
NMR Spectrum: 1H NMR (400.13 MHz, DMSO-d_6) δ 0.29 - 0.31 (2H, m), 0.34 - 0.44 (4H, m), 0.62 - 0.67 (2H, m), 1.21 - 1.27 (3H, m), 2.13 - 2.17 (1H, m), 2.53 - 2.58 (1H, m), 3.14 - 3.21 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.71 (2H, d), 3.75 (1H, s), 3.95 - 3.99 (1H, m), 4.14 - 4.17 (1H, m), 4.49 - 4.51 (1H, m), 6.46 (1H, d), 6.65 (1H, s), 7.47 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.55 (1H, s).

Mass Spectrum; $M+H^+$ 423.

The following compounds were made in an analogous fashion from 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea and the appropriate amine.

Example	Structure	NAME	LCMS MH+
49a		3-cyclopropyl-1-[4-[4-[(2-hydroxyethyl-methyl-amino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	441

Example	Structure	NAME	LCMS MH+
49b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]phenyl]urea	466
49c		3-cyclopropyl-1-[4-[4-[(2-methoxyethylamino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	441
49d		3-cyclopropyl-1-[4-[4-(dimethylaminomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	411
49e		3-cyclopropyl-1-[4-[4-[(3-dimethylaminopropylamino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	468
49f		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(morpholin-4-ylmethyl)pyrimidin-2-yl]phenyl]urea	453
49g		3-cyclopropyl-1-[4-[4-[(2-dimethylaminoethylamino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	454
49h		3-cyclopropyl-1-[4-[4-[(4-methyl-1,4-diazepan-1-yl)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	480

Example	Structure	NAME	LCMS MH+
49i		3-cyclopropyl-1-[4-[4-[[(1-hydroxy-2-methyl-propan-2-yl)amino]methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	455
49j		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(3-oxopiperazin-1-yl)methyl]pyrimidin-2-yl]phenyl]urea	456
49k		3-cyclopropyl-1-[4-[4-[(3-hydroxyazetidin-1-yl)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	439
49l		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[(3S)-3-methylmorpholin-4-yl]methyl]pyrimidin-2-yl]phenyl]urea	467

Example 49a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 - 1.27 (3H, m), 2.30 (3H, s), 2.53 - 2.58 (1H, m), 3.14 - 3.21 (1H, m), 3.46 - 3.58 (7H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.45 (1H, t), 4.48 (1H, s), 6.42 (1H, d), 6.73 (1H, s), 7.47 - 7.49 (2H, m), 8.19 - 8.21 (2H, m), 8.50 (1H, s).

Example 49b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 (3H, d), 2.17 (3H, s), 2.30 - 2.37 (8H, m), 2.53 - 2.58 (1H, m), 3.14 - 3.21 (1H, m), 3.47 - 3.50 (3H, m), 3.63 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.12 - 4.15 (1H, m), 4.45 - 4.47 (1H, m), 6.43 (1H, d), 6.61 (1H, s), 7.46 - 7.50 (2H, m), 8.19 - 8.21 (2H, m), 8.51 (1H, s).

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Example 49c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 - 1.26 (3H, m), 3.14 - 3.22 (1H, m), 3.26 (3H, s), 3.39 - 3.49 (5H, m), 3.62 - 3.66 (2H, m), 3.67 (2H, s), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.16 (1H, d), 4.48 (1H, s), 6.54 (1H, s), 6.66 (1H, s), 7.50 (2H, d), 8.19 (2H, q), 8.62 (1H, s).

Example 49d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 - 1.22 (3H, m), 2.25 (6H, s), 2.52 - 2.57 (1H, m), 3.17 (1H, d), 3.42 (2H, s), 3.46 - 3.50 (1H, m), 3.62 - 3.66 (1H, m), 3.75 (1H, d), 3.95 - 3.98 (1H, m), 4.14 - 4.18 (1H, m), 4.46 - 4.48 (1H, m), 6.44 (1H, d), 6.61 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.53 (1H, s).

Example 49e: no spectrum

Example 49f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 (3H, d), 2.52 - 2.57 (1H, m), 3.14 - 3.21 (1H, m), 3.49 (2H, s), 3.50 (2H, t), 3.63 (7H, m), 3.66 (1H, d), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 - 4.16 (1H, m), 4.49 (1H, d), 6.42 (1H, d), 6.64 (1H, s), 7.47 - 7.49 (2H, m), 8.19 - 8.21 (2H, m), 8.51 (1H, s).

Example 49g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 2.13 (6H, s), 2.32 - 2.35 (2H, m), 2.52 - 2.57 (1H, m), 2.62 (2H, t), 3.14 - 3.22 (1H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.67 (3H, s), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.14 - 4.18 (1H, m), 4.49 (1H, s), 6.42 (1H, d), 6.65 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.50 (1H, s).

Example 49h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.24 (3H, d), 1.46 (1H, d), 1.73 - 1.77 (2H, m), 2.27 (4H, s), 2.37 (1H, d), 2.43 (1H, s), 2.56 - 2.61 (2H, m), 2.73 - 2.76 (3H, m), 3.14 - 3.21 (1H, m), 3.47 - 3.53 (1H, m), 3.59 - 3.68 (3H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.14 - 4.17 (1H, m), 4.45 (1H, s), 6.43 (1H, d), 6.65 (1H, s), 7.47 - 7.49 (2H, m), 8.19 - 8.21 (2H, m), 8.51 (1H, s)

Example 49i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.01 (6H, s), 1.21 - 1.27 (3H, m), 1.36 (1H, t), 2.07 (1H, t), 2.52 - 2.57 (1H, m), 3.15 - 3.21 (1H, m), 3.23 (2H, d), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (3H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.12 - 4.16 (1H, m), 4.50 - 4.52 (1H, m), 6.49 (1H, s), 6.69 (1H, s), 7.47 - 7.50 (2H, m), 8.16 - 8.22 (2H, m), 8.56 (1H, s),

Example 49j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.21 - 1.27 (3H, m), 2.53 - 2.58 (1H, m), 2.68 (2H, q), 3.09 (2H, s), 3.18 (1H, t), 3.20 (2H, t), 3.46 - 3.53 (1H, m), 3.57 (2H, s), 3.62 - 3.66 (1H, m), 3.75 (1H, d), 3.95 - 3.99 (1H, m), 4.15 -

4.18 (1H, m), 4.48 - 4.51 (1H, m), 6.44 (1H, d), 6.63 (1H, s), 7.48 - 7.50 (2H, m), 7.74 (1H, s), 8.19 - 8.22 (2H, m), 8.53 (1H, s),

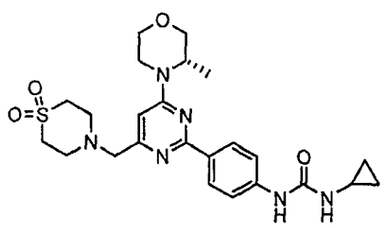
Test(a): Example(49) 0.033 μM; Example(49a) 0.15 μM; Example(49b) 0.014 μM; Example(49c) 0.04 μM; Example(49e) 0.032 μM; Example(49f) 0.2 μM; Example(49g0 0.087 μM; Example(49h) 0.18 μM; Example(49i) 0.016 μM; Example(49k) 0.014 μM; Example(49l) 1.6 μM.

Test(c): Example(49d) 0.62 μM; Example(49j) 0.13 μM.

The preparation of 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 50:

3-Cyclopropyl-1-[4-[4-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (107 mg, 0.23 mmol) was dissolved in DCM (5mL) and added to thiomorpholine (1.16 mmol). Triethylamine (0.162 mL, 1.16 mmol) was added to the solution and stirred at RT for 18 hours. The reaction was evaporated to dryness and dissolved in a 1,4-Dioxane (4 mL) water (1 mL) mixture. Meta-Chloroperbenzoic acid (100 mg, 0.58 mmol) and sodium permanagante (110 mg, 0.69 mmol) were added in single portions to the solution and stirred at RT for 1 hour. The crude solution was loaded onto a SCX-2 column, removed with 7N ammonia in methanol and evaporated to dryness. The solid was purified by prep-HPLC (basic) to give the desired material as a white solid (11 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 2.53 - 2.58 (1H, m), 3.00 (1H, s), 3.02 (3H, t), 3.15 - 3.22 (5H, m), 3.50 (1H,

d), 3.63 - 3.67 (1H, m), 3.70 (2H, s), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.18 (1H, s), 4.53 (1H, s), 6.42 (1H, d), 6.70 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.21 (2H, m), 8.50 (1H, s).

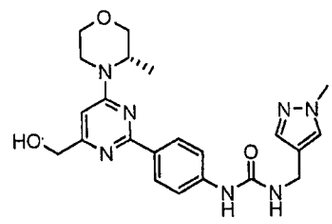
Mass Spectrum; $M+H^+$ 501.

Test(a): 0.0016 μM.

The preparation of 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 51:

1-[4-[4-(Hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea



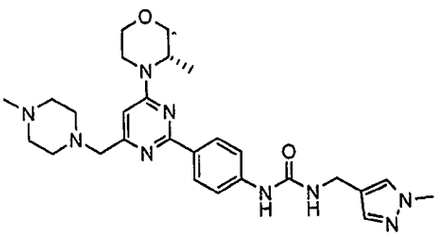
[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (1.00 g, 4.10 mmol) was added to 3-[(1-methylpyrazol-4-yl)methyl]-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (2.193 g, 6.16 mmol) and sodium carbonate (8.21 mL, 16.41 mmol) in 18% DMF in DME:EtOH:Water 7:2:3 (18 mL) and the solution was degassed for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.144 g, 0.21 mmol) was added to the mixture. The resulting solution was stirred at 85°C for 18 hours. The reaction was allowed to cool and neutralised with concentrated hydrochloric acid. The crude product was purified by ion exchange chromatography, using an SCX -2 (50g) column then further purified by flash silica chromatography, elution gradient 0 to 7% methanol in DCM, to give the desired material as a white solid (963 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.19 - 3.23 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.78 (1H, d), 3.79 (3H, s), 3.96 - 3.99 (1H, m), 4.13 (3H, d), 4.45 - 4.50 (3H, m), 5.38 (1H, t), 6.39 (1H, t), 6.66 (1H, s), 7.35 (1H, s), 7.45 - 7.49 (2H, m), 7.59 (1H, s), 8.19 - 8.21 (2H, m), 8.64 (1H, s), m/z LCMS Spectrum: MH+ 438, retention time 1.37 minutes

The preparations of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (1.00 g, 4.10 mmol) and 3-[(1-methylpyrazol-4-yl)methyl]-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea were described earlier.

Example 52:

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(4-methylpiperazin-1-yl)methyl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea

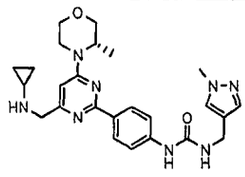
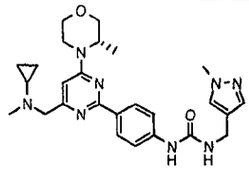


1-Methylpiperazine (0.067 mL, 0.60 mmol) was added to a solution of triethylamine (0.084 mL, 0.60 mmol) and 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea (155 mg, 0.30 mmol) in DCM (5 mL) at RT under nitrogen. The resulting solution was stirred at RT for 18 hours. The reaction mixture was evaporated. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (65 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.17 (3H, s), 2.35 (8H, s), 3.14 - 3.21 (1H, m), 3.47 - 3.50 (3H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, s), 3.79 (3H, s), 3.95 - 3.99 (1H, m), 4.13 (3H, d), 4.46 (1H, d), 6.42 (1H, t), 6.61 (1H, s), 7.35 (1H, s), 7.47 (2H, d), 7.59 (1H, s), 8.20 (2H, d), 8.66 (1H, s).

LCMS Spectrum: MH+ 520, retention time 1.49 minutes.

The following compounds were prepared in an analogous fashion from 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (mins)
52a		1-[4-[4-[(cyclopropylamino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	477	1.66
52b		1-[4-[4-[(cyclopropyl-methyl-amino)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	491	1.89

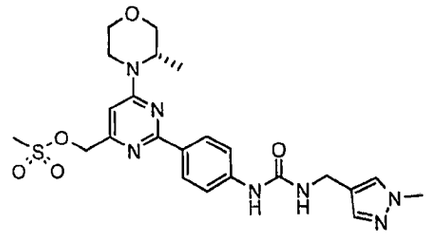
Example 52a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.28 - 0.33 (2H, m), 0.37 - 0.39 (1H, m), 1.21 - 1.26 (3H, m), 1.36 (1H, t), 2.13 - 2.17 (1H, m), 2.82 (1H, s), 3.14 - 3.21 (1H, m), 3.43 - 3.51 (1H, m), 3.62 - 3.65 (1H, m), 3.71 (2H, d), 3.77 - 3.79 (4H, m), 3.95 - 3.99 (1H, m), 4.12 - 4.17 (3H, m), 4.50 (1H, d), 6.55 (1H, s), 6.64 (1H, s), 7.35 (1H, s), 7.48 (2H, d), 7.59 (1H, s), 8.17 - 8.23 (2H, m), 8.79 (1H, s).

Example 52b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 (2H, t), 0.44 - 0.49 (2H, m), 1.20 (3H, d), 1.89 - 1.94 (1H, m), 2.33 (3H, s), 3.16 - 3.20 (2H, m), 3.45 - 3.52 (1H, m), 3.65 (3H, d), 3.79 (3H, s), 3.94 - 3.98 (1H, m), 4.13 (3H, d), 4.46 (1H, s), 6.40 (1H, t), 6.52 (1H, s), 7.35 (1H, s), 7.46 - 7.49 (2H, m), 7.59 (1H, s), 8.21 (2H, d), 8.64 (1H, s).

Test(a): Example(52) 1.4 μM; Example(52a) 0.33 μM; Example(52b) 0.57 μM.

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea is described below

1-[4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea



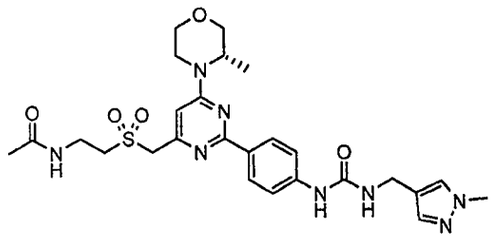
Methanesulfonyl chloride (0.246 mL, 3.15 mmol) was added dropwise over a period of 10 minutes to a solution of triethylamine (0.440 mL, 3.15 mmol) and 1-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea (920 mg, 2.10 mmol) in DCM (30 mL) at 0°C under nitrogen. The resulting solution was stirred at 20°C for 45 minutes. The reaction mixture was washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material which was used without further purification.

LCMS Spectrum: MH+ 516, retention time 1.72 min.

The preparation of -[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea was described earlier.

Example 53:

***N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide**



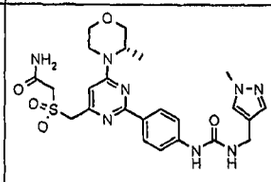
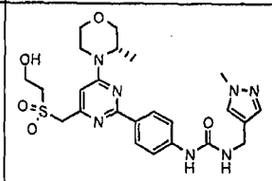
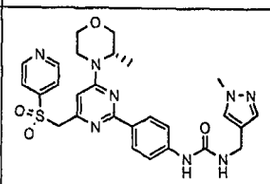
meta-Chloroperbenzoic acid (156 mg, 0.90 mmol) dissolved in Dioxane (2 mL), and sodium permanganate monohydrate (192 mg, 1.20 mmol) dissolved in water (1 mL) were added dropwise to *N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide (162 mg, 0.30 mmol) in dioxane (6 mL) and water (2 mL) at RT under nitrogen. The resulting solution was stirred at RT for 1 hour. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column

using 7M ammonia in methanol and pure fractions were evaporated to dryness. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (61 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.83 (3H, s), 3.18 (1H, m), 3.50 - 3.58 (6H, m), 3.66 - 3.67 (1H, m), 3.76 (1H, s), 3.80 (3H, s), 3.97 (1H, s), 4.13 (2H, d), 4.51 (3H, m), 6.40 (1H, d), 6.78 (1H, s), 7.35 (1H, s), 7.48 - 7.51 (2H, m), 7.59 (1H, s), 8.15 (1H, s), 8.21 (2H, d), 8.69 (1H, s).

LCMS Spectrum: MH+ 571, retention time 1.42 min.

The following compounds were prepared in an analogous fashion from the appropriate sulphides.

Example	Structure	NAME	LCMS MH+	Retention time (mins)
53a		2-[[6-[(3S)-3-methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfonyl]acetamide	543	1.40
53b		1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	530	1.43
52c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	563	1.63

Example 53a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.19 - 3.25 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 - 4.00 (1H, m), 4.13 (3H, d), 4.27 (2H, s), 4.48 (1H, s), 4.67 (2H, s), 6.42 (1H, t), 6.76 (1H, s), 7.35 (1H, s), 7.48 - 7.52 (3H, m), 7.59 (1H, s), 7.79 (1H, s), 8.20 (2H, d), 8.69 (1H, s).

Example 53b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 3.22 (1H, d), 3.51 (3H, t), 3.63 - 3.67 (1H, m), 3.80 (4H, s), 3.92 (2H, q), 3.97 - 4.01 (1H, m), 4.13 (3H, d), 4.50 (3H, s), 5.18 (1H, t), 6.42 (1H, t), 6.76 (1H, s), 7.35 (1H, s), 7.49 - 7.51 (2H, m), 7.59 (1H, s), 8.22 (2H, d), 8.68 (1H, s).

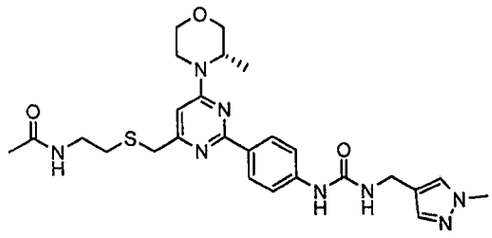
Example 53c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 - 1.26 (3H, m), 3.15 - 3.22 (1H, m), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.78 (1H, s), 3.80 (3H, s), 3.95 - 3.99 (1H, m), 4.12 (3H, d), 4.39 (1H, s), 4.87 (2H, s), 6.39 (1H, t), 6.71 (1H, s), 7.34 - 7.39 (3H, m), 7.59 (1H, s), 7.66 (2H, d), 7.81 - 7.82 (2H, m), 8.64 (1H, s), 8.90 - 8.91 (2H, m).

Test(a): Example(53) 0.64 μM; Example(53a) 0.6 μM; Example(53c) 0.03 μM.

Test(c): Example(53b) 3 μM.

The preparation of *N*-[2-[[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide is described below.

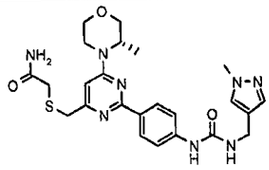
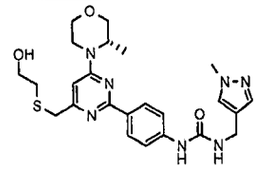
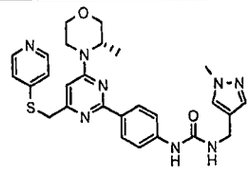
N-[2-[[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide



N-Acetylcysteamine (0.056 mL, 0.53 mmol) was added to DBU (0.091 mL, 0.60 mmol) and 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea (155 mg, 0.30 mmol) in acetonitrile (4 mL) under nitrogen. The resulting solution was stirred at RT for 5 hours. The reaction mixture was evaporated to give the desired material which was used without further purification.

LCMS Spectrum: MH+ 539, retention time 1.66 min.

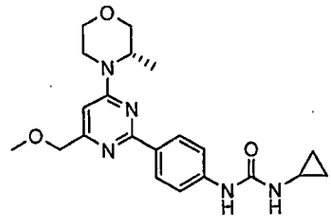
The following sulphides were prepared in an analogous fashion from 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea and the appropriate thiol.

Structure	NAME
	2-[[6-[(3S)-3-methylmorpholin-4-yl]-2-[4-[(1-methylpyrazol-4-yl)methylcarbamoylamino]phenyl]pyrimidin-4-yl]methylsulfanyl]acetamide
	1-[4-[4-(2-hydroxyethylsulfanylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea
	1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea

The preparation of 1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea was described earlier.

Example 54:

3-Cyclopropyl-1-[4-[4-(methoxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea (75 mg, 0.16 mmol) and potassium carbonate (90 mg, 0.65 mmol) were suspended in methanol (3 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 10 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol. The crude product was further purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (15 mg).

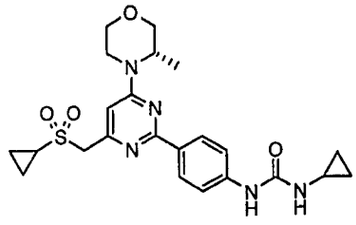
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 2.54 - 2.58 (1H, m), 3.18 - 3.23 (1H, m), 3.40 (3H, s), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.75 (1H, d), 3.95 - 3.98 (1H, m), 4.16 - 4.19 (1H, m), 4.39 (2H, s), 4.50 (1H, s), 6.42 (1H, d), 6.57 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.21 (2H, m), 8.51 (1H, s).
LCMS Spectrum: MH+ 398, retention time 1.86 min.

Test(c): 0.11 μM

The preparation of 3-cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonyloxymethyl)pyrimidin-2-yl]phenyl]urea was described earlier.

Example 55:

3-Cyclopropyl-1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



[4-(3-Cyclopropylureido)phenyl]boronic acid, pinacol ester (80 mg, 0.26 mmol), sodium carbonate (1.055 mL, 2.11 mmol), dichlorobis(triphenylphosphine)palladium(II) (14.8 mg, 0.02 mmol) and 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (70 mg, 0.21 mmol) were suspended in 18% DMF in DME:Ethanol:Water 7:2:3 mixture (4 mL) and sealed into a microwave tube. The reaction was heated to 100°C for

10 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol. The crude product was further purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a colourless gum (33.0 mg).

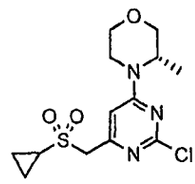
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.43 (2H, m), 0.64 - 0.66 (2H, m), 0.98 - 1.01 (2H, m), 1.04 - 1.08 (2H, m), 1.24 (3H, d), 2.56 (1H, s), 2.86 (1H, d), 3.18 (1H, d), 3.50 (1H, d), 3.67 (1H, d), 3.76 - 3.79 (1H, m), 4.50 (2H, s), 6.43 (1H, d), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 7.55 - 7.57 (1H, m), 7.60 - 7.65 (2H, m), 8.21 - 8.23 (2H, m), 8.53 (1H, s).

LCMS Spectrum: MH+ 472, retention time 1.80 min.

Test(a): 0.062 μM.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine is described below.

2-Chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Cyclopropanesulfinic acid, sodium salt (381 mg, 2.97 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (700 mg, 1.98 mmol) in acetonitrile (20 mL) at RT. The resulting suspension was stirred at 90 °C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (458 mg).

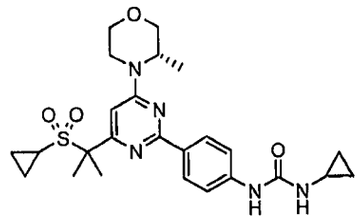
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.95 - 0.98 (2H, m), 1.02 - 1.06 (2H, m), 1.18 - 1.23 (3H, m), 2.77 - 2.83 (1H, m), 3.19 - 3.25 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.30 (1H, s), 4.48 (2H, s), 6.92 (1H, s).

LCMS Spectrum: MH+ 332, retention time 1.68 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 56:

3-Cyclopropyl-1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



[4-(3-Cyclopropylureido)phenyl]boronic acid, pinacol ester (199 mg, 0.66 mmol), 2-chloro-4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (190 mg, 0.53 mmol), sodium carbonate (1.320 mL, 2.64 mmol) and dichlorobis(triphenylphosphine)palladium(II) (37.1 mg, 0.05 mmol) were suspended in 18% DMF in a DME:Water:EtOH 7:3:2 solution (4 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 20 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness. The crude product was further purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (85 mg).

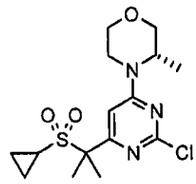
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.78 - 0.83 (1H, m), 0.81 (1H, d), 0.95 (2H, d), 1.23 (3H, d), 1.81 (6H, d), 2.56 (1H, q), 2.73 - 2.77 (1H, m), 3.20 - 3.24 (1H, m), 3.48 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.23 (1H, m), 4.57 - 4.59 (1H, m), 6.42 (1H, d), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 8.23 - 8.25 (2H, m), 8.52 (1H, s).

LCMS Spectrum: MH+ 500, retention time 2.04 min.

Test(a): 2.4 μM.

The preparation of 2-chloro-4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine is described below.

2-Chloro-4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



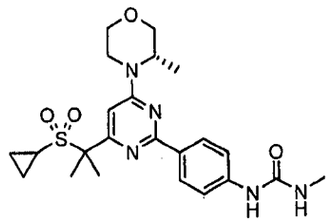
Iodomethane (0.033 mL, 0.53 mmol) was added to sodium tert-butoxide (50.7 mg, 0.53 mmol) and 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (175 mg, 0.53 mmol) in DMF (2 mL) at -10°C. The resulting thick suspension was stirred at RT for 15 minutes to ease the stirring. Iodomethane (0.033 mL, 0.53 mmol) and sodium tert-butoxide (50.7 mg, 0.53 mmol) were again added to the reaction and the resulting suspension stirred at RT for 15 minutes. The reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material (153 mg).

LCMS Spectrum: MH+ 360, retention time 2.13 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 57:

1-[4-[4-(2-Cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



Methylamine (0.699 mL, 1.40 mmol) was added to phenyl *N*-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-

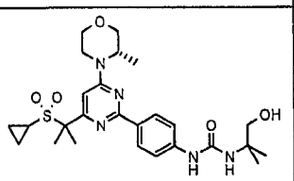
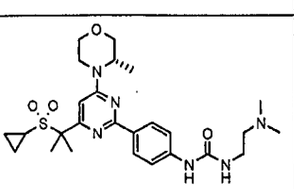
yl]phenyl]carbamate (150 mg, 0.28 mmol) and triethylamine (0.117 mL, 0.84 mmol) in DMF (2 mL). The resulting solution was stirred at 40°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (74.0 mg).

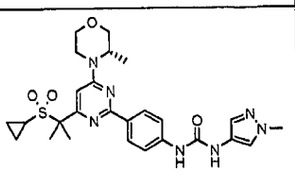
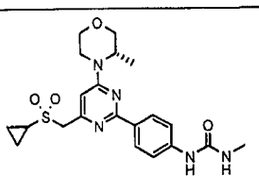
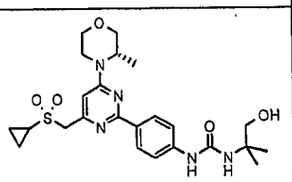
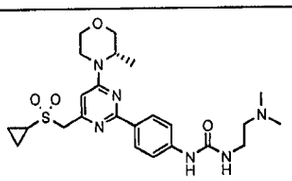
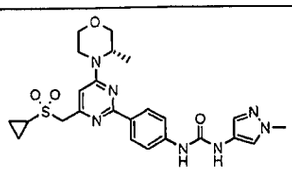
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.77 - 0.85 (2H, m), 0.91 - 0.98 (2H, m), 1.22 - 1.23 (3H, m), 1.81 (6H, d), 2.67 (3H, t), 2.72 - 2.78 (1H, m), 3.20 - 3.24 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.23 (1H, m), 4.57 - 4.59 (1H, m), 6.06 (1H, q), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.22 - 8.25 (2H, m), 8.72 (1H, s).

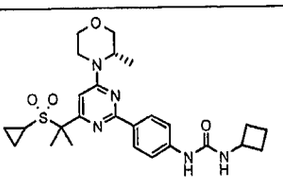
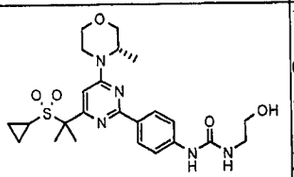
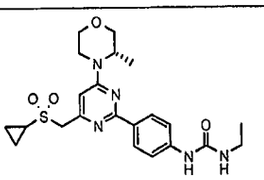
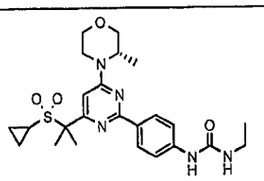
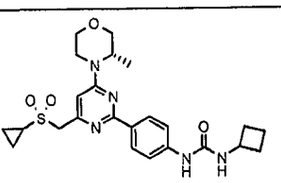
LCMS Spectrum: MH+ 474, retention time 1.92 min.

Test(c): Example(57) 0.25 μM; Example(57a) 0.064 μM; Example(57b) 0.089 μM; Example(57c) 0.36 μM; Example(57d) 0.84 μM; Example(57e) 0.38 μM; Example(57f) 0.72 μM; Example(57g) 0.095 μM; Example(57h) 0.066 μM; Example(57i) 0.27 μM; Example(57j) 0.07 μM; Example(57k) 0.34 μM; Example(57l) 0.088μM.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
57a		1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	532	2.03
57b		1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	531	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
57c		1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	540	1.93
57d		1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	446	1.56
57e		1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	504	1.70
57f		1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	503	1.66
57g		1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	512	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
57h		3-cyclobutyl-1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	514	2.28
57i		1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	504	1.72
57j		1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	460	1.71
57k		1-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	488	2.04
57l		3-cyclobutyl-1-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	486	1.96

Example 57a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.79 - 0.83 (2H, m), 0.94 - 0.97 (2H, m), 1.22 (3H, d), 1.24 (6H, s), 1.81 (6H, d), 2.74 - 2.78 (1H, m), 3.21 (1H, t), 3.39 (2H, d), 3.50 (1H, d), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.23 (1H, m), 4.56 - 4.59 (1H, m), 4.95 (1H, t), 6.00 (1H, s), 6.76 (1H, s), 7.44 - 7.46 (2H, m), 8.22 (2H, d), 8.72 (1H, s).

Example 57b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.79 - 0.84 (2H, m), 0.95 (2H, d), 1.23 (3H, d), 1.81 (6H, d), 2.18 (6H, s), 2.34 (2H, t), 2.73 - 2.77 (1H, m), 3.17 - 3.23 (3H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 - 4.23 (1H, m), 4.58 (1H, d), 6.15 (1H, t), 6.77 (1H, s), 7.47 - 7.50 (2H, m), 8.22 - 8.24 (2H, m), 8.88 (1H, s).

Example 57c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.81 - 0.83 (2H, m), 0.96 (2H, d), 1.22 - 1.24 (3H, m), 1.82 (6H, d), 2.73 - 2.77 (1H, m), 3.21 - 3.25 (1H, m), 3.47 - 3.51 (1H, m), 3.64 - 3.68 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 - 4.00 (1H, m), 4.22 (1H, d), 4.57 - 4.60 (1H, m), 6.78 (1H, s), 7.38 (1H, d), 7.53 - 7.56 (2H, m), 7.76 (1H, s), 8.27 (2H, d), 8.38 (1H, s), 8.82 (1H, s)

Example 57d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.97 - 1.01 (2H, m), 1.03 - 1.09 (2H, m), 1.23 - 1.25 (3H, m), 2.67 (3H, t), 2.83 - 2.90 (1H, m), 3.18 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.20 (1H, d), 4.50 (3H, m), 6.06 (1H, q), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.72 (1H, s).

Example 57e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.98 - 1.01 (2H, m), 1.05 - 1.09 (2H, m), 1.23 (3H, d), 1.25 (6H, s), 2.85 - 2.89 (1H, m), 3.18 (1H, d), 3.39 (2H, d), 3.47 - 3.51 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.15 - 4.18 (1H, m), 4.47 (1H, s), 4.50 (2H, s), 4.95 (1H, t), 6.00 (1H, s), 6.77 (1H, s), 7.43 - 7.47 (2H, m), 8.21 (2H, d), 8.72 (1H, s).

Example 57f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.99 - 1.01 (2H, m), 1.05 - 1.08 (2H, m), 1.24 (3H, d), 2.18 (6H, s), 2.34 (2H, t), 2.86 (1H, d), 3.17 (1H, d), 3.20 (2H, m), 3.51 (1H, s), 3.66 - 3.67 (1H, m), 3.76 - 3.79 (1H, m), 4.02 (1H, d), 4.20 (1H, d), 4.50 (3H, m), 6.15 (1H, s), 6.77 (1H, s), 7.47 - 7.49 (2H, m), 8.20 - 8.23 (2H, m), 8.88 (1H, s).

Example 57g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.99 - 1.02 (2H, m), 1.04 - 1.10 (2H, m), 1.25 (3H, d), 2.85 - 2.89 (1H, m), 3.18 (2H, m), 3.48 - 3.51 (1H, m), 3.64 - 3.68 (1H, m), 3.77 (1H, s), 3.79 (3H, s), 3.97 - 4.01 (1H, m), 4.48 (1H, s), 4.51 (2H, s), 6.78 (1H, d), 7.38 - 7.39 (1H, m), 7.53 - 7.55 (2H, m), 7.76 (1H, s), 8.24 - 8.27 (2H, m), 8.38 (1H, s), 8.82 (1H, s).

Example 57h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.77 - 0.84 (2H, m), 0.91 - 0.96 (2H, m), 1.22 - 1.23 (3H, m), 1.59 - 1.64 (2H, m), 1.80 (6H, s), 1.81 - 1.85 (2H, m), 2.17 - 2.25 (2H, m), 2.73 - 2.77 (1H, m), 3.16 - 3.24 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.11 (1H, m), 4.19 (1H, m), 4.56 - 4.59 (1H, m), 6.46 (1H, d), 6.77 (1H, s), 7.46 - 7.49 (2H, m), 8.24 (2H, d), 8.55 (1H, s).

Example 57i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.77 - 0.83 (2H, m), 0.94 (2H, t), 1.23 (3H, d), 1.81 (6H, d), 2.73 - 2.77 (1H, m), 3.18 (2H, d), 3.20 - 3.24 (1H, m), 3.46 (2H, q),

3.48 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.21 (1H, d), 4.58 (1H, d), 4.72 (1H, t), 6.25 (1H, t), 6.75 (1H, d), 7.47 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.79 (1H, s).

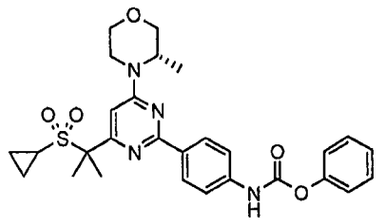
Example 57j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.97 - 1.01 (2H, m), 1.03 - 1.10 (2H, m), 1.04 - 1.09 (3H, m), 1.23 - 1.25 (3H, m), 2.85 - 2.89 (1H, m), 3.09 - 3.16 (2H, m), 3.21 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.15 (1H, d), 4.50 (3H, m), 6.16 (1H, t), 6.77 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.23 (2H, m), 8.65 (1H, s).

Example 57k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.78 - 0.83 (2H, m), 0.95 (2H, d), 1.07 (3H, t), 1.23 (3H, d), 1.81 (6H, d), 2.75 (1H, d), 3.15 (2H, d), 3.18 (1H, s), 3.50 (1H, d), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 - 4.23 (1H, m), 4.58 (1H, d), 6.16 (1H, t), 6.74 - 6.77 (1H, m), 7.48 - 7.50 (2H, m), 8.23 (2H, d), 8.65 (1H, s).

Example 57l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.97 - 1.03 (2H, m), 1.03 - 1.09 (2H, m), 1.23 - 1.25 (3H, m), 1.57 - 1.66 (2H, m), 1.83 - 1.88 (2H, m), 2.17 - 2.24 (2H, m), 2.83 - 2.88 (1H, m), 3.21 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.14 (2H, m), 4.50 (3H, m), 6.45 (1H, d), 6.77 (1H, s), 7.45 - 7.49 (2H, m), 8.20 - 8.23 (2H, m), 8.55 (1H, s).

The preparation of phenyl *N*-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



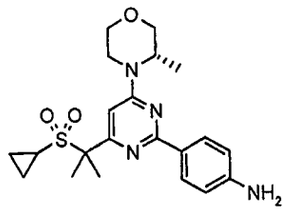
Phenyl chloroformate (0.215 mL, 1.71 mmol) was added dropwise to 4-[4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (712 mg, 1.71 mmol) and sodium bicarbonate (215 mg, 2.56 mmol) in dioxane (15 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was

evaporated to dryness and redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material (983 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.77 - 0.84 (2H, m), 0.95 (2H, t), 1.23 (3H, s), 1.82 (6H, d), 2.74 - 2.78 (1H, m), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.80 (1H, s), 7.22 - 7.30 (3H, m), 7.40 - 7.48 (2H, m), 7.55 - 7.64 (2H, m), 8.35 (2H, d), 10.42 (1H, s).

LCMS Spectrum: MH+ 537, retention time 2.87 min.

4-[4-(2-Cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium(II) (96 mg, 0.14 mmol) was added to (4-aminophenyl)boronic acid pinacol ester (747 mg, 3.41 mmol), 2-chloro-4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (982 mg, 2.73 mmol) and sodium carbonate (6.82 mL, 13.64 mmol) in 18% DMF in DME:water:ethanol 7:3:2 (20 mL). The resulting solution was stirred at 80°C for 16 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol. The crude product was further purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a yellow crystalline solid (712 mg).

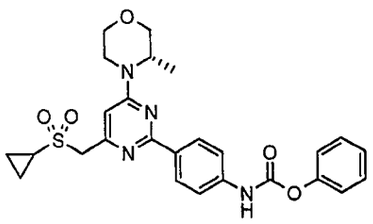
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.79 - 0.83 (2H, m), 0.94 - 0.96 (2H, s), 1.21 (3H, d), 1.79 (6H, d), 2.74 (1H, m), 3.17 (1H, d), 3.49 (1H, d), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.16 - 4.19 (1H, m), 4.54 (1H, d), 5.51 - 5.53 (2H, m), 6.59 (2H, t), 6.67 (1H, s), 8.07 (2H, d).

LCMS Spectrum: MH+ 417, retention time 2.22 min.

The preparation of 2-chloro-4-(2-cyclopropylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

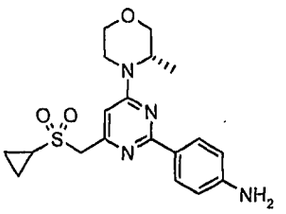


Phenyl chloroformate (0.315 mL, 2.50 mmol) was added dropwise to 4-[4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (972 mg, 2.50 mmol) and sodium bicarbonate (315 mg, 3.75 mmol) in dioxane (20 mL). The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.35 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.98 - 1.03 (2H, m), 1.06 - 1.10 (2H, m), 1.26 (3H, d), 2.86 - 2.93 (1H, m), 3.48 - 3.52 (1H, m), 3.58 (1H, s), 3.64 - 3.68 (1H, m), 3.77 - 3.80 (1H, m), 3.98 - 4.06 (1H, m), 4.17 (1H, d), 4.50 (1H, s), 4.56 (2H, s), 6.86 (1H, s), 7.24 - 7.29 (3H, m), 7.43 - 7.47 (2H, m), 7.65 (2H, d), 8.31 (2H, d), 10.47 (1H, s).

LCMS Spectrum: MH+ 509, retention time 2.29min.

4-[4-(Cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium(II) (96 mg, 0.14 mmol) was added to (4-aminophenyl)boronic acid pinacol ester (747 mg, 3.41 mmol), 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (905 mg, 2.73 mmol) and sodium carbonate (6.82 mL, 13.64 mmol) in 18% DMF in DME:water:ethanol 7:3:2 (20 mL). The resulting solution was stirred at 80°C for 6 hours. The crude reaction was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol. The crude product was further purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (972 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.97 - 1.02 (2H, m), 1.03 - 1.10 (2H, m), 1.23 (3H, d), 2.81 - 2.87 (1H, m), 3.15 - 3.22 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.12 - 4.15 (1H, m), 4.45 (3H, s), 5.53 (2H, d), 6.58 - 6.61 (2H, m), 6.66 (1H, s), 8.03 - 8.07 (2H, m).

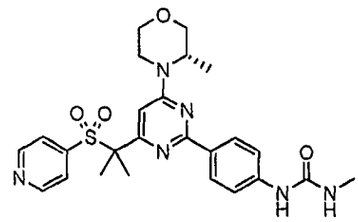
LCMS Spectrum: MH+ 389, retention time 1.82.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

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Example 58:

3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea

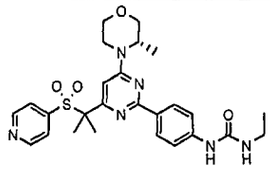


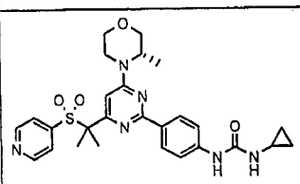
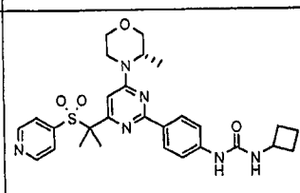
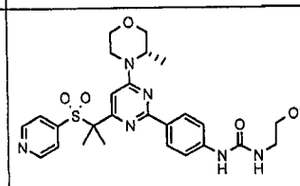
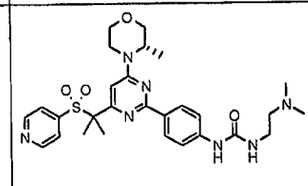
Methylamine (2M solution in THF) (0.55mL, 1.10 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate (125 mg, 0.22 mmol) and triethylamine (0.092 mL, 0.66 mmol) in DMF (4 mL). The resulting solution was stirred at 50°C overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (91 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22-1.23 (3H, d), 1.82-1.83 (6H, d), 2.66-2.67 (3H, d), 3.15-3.23 (1H, td), 3.47-3.53 (1H, td), 3.63-3.53 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.18-4.21 (1H, d), 4.57 (1H, bs), 6.03-6.07 (1H, q), 6.71 (1H, s), 7.35-7.37 (2H, d), 7.47-7.48 (2H, q), 7.65-7.68 (2H, d), 8.70 (1H, s), 8.74-8.75 (2H, q).

LCMS Spectrum: MH+ 511, retention time 2.03 min.

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
58a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	525	2.17

Example	Structure	NAME	LCMS MH+	Retention time (min)
58b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	537	2.19
58c		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	551	2.39
58d		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	541	1.90
58e		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	568	2.36

Example 58a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.05-1.09 (3H, t), 1.22-1.23 (3H, d), 1.82-1.83 (6H, d), 3.09-3.22 (3H, m), 3.47-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.96-3.99 (1H, dd), 4.18-4.22 (1H, d), 4.57 (1H, bs), 6.13-6.15 (1H, t), 6.71 (1H, s), 7.34-7.36 (2H, d), 7.47-7.48 (2H, q), 7.65-7.68 (2H, d), 8.62 (1H, s), 8.74-8.75 (2H, q).

Example 58b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.68 (2H, m), 1.22-1.23 (3H, d), 1.82-1.83 (6H, d), 2.54-2.59 (1H, m), 3.15-3.23 (1H, td), 3.47-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.18-4.21 (1H, d), 4.57 (1H, bs), 6.41-6.42 (1H, d), 6.72 (1H, s), 7.35-7.38 (2H, d), 7.47-7.48 (2H, q), 7.66-7.68 (2H, d), 8.50 (1H, s), 8.74-8.75 (2H, q).

Example 58c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22-1.23 (3H,d), 1.58-1.66 (2H, m), 1.82-1.83 (6H, d), 1.83-1.89 (2H, m), 2.18-2.25 (2H, m), 3.15-3.22 (1H, td), 3.47-3.53 (1H,

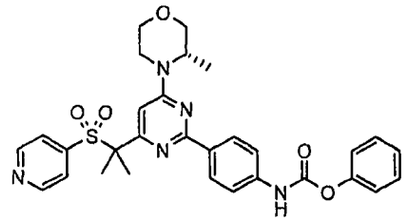
td), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.11-4.21 (2H, m), 4.57 (1H,bs), 6.43-6.45 (1H, d), 6.72 (1H, s), 7.32-7.34 (2H, d), 7.46-7.48 (2H, q), 7.65-7.68 (2H, d), 8.83 (1H, s), 8.74-8.75 (2H, q).

Example 58d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22-1.23 (3H, d), 1.82-1.83 (6H, d), 3.16-3.23 (3H, m), 3.44-3.48 (2H, q), 3.48-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.18-4.22 (1H, d), 4.56 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.25 (1H, t), 6.72 (1H, s), 7.33-7.36 (2H, d), 7.47-7.48 (2H, q), 7.66-7.68 (2H, d), 8.74-8.75 (2H, q), 8.77 (1H, s).

Example 58e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22-123 (3H, d), 1.82-1.83 (6H, d), 2.19 (6H, s), 2.32-2.36 (2H, t), 3.15-3.22 (3H, m), 3.47-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.18-4.21 (1H, d), 4.56 (1H, bs), 6.13-6.15 (1H, t), 6.72 (1H, s), 7.33-7.35 (2H, d), 7.47-7.48 (2H, q), 7.66-7.68 (2H, d), 8.74-8.75 (2H, q), 8.85 (1H, s).

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate



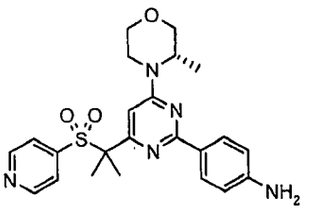
Phenyl chloroformate (0.177 mL, 1.41 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline (0.640 g, 1.41 mmol) and sodium bicarbonate (0.178 g, 2.12 mmol) in dioxane (175 mL) at RT under air. The resulting slurry was stirred at RT for 2 hours. Two more portions of phenyl chloroformate (2 x 0.005 mL) were added and the reaction allowed to stir at RT. Water was then added to the reaction and the solids were filtered and dried in a vacuum oven at 55°C overnight to give the desired material as a tan solid (0.758 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.83-1.84 (6H, d), 3.17-3.24 (1H, td), 3.48-3.53 (1H, td), 3.64-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H,

dd), 4.21-4.24 (1H, d), 4.59 (1H, bs), 6.76 (1H, s), 7.24-7.31 (3H, m), 7.43-7.50 (6H, m), 7.75-7.78 (2H, d), 8.74-8.76 (2H, d), 10.39 (1H, s).

LCMS Spectrum: MH+572, retention time 2.82 min.

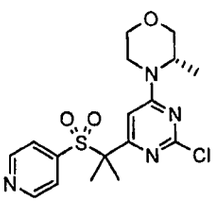
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline



trans-Dichlorobis (triphenylphosphine)palladium (II) (0.050 g, 0.07 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidine (0.560 g, 1.41 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.464 g, 2.12 mmol) and sodium carbonate (3.53 mL, 7.05 mmol) in 18% DMF in a mixture of DME:water:ethanol (7:3:2) (30 mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was allowed to cool and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate twice and the combined organics dried ($MgSO_4$), filtered and evaporated to afford the desired material (0.640 g) which was used without further purification.

LCMS Spectrum: MH+454, retention time 2.18 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-4-ylsulfonylpropan-2-yl)pyrimidine



Iodomethane (0.164 mL, 2.63 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (0.970 g, 2.63 mmol) and sodium *tert*-butoxide (0.253 g, 2.63 mmol) in DMF (15 mL) at 0°C under air. Additional sodium *tert*-butoxide (0.253 g, 2.63 mmol) and iodomethane (0.164 mL, 2.63 mmol) were added and the resulting solution stirred at 0 °C for 1 hour. The solution was allowed to slowly warm up to RT. Water

and ethyl acetate were added and the solution was separated. The aqueous layer was extracted with ethyl acetate twice and the combined organics dried ($MgSO_4$), filtered and evaporated on to silica. The crude product was chromatographed on silica, eluting with 0 - 60% ethyl acetate in DCM, to give the desired material as a yellow oil which solidified on standing (0.56 g).

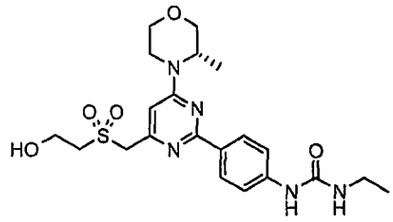
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.27-1.29 (3H, d), 1.71-1.72 (6H, d), 3.22-3.29 (1H, td), 3.48-3.54 (1H, td), 3.64-3.67 (1H, dd), 3.73-3.76 (1H, d), 3.95-3.98 (2H, dd), 4.29 (1H, bs), 6.63 (1H, s), 7.39-7.41 (2H,dd), 8.78-8.79 (2H, dd).

LCMS Spectrum: MH+ 397, retention time 1.73 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine was described earlier.

Example 59:

3-Ethyl-1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

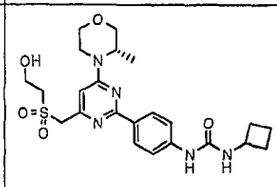
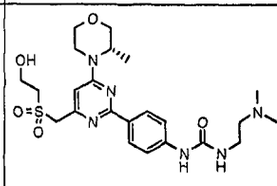


Phenyl *N*-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.073 g, 0.14 mmol), ethylamine (0.70 mmol) and triethylamine (0.42 mmol) were combined and heated at 50°C under an atmosphere of air overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents to give the desired material as a white solid (0.047 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.06-1.09 (3H, t), 1.24-1.25 (3H, d), 3.10-3.17 (2H, m), 3.19-3.26 (1H, td), 3.47-3.53 (3H, m), 3.64-3.67 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.94 (2H, q), 3.97-4.01 (1H, dd), 4.15-4.19 (1H, d), 4.48 (1H, bs), 4.50 (2H, s), 5.17-5.20 (1H, t), 6.15-6.18 (1H, t), 6.76 (1H, s), 7.49-7.51 (2H, d), 8.20-8.23 (2H, d), 8.66 (1H, s).

LCMS Spectrum: MH+ 464, retention time 1.62 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
59a		3-cyclobutyl-1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	490	1.84
59b		3-(2-dimethylaminoethyl)-1-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	507	1.61

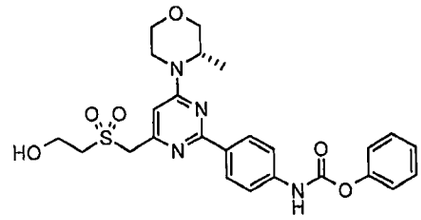
Example 59a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.57-1.69 (2H, m), 1.82-1.92 (2H, m), 2.18-2.25 (2H, m), 3.18-3.27 (1H, td), 3.47-3.53 (3H, m), 3.64-3.67 (1H, dd), 3.77-3.79 (1H, d), 3.90-3.94 (2H, q), 3.97-4.01 (1H, dd), 4.10-4.18 (2H, m), 4.47 (1H, bs), 4.50 (2H, s), 5.17-5.20 (1H, t), 6.46-6.48 (1H, d), 6.76 (1H, s), 7.47-7.49 (2H, d), 8.20-8.22 (2H, d), 8.56 (1H, s).

Example 59b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.35-1.37 (3H, d), 3.37 (6H, s), 2.56-2.59 (2H, t), 3.31-3.38 (5H, m), 3.49 (2H, s), 3.56-3.63 (1H, td), 3.72-3.76 (1H, dd), 3.82-3.85 (1H, d), 4.03-4.07 (1H, dd), 4.14-4.17 (2H, t), 4.17-4.20 (1H, d), 4.42-4.43 (2H, d), 4.48 (1H, bs), 5.61 (1H, bs), 6.45 (1H, s), 7.46-7.48 (2H, d), 8.19-8.21 (2H, d).

Test(c): Example(59a) 0.037 μM; Example(57b) 0.043 μM.

The preparation of phenyl *N*-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

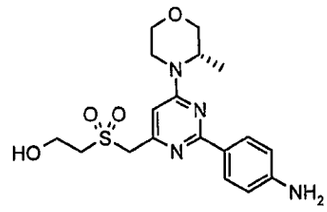
Phenyl *N*-[4-[4-(2-hydroxyethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.046 mL, 0.36 mmol) was added to 2-[[2-(4-aminophenyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol (0.143 g, 0.36 mmol) and sodium bicarbonate (0.046 g, 0.55 mmol) in dioxane (20 mL) at RT under air. The resulting slurry was stirred at RT for 2 hours. Water was added and the misture extracted with DCM three times. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a yellow solid (0.228 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 3.20-3.26 (1H, td), 3.51-3.54 (3H, m), 3.58 (1H, s), 3.64-3.68 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.95 (2H, m), 3.97-4.01 (1H, dd), 4.18-4.21 (1H, d), 4.48 (1H, bs), 4.52 (2H, s), 5.18-5.20 (1H, t), 6.80 (1H, s), 7.25-7.30 (3H, m), 7.43-7.47 (2H, t), 7.63-7.65 (3H, d), 8.31-8.33 (2H, d), 10.44 (1H, s).
LCMS Spectrum: MH+ 513, retention time 2.28 min.

2-[[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol

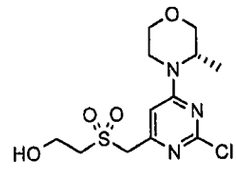


trans-Dichlorobis(triphenylphosphine)palladium (II) (0.013 g, 0.02 mmol) was added to 2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol (0.122 g, 0.36 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.119 g, 0.54 mmol) and sodium carbonate (0.908 mL, 1.82 mmol) in 18% DMF in a mixture of DME:water:ethanol (7:3:2) (10 mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 2 hours. The reaction was cooled and partitioned between ethyl acetate and water. The reaction

mixture was extracted with ethyl acetate twice and the combined organics dried ($MgSO_4$) filtered and concentrated *in vacuo* to give the desired (0.143 g).

LCMS Spectrum: MH+ 393, retention time 1.30 min.

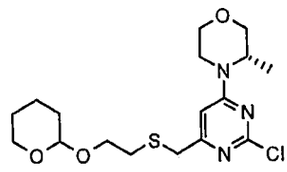
2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol



A 30% aqueous solution of hydrogen peroxide (0.225 mL, 7.29 mmol) (was added to a stirred solution of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfanylmethyl]pyrimidine (0.141 g, 0.36 mmol), sodium tungstate dihydrate (2.4 mg, 0.0073 mmol) in water (0.2 mL) and 2N sulfuric acid (0.011 mL) in 1,4-dioxane (1.4 mL) and methanol (1.4 mL) and warmed to 55°C under air. The resulting solution was stirred at 55°C for 4 hours then water (50 mL) added and the reaction cooled. A 10% aqueous solution of sodium metabisulfite was added and then the whole solution extracted with DCM. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as an opaque oil (0.198 g).

LCMS Spectrum: MH+ 336, retention time 1.18 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfanylmethyl]pyrimidine



DIPEA (0.211 g, 1.63 mmol) was added dropwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.231 g, 0.65 mmol) and 2-(tetrahydro-2H-pyran-2-yloxy)ethanethiol (0.133 g, 0.82 mmol) in acetonitrile at RT under air. The resulting solution was stirred at RT for 1 hour. The solvent was removed and the reaction mixture diluted with DCM and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography,

eluting with 0 - 2% methanol in DCM, to give the desired material as a colourless oil (0.141 g).

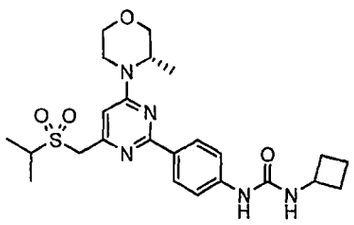
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.24-1.26 (3H, d), 1.40-1.55 (4H, m), 1.60-1.67 (1H, m), 1.69-1.77 (1H, m), 2.68-2.71 (2H, t), 3.17-3.24 (1H, td), 3.41-3.47 (2H, m), 3.50-3.58 (1H, m), 3.59 (2H, s), 3.62-3.63 (1H, d), 3.69-3.72 (1H, d), 3.76-3.86 (2H, m), 3.91-3.95 (1H, dd), 3.97 (1H, bs), 4.25 (1H, bs)< 4.52-4.54 (1H, t), 6.44 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=386; HPLC tR=2.11 min. MH+ 386, retention time 2.11 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 60:

3-Cyclobutyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea

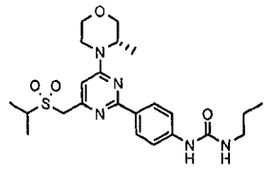
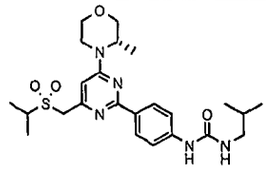
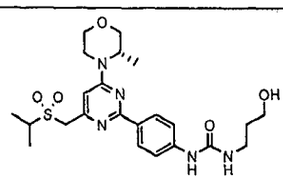
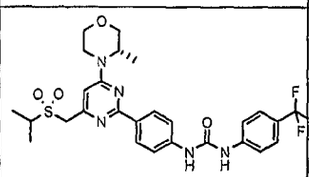
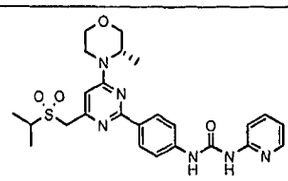


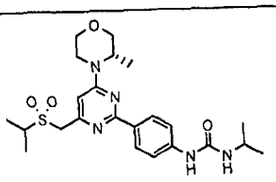
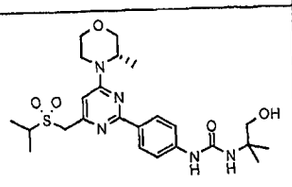
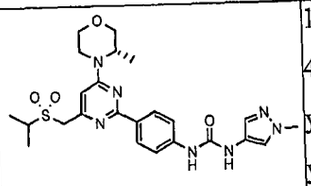
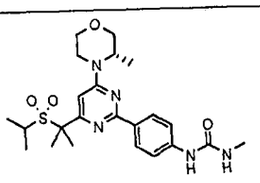
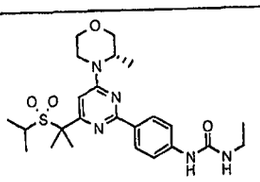
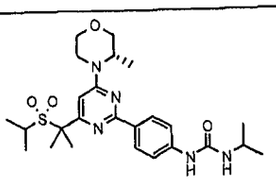
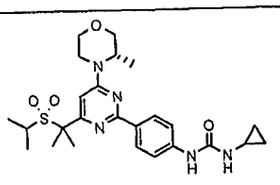
Cyclobutylamine (70 mg, 0.98 mmol) was added to phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate (100 mg, 0.20 mmol) and triethylamine (0.082 mL, 0.59 mmol) in DMF (2 mL). The resulting solution was stirred at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (57 mg).

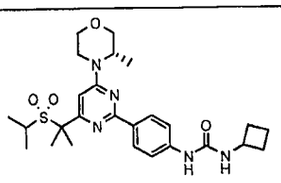
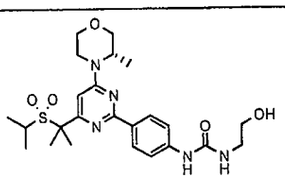
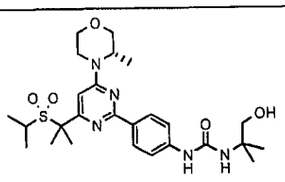
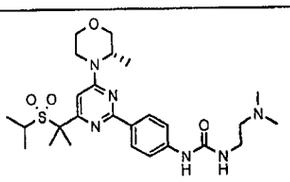
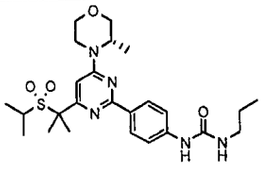
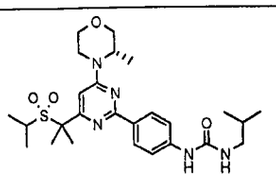
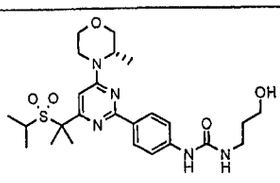
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.57 - 1.68 (2H, m), 1.81 - 1.91 (2H, m), 2.18 - 2.25 (2H, m), 3.18 - 3.25 (1H, m), 3.25 - 3.27 (1H, m), 3.47 - 3.54 (2H, m), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.11 - 4.17 (2H, m), 4.46 (2H, s), 6.47 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.55 (1H, s)

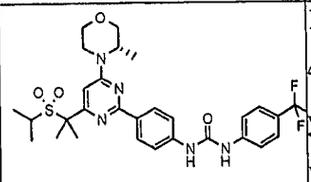
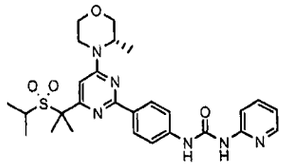
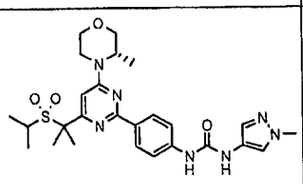
LCMS Spectrum: MH+ 488, retention time 1.99min.

The following compounds were made in an analogous fashion from either phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
60a		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-1-propyl-urea	476	1.91
60b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	490	2.10
60c		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	492	1.45
60d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	578	2.70
60e		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	511	2.16

Example	Structure	NAME	LCMS MH+	Retention time (min)
60f		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	476	2.00
60g		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	506	1.81
60h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	514	1.71
60i		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	476	1.96
60j		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	490	2.14
60k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	504	2.29
60l		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	502	2.12

Example	Structure	NAME	LCMS MH+	Retention time (min)
60m		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	516	2.34
60n		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	506	1.78
60o		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	534	2.07
60p		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	533	2.07
60q		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-1-propyl-urea	504	2.26
60r		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	518	2.43
60s		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	520	1.82

Example	Structure	NAME	LCMS MH+	Retention time (min)
60t		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	606	2.95
60u		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	539	2.54
60v		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	542	1.97

Example 60a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.25 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.43 - 1.49 (2H, m), 3.04 - 3.07 (1H, m), 3.21 - 3.26 (1H, m), 3.47 - 3.52 (2H, m), 3.64 - 3.67 (1H, m), 3.67 - 3.87 (3H, m), 3.98 - 4.00 (1H, m), 4.20 (1H, d), 4.47 (2H, s), 6.23 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Example 60b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.25 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.71 (1H, quintet), 2.95 (2H, t), 3.20 - 3.27 (1H, m), 3.47 - 3.54 (3H, m), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.19 (1H, d), 4.47 (2H, s), 6.27 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Example 60c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.35 - 1.37 (6H, m), 1.60 (2H, quintet), 3.17 (2H, q), 3.21 - 3.25 (1H, m), 3.45 - 3.54 (4H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.17 (1H, d), 4.46 - 4.49 (3H, m), 6.21 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.70 (1H, s)

Example 60d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.36 (3H, d), 1.38 (3H, d), 3.20 - 3.27 (2H, m), 3.48 - 3.55 (2H, m), 3.66 (1H, dd), 3.79 (1H, d), 4.00 (1H, dd),

4.19 (1H, d), 4.48 (2H, s), 6.80 (1H, s), 7.59 (2H, d), 7.64 - 7.70 (4H, m), 8.27 (2H, d), 9.04 (1H, s), 9.15 (1H, s)

Example 60e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.37 (3H, d), 1.38 (3H, d), 3.20 - 3.24 (1H, m), 3.27 (1H, s), 3.48 - 3.56 (2H, m), 3.66 (1H, dd), 3.79 (1H, d), 4.00 (1H, dd), 4.19 (1H, d), 4.49 (2H, s), 6.81 (1H, s), 7.02 - 7.05 (1H, m), 7.55 (1H, d), 7.65 (2H, d), 7.75 - 7.79 (1H, m), 8.27 - 8.31 (3H, m), 9.47 (1H, s), 10.63 (1H, s)

Example 60f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 3.19 - 3.25 (2H, m), 3.47 - 3.54 (2H, m), 3.65 (1H, dd), 3.73 - 3.82 (2H, m), 3.99 (1H, dd), 4.17 (1H, d), 4.46 (2H, s), 6.07 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.52 (1H, s)

Example 60g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.24 (6H, s), 1.35 (3H, d), 1.37 (3H, d), 3.18 (1H, d), 3.22 - 3.27 (1H, m), 3.39 (1H, d), 3.47 - 3.55 (2H, m), 3.64 - 3.66 (1H, m), 3.78 (1H, d), 3.98 - 4.00 (1H, m), 4.17 (1H, d), 4.46 (2H, s), 4.95 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.46 (2H, d), 8.17 (2H, d), 8.73 (1H, s)

Example 60h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.36 (3H, d), 1.38 (3H, d), 3.18 - 3.25 (2H, m), 3.48 - 3.54 (2H, m), 3.66 (1H, dd), 3.78 (1H, d), 3.79 (3H, s), 3.99 (1H, dd), 4.18 (1H, d), 4.47 (2H, s), 6.78 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.22 (2H, d), 8.40 (1H, s), 8.83 (1H, s)

Example 60i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 2.66 (3H, d), 3.16 - 3.24 (1H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.06 - 6.08 (1H, m), 6.78 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.74 (1H, s)

Example 60j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 3.10 - 3.15 (2H, m), 3.16 - 3.24 (1H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.66 (1H, s)

Example 60k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 - 1.13 (12H, m), 1.22 (3H, d), 1.79 (6H, d), 3.18 - 3.24 (2H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.82 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.06 (1H, d), 6.78 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.53 (1H, s)

Example 60l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.33 - 0.37 (2H, m), 0.56 - 0.60 (2H, m), 1.02 (3H, d), 1.05 (3H, d), 1.15 (3H, d), 1.73 (6H, d), 2.47 - 2.52 (1H, m), 3.14 (1H,

dt), 3.43 (1H, dt), 3.58 (1H, dd), 3.63 - 3.72 (2H, m), 3.89 - 3.92 (1H, m), 4.16 (1H, d), 4.50 (1H, s), 6.36 (1H, d), 6.72 (1H, s), 7.44 (2H, d), 8.16 (2H, d), 8.46 (1H, s)

Example 60m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.57 - 1.66 (2H, m), 1.79 (6H, d), 1.83 - 1.90 (2H, m), 2.18 - 2.25 (2H, m), 3.20 (1H, dt), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.12 - 4.18 (1H, m), 4.22 (1H, d), 4.55 (1H, s), 6.46 (1H, d), 6.78 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.56 (1H, s)

Example 60n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 3.16 - 3.24 (2H, m), 3.44 - 3.53 (3H, m), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.24 (2H, s), 8.80 (1H, s)

Example 60o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.13 (3H, d), 1.22 (3H, d), 1.24 (6H, s), 1.79 (6H, d), 3.17 - 3.24 (1H, m), 3.39 (2H, d), 3.50 (1H, dt), 3.65 (1H, dd), 3.71 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.78 (1H, s), 7.46 (2H, d), 8.22 (2H, d), 8.73 (1H, s)

Example 60p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 2.18 (6H, s), 2.32 - 2.35 (2H, m), 3.17 - 3.22 (3H, m), 3.50 (1H, dt), 3.66 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.89 (1H, s)

Example 60q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.41 - 1.50 (2H, m), 1.79 (6H, d), 3.04 - 3.09 (2H, m), 3.18 - 3.24 (2H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.78 (1H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.21 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.65 (1H, s)

Example 60r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.67 - 1.74 (1H, m), 1.79 (6H, d), 2.95 (2H, t), 3.22 (1H, dd), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 - 3.79 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.25 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.64 (1H, s)

Example 60s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.60 (2H, quintet), 1.79 (6H, d), 3.15 - 3.24 (3H, m), 3.45 - 3.53 (3H, m), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.47 (1H, t), 4.55 (1H, s), 6.21 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.71 (1H, s)

Example 60t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (3H, d), 1.13 (3H, d), 1.23 (3H, d), 1.81 (6H, d), 3.22 - 3.25 (1H, m), 3.66 (1H, dd), 3.71 - 3.79 (1H, m), 3.97 - 4.00 (2H, m), 4.04 - 4.08 (1H, m), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.59 (2H, d), 7.64 - 7.70 (4H, m), 8.31 (2H, d), 9.04 (1H, s), 9.14 (1H, s)

Example 60u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (3H, d), 1.14 (3H, d), 1.24 (3H, d), 1.81 (6H, d), 3.18 - 3.27 (1H, m), 3.51 (1H, dt), 3.66 (1H, ddd), 3.73 - 3.80 (2H, m), 3.99 (1H, dd), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.02 - 7.05 (1H, m), 7.57 (1H, t), 7.65 (2H, d), 7.74 - 7.79 (1H, m), 8.29 - 8.33 (3H, m), 9.45 (1H, s), 10.59 (1H, s)

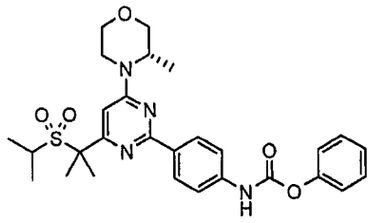
Example 60v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.13 (3H, d), 1.23 (3H, d), 1.80 (6H, d), 3.18 - 3.24 (2H, m), 3.51 (1H, dt), 3.64 - 3.68 (1H, m), 3.71 - 3.78 (1H, m), 3.79 (3H, s), 3.98 (1H, dd), 4.23 (1H, d), 4.56 (1H, s), 6.80 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.27 (2H, d), 8.39 (1H, s), 8.84 (1H, s)

Test(c): Example(60) 1.0μM; Example(60a) 3.3 μM; Example(60b) 1.8 μM; Example(60b) 1.8 μM; Example(60c) 0.77 μM; Example(60d) 0.59 μM; Example(60e) 1.3 μM; Example(60f) 0.87 μM; Example(60g) 0.22 μM; Example(60h) 1.9 μM; Example(60i) 0.12 μM; Example(60j) 0.19 μM; Example(60k) 0.18 μM; Example(60l) 0.064 μM; Example(60m) 0.059 μM; Example(60n) 0.15 μM; Example(60o) 0.086 μM; Example(60p) 0.14 μM; Example(60q) 0.16 μM; Example(60r) 0.21 μM; Example(60s) 0.3 μM; Example(60t) 1.4 μM; Example(60u) 0.16 μM; Example(60v) 0.27μM.

The preparation of phenyl (4-{4-[(isopropylsulfonyl)methyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl}phenyl)carbamate was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate

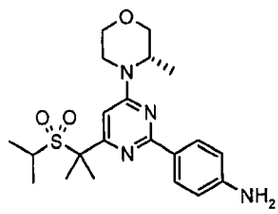


Phenyl chloroformate (0.42 mL, 3.34 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline (1.4 g, 3.34 mmol) and sodium carbonate (0.421g, 5.02 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give crude product which was triturated with diethyl ether to give the desired product (1.57 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.23 (3H, d), 1.80 (6H, d), 3.17 - 3.25 (1H, m), 3.47 - 3.54 (1H, m), 3.66 (1H, dd), 3.72 - 3.79 (2H, m), 3.97 - 4.00 (1H, m), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.25 (3H, d), 7.45 (2H, t), 7.64 (2H, d), 8.34 (2H, d), 10.43 (1H, s)

LCMS Spectrum: MH+ 539, retention time 2.76 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium(II) (116 mg, 0.17 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidine (1.2 g, 3.32 mmol), and sodium carbonate (5 mL, 10.00 mmol) in 18% DMF in a mixture of DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 90°C for 4 hours.

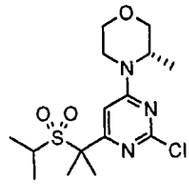
The reaction mixture was diluted with ethyl acetate (20 mL), and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (1.40 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.21 (3H, d), 1.77 (6H, d), 3.13 - 3.21 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.69 - 3.77 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.53 (1H, d), 5.55 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.06 (2H, d)

LCMS Spectrum: MH+ 419, retention time 2.11 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-propan-2-ylsulfonylpropan-2-yl)pyrimidine



Iodomethane (0.23 mL, 3.75 mmol) was added to sodium tert-butoxide (360 mg, 3.75 mmol) and (3*S*)-4-{2-Chloro-6-[(isopropylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine (2.5 g, 7.49 mmol) in DMF (2 mL) at -10°C. The resulting thick suspension was stirred at RT for 15 minutes to ease the stirring. Iodomethane (0.23 mL, 3.75 mmol) and sodium tert-butoxide (360 mg, 3.75 mmol) were again added to the reaction and the resulting suspension stirred at RT for 15 minutes. The reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige solid (1.20 g).

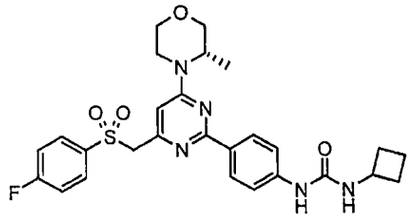
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.14 (3H, d), 1.20 (3H, d), 1.70 (6H, s), 3.16 - 3.24 (1H, m), 3.41 - 3.48 (1H, m), 3.59 (1H, dd), 3.67 (1H, q), 3.72 (1H, d), 3.94 (1H, dd), 4.06 (1H, d), 4.42 (1H, s), 6.91 (1H, s)

LCMS Spectrum: MH+ 362, retention time 2.08 min.

The preparation of (3*S*)-4-{2-Chloro-6-[(isopropylsulfonyl)methyl]pyrimidin-4-yl}-3-methylmorpholine was described earlier.

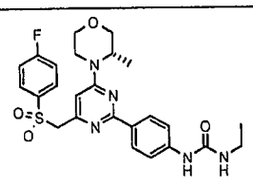
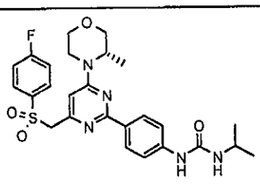
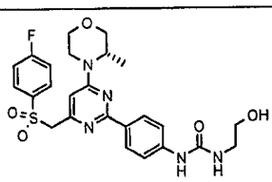
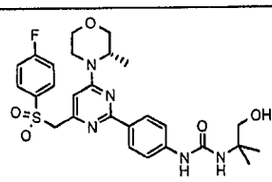
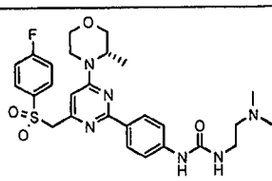
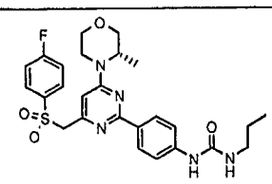
Example 61:

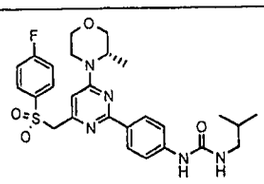
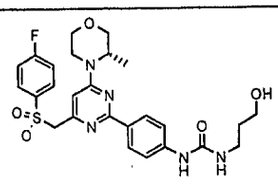
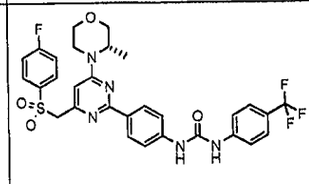
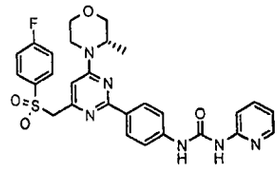
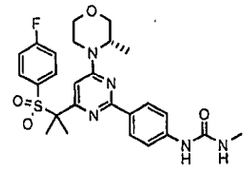
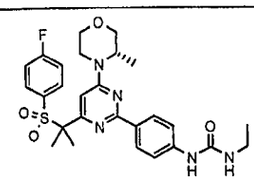
3-Cyclobutyl-1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

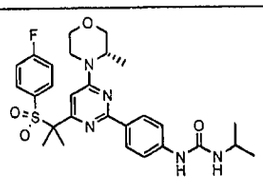
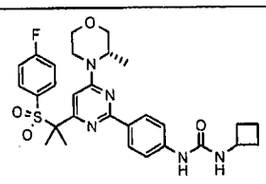
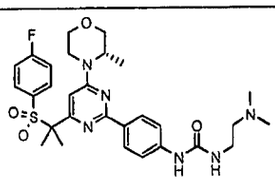
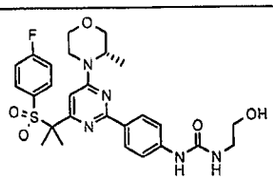
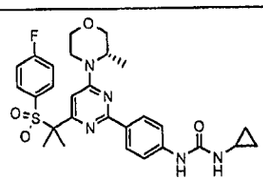


Cyclobutylamine (0.96 mmol) was added to phenyl *N*-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.21 mmol) and triethylamine (0.090 mL, 0.59 mmol) in DMF (2 mL). The resulting solution was stirred at 50°C for 3 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (117 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.57 - 1.66 (2H, m), 1.81 - 1.91 (2H, m), 2.18 - 2.24 (2H, m), 3.17 (1H, dt), 3.47 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.08 - 4.19 (2H, m), 4.38 (1H, s), 4.71 (2H, s), 6.42 (1H, d), 6.64 (1H, s), 7.36 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 - 7.89 (2H, m), 8.53 (1H, s)
LCMS Spectrum: MH+ 540, retention time 2.25 min.

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
61a		1-ethyl-3-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	514	2.02
61b		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	528	2.17
61c		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	530	1.72
61d		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	558	1.99
61e		3-(2-dimethylaminoethyl)-1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	557	1.98
61f		3-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	528	2.18

Example	Structure	NAME	LCMS MH+	Retention time (min)
61g		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	542	2.34
61h		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	544	1.76
61i		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	630	2.82
61j		1-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	563	2.40
61k		1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	528	2.19
61l		1-ethyl-3-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	542	2.34

Example	Structure	NAME	LCMS MH+	Retention time (min)
61m		1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	556	2.49
61n		3-cyclobutyl-1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	568	2.57
61o		3-(2-dimethylaminoethyl)-1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	585	1.91
61p		1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	558	2.01
61q		3-cyclopropyl-1-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.35

Example 61a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 3.09 - 3.21 (3H, m), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H,

s), 4.71 (2H, s), 6.13 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 - 7.88 (2H, m), 8.64 (1H, s)

Example 61b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.20 (3H, d), 3.18 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.73 - 3.81 (2H, m), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.71 (2H, s), 6.03 (1H, d), 6.64 (1H, s), 7.36 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 - 7.89 (2H, m), 8.51 (1H, s)

Example 61c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 3.13 - 3.21 (3H, m), 3.44 - 3.50 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H, s), 4.71 - 4.74 (3H, m), 6.22 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 - 7.89 (2H, m), 8.78 (1H, s)

Example 61d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.24 (6H, s), 3.14 - 3.20 (2H, m), 3.39 (1H, d), 3.48 (1H, t), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.11 (1H, d), 4.37 (1H, s), 4.72 (2H, s), 4.95 (1H, s), 5.98 (1H, s), 6.64 (1H, s), 7.34 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.86 - 7.89 (2H, m), 8.72 (1H, s)

Example 61e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.18 (6H, s), 2.34 (2H, t), 3.14 - 3.21 (3H, m), 3.48 (1H, dt), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.04 - 4.12 (1H, m), 4.37 (1H, s), 4.71 (2H, s), 6.13 (1H, t), 6.64 (1H, s), 7.37 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 - 7.89 (2H, m), 8.86 (1H, s)

Example 61f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.20 (3H, d), 1.46 (2H, sextet), 3.06 (2H, q), 3.17 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H, s), 4.71 (2H, s), 6.17 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.86 - 7.89 (2H, m), 8.62 (1H, s)

Example 61g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.20 (3H, d), 1.67 - 1.72 (1H, m), 2.94 (2H, t), 3.17 (1H, t), 3.48 (1H, t), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.72 (2H, s), 6.21 (1H, t), 6.65 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 - 7.89 (2H, m), 8.62 (1H, s)

Example 61h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 (2H, quintet), 3.14 - 3.21 (3H, m), 3.45 - 3.51 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.47 (1H, t), 4.71 (2H, s), 6.17 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 - 7.89 (2H, m), 8.68 (1H, s)

Example 61i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 9.10 (1H, s), 9.02 (1H, s), 7.86 - 7.89 (4H, m), 7.64 - 7.70 (4H, m), 7.45 - 7.49 (4H, m), 6.68 (1H, s), 4.73 (2H, s), 4.39 (1H, s),

4.13 (1H, d), 3.98 (1H, d), 3.77 (1H, d), 3.64 (1H, dd), 3.49 (1H, td), 3.19 (1H, td), 1.21 (3H, d)

Example 61j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 3.19 (1H, dt), 3.50 (1H, dt), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.12 (1H, d), 4.39 (1H, s), 4.74 (2H, s), 6.68 (1H, s), 7.02 - 7.05 (1H, m), 7.45 - 7.59 (5H, m), 7.75 - 7.79 (1H, m), 7.86 - 7.90 (4H, m), 8.30 (1H, d), 9.42 (1H, s), 10.52 (1H, s)

Example 61k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.27 (3H, d), 1.84 (6H, d), 2.71 (3H, d), 3.19 - 3.26 (1H, m), 3.52 - 3.57 (1H, m), 3.70 (1H, dd), 3.82 (1H, d), 4.02 (1H, dd), 4.22 (1H, d), 4.59 (1H, s), 6.09 - 6.10 (1H, m), 6.73 (1H, s), 7.36 (2H, t), 7.44 (2H, d), 7.60 - 7.63 (2H, m), 7.83 (2H, d), 8.76 (1H, s)

Example 61l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.22 (3H, d), 1.79 (6H, d), 3.09 - 3.20 (3H, m), 3.50 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.17 (1H, d), 4.55 (1H, s), 6.13 (1H, t), 6.68 (1H, s), 7.31 (2H, t), 7.38 (2H, d), 7.54 - 7.58 (2H, m), 7.78 (2H, d), 8.62 (1H, s)

Example 61m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.22 (3H, d), 1.79 (6H, d), 3.11 - 3.20 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.75 - 3.80 (2H, m), 3.98 (1H, d), 4.17 (1H, d), 4.54 (1H, s), 6.03 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.36 (2H, d), 7.54 - 7.58 (2H, m), 7.78 (2H, d), 8.50 (1H, s)

Example 61n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.66 (2H, m), 1.78 (6H, d), 1.82 - 1.91 (2H, m), 2.14 - 2.25 (2H, m), 3.17 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.09 - 4.18 (2H, m), 4.54 (1H, s), 6.43 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.36 (2H, d), 7.54 - 7.58 (2H, m), 7.78 (2H, d), 8.53 (1H, s)

Example 61o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.79 (6H, d), 2.18 (6H, s), 2.34 (2H, t), 3.13 - 3.21 (3H, m), 3.50 (1H, t), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.17 (1H, d), 4.55 (1H, s), 6.14 (1H, t), 6.67 (1H, s), 7.31 (2H, t), 7.37 (2H, d), 7.54 - 7.58 (2H, m), 7.78 (2H, d), 8.85 (1H, s)

Example 61p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.79 (6H, d), 3.14 - 3.21 (3H, m), 3.44 - 3.53 (3H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.68 (1H, s), 7.31 (2H, t), 7.37 (2H, d), 7.54 - 7.58 (2H, m), 7.78 (2H, d), 8.77 (1H, s)

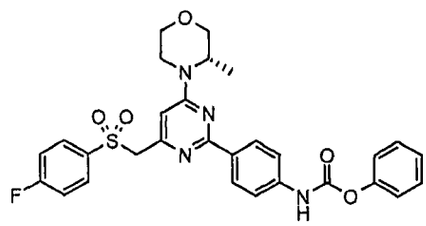
Example 61q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 1.79 (6H, d), 2.54 - 2.58 (1H, m), 3.17 (1H, dt), 3.49 (1H, dt), 3.65 (1H,

dd), 3.77 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 6.40 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.39 (2H, d), 7.54 - 7.58 (2H, m), 7.79 (2H, d), 8.50 (1H, s)

Test (c): Example(61) 0.33 μM; Example(61a) 0.75 μM; Example(61b) 0.038 μM; Example(61c) 0.41 μM; Example(61d) 0.18 μM; Example(61e) 0.12 μM; Example(61g) 0.45 μM; Example(61h) 0.79 μM; Example(61k) 0.12 μM; Example(61l) 0.099 μM; Example(61m) 0.03 μM; Example(61n) 0.038 μM; Example(61o) 0.045 μM; Example(61q) 0.077 μM;

The preparation of phenyl *N*-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

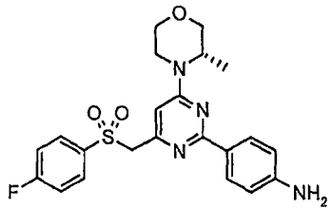


Phenyl chloroformate (0.474 mL, 3.77 mmol) was added dropwise to 4-[4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.67 g, 3.77 mmol) and sodium bicarbonate (476 mg, 5.66 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give crude product which was triturated with diethyl ether to give the desired product (1.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 3.15 - 3.22 (1H, m), 3.35 (1H, s), 3.45 - 3.52 (1H, m), 3.63 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.39 (1H, s), 4.73 (2H, s), 6.69 (1H, s), 7.24 - 7.26 (2H, m), 7.43 - 7.48 (4H, m), 7.53 (2H, d), 7.86 - 7.90 (4H, m), 10.39 (1H, s)

LCMS Spectrum: MH+ 563, retention time 2.65 min.

4-[4-[(4-Fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

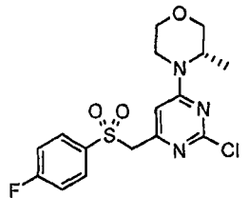


Dichlorobis(triphenylphosphine)palladium(II) (136 mg, 0.19 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.107 g, 5.05 mmol) and 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.50 g, 3.89 mmol) and sodium carbonate (5 mL, 10.00 mmol) in 18% DMF in DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 90°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (1.670 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.10 - 3.18 (1H, m), 3.44 - 3.50 (1H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.07 (1H, d), 4.35 (1H, s), 4.67 (2H, s), 5.52 (2H, s), 6.49 (2H, d), 6.53 (1H, s), 7.45 (2H, t), 7.62 (2H, d), 7.84 - 7.88 (2H, m)

LCMS Spectrum: MH+ 443, retention time 1.96 min.

2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



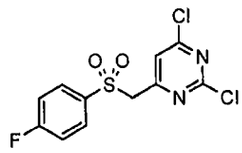
Triethylamine (1.117 ml, 8.01 mmol) was added to 2,4-dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine (2.34 g, 7.29 mmol) in DCM (36.4 mL) at 0°C followed by (3*S*)-3-methylmorpholine (0.737 g, 7.29 mmol) in DCM (20 mL) over 15 minutes. The reaction was then stirred at RT for 16 hours. The reaction mixture was washed with water (50 mL), the organic layer dried ($MgSO_4$), filtered and evaporated to

afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige solid (1.530 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.13 - 3.20 (1H, m), 3.27 - 3.28 (1H, m), 3.39 - 3.46 (1H, m), 3.57 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.17 (1H, s), 4.65 (2H, s), 6.71 (1H, s), 7.48 (2H, t), 7.83 - 7.87 (2H, m)

LCMS Spectrum: MH+ 386, retention time 1.94 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine

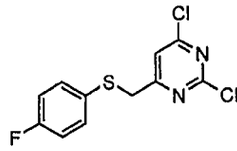


3-Chloroperoxybenzoic acid (3.78 g, 21.89 mmol) was added portionwise to 2,4-dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine (2.11 g, 7.30 mmol), in DCM (36.5 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated aqueous solution ofsodium hydrogen carbonate (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford desired product (2.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.99 (2H, s), 7.48 - 7.52 (2H, m), 7.76 (1H, s), 7.85 - 7.88 (2H, m)

LCMS Spectrum: MH+ 319, retention time 2.01 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine



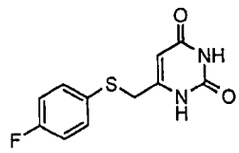
Phosphorus oxychloride (15.2 g, 99.1 mmol) was added to 6-[(4-fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (2.5 g, 9.91 mmol), and the resulting solution was stirred at reflux for 7 hours. The reaction was allowed to cool and the phosphorus oxychloride removed under reduced pressure to give a brown oil. This was dissolved in DCM and ice water (50 mL) added followed by solid sodium bicarbonate (until effervescence stops). The aqueous layer was extracted with DCM (2 x 50 mL) and

the organics dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.11 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.21 (2H, s), 7.09 - 7.14 (2H, m), 7.34 - 7.38 (2H, m), 7.58 (1H, s)

LCMS Spectrum: M-H+ 287, retention time 2.51 min.

6-[(4-Fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione



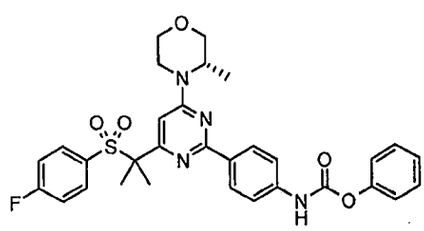
DBU (4.02 mL, 26.91 mmol) was added to 4-fluorobenzenethiol (3.45 g, 26.91 mmol), in DMF (90 mL) at RT. The resulting solution was stirred at 20°C for 15 minutes. 6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (2.88 g, 17.94 mmol) was then added and the reaction stirred for 4 hours. The reaction mixture was concentrated and diluted with DCM (100 mL), and washed with water (100 mL). The aqueous layer was acidified with 2M hydrochloric acid to give a white solid which was filtered and washed with water then dried under vacuum to give desired product (2.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.80 (2H, s), 5.20 (1H, s), 7.18 - 7.23 (2H, m), 7.45 - 7.49 (2H, m), 10.90 (1H, s), 10.93 (1H, s)

LCMS Spectrum: M-H- 251, retention time 0.80 min.

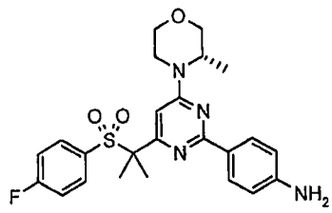
The preparation of phenyl *N*-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.482 mL, 3.83 mmol) was added dropwise to 4-[4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.8 g, 3.83 mmol) and sodium bicarbonate (0.482 g, 5.74 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give crude product which was triturated with diethyl ether to give the desired material as a white solid (2.26 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.80 (6H, d), 3.18 (1H, dt), 3.50 (1H, dt), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.55 (1H, s), 6.72 (1H, s), 7.24 - 7.33 (5H, m), 7.45 (2H, t), 7.52 (2H, d), 7.55 - 7.58 (2H, m), 7.88 (2H, d), 10.39 (1H, s)
LCMS Spectrum: MH+ 591, retention time 3.10 min.

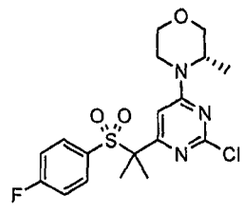
4-[4-[2-(4-Fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium(II) (170 mg, 0.24 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.376 g, 6.28 mmol) and 2-chloro-4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2 g, 4.83 mmol), and sodium carbonate (5 mL, 10.00 mmol) in 18% DMF in DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 90°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed with water (2 x 20 mLl). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (1.80 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.76 (6H, d), 3.14 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.51 (1H, d), 5.50 (2H, s), 6.49 (2H, d), 6.58 (1H, s), 7.31 (2H, t), 7.54 - 7.57 (2H, m), 7.62 (2H, d)

LCMS Spectrum: MH+ 471, retention time 2.57 min.

2-Chloro-4-[2-(4-fluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

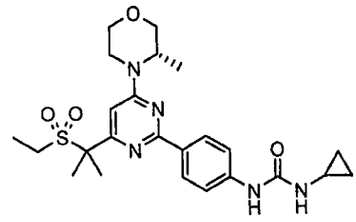


Iodomethane (0.32 mL, 5.20 mmol) was added to sodium tert-butoxide (498 mg, 5.20 mmol) and 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2 g, 5.18 mmol) in DMF (2 mL) at -10°C. The resulting thick suspension was stirred at RT for 15 minutes to ease the stirring. Iodomethane (0.32 mL, 5.20 mmol) and sodium tert-butoxide (498 mg, 5.20 mmol) were again added to the reaction and the resulting suspension stirred at RT for 15 minutes. The reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM. Pure fractions were evaporated to dryness to give the desired product as a white solid (2.00 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 (6H, d), 3.17 (1H, dt), 3.43 (1H, dt), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.01 (1H, d), 4.38 (1H, s), 6.75 (1H, s), 7.44 (2H, t), 7.58 - 7.61 (2H, m)
LCMS Spectrum: MH+ 414, retention time 2.35 min.

The preparation of 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 62:

3-Cyclopropyl-1-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

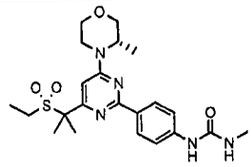


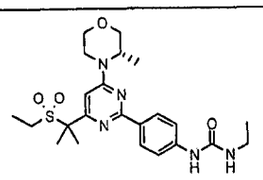
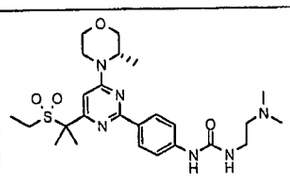
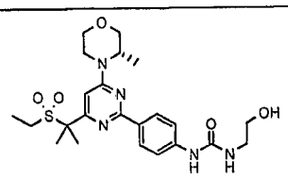
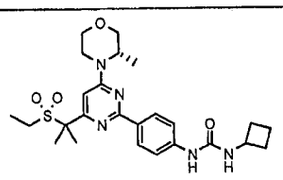
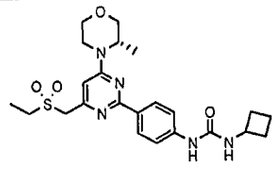
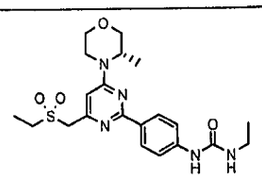
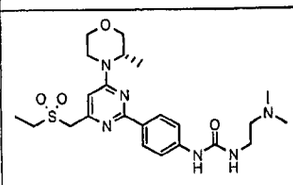
To a solution of phenyl *N*-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.29 mmol) in DMF (2 mL) was added triethylamine (0.120 mL, 0.86 mmol) followed by cyclopropylamine (0.100 mL, 1.44 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (85 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.14 (3H, t), 1.23 (3H, d), 1.79 (6H, s), 2.55 (1H, m), 3.17 - 3.21 (1H, m), 3.23 (2H, d), 3.46 - 3.50 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.43 (1H, d), 6.75 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.54 (1H, s).

LCMS Spectrum: MH+ 488, retention time 2.19min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
62a		1-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	502	2.42

Example	Structure	NAME	LCMS MH+	Retention time (min)
62b		1-ethyl-3-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	476	2.16
62c		3-(2-dimethylaminoethyl)-1-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	519	2.10
62d		1-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	492	1.83
62e		3-cyclobutyl-1-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	462	2.00
62f		3-cyclobutyl-1-[4-[4-(ethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	474	2.14
62g		1-ethyl-3-[4-[4-(ethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	448	1.87
62h		3-(2-dimethylaminoethyl)-1-[4-[4-(ethylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	491	1.83

Example 62a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.23 (3H, d), 1.54 - 1.68 (2H, m), 1.78 (6H, s), 1.83 -1.90 (2H, d), 2.18 - 2.25 (2H, m), 3.17 - 3.21 (1H, m), 3.23 (2H, q), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.15 (1H, q), 4.22 (1H, d), 4.59 (1H, s), 6.46 (1H, d), 6.75 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.56 (1H, s)

Example 62b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.14 (3H, t), 1.23 (3H, d), 1.78 (6H, d), 3.09 - 3.16 (2H, m), 3.18 (1H, m), 3.22 (2H, t), 3.46 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.58 (1H, s), 6.16 (1H, t), 6.75 (1H, d), 7.50 (2H, d), 8.22 (2H, d), 8.66 (1H, s)

Example 62c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.14 (3H, t), 1.23 (3H, d), 1.78 (6H, d), 3.09 - 3.16 (2H, m), 3.18 (1H, m), 3.22 (2H, t), 3.46 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.58 (1H, s), 6.16 (1H, t), 6.75 (1H, d), 7.50 (2H, d), 8.22 (2H, d), 8.66 (1H, s)

Example 62d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.22 - 1.24 (3H, m), 1.78 (6H, s), 3.17 (1H, t), 3.20 - 3.22 (2H, s), 3.24 (2H, m), 3.46 (2H, q), 3.48 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.21 - 4.24 (1H, m), 4.57 - 4.60 (1H, m), 4.73 (1H, t), 6.25 (1H, t), 6.75 (1H, s), 7.48 - 7.51 (2H, m), 8.23 (2H, d), 8.80 (1H, s)

Example 62e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.27 (3H, d), 1.78 (6H, m), 2.68 (3H, d), 3.18 (1H, m), 3.24 (2H, m), 3.46 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.07 (1H, t), 6.75 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.74 (1H, s)

Example 62f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 - 1.25 (3H, m), 1.35 (3H, t), 1.59 - 1.66 (2H, m), 1.83 - 1.86 (2H, m), 2.19 - 2.23 (2H, m), 3.18 (1H, m), 3.33 (2H, m), 3.47 - 3.50 (1H, m), 3.66 (1H, d), 3.76 - 3.79 (1H, m), 3.96 (1H, d), 4.14 (2H, d), 4.45 (3H, m), 6.47 (1H, d), 6.78 (1H, s), 7.47 - 7.49 (2H, m), 8.18 - 8.20 (2H, m), 8.56 (1H, s)

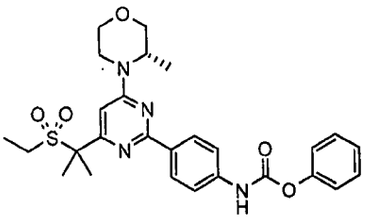
Example 62g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.35 (3H, t), 3.09 - 3.16 (2H, m), 3.21 - 3.26 (1H, m), 3.33 (2H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.14 (1H, d), 4.45 (3H, s), 6.17 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.18 - 8.20 (2H, m), 8.66 (1H, s)

Example 62h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 - 1.25 (3H, m), 1.35 (3H, t), 2.18 (6H, s), 2.34 (2H, t), 3.20 (3H, q), 3.33 (2H, d), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m),

3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.14 (1H, d), 4.45 (3H, s), 6.16 (1H, t), 6.77 (1H, s), 7.47 - 7.51 (2H, m), 8.18 - 8.20 (2H, m), 8.89 (1H, s)

The preparation of phenyl *N*-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

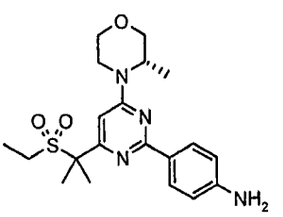


Phenyl chloroformate (0.373 mL, 2.97 mmol) was added dropwise to 4-[4-(2-ethylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.20 g, 2.97 mmol) and sodium bicarbonate (0.374 g, 4.45 mmol) in dioxane (25 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and partitioned between ethyl acetate (150 mL) and water (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a white solid (1.40 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.79 (6H, d), 3.24 (3H, q), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 6.74 - 6.79 (2H, m), 7.24 - 7.27 (2H, m), 7.43 - 7.47 (2H, m), 7.61 - 7.64 (2H, m), 8.33 (2H, d), 10.43 (1H, s)

LCMS Spectrum: MH+ 525, retention time 2.84min.

4-[4-(2-Ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

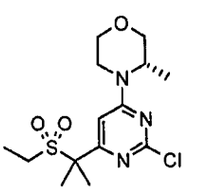


Dichlorobis(triphenylphosphine)palladium(II) (0.360 g, 0.51 mmol) was added to a degassed solution of 2-chloro-4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.784 g, 5.13 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.404 g, 6.41 mmol) and sodium carbonate (12.82 mL, 25.64 mmol) in a mixture of 18% DMF in DME:water:ethanol (7:3:2) (25 mL). The resulting solution was stirred at 85°C for 2 hours. The reaction mixture was concentrated and partitioned between DCM (150 mL), and water (100 mL) and the organics washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a brown solid (1.20 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.13 (3H, t), 1.21 (3H, d), 1.76 (6H, d), 3.14 - 3.18 (1H, m), 3.23 (2H, q), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.21 (1H, m), 4.54 - 4.56 (1H, m), 5.54 (2H, d), 6.61 (1H, d), 6.62 (2H, t), 8.06 (2H, d)

LCMS Spectrum: MH+ 405, retention time 2.14 min.

2-Chloro-4-(2-ethylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

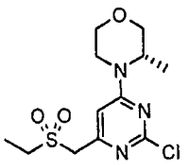


Iodomethane (0.321 mL, 5.13 mmol) was added to sodium *tert*-butoxide (0.493 g, 5.13 mmol) and 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.64 g, 5.13 mmol) in DMF (75 mL) at -5°C. The solution was stirred at -5°C for 15 minutes. Further iodomethane (0.321 mL, 5.13 mmol) and sodium *tert*-butoxide (0.493 g, 5.13 mmol) were added and the reaction stirred at -5°C for 15 minutes. The reaction mixture was diluted with DCM (200 mL) and washed with water (2 x 100 mL) and brine (100 mL). The organics were dried ($MgSO_4$), filtered and evaporated to give the desired material as a brown solid (1.784 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.16 (3H, t), 1.21 (3H, d), 1.69 (6H, s), 3.15 - 3.19 (2H, m), 3.14 - 3.24 (1H, m), 3.41 - 3.48 (1H, m), 3.57 - 3.61 (1H, m), 3.72 (1H, d), 3.92 - 3.95 (1H, m), 4.05 - 4.44 (2H, m), 6.87 (1H, s)

LCMS Spectrum: MH+ 348, retention time 1.79 min.

2-Chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Ethane sulfinic acid sodium salt (3.94 g, 33.94 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (12.0 g, 33.94 mmol) in acetonitrile (250 mL) at RT. The resulting suspension was stirred at 80°C for 16 hours. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (250 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow solid (5.94 g).

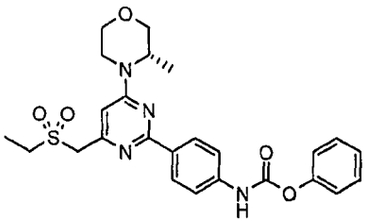
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, m), 1.28 (3H, t), 3.22 (2H, d), 3.32 (1H, s), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.25 - 4.31 (1H, m), 4.43 (2H, s), 6.92 (1H, s)

LCMS Spectrum: MH+ 320, retention time 1.46 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

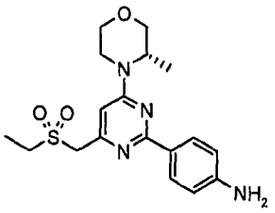


Phenyl chloroformate (0.207 mL, 1.65 mmol) was added dropwise to 4-[4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (620 mg, 1.65 mmol) and sodium bicarbonate (208 mg, 2.47 mmol) in dioxane (15 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a white solid (885 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 - 1.29 (3H, m), 1.35 (3H, t), 3.20 - 3.28 (2H, m), 3.47 - 3.54 (2H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.20 (1H, d), 4.48 (3H, s), 6.83 (1H, s), 7.24 - 7.30 (3H, m), 7.42 - 7.48 (2H, m), 7.64 (2H, d), 8.28 - 8.30 (2H, m), 10.45 (1H, s)

LCMS Spectrum: MH+ 497, retention time 2.57 min.

4-[4-(Ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium(II) (0.162 g, 0.23 mmol) was added to a degassed solution of 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.74 g, 2.31 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.634 g, 2.89 mmol) and sodium carbonate (5.78 mL, 11.57 mmol) in a mixture of 18% DMF in DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 85°C for 30 minutes. The reaction mixture was concentrated and diluted with DCM (100 mL) then washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica

chromatography, elution gradient 0 to 2.5% methanol in DCM. The material obtained was further purified using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a yellow solid (0.62 g).

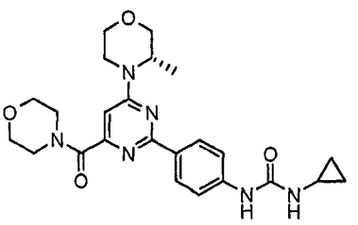
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.34 (3H, t), 3.16 - 3.19 (1H, m), 3.32 (2H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.12 (1H, s), 4.42 (3H, d), 5.56 (2H, s), 6.59 - 6.62 (2H, m), 6.67 (1H, s), 8.01 - 8.04 (2H, m)

LCMS Spectrum: MH+ 377, retention time 1.83 min.

The preparation of 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 63:

3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(morpholine-4-carbonyl)pyrimidin-2-yl]phenyl]urea

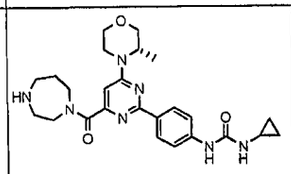
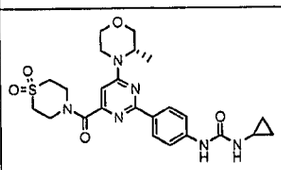
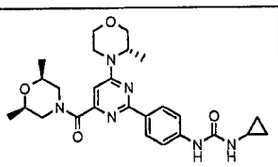
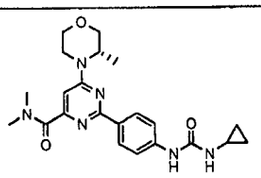
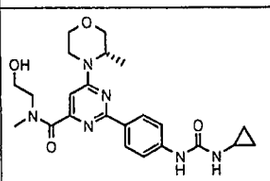


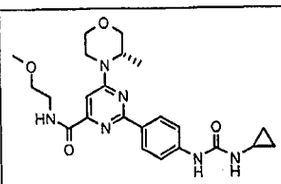
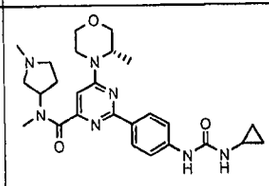
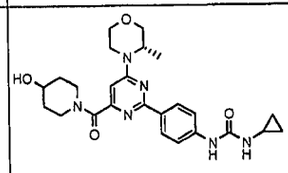
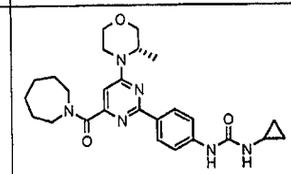
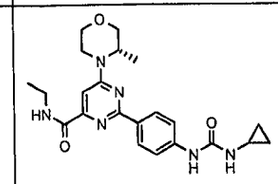
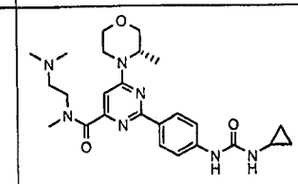
2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid (100 mg, 0.25 mmol) was added to morpholine (0.066 mL, 0.75 mmol), DIPEA (0.132 mL, 0.75 mmol) and HATU (144 mg, 0.38 mmol) in dry DMF (3 mL) at RT over a period of 30 minutes under nitrogen. The resulting solution was stirred at RTfor 3 hours and the crude product purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (98 mg).

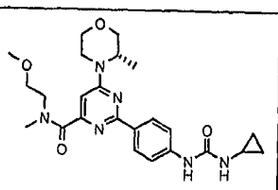
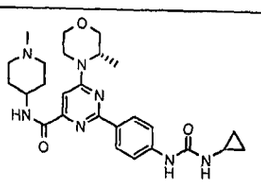
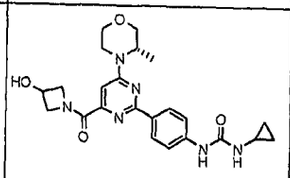
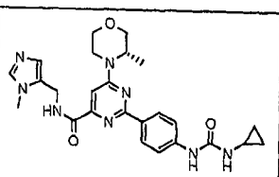
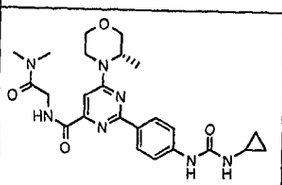
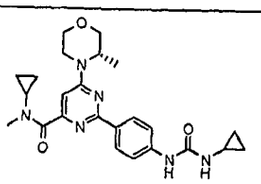
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 2.54-2.59 (1H, m), 3.18-3.27 (1H, m), 3.46-3.49 (3H, m), 3.60-3.69 (7H, m), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.56 (1H, s), 6.43-6.44 (1H, d), 6.77 (1H, s), 7.50-7.52 (2H, d), 8.18-8.20 (2H, d), 8.54 (1H, s)

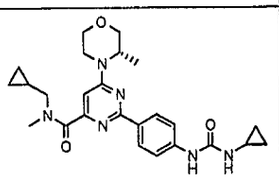
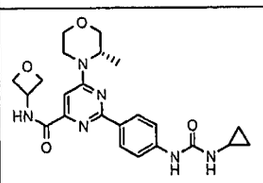
LCMS Spectrum: MH+ 467, retention time 1.69 min

The following compounds were prepared in an analogous fashion from 2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
63a		3-cyclopropyl-1-[4-[4-(1,4-diazepane-1-carbonyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	479	1.6
63b		3-cyclopropyl-1-[4-[4-(1,1-dioxo1,4-thiazinane-4-carbonyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	514	1.74
63c		3-cyclopropyl-1-[4-[4-[(2R,6S)-2,6-dimethylmorpholine-4-carbonyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	494	1.93
63d		2-[4-(cyclopropylcarbamoylamino)phenyl]-N,N-dimethyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	424	1.69
63e		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-(2-hydroxyethyl)-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	455	1.53

Example	Structure	NAME	LCMS MH+	Retention time (min)
63f		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-(2-methoxyethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	455	1.92
63g		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]-N-(1-methylpyrrolidin-3-yl)pyrimidine-4-carboxamide	494	1.72
63h		3-cyclopropyl-1-[4-[4-(4-hydroxypiperidine-1-carbonyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	481	1.54
63i		1-[4-[4-(azepane-1-carbonyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea	479	2.15
63j		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-ethyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	425	2.00
63k		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-(2-dimethylaminoethyl)-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	482	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
63l		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-(2-methoxyethyl)-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	469	1.77
63m		2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]-N-(1-methyl-4-piperidyl)pyrimidine-4-carboxamide	494	1.93
63n		3-cyclopropyl-1-[4-[4-(3-hydroxyazetidine-1-carbonyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	453	1.62
63o		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-[(3-methylimidazol-4-yl)methyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	491	1.79
63p		2-[4-(cyclopropylcarbamoylamino)phenyl]-N-(dimethylcarbamoylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	482	1.80
63q		N-cyclopropyl-2-[4-(cyclopropylcarbamoylamino)phenyl]-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	451	1.85

Example	Structure	NAME	LCMS MH+	Retention time (min)
63r		2-[4-(cyclopropylcarbamoylamino) phenyl]-N-(cyclopropylmethyl)-N-methyl-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine-4-carboxamide	465	2.02
63s		2-[4-(cyclopropylcarbamoylamino) phenyl]-6-[(3S)-3-methylmorpholin-4-yl]-N-(oxetan-3-yl)pyrimidine-4-carboxamide	453	1.84

Example 63a: ^{1}H NMR (400MHz, $CDCl_3$) δ 0.68-0.68 (2H, d), 0.86-0.87 (2H, d), 1.34-1.35 (3H, d), 1.86-1.90 (1H, m), 1.94-2.02 (1H, m), 2.62-2.64 (1H, t), 2.99-3.04 (2H, m), 3.06-3.11 (2H, m), 3.30-3.37 (1H, td), 3.56-3.59 (1H, d), 3.63-3.68 (3H, m), 3.72-3.75 (1H, d), 3.78-3.84 (3H, m), 4.02-4.06 (1H, dd), 4.15-4.18 (1H, d), 4.49 (1H, s), 4.98-4.99 (1H, d), 6.62-6.64 (1H, d), 7.07-7.08 (1H, d), 7.48-7.50 (2H, d), 8.30-8.33 (2H, m)

Example 63b: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.23-1.24 (3H, d), 1.64-1.70 (2H, m), 1.75-1.80 (2H, m), 2.54-2.58 (1H, m), 3.2-3.21 (1H, d), 3.36-3.44 (2H, dt), 3.46-3.53 (1H, m), 3.57-3.60 (1H, q), 3.62-3.65 (2H, m), 3.74-3.77 (1H, d), 3.95-3.98 (1H, dd), 4.21-4.24 (1H, d), 4.54 (1H, s), 6.43-6.44 (1H, d), 6.70-6.71 (1H, d), 7.49-7.51 (2H, d), 8.18-8.20 (2H, d), 8.45 (1H, s)

Example 63c: ^{1}H NMR (400MHz, $CDCl_3$) δ 0.68-0.72 (2H, m), 0.86-0.90 (2H, m), 1.13-1.15 (3H, dd), 1.27-1.29 (3H, d), 1.35-1.37 (3H, d), 2.54-2.61 (1H, t), 2.62-2.66 (1H, m), 2.82-2.91 (1H, m), 3.31-3.39 (1H, td), 3.57-3.63 (1H, td), 3.73-3.76 (3H, m), 3.82-3.85 (1H, d), 4.03-4.07 (1H, dd), 4.11-4.18 (2H, m), 4.51 (1H, s), 4.56-4.60 (1H, dd), 4.96 (1H, s), 6.69 (1H, s), 7.069 (1H, s), 7.51-7.53 (2H, d), 8.31-8.33 (2H, d),

Example 63d: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.42-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 2.54-2.59 (1H, m), 2.99-3.01 (6H, d), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.55 (1H, s), 6.43-6.44 (1H, d), 6.71 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.54 (1H, s)

Example 63e: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.67 (2H, m), 1.23-1.25 (3H, d), 2.32-2.34 (1H, m), 2.54-2.61 (1H, m), 3.03 (3H, s), 3.18-3.25 (1H, td), 3.36-3.41 (1H, q), 3.49-3.50 (1H, d), 3.52-3.54 (1H, d), 3.57 (1H, s), 3.63-3.66 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.21-4.23 (1H, d), 4.52 (1H, s), 4.74 (1H, s), 6.45-6.46 (1H, d), 6.70 (1H, s), 7.50-7.52 (2H, d), 8.17-8.20 (2H, m), 8.56 (1H, s)

Example 63f: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.45 (2H, m), 0.63-0.68 (2H, m), 1.24-1.26 (3H, d), 2.33-2.35 (1H, m), 2.67-2.69 (1H, m), 2.70 (1H, s), 2.74 (2H, s), 2.90 (3H, s), 3.49-3.53 (2H, m), 3.63-3.67 (1H, dd), 3.76-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.35 (1H, s), 4.56-4.58 (1H, d), 6.43-6.44 (1H, d), 7.13 (1H, s), 7.52-7.54 (2H, d), 7.96 (1H, s), 8.38-8.40 (2H, d), 8.57 (1H, s)

Example 63g: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 2.20 (2H, s), 2.27 (1H, s), 2.33-2.35 (2H, m), 2.67-2.69 (3H, m), 2.74 (1H, s), 2.90-2.91 (2H, d), 2.97 (2H, s), 3.17-3.21 (1H, m), 3.47-3.52 (1H, m), 3.63-3.66 (1H, dd), 3.74-3.77 (1H, d), 3.96-3.98 (1H, dd), 4.22-4.24 (1H, d), 4.32-4.34 (1H, d), 4.56 (1H, s), 6.43-6.45 (1H, m), 6.69-6.70 (1H, d), 7.49-7.53 (2H, dd), 8.19-8.21 (2H, dd), 8.54 (1H, s),

Example 63h: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.23-1.24 (3H, d), 1.43 (2H, s), 1.74-1.84 (2H, d), 2.53-2.57 (1H, m), 3.14-3.18 (1H, m), 3.21-2.24 (2H, m), 3.46-3.52 (1H, td), 3.56 (1H, m), 3.62-3.66 (1H, dd), 3.74-3.77 (2H, d), 3.95-3.98 (1H, dd), 4.00-4.04 (1H, m), 4.21 (1H, d), 4.55 (1H, s), 4.77-4.78 (1H, d), 6.43-6.44 (1H, d), 6.71 (1H, s), 7.49-7.52 (2H, d), 8.18-8.20 (2H, d), 8.54 (1H, s)

Example 63i: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.24 (3H, d), 1.60-1.61 (4H, d), 1.74-1.75 (4H, d), 2.67-2.69 (1H, m), 3.17-3.25 (1H, m), 3.37-3.40 (1H, t)3.56-3.59 (1H, t), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.99 (1H, dd), 4.22-4.24 (1H, d), 4.54 (1H, s), 6.43-6.44 (1H, d), 6.69 (1H, s), 7.49-7.51 (2H, d), 8.18-2.20 (2H, d), 8.53 (1H, s)

Example 63j: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.45 (2H, m), 0.63-0.68 (2H, m), 1.15-1.19 (3H, t), 1.24-1.26 (3H, d), 2.56-2.60 (1H, m), 3.25-3.26 (1H, m), 3.33-3.42 (2H,

m), 3.47-3.53 (1H, td), 3.64-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.35-4.27 (1H, d), 4.57 (1H, s), 6.43-6.44 (1H, d), 7.13 (1H, s), 7.52-7.54 (2H, d), 8.40-8.42 (2H, d), 8.57 (1H, s)8.91-8.93 (1H, t)

Example 63k: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.68 (2H, m), 1.22-1.25 (3H, m), 2.01 (2H, s), 2.24 (2H, s), 2.55-2.58 (1H, m), 2.99-3.01 (3H, d), 3.27 (3H, s), 3.35-3.39 (3H, m), 3.46-3.49 (1H, dd), 3.52-3.56 (1H, td), 3.62-3.66 (1H, dd), 3.74-3.77 (1H, d), 3.96-3.98 (1H, d), 4.21-4.24 (1H, d), 4.55 (1H, s), 6.43-6.44 (1H, d), 6.68-6.70 (1H, d), 7.50-7.52 (2H, d), 8.20-8.22 (2H, d), 8.54 (1H, s)

Example 63l: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 2.55-2.58 (1H, m), 3.02 (3H, s), 3.19 (2H, s), 3.24-3.25 (1H, m), 3.46-3.47 (1H, d), 3.49-3.54 (3H, m), 3.59-3.60 (1H, d), 3.61-3.66 (2H, dd), 3.74-3.78 (1H, d), 3.95-3.98 (1H, dd), 4.21-4.22 (1H, d), 4.51 (1H, s), 6.44 (1H, s), 6.69-6.71 (1H, s), 7.50-7.52 (2H, d), 8.18-8.20 (2H, d), 8.55 (1H, s)

Example 63m: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.45 (2H, m), 0.63-0.68 (2H, m), 1.24-1.25 (3H, d), 1.74-1.78 (4H, m), 1.97-2.04 (3H, m), 2.55-2.61 (1H, m), 2.76-2.79 (2H, d), 3.21-3.26 (1H, m), 3.27 (1H, s), 3.47-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.73-3.78 (2H, d), 3.80-3.84 (1H, m), 3.96-4.00 (1H, dd), 4.24-4.27 (1H, d), 4.58 (1H, s), 6.44-6.45 (1H, d), 7.12 (1H, s), 7.52-7.54 (2H, d), 8.38-8.40 (2H, d), 8.51-8.54 (1H, d), 8.57 (1H, s)

Example 63n: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H,m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 2.56-2.59 (1H, m), 3.19-3.23 (1H, dd), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.75-3.78 (1H, d), 3.80-3.84 (1H, m), 3.96-3.99 (1H, dd), 4.23 (1H, s), 4.26-4-31 (1H, qd), 4.42-4.47 (1H, m), 4.53-4.58 (2H, m), 4.88-4.94 (1H, m), 5.72-5.73 (1H, d), 6.44-6.45 (1H, d), 7.04 (1H, s), 7.52-7.54 (2H, d), 8.20-8.23 (2H, d), 8.56 (1H, s)

Example 63o: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.68 (2H, m), 1.24-1.26 (3H, d), 2.55-2.59 (1H, m), 3.21-3.25 (1H, m), 3.47-3.53 (1H, td), 3.63-3.64 (1H, d), 3.66 (3H, s), 3.75-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.24-4.28 (1H, d), 4.52-4.54 (2H, d), 4.58 (1H, s), 6.42-6.44 (1H, d), 6.65 (1H, s), 7.15 (1H, s), 7.50-7.51 (1H, t), 7.52-7.53 (2H, d), 8.38-8.40 (2H, d), 8.56 (1H, s)

Example 63p: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.45 (2H, m), 0.63-0.68 (2H, m), 1.25-1.27 (3H, d), 2.56-2.59 (1H, m), 2.91 (3H, s), 3.03 (3H, s), 3.20-3.24 (1H, m), 2.48-3.54 (1H, td), 3.64-3.68 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.18-4.20 (2H, d),

4.26 (1H, d), 4.59 (1H, s), 6.46-6.47 (1H, d), 7.14 (1H, s), 7.54-7.56 (2H, d), 8.34-8.36 (2H, d), 8.59 (1H, s), 8.99-9.02 (1H, t)

Example 63q: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.49-0.53 (4H, m), 0.63-0.67 (2H, m), 1.22-1.24 (3H, d), 2.55-2.61 (2H, m), 2.87-2.88 (1H, d), 2.93 (2.95 (1H, m), 3.17-3.25 (1H, td) , 3.27 (1H, s), 3.47-3.54 (1H, td), 3.62-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.94-3.98 (1H, dd), 4.21-4.24 (1H, d), 4.52 (1H, s), 6.42-6.43 (1H, d), 6.73 (1H, s), 7.49-7.51 (2H, d), 8.19-8.22 (2H, d), 8.53 (1H, s)

Example 63r: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.14-0.18 (1H, m), 0.30-0.34 (1H, m), 0.40-0.43 (2H, m), 0.44-0.48 (1H, dq), 0.51-0.56 (1H, dq), 0.63-0.67 (2H, m), 1.06-1.10 (1H, m), 1.22-1.25 (3H, m), 2.54-2.59 (1H, m), 3.03-3.06 (3H, d), 3.16-3.19 (1H, m), 3.20-3.25 (1H, m), 3.35-3.37 (1H, m), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.98 (1H, dd), 4.22-4.24 (1H, d), 4.55 (1H, s)6.44-6.45 (1H, d), 6.70-6.71 (1H, d), 7.49-7.59 (2H, dd), 8.18-8.21 (2H, dd), 8.54-8.55 (1H, d)

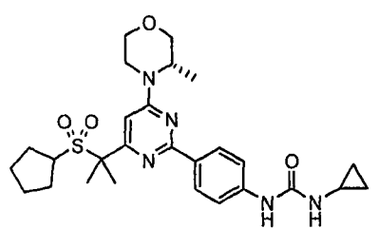
Example 63s: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.45 (2H, m), 0.64-0.68 (2H, m), 1.24-1.25 (3H, d), 2.55-2.60 (1H, m), 3.17-3.25 (1H, m), 3.47-3.54 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.25-4.27 (1H, d), 4.57 (1H, s), 4.74-4.80 (4H, m), 5.04-5.13 (1H, m), 6.44-6.45 (1H, d), 7.11 (1H, s), 7.53-7.55 (2H, d), 8.46-8.48 (2H, d), 8.58 (1H, s), 9.38-9.40 (1H, d)

Test (c): Example(63) 0.41 μM; Example(63a) 0.092 μM; Example(63b) 0.5 μM; Example(63c) 0.26 μM.

The preparation of 2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylic acid was described earlier.

Example 64:

1-[4-[4-(2-Cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea

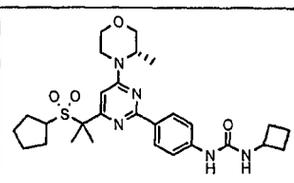
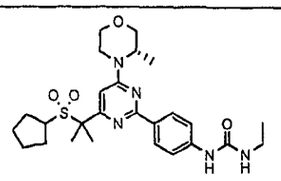
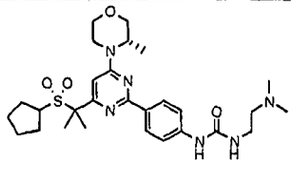


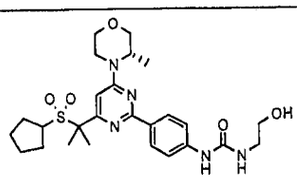
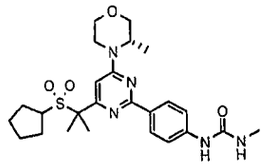
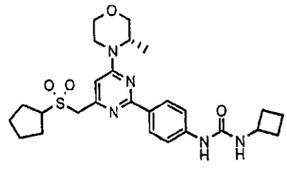
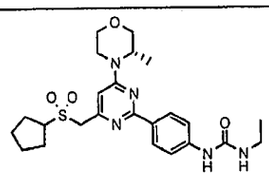
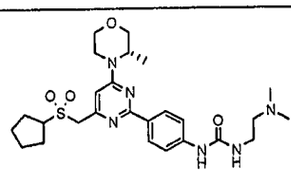
Triethylamine (0.175 mL, 1.25 mmol) was added to a mixture of phenyl *N*-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (200 mg,0.31 mmol) and cyclopropylamine (1.25 mmol) in NMP (2 mL) and heated at 75°C for 6 hours. The reaction mixture was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (136 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.22 (3H, d), 1.40 - 1.48 (4H, m), 1.52 - 1.59 (4H, m), 1.70 - 1.80 (6H, m), 3.16 - 3.24 (1H, m), 3.46 - 3.54 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.91 - 4.01 (2H, m), 4.23 (1H, d), 4.60 (1H, s), 6.44 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.24 (2H, d), 8.55 (1H, s)

LCMS Spectrum: MH+ 528, retention time 2.43 min

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
64a		3-cyclobutyl-1-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	542	2.7
64b		1-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	516	2.42
64c		1-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	559	2.35

Example	Structure	NAME	LCMS MH+	Retention time (min)
64d		1-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	532	2.04
64e		1-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	502	2.26
64f		3-cyclobutyl-1-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	514	2.36
64g		1-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	488	2.13
64h		1-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	531	2.08

Example 64a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.39 - 1.68 (10H, m), 1.69 - 1.80 (6H, m), 1.86 (2H, q), 2.17 - 2.25 (2H, m), 3.16 - 3.24 (1H, m), 3.46 - 3.55 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.95 (1H, quintet), 4.14 (1H, q), 4.22 (1H, d), 4.60 (1H, s), 6.46 (1H, d), 6.78 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.57 (1H, s)

Example 64b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.22 (3H, d), 1.41 - 1.48 (4H, m), 1.51 - 1.57 (4H, m), 1.70 - 1.79 (6H, m), 3.12 (2H, q), 3.16 - 3.24 (1H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.91 - 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 6.17 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.67 (1H, s)

Example 64c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.41 - 1.48 (4H, m), 1.52 - 1.58 (4H, m), 1.69 - 1.79 (6H, m), 2.19 (6H, s), 2.33 (2H, t), 3.16 - 3.24 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.90 - 4.01 (2H, m), 4.22 (1H, d), 4.59 (1H, s), 6.15 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.90 (1H, s)

Example 64d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.41 - 1.47 (4H, m), 1.50 - 1.58 (4H, m), 1.70 - 1.79 (6H, m), 3.15 - 3.24 (3H, m), 3.44 - 3.54 (3H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.91 - 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s)

Example 64e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.41 - 1.49 (4H, m), 1.51 - 1.58 (4H, m), 1.68 - 1.81 (6H, m), 2.67 (3H, d), 3.16 - 3.24 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.91 - 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 6.07 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.75 (1H, s)

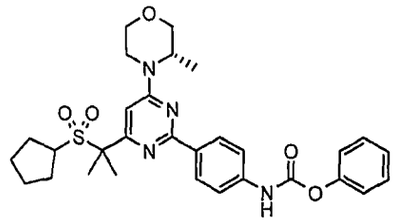
Example 64f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.57 - 1.74 (6H, m), 1.82 - 1.90 (2H, m), 1.93 - 2.07 (4H, m), 2.17 - 2.25 (2H, m), 3.16 - 3.27 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.73 - 3.83 (1H, m), 3.99 (1H, dd), 4.10 - 4.20 (2H, m), 4.45 (2H, s), 4.49 (1H, s), 6.47 (1H, d), 6.79 (1H, s), 7.47 (2H, d), 8.19 (2H, d), 8.56 (1H, s)

Example 64g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.60 - 1.74 (4H, m), 1.89 - 2.06 (4H, m), 3.09 - 3.16 (2H, m), 3.18 - 3.26 (1H, m), 3.46 - 3.54 (1H, m), 3.65 (1H, dd), 3.75 - 3.83 (2H, m), 3.99 (1H, dd), 4.17 (1H, d), 4.43 (2H, s), 4.49 (1H, s), 6.16 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.66 (1H, s)

Example 64h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.60 - 1.74 (4H, m), 1.91 - 2.07 (4H, m), 2.19 (6H, s), 2.34 (2H, t), 3.16 - 3.22 (3H, m), 3.50 (2H, td), 3.65 (2H, dd), 3.74 - 3.83 (2H, m), 3.99 (2H, dd), 4.16 (1H, d), 4.44 (2H, s), 4.51 (1H, s), 6.17 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.89 (1H, s)

The preparation of phenyl *N*-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

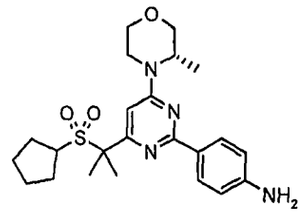


Phenyl chloroformate (0.635 mL, 5.06 mmol) was added to 4-[4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.5 g, 3.37 mmol) and sodium hydrogen carbonate (0.425 g, 5.06 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL).The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.30 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.41 - 1.47 (2H, m), 1.50 - 1.57 (2H, m), 1.69 - 1.78 (4H, m), 1.79 (6H, d), 3.21 (1H, td), 3.51 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.92 - 4.01 (2H, m), 4.24 (1H, d), 4.62 (1H, s), 6.82 (1H, s), 7.23 - 7.31 (3H, m), 7.42 - 7.48 (2H, m), 7.64 (2H, d), 8.34 (2H, d), 10.45 (1H, s)

LCMS Spectrum: MH+ 565, retention time 3.0 mins

4-[4-(2-Cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



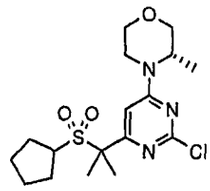
Bis(triphenylphosphine)palladium(II) chloride (200 mg, 0.28 mmol) was added to 2-chloro-4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.66 g, 4.28 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.406 g, 6.42 mmol) and sodium carbonate (10 mL, 20.00 mmol) in a mixture of ethanol (5 mL), DMF

(10 mL), water (7 mL) and DME (25 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction mixture was allowed to cool and diluted with ethyl acetate (200 mL) then washed with water (2 x 150 mL), and brine (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, and the residue obtained was triturated with a mixture of diethyl ether and isohexane to give the desired material as a pale pink solid (1.52 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.41 - 1.50 (2H, m), 1.52 - 1.60 (2H, m), 1.69 - 1.80 (10H, m), 3.17 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.90 - 3.99 (2H, m), 4.18 (1H, d), 4.56 (1H, s), 5.57 (2H, s), 6.61 (2H, d), 6.68 (1H, s), 8.06 (2H, d)

LCMS Spectrum: MH+ 445, retention time 2.42 mins

2-Chloro-4-(2-cyclopentylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

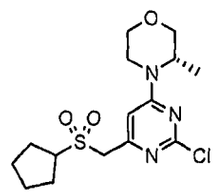


Sodium *tert*-butoxide (5.56 mmol) was added to a solution of 2-chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2 g, 5.56 mmol) in DMF (10 mL) at –5°C, followed by dropwise addition of iodomethane (0.365 mL) at –5°C. Additional sodium *tert*-butoxide (5.56 mmol) and iodomethane (0.365 mL) were added and the reaction stirred at –5°C overnight. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.66 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (4H, d), 1.46 - 1.61 (6H, m), 1.69 - 1.84 (12H, m), 1.70 (9H, s), 3.20 (3H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.75 (1H, s), 3.85 (2H, q), 3.96 (1H, d), 4.06 (1H, d), 4.46 (1H, s), 6.90 (1H, s)

LCMS Spectrum: MH+ 388, retention time 2.47 mins

2-Chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

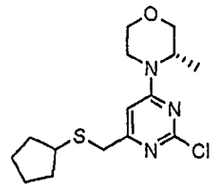


Hydrogen peroxide (19.54 mL, 632 mmol) was added to 2-chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (10.36 g, 31.60 mmol), sodium tungstate dihydrate (0.208 g, 0.63 mmol) (dissolved in minimum quantity of water) and 2M sulphuric acid solution (0.177 mL) in dioxane (100 mL) at 55°C under air. The resulting solution was stirred at 55°C for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water then a 10% aqueous solution of sodium metabisulfite. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 70% ethyl acetate in isohexane, to give the desired material as a colourless gum (9.7 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.64 (4H, m), 1.95 (4H, m), 3.24 (1H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.71 (1H, m), 3.95 (2H, m), 4.35 (1H, s), 4.40 (2H, s), 6.91 (1H, s)

Mass Spectrum: MH+360

2-Chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



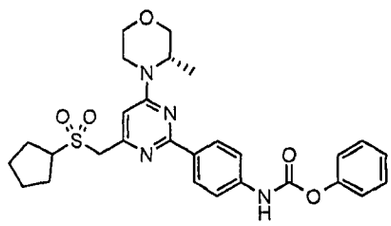
DIPEA (9.62 mL, 55.57 mmol) was added to cyclopentanethiol (5.93 mL, 55.57 mmol), in DMF (80 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13.1g, 37.05 mmol) was added to the reaction and stirred for 2 hours at RT. The reaction mixture was diluted with ethyl acetate (500 mL), and washed with water (2 x 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude

product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in isohexane, to give the desired material as a colourless gum (11.13 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.43 (2H, m), 1.53 (2H, m), 1.65 (2H, m), 1.94 (2H, m), 3.16 (2H, m), 3.44 (1H, td), 3.71 (1H, d), 3.95 (2H, m), 4.35 (1H, s), 6.79 (1H, s)
Mass Spectrum: MH+ 328

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

The preparation of phenyl *N*-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below

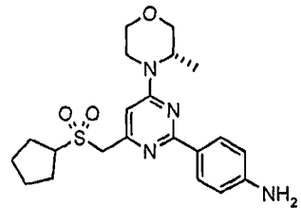
Phenyl *N*-[4-[4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.759 mL, 6.05 mmol) was added to 4-[4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.68 g, 4.03 mmol) and sodium hydrogen carbonate (0.508 g, 6.05 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (2.10 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.57 - 1.76 (4H, m), 1.93 - 2.08 (4H, m), 3.24 (1H, td), 3.47 - 3.54 (1H, m), 3.66 (1H, dd), 3.75 - 3.84 (2H, m), 3.99 (1H, dd), 4.20 (1H, d), 4.47 (2H, s), 4.52 (1H, s), 6.84 (1H, s), 7.24 - 7.31 (3H, m), 7.42 - 7.48 (2H, m), 7.64 (2H, d), 8.29 (2H, d), 10.47 (1H, s)

LCMS Spectrum: MH+ 537, retention time 2.75 mins

4-[4-(Cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (118 mg, 0.17 mmol) was added to 2-chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.67 g, 4.64 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.525 g, 6.96 mmol) and sodium carbonate (10 mL, 20.00 mmol) in a mixture of ethanol (6 mL), DMF (10 mL), water (6 mL) and DME (20 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed with water (2 x 150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a cream crystalline solid (1.680g).

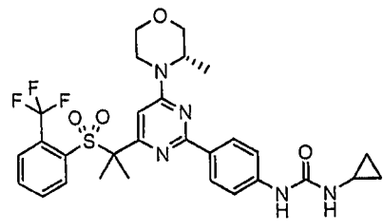
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.58 - 1.73 (4H, m), 1.93 - 2.06 (4H, m), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.74 - 3.82 (2H, m), 3.97 (1H, dd), 4.14 (1H, d), 4.39 (2H, s), 4.47 (1H, s), 5.57 (2H, s), 6.60 (2H, d), 6.67 (1H, s), 8.03 (2H, d)

LCMS Spectrum: MH+ 417, retention time 2.09 mins

The preparation of 2-chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 65:

3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea

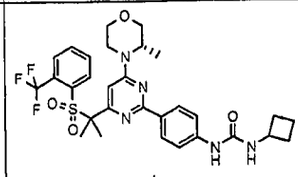


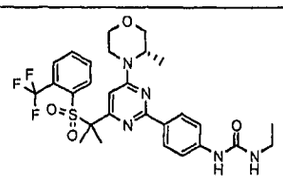
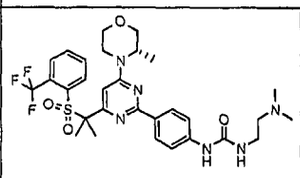
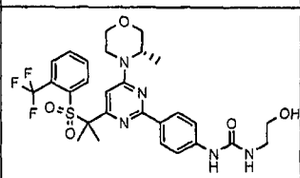
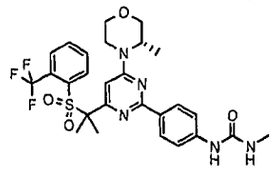
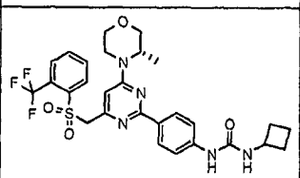
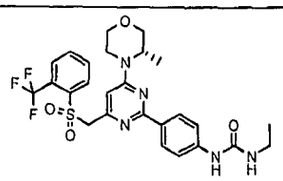
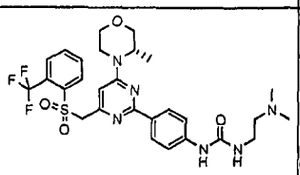
Triethylamine (0.197 mL, 1.40 mmol) was added to a mixture of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]carbamate (200mg,0.35 mmol) and cyclopropylamine (1.40 mmol) in NMP (2 mL) and heated at 75°C for 6 hours. The reaction mixture was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (163 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.63 - 0.66 (2H, m), 1.20 (3H, d), 1.84 (6H, d), 3.11 - 3.19 (1H, m), 3.49 (1H, dd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.62 (1H, s), 6.41 (1H, d), 6.67 (1H, s), 7.32 (2H, d), 7.59 (2H, d), 7.78 (1H, d), 7.82 - 7.91 (2H, m), 7.97 (1H, d), 8.48 (1H, s)

LCMS Spectrum: MH+ 604, retention time 2.59 min

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
65a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea	618	2.83

Example	Structure	NAME	LCMS MH+	Retention time (min)
65b		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea	592	2.60
65c		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea	635	2.53
65d		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea	608	2.22
65e		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]urea	578	2.42
65f		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	590	2.56
65g		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	564	2.39
65h		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	607	1.32

Example 65a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.57 - 1.68 (4H, m), 1.84 (6H, d), 2.18 - 2.25 (2H, m), 3.12 - 3.18 (1H, m), 3.45 - 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.09 - 4.18 (2H, m), 4.60 (1H, s), 6.43 (1H, d), 6.66 (1H, s), 7.29 (2H, d), 7.59 (2H, d), 7.78 (1H, d), 7.82 - 7.91 (2H, m), 7.97 (1H, d), 8.50 (1H, s)

Example 65b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.20 (3H, d), 1.82 (6H, d), 3.08 - 3.19 (2H, m), 3.49 (1H, dd), 3.64 (1H, dd), 3.77 (1H, d), 3.94 - 3.99 (1H, m), 4.12 (1H, d), 4.62 (1H, s), 6.14 (1H, t), 6.68 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.77 - 7.80 (1H, m), 7.82 - 7.91 (2H, m), 7.97 (1H, d), 8.60 (1H, s)

Example 65c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.84 (6H, d), 2.20 (6H, s), 2.34 (2H, t), 3.09 - 3.21 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.61 (1H, s), 6.14 (1H, t), 6.67 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.78 (2H, dd), 7.82 - 7.91 (2H, m), 7.97 (2H, d), 8.83 (1H, s)

Example 65d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.85 (6H, d), 3.11 - 3.20 (3H, m), 3.43 - 3.53 (3H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.60 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.67 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.78 (1H, dd), 7.82 - 7.91 (2H, m), 7.95 - 7.99 (1H, m), 8.74 (1H, s)

Example 65e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.84 (6H, d), 2.66 (3H, d), 3.15 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.61 (1H, s), 6.02 - 6.07 (1H, m), 6.66 (1H, s), 7.31 (2H, d), 7.59 (2H, d), 7.76 - 7.80 (1H, m), 7.82 - 7.91 (2H, m), 7.95 - 7.99 (1H, m), 8.67 (1H, s)

Example 65f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (3H, t), 1.20 (3H, d), 1.58 - 1.67 (2H, m), 1.81 - 1.92 (2H, m), 2.16 - 2.25 (2H, m), 3.12 - 3.22 (1H, m), 3.44 - 3.52 (1H, m), 3.63 (1H, d), 3.97 (1H, d), 4.06 - 4.17 (2H, m), 4.44 (1H, s), 4.77 (2H, s), 6.45 (1H, d), 6.71 (1H, s), 7.33 (2H, d), 7.71 (2H, d), 7.76 - 7.82 (1H, m), 7.87 - 7.93 (2H, m), 8.09 (1H, d), 8.52 (1H, s)

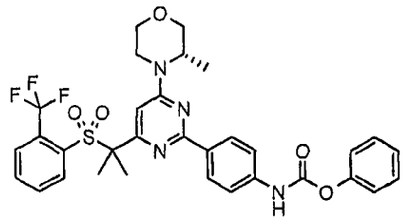
Example 65g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 3.08 - 3.22 (3H, m), 3.48 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.44 (1H, s), 4.78 (2H, s), 6.15 (1H, t), 6.70 (1H, s), 7.35 (2H, d), 7.72 (2H, d), 7.79 (1H, t), 7.87 - 7.93 (2H, m), 8.08 (1H, d), 8.61 (1H, s)

Example 65h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.19 (6H, s), 2.33 (2H, t), 3.13 - 3.22 (3H, m), 3.44 - 3.53 (1H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.10

(1H, d), 4.44 (1H, s), 4.76 (2H, s), 6.14 (1H, t), 6.70 (1H, s), 7.34 (2H, d), 7.71 (2H, d), 7.79 (1H, t), 7.87 - 7.92 (2H, m), 8.08 (1H, d), 8.84 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]phenyl]carbamate

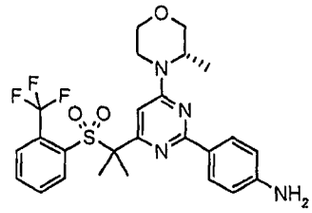


Phenyl chloroformate (0.542 mL, 4.32 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]aniline line (1.5 g, 2.88 mmol) and sodium hydrogen carbonate (0.363 g, 4.32 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours then diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.38 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.85 (6H, d), 3.16 (1H, td), 3.45 - 3.54 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.63 (1H, s), 6.71 (1H, s), 7.23 - 7.29 (3H, m), 7.42 - 7.47 (4H, m), 7.69 (2H, d), 7.78 (1H, d), 7.82 - 7.92 (2H, m), 7.98 (1H, d), 10.37 (1H, s)

LCMS Spectrum: MH+ 641, retention time 3.08 mins

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidin-2-yl]aniline

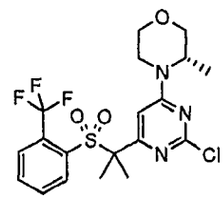


Bis(triphenylphosphine)palladium(II) chloride (200 mg, 0.28 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidine (1.91 g, 4.12 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.353 g, 6.18 mmol) and sodium carbonate (10 mL, 20.00 mmol) in a mixture of ethanol (5 mL), DMF (10 mL), water (7 mL) and DME (25 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction mixture was allowed to cool and diluted with ethyl acetate (200 mL), and washed with water (2 x 200 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, and the resultant material triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.82 (6H, d), 3.12 (1H, td), 3.47 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.57 (1H, s), 5.47 (2H, s), 6.42 (2H, d), 6.56 (1H, s), 7.44 (2H, d), 7.78 - 7.89 (3H, m), 7.92 - 7.96 (1H, m)

LCMS Spectrum: MH+ 521, retention time 2.56 mins

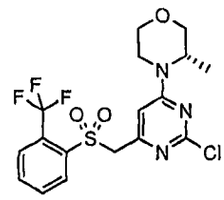
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[2-(trifluoromethyl)phenyl]sulfonylpropan-2-yl]pyrimidine



Sodium *tert*-butoxide (4.59 mmol) was added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine (2 g, 4.59 mmol) in DMF(10 mL) at –5°C, followed by dropwise addition of iodomethane (0.030 mL) at –5°C. Additional sodium tert-butoxide (4.59 mmol) and iodomethane (0.030 mL) were added and the reaction stirred at –5°C for overnight. The organics were removed *in vacuo* and the residue partitioned between ethyl acetate (200 mL) and water (100 mL). The organic layer was washed with water (100 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.91 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.13 (1H, td), 3.41 (1H, td), 3.57 (1H, dd), 3.71 (1H, d), 3.89 - 3.98 (2H, m), 4.46 (1H, s), 6.72 (1H, s), 7.87 - 8.02 (4H, m)

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine

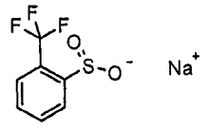


Sodium 2-(trifluoromethyl)benzenesulfinate (10.24 g, 44 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13 g, 36.77 mmol), in acetonitrile (500 mL) at RT under nitrogen. The resulting mixture was stirred at 80°C for 3 hours. Additional sodium 2-(trifluoromethyl)benzenesulfinate (10.2 g, 44 mmol) was added and reaction heated at 80°C for 1 hour. The reaction mixture allowed to cool and concentrated *in vacuo*. The material was dissolved in ethyl acetate (500 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as an orange/cream solid (9.48 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.17 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.27 (1H, s), 4.68 (2H, s), 6.79 (1H, s), 7.94 (3H, m), 8.08 (1H, d)

LCMS Spectrum: MH+ 436; retention time 2.35 min.

Sodium 2-(trifluoromethyl)benzenesulfinate



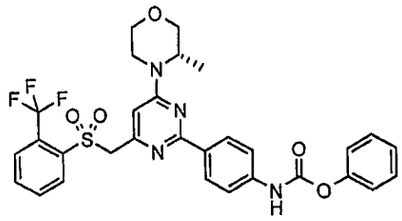
Sodium sulfite (3.92 mL, 81.88 mmol) was dissolved in water and stirred at RT 10 minutes. Sodium bicarbonate (13.74 g, 163.52 mmol) was added and the mixture stirred at 50°C for 1 hour. 2-(Trifluoromethyl)benzene-1-sulfonyl chloride (12.62 mL, 81.76 mmol) was added dropwise to the reaction mixture which was then stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and the residue suspended in methanol (250 mL) and stirred at RT for 20 minutes. The solid was removed by filtration and the filtrate evaporated to give the desired material (20.00 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.40 (1H, d), 7.51 (1H, d), 7.64 (1H, d), 8.05 (1H, d)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate

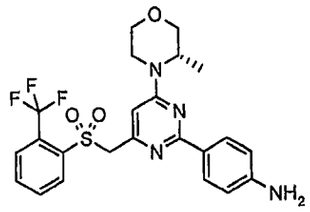


Phenyl chloroformate (0.535 mL, 4.26 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]aniline (1.4 g, 2.84 mmol) and sodium hydrogen carbonate (0.358 g, 4.26 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours then the reaction mixture diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.70 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 (1H, d), 4.47 (1H, s), 4.79 (2H, s), 6.75 (1H, s), 7.23 - 7.31 (3H, m), 7.42 - 7.51 (4H, m), 7.77 - 7.83 (2H, m), 7.87 - 7.92 (2H, m), 8.09 (1H, d), 10.39 (1H, s)

LCMS Spectrum: MH+ 613, retention time 2.92 mins

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.43 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine (1.66 g, 3.81 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.252 g, 5.71 mmol) and sodium carbonate

(10 mL, 20.00 mmol) in a mixture of ethanol (6 mL), DMF (10 mL), water (6 mL) and DME (20 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction mixture was allowed to cooll then diluted with ethyl acetate (400 mL), and washed with water (2 x 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a cream crystalline solid (1.40 g).

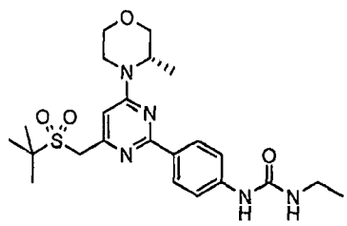
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 3.14 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.04 - 4.11 (1H, m), 4.41 (1H, s), 4.72 (2H, s), 5.51 (2H, s), 6.47 (2H, d), 6.59 (1H, s), 7.56 (2H, d), 7.76 - 7.81 (1H, m), 7.86 - 7.92 (2H, m), 8.07 (1H, d)

LCMS Spectrum: MH+ 493, retention time 2.35 mins

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine was described earlier.

Example 66:

3-Ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea

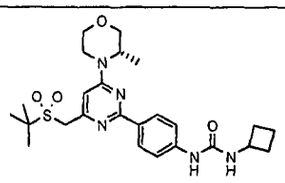
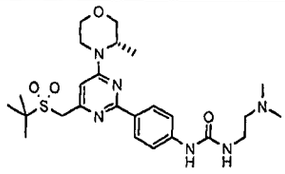
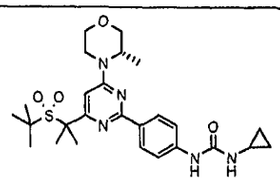
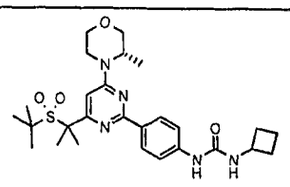


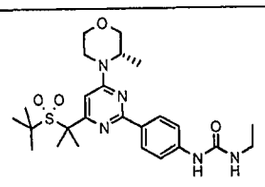
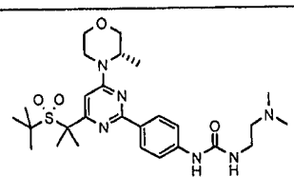
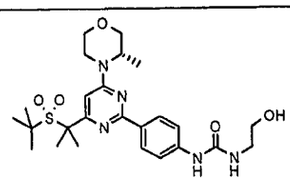
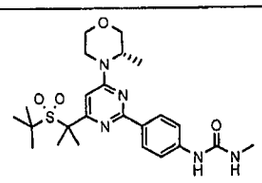
Ethylamine hydrochloride (86.4 mg, 1.03 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.23 mmol) and triethylamine (0.21 mL, 1.49 mmol) in DMF (2 mL). The reaction mixture was allowed to stand at RT for 65 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a colourless solid (79.0 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.25 (3H, d), 1.39 (9H, s), 3.10 - 3.25 (3H, m), 3.45 - 3.54 (1H, m), 3.63 - 3.69 (1H, m), 3.79 (1H, d), 3.95 - 4.03 (1H, m), 4.18 (1H, d), 4.46 (3H, s), 6.18 (1H, t), 6.75 (1H, s), 7.50 (2H, m), 8.21 (2H, d), 8.68 (1H, s)

LCMS Spectrum: MH+ 476, retention time 2.04 min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
66a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	502	2.25
66b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea	519	1.97
66c		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	516	2.36
66d		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	530	2.64

Example	Structure	NAME	LCMS MH+	Retention time (min)
66e		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	504	2.34
66f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	547	2.27
66g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	520	1.98
66h		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea	490	2.27

Example 66a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.39 (9H, s), 1.54 - 1.69 (2H, m), 1.79 – 1.92 (2H, m), 2.15 – 2.27 (2H, m), 3.15 – 3.25 (1H, m), 3.51 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.10 – 4.22 (2H, m), 4.46 (3H, s), 6.46 (1H, d), 6.75 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.1 (1H, s)

Example 66b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 - 1.25 (3H, m), 1.39 (9H, s), 2.19 (6H, s), 2.34 (2H, t), 3.19 - 3.25 (1H, m), 3.45 - 3.56 (1H, m), 3.62 - 3.68 (1H, m), 3.79 (1H, d), 3.95 - 4.02 (1H, m), 4.08 (2H, q), 4.18 (1H, d), 4.46 (3H, s), 6.17 (1H, t), 6.75 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.90 (1H, s)

Example 66c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.55 - 2.59 (1H, m), 3.18 (1H, dt), 3.51 (1H, dt), 3.66 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.22 (1H, d), 4.51 (1H, br, s), 6.44 (1H, d), 6.88 (1H, s), 7.52 (2H, d), 8.27 (2H, d), 8.55 (1H, s)

Example 66d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.58 - 1.68 (2H, m), 1.80 - 1.91 (8H, m), 2.15 - 2.25 (2H, m), 3.12 - 3.23 (1H, m), 3.45 – 3.55 (1H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.94 – 4.02 (1H, m), 4.08 – 4.26 (2H, m), 4.51 (1H, br, s), 6.47 (1H, d), 6.88 (1H, s), 7.49 (2H, d), 8.26 (2H, d), 8.58 (1H, s)

Example 66e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 3.10 - 3.24 (3H, m), 3.44 - 3.55 (1H, m), 3.62 - 3.68 (1H, m), 3.78 (1H, d), 3.94 – 4.01 (1H, m), 4.22 (1H, d), 4.51 (1H, br, s), 6.17 (1H, t), 6.88 (1H, s), 7.51 (2H, d), 8.26 (2H, d), 8.67 (1H, s)

Example 66f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.19 (6H, s), 2.35 (2H, t), 3.13 - 3.23 (3H, m), 3.45 - 3.54 (1H, m), 3.62 - 3.68 (1H, m), 3.78 (1H, d), 3.94 - 4.01 (1H, m), 4.22 (1H, d), 4.52 (1H, br, s), 6.17 (1H, t), 6.88 (1H, s), 7.50 (2H, d), 8.26 (2H, d), 8.91 (1H, s)

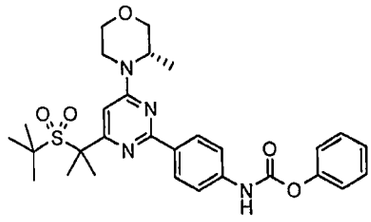
Example 66g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 3.12 – 3.22 (3H, m), 3.43 - 3.54 (3H, m), 3.62 - 3.68 (1H, m), 3.78 (1H, d), 3.95 - 4.01 (1H, m), 4.22 (1H, d), 4.51 (1H, br, s), 4.74 (1H, t), 6.27 (1H, t), 6.88 (1H, s), 7.50 (2H, d), 8.27 (2H, d), 8.82 (1H, s)

Example 66h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.67 (3H, d), 3.14 - 3.23 (1H, m), 3.46 - 3.55 (1H, m), 3.63 - 3.69 (1H, m), 3.78 (1H, d), 3.96 - 4.02 (1H, m), 4.22 (1H, d), 4.52 (1H, br, s), 6.06 – 6.12 (1H, m), 6.88 (1H, s), 7.52 (2H, d), 8.26 (2H, d), 8.77 (1H, s)

Test (c): Example(66c) 0.15 μM; Example(66d) 0.16 μM; Example(66e) 0.26 μM; Example(66f) 0.04 μM; Example(66g) 0.3 μM.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate

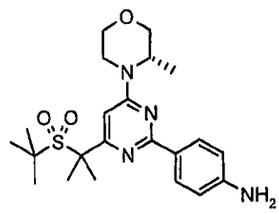


Phenyl chloroformate (0.368 mL, 2.93 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline (1.153 g, 2.67 mmol) and sodium hydrogen carbonate (0.336 g, 4.00 mmol) in dioxane (20 mL) at RT. The resulting slurry was stirred at RT for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 20%-70% ethyl acetate in isohexane, to give the desired material as a near colourless solid (1.42 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.25 (9H, s), 1.32 (3H, d), 1.95 (3H, s), 1.97 (3H, s), 3.31 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.18 (1H, d), 4.47 (1H, br), 6.88 (1H, s), 7.10 (1H, br, s), 7.20 - 7.27 (3H, m), 7.41 (2H, t), 7.55 (2H, d), 8.43 (2H, d)

LCMS Spectrum: MH+ 553, retention time 3.05 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline



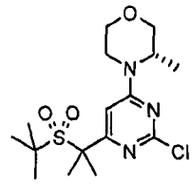
Dichlorobis(triphenylphosphine)-palladium(II) (0.103 g, 0.15 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidine (1.10 g, 2.93 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.833 g, 3.80 mmol) and 2M aqueous sodium carbonate (5.27 mL, 10.53 mmol) in DMF (6 mL), DME

(5 mL), ethanol (5 mL) and water (12.5 mL) at RT under nitrogen. The reaction was purged with nitrogen for 15 minutes and the resulting mixture was stirred at 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with water. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-100% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.19 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (9H, s), 1.30 (3H, d), 1.93 (3H, s), 1.95 (3H, s), 3.28 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 3.90 (2H, s), 4.03 (1H, dd), 4.16 (1H, d), 4.46 (1H, br), 6.72 (2H, d), 6.79 (1H, s), 8.26 (2H, d)

LCMS Spectrum: MH+ 433, retention time 2.42 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-tert-butylsulfonylpropan-2-yl)pyrimidine

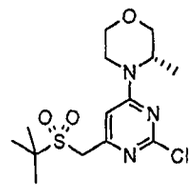


Sodium *tert*-butoxide (0.345 g, 3.59 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidine (1.250 g, 3.59 mmol) in DMF (30 mL) at 0°C under nitrogen. Iodomethane (0.224 mL, 3.59 mmol) was added and the resulting solution was stirred at 0°C for 15 minutes. Further sodium *tert*-butoxide (0.345 g, 3.59 mmol) was added followed by iodomethane (0.224 mL, 3.59 mmol) and the resulting solution was stirred at 0°C for 1 hour. The reaction was diluted with DCM (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated to give a gum which slowly crystallised. The crude product was chromatographed on silica, eluting with 0-40% ethyl acetate in DCM, to give the desired material as a colourless solid (1.14 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (9H, s), 1.30 (3H, d), 1.84 (3H, s), 1.86 (3H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.99 - 4.05 (2H, m), 4.30 (1H, br, s), 6.89 (1H, s).

LCMS Spectrum: MH+ 376, 378, retention time 2.52 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidine

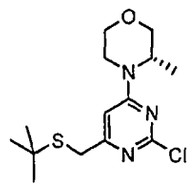


A solution of hydrogen peroxide (9.48 mL, 107.30 mmol) (35% aqueous solution) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfanylmethyl)pyrimidine (9.82 g, 31.1 mmol), sodium tungstate dihydrate (0.205 g, 0.62 mmol) and sulfuric acid (0.6 mL, 1M, 0.6 mmol) in dioxane (80 mL). The mixture was heated at 55°C under air for 1 hour. When the reaction was complete, the solution was diluted with water and cooled. A solution of sodium metabisulfite (10% w/v) was added to destroy remaining peroxide. The solution was extracted with DCM, dried ($MgSO_4$) and filtered to give the desired material as a near colourless gum (9.34 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.44 (9H, s), 3.29 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.78 (1H, d), 3.97 - 4.13 (2H, m), 4.21 (2H, s), 4.30 (1H, br, s), 6.71 (1H, s).

LCMS Spectrum: MH+ 348, 350, retention time 1.82 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfanylmethyl)pyrimidine



N-Ethyldiisopropylamine (8.61 mL, 49.78 mmol) was added to 2-methyl-2-propanethiol (4.21 mL, 37.33 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT. The reaction mixture was placed in a water bath at 60°C for 1.5 hours then partitioned between ethyl acetate and water. The organic layer was washed with additional water and then was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow gum (10.02 g).

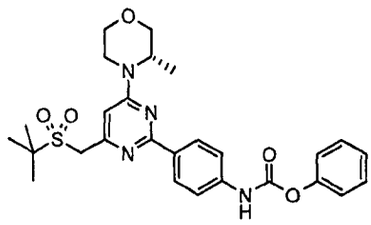
NMR Spectrum: 1H NMR (399.9 MHz, CDCl3) δ 1.31 (3H, d), 1.34 (9H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.66 - 3.71 (3H, m), 3.78 (1H, d), 3.97 - 4.07 (2H, m), 4.31 (1H, br, s), 6.56 (1H, s)

LCMS Spectrum: MH+ 316, 318, retention time 2.61 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate

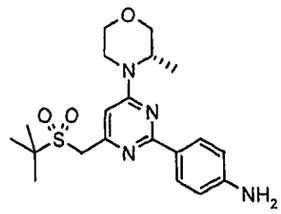


Phenyl chloroformate (0.227 mL, 1.81 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]aniline (665 mg, 1.64 mmol) and sodium hydrogen carbonate (207 mg, 2.47 mmol) in dioxane (12 mL). The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-80% ethyl acetate in isohexane, to give the desired material as a yellow dry film (860 mg).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 (9H, s), 3.32 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.20 (1H, d), 4.34 (2H, s), 4.46 (1H, br), 6.68 (1H, s), 7.10 (1H, s), 7.19 - 7.27 (3H, m), 7.40 (2H, t), 7.53 (2H, d), 8.37 (2H, d)

LCMS Spectrum: MH+ 525, retention time 2.69 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)-palladium(II) (63 mg, 0.09 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidine (626 mg, 1.8 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (513 mg, 2.34 mmol) and 2M aqueous sodium carbonate (3.24 mL, 6.48 mmol) in DMF (3.75 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at RT under nitrogen. The reaction mixture was purged with nitrogen for 15 minutes and the resulting mixture was stirred at 80°C for 16 hours. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-100% ethyl acetate in isohexane, to give the desired material as a yellow solid (681 mg).

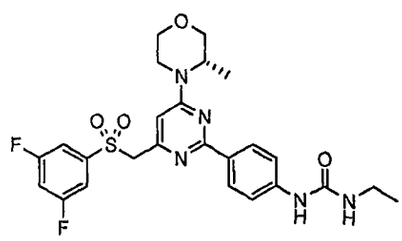
NMR Spectrum: ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.43 (9H, s), 3.30 (1H, m), 3.60 (1H, m), 3.74 (1H, dd), 3.81 (1H, d), 3.89 (2H, s), 4.03 (1H, dd), 4.18 (1H, d), 4.31 (2H, d), 4.44 (1H, br), 6.61 (1H, s), 6.71 (2H, d), 8.21 (2H, d)

LCMS Spectrum: MH+ 405, retention time 1.98 min .

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(tert-butylsulfonylmethyl)pyrimidine was described earlier.

Example 67:

1-[4-[4-[(3,5-Difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea

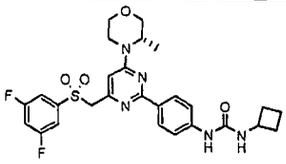
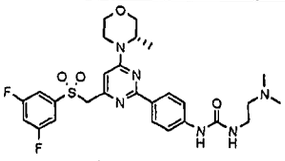


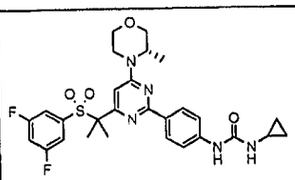
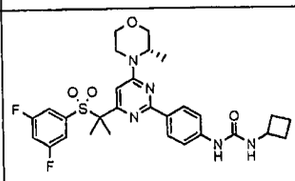
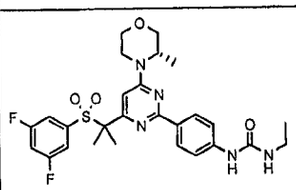
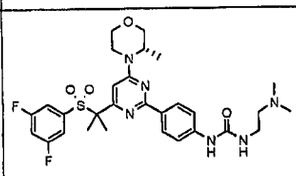
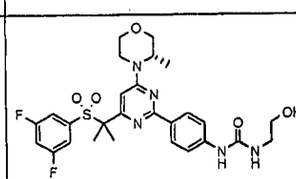
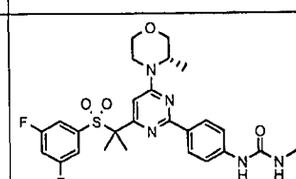
Phenyl *N*-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.207 mmol) was added to a mixture of ethylamine hydrochloride (86 mg, 1.03 mmol) and triethylamine (0.2 mL, 1.49 mmol) in DMF (1.5 mL) at RT. The reaction mixture was allowed to stand at RT for 65 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (19.0 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.22 (3H, d), 3.09 - 3.3 (3H, m), 3.44 - 3.3 (1H, m), 3.61 - 3.67 (1H, m), 3.78 (1H, d), 3.94 - 4.01 (1H, m), 4.09 – 4.18 (1H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.16 (1H, t), 6.71 (1H, s), 7.40 (2H, d), 7.58 - 7.64 (2H, m), 7.72 - 7.83 (3H, m), 8.65 (1H, s).

LCMS Spectrum: MH+ 532, retention time 2.29 min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
67a		3-cyclobutyl-1-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	558	2.51
67b		1-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	575	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
67c		3-cyclopropyl-1-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	572	2.60
67d		3-cyclobutyl-1-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	586	2.81
67e		3-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	560	2.59
67f		1-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	603	2.57
67g		1-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	576	2.23
67h		1-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	546	2.44

Example 67a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 – 1.70 (2H, m), 1.80 - 1.94 (2H, m), 2.15 - 2.27 (2H, m), 3.14 - 3.24 (1H, m), 3.44 – 3.53 (1H, m), 3.61 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.02 (1H, m), 4.08 – 4.20 (2H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.46 (1H, d), 6.71 (1H, s), 7.38 (2H, d), 7.59 - 7.64 (2H, m), 7.72 - 7.83 (3H, m), 8.55 (1H, s).

Example 67b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 (3H, d), 2.19 (6H, s), 2.34 (2H, t), 3.14 - 3.23 (3H, m), 3.44 - 3.54 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.94 - 4.00 (1H, m), 4.06 - 4.14 (1H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.16 (1H, t), 6.71 (1H, s), 7.39 (2H, d), 7.58 - 7.64 (2H, m), 7.74 - 7.83 (3H, m), 8.88 (1H, s).

Example 67c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.39 - 0.45 (2H, m), 0.62 - 0.69 (2H, m), 1.23 (3H, d), 1.82 (6H, s), 2.54 - 2.60 (1H, m), 3.13 - 3.22 (1H, m), 3.46 - 3.54 (1H, m), 3.62 - 3.68 (1H, m), 3.78 (1H, d), 3.95 - 4.00 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 6.43 (1H, s), 6.71 (1H, s), 7.16 – 7.23 (2H, d), 7.41 (2H, d), 7.60 - 7.67 (1H, m), 7.84 (2H, d), 8.53 (1H, s).

Example 67d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 – 1.69 (2H, m), 1.78 - 1.92 (8H, m), 2.17 - 2.26 (2H, m), 3.12 - 3.22 (1H, m), 3.46 - 3.53 (1H, m), 3.61 - 3.68 (1H, m), 3.78 (1H, d), 3.95 - 4.02 (1H, m), 4.10 - 4.22 (2H, m), 4.59 (1H, br, s), 6.46 (1H, d), 6.71 (1H, s), 7.15 - 7.23 (2H, m), 7.38 (2H, d), 7.60 - 7.68 (1H, m), 7.84 (2H, d), 8.55 (1H, s).

Example 67e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.08 (3H, t), 1.23 (3H, d), 1.83 (6H, s), 3.09 – 3.22 (3H, m), 3.50 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.19 (1H, d), 4.60 (1H, br, s), 6.16 (1H, s), 6.71 (1H, s), 7.21 (2H, s), 7.41 (2H, d), 7.59 - 7.69 (1H, m), 7.84 (2H, d), 8.65 (1H, s).

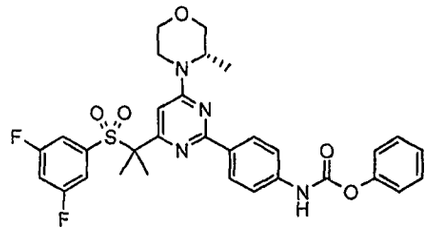
Example 67f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.80 - 1.83 (6H, m), 2.18 (6H, s), 2.34 (2H, t), 3.12 - 3.23 (3H, m), 3.44 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.94 - 4.01 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 6.15 (1H, t), 6.70 (1H, s), 7.15 – 7.23 (2H, m), 7.39 (2H, d), 7.59 - 7.66 (1H, m), 7.84 (2H, d), 8.86 (1H, s).

Example 67g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.80 - 1.83 (6H, m), 3.12 - 3.23 (3H, m), 3.40 - 3.53 (3H, m), 3.62 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 4.73 (1H, t), 6.24 (1H, t), 6.70 (1H, s), 7.16 – 7.23 (2H, m), 7.39 (2H, d), 7.59 - 7.66 (1H, m), 7.84 (2H, d), 8.78 (1H, s).

Example 67h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.82 (6H, s), 2.66 (3H, d), 3.12 - 3.22 (1H, m), 3.44 - 3.54 (1H, m), 3.60 – 3.68 (1H, m), 3.77 (1H, d), 3.93 – 4.00 (1H, m), 4.18 (1H, d), 4.58 (1H, br, s), 6.03 – 6.09 (1H, m), 6.70 (1H, s), 7.14 – 7.23 (2H, m), 7.40 (2H, d), 7.63 (1H, t), 7.83 (2H, d), 8.71 (1H, s).

The preparation of phenyl *N*-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

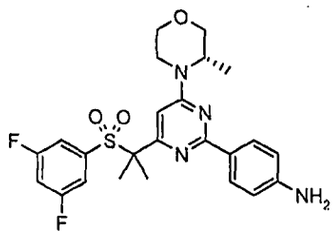


Phenyl chloroformate (0.413 mL, 3.29 mmol) was added to 4-[4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.46 g, 2.99 mmol) and sodium hydrogen carbonate (0.377 g, 4.48 mmol) in dioxane (25 mL). The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-80% ethyl acetate in isohexane, to give a colourless gum. This material was triturated with diethyl ether to give the desired material as a colourless crystalline solid (1.808 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.36 (3H, d), 1.89 (6H, s), 3.34 (1H, dt), 3.63 (1H, dt), 3.79 (1H, dd), 3.86 (1H, d), 4.08 (1H, dd), 4.14 (1H, d), 4.48 - 4.58 (1H, m), 6.66 (1H, s), 6.88 - 6.95 (1H, m), 7.04 (1H, s), 7.08 - 7.13 (2H, m), 7.19 - 7.28 (3H, m), 7.38 - 7.44 (4H, m), 7.98 (2H, d).

LCMS Spectrum: MH+ 609, retention time 3.26 min.

4-[4-[2-(3,5-Difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

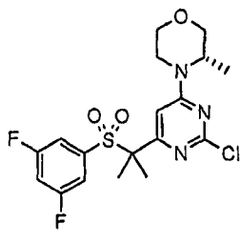


A stream of nitrogen was passed through a mixture of 2-chloro-4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.4 g, 3.24 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.923 g, 4.21 mmol) and 2M aqueous sodium carbonate (5.83 mL, 11.67 mmol) in DMF (6 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at RT. The reaction mixture was treated with dichlorobis(triphenylphosphine)palladium(II) (0.114 g, 0.16 mmol) and was stirred at 80°C for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-60% ethyl acetate in isohexane, to give the desired material as a pale yellow solid (1.496 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.88 (6H, s), 3.32 (1H, dt), 3.63 (1H, dt), 3.77 (1H, dd), 3.82 (1H, s), 3.86 (2H, s), 4.05 (1H, dd), 4.12 (1H, d), 4.46 - 4.54 (1H, m), 6.57 - 6.62 (3H, m), 6.88 - 6.93 (1H, m), 7.08 - 7.12 (2H, m), 7.82 (2H, d).

LCMS Spectrum: MH+ 489, retention time 2.77 min.

2-Chloro-4-[2-(3,5-difluorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



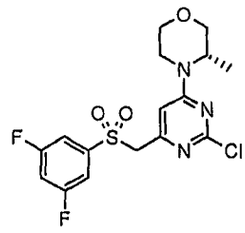
Sodium *tert*-butoxide (0.336 g, 3.49 mmol) was added to 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.41 g, 3.49 mmol) in DMF (30 mL) at 0°C under nitrogen. Iodomethane (0.217 mL, 3.49 mmol) was added and the resulting solution was stirred at 0°C for 15 minutes. Sodium *tert*-butoxide (0.336 g, 3.49 mmol) was added followed by iodomethane (0.217 mL, 3.49 mmol) and the

resulting solution was stirred at 0°C for 1 hour. The reaction was poured into water (100 mL). The resulting precipitate was isolated by filtration and dried *in vacuo*, to give the desired product as a colourless solid (1.434 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.77 (6H, s), 3.32 (1H, dt), 3.58 (1H, dt), 3.72 (1H, dd), 3.81 (1H, d), 3.97 - 4.05 (2H, m), 4.36 (1H, br, s), 6.69 (1H, s), 7.07 - 7.16 (3H, m).

LCMS Spectrum: MH+ 432, 434, retention time 2.78 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

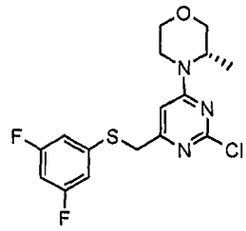


A solution of sodium tungstate dihydrate (199 mg, 0.60 mmol) in water (2 mL) was added to a stirred solution of 2-chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.23 g, 30.2 mmol) and 2M sulfuric acid (0.302 mL, 0.60 mmol) in dioxane (40 mL). Hydrogen peroxide (3.22 mL, 104.19 mmol) was added and the mixture was stirred at RT overnight. A precipitate was collected by filtration and dried *in vacuo*. The filtrate was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 5% - 20% ethyl acetate in DCM, and the product obtained combined with the precipitated material to give the desired material as a near colourless solid (11.27 g).

NMR Spectrum: 1H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 3.31 (1H, dt), 3.56 (1H, dt), 3.71 (1H, dd), 3.80 (1H, d), 3.98 - 4.10 (2H, m), 4.31 (2H, s), 6.55 (1H, s), 7.12 (1H, tt), 7.30 - 7.36 (2H, m).

LCMS Spectrum: MH+ 404,406, retention time 2.32 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



DIPEA (8.07 mL, 46.67 mmol) was added to 3,5-difluorobenzenethiol (5.00 g, 34.22 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT. The reaction mixture was heated in a water bath at 60°C for 1.5 hours before being partitioned between ethyl acetate and water. The organic solution was washed with further water, dried ($MgSO_4$), filtered and evaporated to afford the desired material as a gum (12.24 g).

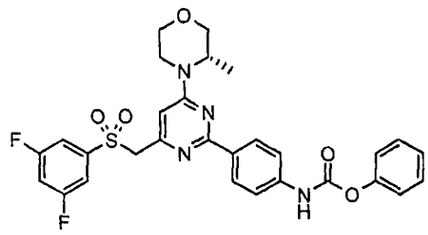
NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.27 (3H, d), 3.24 (1H, dt), 3.52 (1H, dt), 3.66 (1H, dd), 3.76 (1H, d), 3.96 - 4.04 (4H, m), 4.21 (1H, br, s), 6.41 (1H, s), 6.59 - 6.66 (1H, m), 6.80 - 6.86 (2H, m).

LCMS Spectrum: MH+ 372,374, retention time 2.66 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

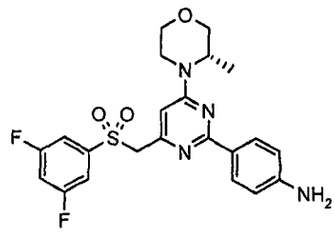


Phenyl chloroformate (0.208 mL, 1.66 mmol) was added to 4-[4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (693 mg, 1.50 mmol) and sodium hydrogen carbonate (190 mg, 2.26 mmol) in dioxane (10 mL). The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-80% ethyl acetate in isohexane, to give the desired product as a yellow dry film (827 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.35 (3H, d), 3.33 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.83 (1H, d), 4.16 (1H, d), 4.38 - 4.48 (3H, m), 6.48 (1H, s), 6.98 - 7.08 (2H, m), 7.19 - 7.28 (4H, m), 7.32 - 7.47 (5H, m), 8.02 (2H, d).

LCMS Spectrum: MH+ 581, retention time 2.91 min.

4-[4-[(3,5-Difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



A stream of nitrogen was passed through 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.727 g, 1.8 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.513 g, 2.34 mmol) and 2M aqueous sodium carbonate (3.24 mL, 6.48 mmol) in DMF (3.75 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)palladium(II) (0.063 g, 0.09 mmol) and the mixture was stirred at 80°C for 16 hours. The mixture was partitioned between ethyl acetate and water.

The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 25%-60% ethyl acetate in isohexane, to give the desired product as a yellow solid (0.735 g).

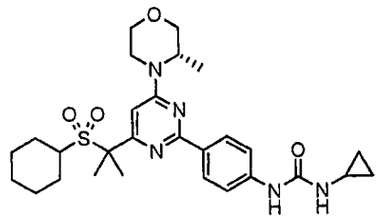
NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t), 3.31 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.80 - 3.93 (3H, m), 4.01 - 4.08 (1H, dd), 4.15 (1H, d), 4.40 (3H, s), 6.40 (1H, s), 6.62 (2H, d), 7.01 (1H, tt), 7.32 - 7.38 (2H, m), 7.85 (2H, d).

LCMS Spectrum: MH+ 461, retention time 2.46 min.

The preparation of 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 68:

1-[4-[4-(2-Cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea

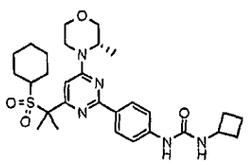
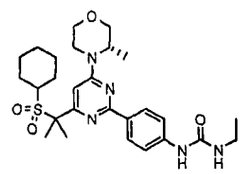
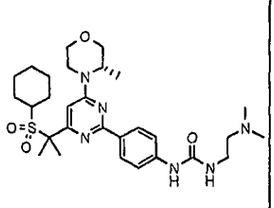
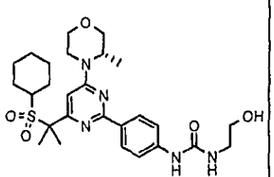


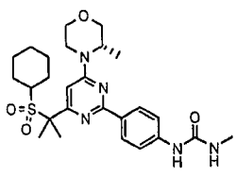
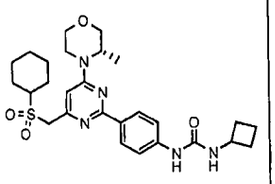
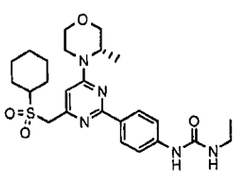
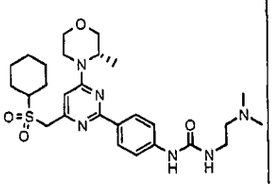
To a solution of cyclopropylamine (53 mg, 0.93 mmol) in DMF (2 mL) was added triethylamine (0.09 mL, 0.64 mmol) followed by phenyl *N*-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (118 mg, 0.20 mmol). The resultant mixture was heated to 50°C and stirred for 2 hours. The reaction mixture was cooled and diluted with further DMF (1 mL) before purifying crude reaction mixture by preparative HPLC, using decreasingly polar mixtures of water (containing 1% aq. ammonia solution) and acetonitrile as eluents, to give the desired material as a white solid (75 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.00 - 1.19 (3H, m), 1.22 (3H, d), 1.24 - 1.37 (2H, m), 1.47 - 1.53 (1H, m), 1.64 - 1.82 (10H, m), 2.53 - 2.59 (1H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 - 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 - 4.62 (1H, m), 6.44 (1H, d), 6.75 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.55 (1H, s).

LCMS Spectrum: MH+ 542, retention time 2.37 min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
68a		3-cyclobutyl-1-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	556	2.59
68b		3-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	530	2.35
68c		1-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	573	2.26
68d		1-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	546	1.99

Example	Structure	NAME	LCMS MH+	Retention time (min)
68e		1-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	516	2.19
68f		3-cyclobutyl-1-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	529	2.57
68g		3-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	503	2.32
68h		1-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	545	2.25

Example 68a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.02 - 1.18 (3H, m), 1.22 (3H, d), 1.25 - 1.35 (2H, m), 1.47 - 1.53 (1H, m), 1.57 - 1.91 (14H, m), 2.18 - 2.25 (2H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.11 - 4.26 (2H, m), 4.55 - 4.61 (1H, m), 6.48 (1H, d), 6.75 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.58 (1H, s).

Example 68b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 - 1.17 (6H, m), 1.22 (3H, d), 1.25 - 1.36 (2H, m), 1.47 - 1.53 (1H, m), 1.64 - 1.84 (10H, m), 3.10 - 3.16 (2H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 - 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.55 - 4.62 (1H, m), 6.17 (1H, t), 6.75 (1H, s), 7.51 (2H, d), 8.25 (2H, d), 8.68 (1H, s).

Example 68c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 - 1.19 (3H, m), 1.22 (3H, d), 1.25 - 1.37 (2H, m), 1.48 - 1.53 (1H, m), 1.64 - 1.84 (10H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 - 3.24 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 - 4.62 (1H, m), 6.17 (1H, t), 6.75 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.91 (1H, s).

Example 68d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 - 1.18 (3H, m), 1.22 (3H, d), 1.25 - 1.37 (2H, m), 1.47 - 1.53 (1H, m), 1.63 - 1.84 (10H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.53 (3H, m), 3.65 (1H, dd), 3.70 - 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 - 4.63 (1H, m), 4.73 (1H, t), 6.26 (1H, t), 6.75 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.82 (1H, s).

Example 68e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.00 - 1.18 (3H, m), 1.22 (3H, d), 1.25 - 1.36 (2H, m), 1.47 - 1.52 (1H, m), 1.64 - 1.84 (10H, m), 2.66 (3H, d), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 - 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 - 4.61 (1H, m), 6.08 (1H, q), 6.75 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.76 (1H, s).

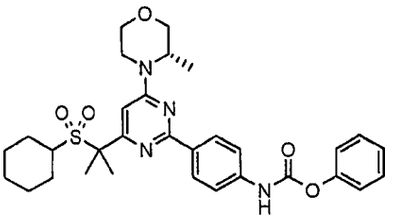
Example 68f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 - 1.31 (6H, m), 1.41 - 1.49 (2H, m), 1.57 - 1.69 (3H, m), 1.82 - 1.92 (4H, m), 2.18 - 2.28 (4H, m), 3.22 (1H, td), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.09 - 4.22 (2H, m), 4.40 - 4.51 (3H, m), 6.48 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.58 (1H, s).

Example 68g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.15 - 1.33 (6H, m), 1.39 - 1.50 (2H, m), 1.65 - 1.71 (1H, m), 1.86 - 1.92 (2H, m), 2.21 - 2.28 (2H, m), 3.09 - 3.16 (2H, m), 3.22 (1H, td), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.13 - 4.21 (1H, m), 4.40 - 4.51 (3H, m), 6.18 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.68 (1H, s).

Example 68h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.33 (6H, m), 1.39 - 1.50 (2H, m), 1.65 - 1.71 (1H, m), 1.86 - 1.92 (2H, m), 2.18 (6H, s), 2.21 - 2.27 (2H, m), 2.34 (2H, t), 3.17 - 3.26 (3H, m), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.14 - 4.21 (1H, m), 4.40 - 4.51 (3H, m), 6.18 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.90 (1H, s).

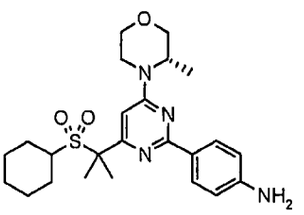
The preparation of phenyl *N*-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



To a solution of 4-[4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.1 g, 2.40 mmol) in 1,4-dioxane (12 mL) was added sodium bicarbonate (0.302 g, 3.60 mmol). Phenyl chloroformate (0.316 mL, 2.52 mmol) was then added dropwise and the resulting mixture was stirred at RT for 3 hours. The resulting mixture was evaporated to dryness and the residue partitioned between water (10 mL) and DCM (10 mL). The organic layer was separated and evaporated to dryness. The residue was triturated with diethyl ether to give the desired material as a solid (1.328 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 - 1.18 (3H, m), 1.20 - 1.37 (5H, m), 1.46 - 1.52 (1H, m), 1.63 - 1.83 (10H, m), 3.21 (1H, td), 3.51 (1H, td), 3.65 (1H, dd), 3.69 - 3.79 (3H, m), 3.98 (1H, dd), 4.21 - 4.28 (1H, m), 4.56 - 4.64 (1H, m), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.65 (2H, d), 8.36 (2H, d), 10.43 (1H, s).
LCMS Spectrum: MH+ 579, retention time 3.11 min.

4-[4-(2-Cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



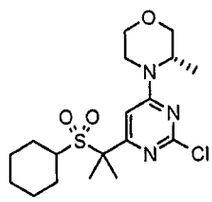
A mixture of 2-chloro-4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.18 g, 2.94 mmol), 2M aqueous sodium carbonate solution (5.5 mL, 11.00 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.907 g, 4.14 mmol) in

a mixture of DMF (5 mL), water (12.50 mL), ethanol (5.00 mL) and DME (5.00 mL) was purged with nitrogen for 10 minutes before being treated with bis(triphenylphosphine)palladium(II) chloride (0.111 g, 0.16 mmol). The stirred mixture was heated to 80°C and stirred under nitrogen for 2.5 hours. The reaction mixture was cooled and treated with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated and the aqueous re-extracted with ethyl acetate (2 x 30 mL). The combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material (1.130 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 - 1.23 (6H, m), 1.25 - 1.36 (2H, m), 1.47 - 1.53 (1H, m), 1.65 - 1.83 (10H, m), 3.18 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.73 - 3.81 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.52 - 4.58 (1H, m), 5.54 - 5.57 (2H, m), 6.62 (2H, d), 6.64 (1H, s), 8.08 (2H, d).

LCMS Spectrum: MH+ 459, retention time 2.56 min.

2-Chloro-4-(2-cyclohexylsulfonylpropan-2-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



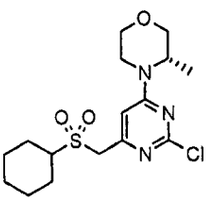
A cooled (ice/water bath) solution of 2-chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.26 g, 3.37 mmol) in DMF (16 mL) was treated with sodium tert-butoxide (0.324 g, 3.37 mmol). The mixture was stirred at 0°C for 5 minutes. Iodomethane (0.210 mL, 3.37 mmol) was then added and mixture stirred at 0°C for a further 10 minutes. Further sodium tert-butoxide (0.324 g, 3.37 mmol) was then added and stirring continued for a further 5 minutes before addition of more iodomethane (0.210 mL, 3.37 mmol). The resultant mixture was stirred at 0°C for a further 15 minutes. The cooling bath was then removed and reaction allowed to warm, with stirring to RT. Water (75 mL) was added to reaction mixture and resultant precipitate collected by suction filtration, washed with more water (40 mL) and dried to afford the desired material (1.180 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 - 1.15 (1H, m), 1.19 - 1.37 (7H, m), 1.54 - 1.60 (1H, m), 1.69 (6H, s), 1.70 - 1.80 (4H, m), 3.17 - 3.25 (1H, m), 3.45

(1H, td), 3.52 - 3.62 (2H, m), 3.72 (1H, d), 3.94 (1H, dd), 4.07 (1H, d), 4.39 - 4.48 (1H, m), 6.89 (1H, s).

LCMS Spectrum: MH+ 402, retention time 2.72 min.

2-Chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

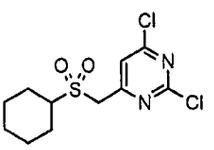


To a cooled (ice/water bath) solution of 2,4-dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine (1.65 g, 5.34 mmol) in DCM (25 mL) was added triethylamine (0.820 mL, 5.88 mmol). The resulting solution was treated, dropwise over 8 minutes, with a solution of (3S)-3-methylmorpholine (609 mg, 6.02 mmol) in DCM (5 mL). The mixture was stirred at 6°C for 30 minutes. The cooling bath was then removed and reaction mixture left to stir overnight. Water (25 mL) was then added and reaction mixture stirred for 5 minutes. The organic layer was then separated, dried ($MgSO_4$) and evaporated to give a crude brown oil, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material (1.440 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 - 1.45 (8H, m), 1.63 - 1.68 (1H, m), 1.81 - 1.87 (2H, m), 2.11 - 2.17 (2H, m), 3.15 - 3.25 (2H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.73 (1H, d), 3.92 - 4.01 (2H, m), 4.30 (1H, br s), 4.39 (2H, s), 6.90 (1H, s).

LCMS Spectrum: MH+ 374, retention time 2.24 min.

2,4-Dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine



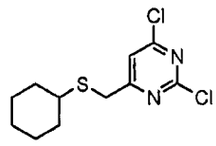
To a stirred solution of 2,4-dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine (1.53 g, 5.52 mmol) in DCM (28 mL) was added, portionwise, 3-chloroperoxybenzoic acid (3.09 g, 13.80 mmol) over a period of 20 minutes under nitrogen, so as to control temperature

below 28°C. The resulting suspension was stirred at RT for 3 hours then saturated aqueous sodium hydrogen carbonate solution (40 mL) added and the reaction mixture stirred for 5 minutes. The organic layer was then separated, dried ($MgSO_4$) and evaporated to dryness. The resultant solid was redissolved in DCM (40 mL) and saturated aqueous sodium hydrogen carbonate solution (40 mL) added. The mixture was stirred for 15 minutes before separating organic layer, drying over ($MgSO_4$) and evaporating to afford the desired material (1.650 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 - 1.46 (5H, m), 1.61 - 1.69 (1H, m), 1.80 - 1.88 (2H, m), 2.10 - 2.17 (2H, m), 3.22 (1H, tt), 4.73 (2H, s), 7.85 (1H, s).

LCMS Spectrum: M-H- 307, retention time 2.26 min.

2,4-Dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine



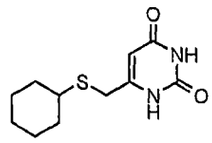
A suspension of 6-(cyclohexylsulfanylmethyl)-1H-pyrimidine-2,4-dione (3.6 g, 14.98 mmol) in phosphorus oxychloride (15 mL, 160.93 mmol) was warmed to 100°C, over a period of 15 minutes. The resulting dark orange solution was stirred at 100°C for 7 hours. The reaction mixture was then cooled before evaporating to a viscous brown oil which was partitioned between DCM (20 mL) and iced water (20 mL). Solid sodium hydrogen carbonate was then added carefully and portionwise, over 30 minutes so as to control effervescence. Further aliquots of water (30 mL) and DCM were added during addition. Once effervescence had ceased and pH had been adjusted to 8, mixture was transferred to a separating funnel and organic layer seperated. The aqueous layer was re-extracted with DCM (2 x 50 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$) and evaporated to afford crude product, which was purified by flash silica chromatography, elution gradient 10 to 40% ethyl acetate in isohexane, to give the desired material (1.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 - 1.31 (5H, m), 1.51 - 1.58 (1H, m), 1.63 - 1.71 (2H, m), 1.86 - 1.93 (2H, m), 2.70 - 2.77 (1H, m), 3.85 (2H, s), 7.81 (1H, s).

LCMS Spectrum: M-H- 275, retention time 3.04 min.

431

6-(Cyclohexylsulfanylmethyl)-1*H*-pyrimidine-2,4-dione



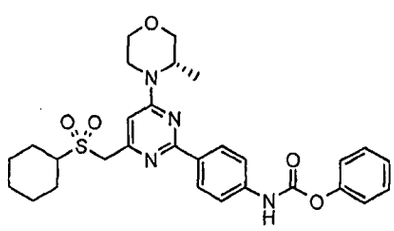
A solution of cyclohexanethiol (10 mL, 81.74 mmol) in DMF (150 mL) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (14 mL, 93.80 mmol). The resulting solution was stirred at RT for 20 minutes. 6-(chloromethyl)pyrimidine-2,4(1H,3H)-dione (10 g, 62.28 mmol) was then added, portionwise, over a period of 30 minutes, under nitrogen, so as to maintain the internal temperature below 35°C. The resulting solution was stirred at RT overnight. The reaction mixture was then evaporated to dryness and the residue was partitioned between DCM (100 mL) and water (150 mL). On mixing a precipitate formed, this was removed by suction filtration, and dried under vacuum, at 55°C for 2 hours to afford the desired material (6.45 g). Additional desired material (3.62 g) was obtained by adjusting the filtrate to pH2 by the dropwise addition of 2M hydrochloric acid and removing the precipitate, washing the precipitate with water (100 mL) and drying in a vacuum oven.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.34 (5H, m), 1.51 - 1.58 (1H, m), 1.63 - 1.72 (2H, m), 1.87 - 1.96 (2H, m), 2.65 - 2.72 (1H, m), 3.41 (2H, s), 5.49 (1H, s), 10.75 - 10.96 (2H, m).

LCMS Spectrum: MH+ 241, retention time 0.99 min.

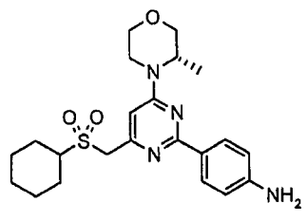
The preparation of phenyl *N*-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Sodium bicarbonate (113 mg, 1.35 mmol) was added to a solution of 4-[4-(cyclohexylsulfonylmethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (370 mg, 0.86 mmol) in 1,4-dioxane (5 mL). Phenyl chloroformate (0.124 mL, 0.99 mmol) was added dropwise and the resultant mixture was stirred at RT for 5 hours. The resulting mixture was evaporated to dryness and the residue partitioned between DCM (5 mL) and water (5 mL). The organic layer was separated and evaporated to dryness. The crude residue was triturated with diethyl ether to give the desired material (429 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.33 (6H, m), 1.40 - 1.50 (2H, m), 1.64 - 1.70 (1H, m), 1.85 - 1.92 (2H, m), 2.21 - 2.28 (2H, m), 3.19 - 3.36 (2H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.16 - 4.23 (1H, m), 4.43 - 4.52 (3H, m), 6.81 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.30 (2H, d), 10.44 (1H, s).
LCMS Spectrum: MH+ 551, retention time 2.88 min.

4-[4-(Cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



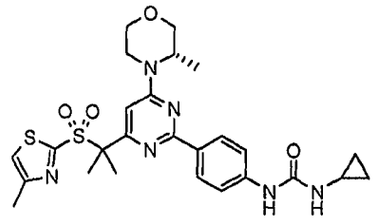
A mixture of 2-chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (437 mg, 1.17 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (381 mg, 1.74 mmol) and 2M aqueous sodium carbonate solution (0.60 mL, 1.20 mmol) in a mixture of DMF (2 mL), ethanol (2 mL), water (5 mL) and DME (2 mL) was purged with nitrogen for 5 minutes before addition of bis(triphenylphosphine)palladium(II) chloride (41.0 mg, 0.06 mmol). The reaction mixture was heated to 80°C, under nitrogen, and stirred for 3.5 hours. The reaction mixture was cooled and partitioned between ethyl acetate (25 mL) and water (30 mL). The organic layer was separated and aqueous re-extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with saturated brine (50 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material (402 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.32 (6H, m), 1.38 - 1.50 (2H, m), 1.64 - 1.70 (1H, m), 1.85 - 1.92 (2H, m), 2.20 - 2.27 (2H, m), 3.19 (1H, td), 3.31 - 3.40 (1H, m), 3.48 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.10 - 4.18 (1H, m), 4.38 (2H, s), 4.40 - 4.48 (1H, m), 5.57 (2H, s), 6.61 (2H, d), 6.66 (1H, s), 8.04 (2H, d).
LCMS Spectrum: MH+ 431, retention time 2.33 min.

The preparation of 2-chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 69:

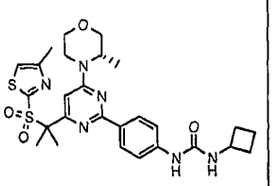
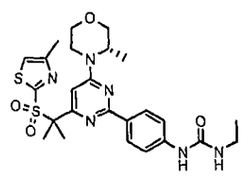
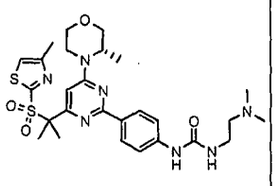
3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea

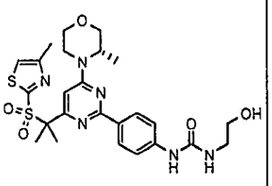
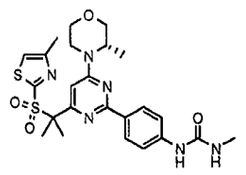
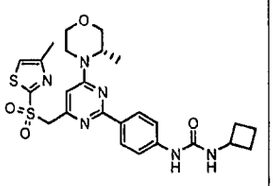
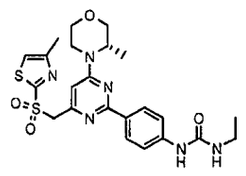
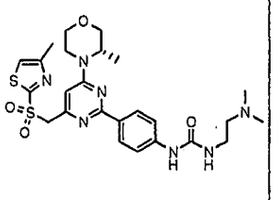


To cyclopropylamine (53 mg, 0.93 mmol) was added a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]carbamate (54 mg, 0.09 mmol) in DMA (2 mL) and triethylamine (0.045 mL, 0.32 mmol). The resultant mixture was heated to 50°C for 16 hours. The reaction mixture was cooled and poured into water (30 mL). The resultant precipitate was collected by suction filtration and dried under suction to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane. Product containing fractions were evaporated to dryness, triturated with isohexane/diethyl ether and dried under vacuum, at 50°C, for 1 hour to afford the desired material as a white solid (38 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.21 (3H, d), 1.92 (6H, s), 2.42 (3H, s), 2.53 - 2.59 (1H, m), 3.16 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 - 4.20 (1H, m), 4.52 - 4.58 (1H, m), 6.40 - 6.42 (1H, m), 6.69 (1H, s), 7.42 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.51 (1H, s)
LCMS Spectrum: MH+ 557, retention time 2.33 min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
69a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea	571	2.53
69b		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea	545	2.3
69c		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea	588	2.44

Example	Structure	NAME	LCMS MH+	Retention time (min)
69d		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea	561	1.99
69e		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]urea	531	2.15
69f		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	543	2.28
69g		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	517	2.04
69h		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]urea	560	2.14

Example 69a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.68 (2H, m), 1.80 - 1.92 (2H, m), 1.92 (6H, s), 2.18 - 2.25 (2H, m), 2.41 - 2.42 (3H, m), 3.16 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 - 4.19 (2H, m), 4.51 - 4.58 (1H, m), 6.44 (1H, d), 6.69 (1H, s), 7.39 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.53 (1H, s).

Example 69b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.92 (6H, s), 2.41 - 2.42 (3H, m), 3.09 - 3.20 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.14 - 4.19 (1H, m), 4.52 - 4.58 (1H, m), 6.14 (1H, t), 6.69 (1H, s), 7.41 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.63 (1H, s).

Example 69c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.20 (6H, s), 2.33 - 2.40 (2H, m), 2.42 (3H, s), 3.12 - 3.22 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.16 (1H, d), 4.51 - 4.57 (1H, m), 6.15 (1H, t), 6.69 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.87 (1H, s).

Example 69d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.41 (3H, s), 3.13 - 3.21 (3H, m), 3.44 - 3.52 (3H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 - 4.19 (1H, m), 4.52 - 4.57 (1H, m), 4.72 (1H, t), 6.24 (1H, t), 6.69 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.78 (1H, s).

Example 69e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.41 - 2.42 (3H, m), 2.66 (3H, d), 3.12 - 3.20 (1H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 - 4.19 (1H, m), 4.51 - 4.57 (1H, m), 6.05 (1H, q), 6.69 (1H, s), 7.42 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.72 (1H, s).

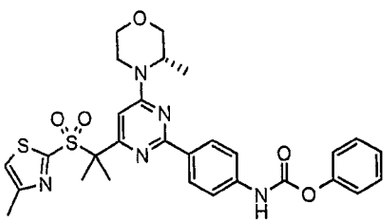
Example 69f: No NMR spectrum

Example 69g: No NMR spectrum

Example 69h: No NMR spectrum

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]phenyl]carbamate

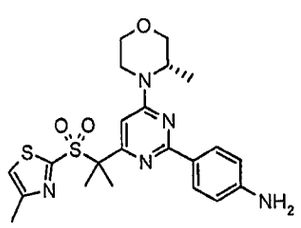


To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]aniline (340 mg, 0.72 mmol) in 1,4-dioxane (4 mL) was added sodium bicarbonate (90 mg, 1.08 mmol). Phenyl chloroformate (0.104 mL, 0.83 mmol) was then added dropwise and the resulting mixture was stirred at RT for 6 hours. Reaction mixture was then evaporated and the residue was partitioned between DCM (5 mL) and water (5 mL). The organic layer was seperated and aqueous re-extracted with more DCM (5 mL). The combined organic layers were combined and evaporated to dryness to afford an amber gum, which was taken up in diethyl ether (5 mL) and triturated with sonication. The resultant solid was collected by suction filtration and dried to afford the desired material (334 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.93 (6H, s), 2.41 (3H, s), 3.17 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.15 - 4.22 (1H, m), 4.53 - 4.59 (1H, m), 6.73 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.55 (2H, d), 7.68 (1H, m), 7.97 (2H, d), 10.39 (1H, s).

LCMS Spectrum: MH+ 594, retention time 2.91 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidin-2-yl]aniline



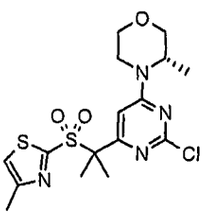
A mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidine (480 mg, 1.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (378 mg, 1.73 mmol) and 2M aqueous sodium carbonate

solution (2.8 mL, 5.60 mmol) in a mixture of DMF (2 mL), 1,2-dimethoxyethane (2 mL), ethanol (2 mL) and water (5 mL) was purged with nitrogen for 10 minutes prior to addition of bis(triphenylphosphine)palladium(II) chloride (54 mg, 0.08 mmol). The reaction mixture was heated to 85°C and stirred at that temperature, under nitrogen for 3 hours. The reaction mixture was then cooled and partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was separated and the aqueous layer re-extracted with ethyl acetate (25 mL). Combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material (367 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.90 (6H, s), 2.43 (3H, s), 3.13 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.09 - 4.15 (1H, m), 4.47 - 4.54 (1H, m), 5.50 (2H, s), 6.52 (1H, d), 6.58 (2H, s), 7.68 - 7.72 (3H, m).

LCMS Spectrum: MH+ 474, retention time 2.31 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]propan-2-yl]pyrimidine



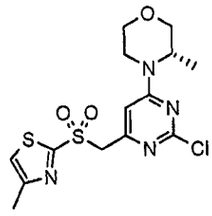
To a cooled (ice/water bath) solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (612 mg, 1.57 mmol) in DMF (8 mL) was added sodium tert-butoxide (157 mg, 1.63 mmol). The mixture was stirred for 5 minutes, under nitrogen, before addition of iodomethane (0.100 mL, 1.61 mmol). The reaction mixture was allowed to stir, in cooling bath, for a further 10 minutes before addition of further sodium tert-butoxide (157 mg, 1.63 mmol). After a further 5 minutes stirring more iodomethane (0.100 mL, 1.61 mmol) was added and reaction mixture stirred, under nitrogen, in cooling bath for 20 minutes. Cooling bath was then removed and stirring continued for a further 2 hours. Water (25 mL) was then added and resultant precipitate

collected by filtration, washed with water (50 mL) and dried under vacuum, at 50°C, for 2 hours to afford the desired material (487 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.79 (6H, d), 2.46 (3H, s), 3.15 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.96 - 4.03 (1H, m), 4.35 - 4.44 (1H, m), 6.78 (1H, s), 7.89 (1H, s).

LCMS Spectrum: MH+ 417, retention time 2.28 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

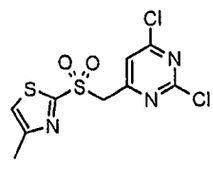


To a cooled (ice/water bath) solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (901 mg, 2.78 mmol) in DCM (12 mL) was added triethylamine (0.45 mL, 3.23 mmol). The resulting solution was treated dropwise, over 3 minutes, with a solution of (3S)-3-methylmorpholine (319 mg, 3.15 mmol) in DCM (2.5 mL). The reaction mixture was stirred, under nitrogen for 24 hours, allowing reaction to warm to RT. Water (20 mL) was added to reaction mixture and stirred for 15 minutes. The organic layer was then separated, dried ($MgSO_4$) and evaporated to give crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material (615 mg).

NMR Spectrum : ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 2.49 (3H, s), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.86 - 3.96 (2H, m), 4.16 - 4.28 (1H, m), 4.82 (2H, s), 6.80 (1H, s), 7.89 (1H, d).

LCMS Spectrum: MH+ 389, retention time 1.89 min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

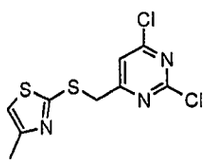


To a cooled (ice/water bath) solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine (867 mg, 2.97 mmol) in DCM (15 mL) was added portionwise, over 10 minutes, 3-chloroperoxybenzoic acid (1.42 g, 6.34 mmol). The resulting suspension was stirred in cooling bath for 15 minutes. Cooling bath was then removed and reaction mixture allowed to warm to RT and stirred for 22 hours. The reaction was incomplete and further 3-chloroperoxybenzoic acid (162 mg, 0.72 mmol) was added and the mixture stirred for a further 1 hour. Saturated aqueous sodium bicarbonate solution (20 mL) was added to the reaction mixture and stirred for 30 minutes. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to afford the desired material (912 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.48 (3H, d), 5.19 (2H, s), 7.84 (1H, s), 7.94 - 7.95 (1H, m).

LCMS Spectrum: M-H- 322, retention time 1.47 min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine

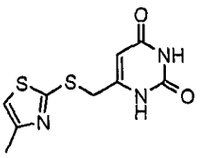


A suspension of 6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (1.4 g, 5.48 mmol) in phosphorus oxychloride (6 mL, 64.37 mmol) was warmed to 100°C and stirred for 6 hours. The reaction mixture was cooled before evaporating and the residue was partitoned between DCM (30 mL) and iced water (30 mL). Sodium hydrogen carbonate was then added carefully and portionwise, over 30 minutes, so as to control effervescence. Once effervescence had ceased and pH had been adjusted to 8, mixture was treated with more DCM (30 mL) and water (20 mL), transferred to a separating funnel and organic layer separated. The aqueous layer was re-extracted with further DCM (2 x 25 mL) and the combined organic extracts washed with brine, dried ($MgSO_4$) and evaporated to dryness to afford the crude product, which was purified by flash silica chromatography, elution gradient 10 to 20% ethyl acetate in isohexane, to give the desired material (0.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.31 (3H, d), 4.55 (2H, s), 7.23 - 7.24 (1H, m), 7.83 (1H, s).

LCMS Spectrum: MH+ 292, retention time 2.33 min.

6-[(4-Methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione



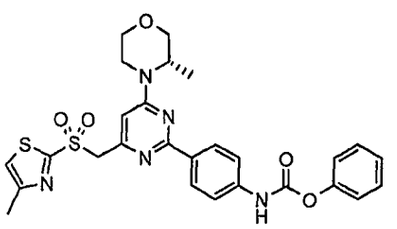
A solution of 4-methylthiazole-2-thiol (1.01 g, 7.70 mmol) in DMF (15 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (1.4 mL, 9.38 mmol). The resulting solution was stirred at RT for 30 minutes. 6-(chloromethyl)pyrimidine-2,4(1H,3H)-dione (1 g, 6.23 mmol) was then added portionwise, over a period of 10 minutes, under nitrogen. The resulting solution was stirred at RT for 19 hours. The reaction mixture was then evaporated to dryness and the residue partitioned between DCM (20 mL) and water (20 mL). A solid precipitated which was collected by suction filtration, washed with water (20 mL) and dried, under vacuum, at 60°C, for 2 hours to afford the desired material (1.07 g, 67 %). Additonal desired material (0.330 g) was obtained by adjusting the filtrate to pH2 with 2M hydrochloric acid, filtering the precipitate, washing it with water (20 mL) and drying in a vacuum oven.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.34 (3H, d), 4.08 (2H, s), 5.43 (1H, s), 7.27 (1H, m), 11.01 (2H, s).

LCMS Spectrum: MH+ 256, retention time 0.53 min.

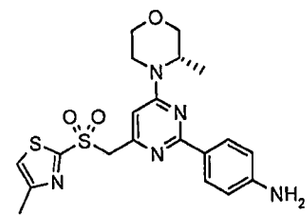
The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.190 mL, 1.51 mmol) was added to 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]aniline (450 mg, 1.01 mmol), sodium hydrogen carbonate (127 mg, 1.51 mmol) in dioxane (10 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product, which was triturated with a mixture of diethyl ether and isohexane to afford the desired material (360 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 2.53 (3H, s) [obscured by DMSO], 3.20 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.45 (1H, s), 4.93 (2H, s), 6.77 (1H, s), 7.22 - 7.32 (3H, m), 7.43 - 7.47 (2H, m), 7.56 (2H, d), 7.84 (1H, s), 7.97 (2H, d), 10.43 (1H, s).
LCMS Spectrum: MH+ 566, retention time 2.66mins

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidin-2-yl]aniline



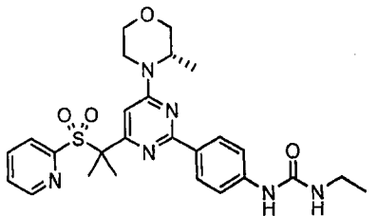
Bis(triphenylphosphine)palladium(II) chloride (54.4 mg, 0.08 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (600 mg, 1.55 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (510 mg, 2.33 mmol) and sodium carbonate (5 mL, 10.00 mmol) in a mixture of DMF (6 mL), DME (12 mL), ethanol (3 mL) and water (3.5 mL) at RT under nitrogen. The reaction mixture was evacuated and refilled with nitrogen several times and the resulting mixture stirred at 95°C for 18 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product, which was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to the desired material (450 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.53 (3H, s), 3.15 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.09 (1H, d), 4.40 (1H, s), 4.83 (2H, s), 5.54 (2H, s), 6.52 (2H, d), 6.60 (1H, s), 7.70 (2H, d), 7.81 (1H, s).
LCMS Spectrum: MH+ 446, retention time 2.0mins

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described earlier.

Example 70:

3-Ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]urea

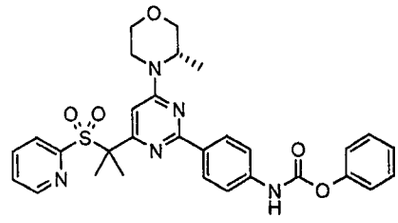


A 2M solution of Ethylamine in methanol (0.471 mL, 0.94 mmol) was added in one portion to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.21 mmol), in DMF (2 mL) at RT under nitrogen. The resulting solution was stirred at RT for 60 minutes. The reaction mixture was evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanol in DCM, to give the desired material as a white foam (103 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (t, 3H), 1.21 (d, 3H), 1.88 (s, 6H), 3.09 - 3.21 (m, 3H), 3.45 - 3.53 (m, 1H), 3.61 - 3.66 (m, 1H), 3.77 (d, 1H), 3.95 - 4.00 (m, 1H), 4.15 (d, 1H), 4.53 (s, 1H), 6.15 (t, 1H), 6.66 (s, 1H), 7.35 (d, 2H), 7.61 - 7.66 (m, 2H), 7.71 (d, 2H), 7.88 - 7.93 (m, 1H), 8.61 (s, 1H), 8.74 - 8.76 (m, 1H)
LCMS Spectrum: MH+ 525.56, retention time 2.14 min.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]phenyl]carbamate

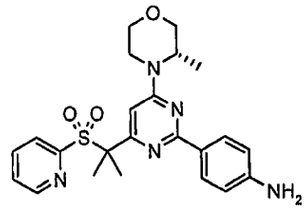


Phenyl chloroformate (0.432 mL, 3.44 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline (1.3 g, 2.87 mmol) and sodium hydrogen carbonate (0.482 g, 5.73 mmol) in dioxane (20 mL) at RT. The resulting slurry was stirred at RT for 1 hour and then the reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 0%-20% ethyl acetate in DCM, to give the desired material as a yellow dry film (1.62 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.27 (d, 3H), 1.90 (s, 6H), 3.25 (m, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 4.03 (m, 2H), 4.39 - 4.46 (m, 1H), 6.60 (s, 1H), 6.93 (s, 1H), 7.12 - 7.22 (m, 12H), 7.32 (m, 5H), 7.57 (m, 2H), 7.82 (d, 2H).

LCMS Spectrum: MH+ 574.52, retention time 2.85 min. (monitor acidic).

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidin-2-yl]aniline



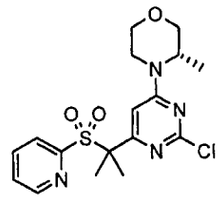
Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.773 g, 3.53 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidine (1.4 g, 3.53 mmol) were suspended in a mixture of DME (10 mL), ethanol (10.00 mL), DMF (10.00 mL) and water (10 mL) at RT under nitrogen. The mixture was purged with nitrogen and bis(triphenylphosphine)palladium(II) chloride (0.124 g, 0.18 mmol) was added. The resulting suspension was stirred at 80°C for 90 minutes under an atmosphere of nitrogen.

The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), and washed with water (2x150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow foam (1.210 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.25 (d, 3H), 1.89 (s, 6H), 3.22 (m, 1H), 3.54 (m, 1H), 3.66 - 3.80 (m, 4H), 3.97 (m, 1H), 4.05 (m, 1H), 4.42 (s, 1H), 6.46 - 6.53 (m, 3H), 7.28 (m, 1H), 7.55 (m, 2H), 7.64 (d, 2H), 8.61 (d, 1H).

LCMS Spectrum: MH+ 454.58, retention time 1.88 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(2-pyridin-2-ylsulfonylpropan-2-yl)pyrimidine

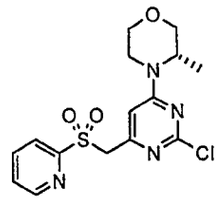


Iodomethane (1.266 mL, 20.33 mmol) was added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (2.5 g, 6.78 mmol) and sodium tert-butoxide (1.954 g, 20.33 mmol) in DMF (50 mL) at 0°C under nitrogen. The solution was allowed to slowly warm up to RT and stirred at RT for 1 hour. Water and ethyl acetate were added and the solution was shaken and separated. The combined ethyl acetate layers were dried ($MgSO_4$) and filtered. The filtrate was evaporated and the crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a yellow oil which solidified on standing (1.77 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.26 (d, 3H), 1.77 (s, 6H), 3.22 (m, 1H), 3.49 (m, 1H), 3.64 (m, 1H), 3.74 (d, 1H), 3.89 - 3.98 (m, 2H), 4.27 (s, 1H), 6.67 (s, 1H), 7.46 (m, 1H), 7.73 (m, 1H), 7.80 (d, 1H), 7.82 (m, 1H).

LCMS Spectrum: MH+ 397.38, retention time 2.04 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine

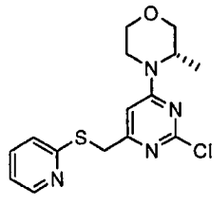


A 35% aqueous solution of hydrogen peroxide (8.26 mL, 93.53 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine (10.5g, 31.17 mmol), sodium tungstate dihydrate (0.206 g, 0.62 mmol) and 2N Sulfuric acid (0.6 mL) in dioxane (300 mL) and then the solution warmed to 55°C. The solution was stirred at 55°C for 4 hours. Further hydrogen peroxide (8.26 mL) was added and the mixture stirred at 50°C for 18 hours. 3-Chloroperoxybenzoic acid (5.38 g, 31.17 mmol) was added and the mixture stirred at RT for 2 hours. The solution was diluted with water (500 mL) and cooled to 20°C. A 10% solution of sodium metabisulfite was added to destroy any remaining peroxide and the solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a yellow gum (10.5 g,).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 3H), 3.20 (m, 1H), 3.46 (m, 1H), 3.61 (d, 1H), 3.71 (d, 1H), 3.90 - 3.98 (m, 2H), 4.21 (s, 1H), 4.51 (s, 2H), 6.50 (s, 1H), 7.51 - 7.53 (m, 1H), 7.86 - 7.95 (m, 2H), 8.72 - 8.74 (m, 1H)

LCMS Spectrum: MH+ 369.37, retention time 1.73 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine



DIPEA (8.77 ml, 50.71 mmol) was added to 2-mercaptopyridine (3.80 g, 34.22 mmol), in DMF (300 mL) at RT in an atmosphere of nitrogen. The resulting solution was stirred at RT for 15 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11 g, 31.11 mmol) was added portionwise over 5 minutes and the mixture stirred at RT for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200

mL) and washed sequentially with saturated sodium hydrogen carbonate solution (100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a tan oil (10.50 g). NMR shows the presence of 0.6 eq. of m-chlorobenzoic acid. This material was used in the subsequent step without further purification.

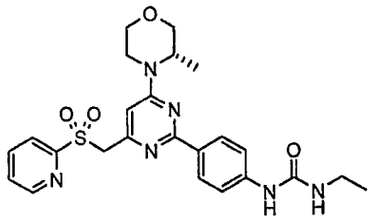
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.17 - 3.25 (m, 1H), 3.46 - 3.54 (m, 1H), 3.62 - 3.67 (m, 1H), 3.74 (d, 1H), 3.93 - 4.01 (m, 2H), 4.20 (s, 1H), 4.29 - 4.38 (m, 2H), 6.60 (s, 1H), 6.99 - 7.02 (m, 1H), 7.20 (d, 1H), 7.47 - 7.51 (m, 1H), 8.40 - 8.42 (m, 1H).

LCMS Spectrum: MH+ 337.48, retention time 2.19 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 71:

3-Ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]urea



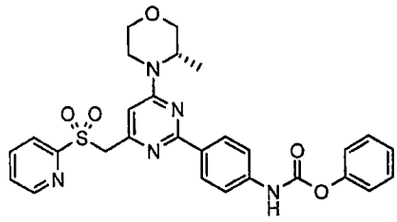
A 2M solution of ethylamine in methanol (0.495 mL, 0.99 mmol) was added in one portion to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) in DMF (2 mL) at RT under nitrogen. The resulting solution was stirred at RT for 60 minutes. The reaction mixture was evaporated to dryness and the crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanol in DCM, to give the desired material as a white foam (83 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (t, 3H), 1.20 (d, 3H), 3.09 - 3.22 (m, 3H), 3.44 - 3.52 (m, 1H), 3.61 - 3.65 (m, 1H), 3.76 (d, 1H), 3.95 - 4.00 (m, 1H), 4.12 (d, 1H), 4.40 (s, 1H), 4.85 (q, 2H), 6.14 (t, 1H), 6.69 (s, 1H), 7.35 (d, 2H), 7.66 (d, 2H), 7.79 - 7.82 (m, 1H), 7.90 (d, 1H), 8.08 - 8.13 (m, 1H), 8.62 (s, 1H), 8.93 (d, 1H).

LCMS Spectrum: MH+ 497.49, retention time 1.66 min.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate

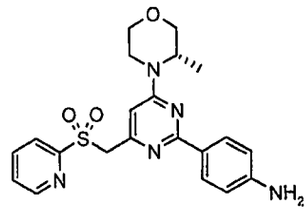


Phenyl chloroformate (0.390 mL, 3.10 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]aniline (1.1 g, 2.59 mmol) and sodium hydrogen carbonate (0.434 g, 5.17 mmol) in dioxane (25 mL) at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash silica chromatography using gradient elution 0%-20% ethyl acetate in DCM, to give the desired material as a yellow foam (1.130 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.25 (d, 3H), 3.23 (m, 1H), 3.52 (m, 1H), 3.65 - 3.68 (m, 1H), 3.75 (d, 1H), 3.95 - 3.99 (m, 1H), 4.05 - 4.11 (m, 2H), 4.31 - 4.38 (m, 1H), 4.63 (q, 2H), 6.39 (s, 1H), 6.95 (s, 1H), 7.13 (m, 2H), 7.17 - 7.21 (m, 1H), 7.34 (m, 4H), 7.48 (m, 1H), 7.75 - 7.85 (m, 4H), 8.77 - 8.79 (m, 1H).

LCMS Spectrum: MH+ 546.49, retention time 2.54 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidin-2-yl]aniline



Sodium carbonate (7.32 mL, 14.64 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.891 g, 4.07 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (1.5 g, 4.07 mmol) in a mixture of DME (10 mL), ethanol (10.00 mL), DMF (10.00 mL) and water (10 mL) at RT under nitrogen. The mixture was purged with nitrogen three times, bis(triphenylphosphine)palladium(II) chloride (0.143 g, 0.20 mmol) was added and the mixture purged with nitrogen again. The resulting suspension was stirred at 80°C for 90 minutes. The reaction mixture was evaporated to dryness and suspended in ethyl acetate (150 mL), and washed with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow foam (1.21 g).

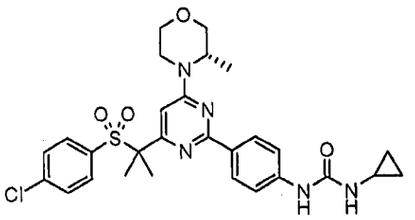
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.16 - 3.24 (m, 1H), 3.47 - 3.55 (m, 1H), 3.63 - 3.68 (m, 1H), 3.71 - 3.80 (m, 3H), 3.92 - 3.98 (m, 1H), 4.02 - 4.09 (m, 1H), 4.30 - 4.37 (m, 1H), 4.59 (q, 2H), 6.32 (s, 1H), 6.48 - 6.53 (m, 2H), 7.44 - 7.49 (m, 1H), 7.67 (d, 2H), 7.73 - 7.83 (m, 2H), 8.77 - 8.79 (m, 1H).

LCMS Spectrum: MH+ 426.48, retention time 1.24 min. (monitor acidic).

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine was described earlier.

Example 72:

1-[4-[4-[2-(4-Chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea

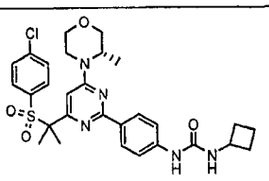
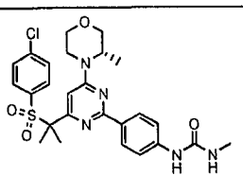
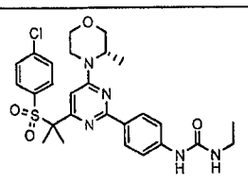
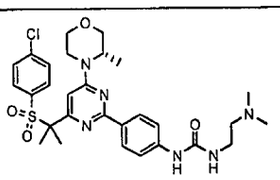
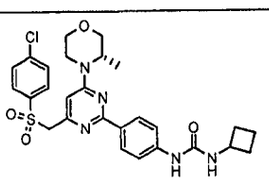
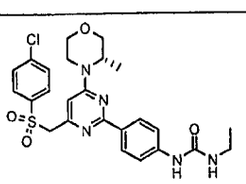


Cyclopropylamine (0.139 mL, 1.98 mmol) was added to phenyl *N*-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol) in DMF (2 mL). The resulting solution was stirred at 60°C for 5 hours. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with water (2 x 30 mL) and saturated brine (30 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane. Pure fractions were evaporated to dryness and the residue triturated with diethyl ether to give the desired material as a white solid (92 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 0.70 (2H, s), 0.88 (2H, s), 1.34 (3H, d), 1.86 (6H, s), 2.63 (1H, t), 3.33 (1H, td), 3.63 (1H, td), 3.78 (2H, dd), 3.85 (2H, d), 4.06 (1H, dd), 4.14 (1H, d), 4.49 (1H, d), 4.88 (1H, s), 6.63 (1H, s), 6.93 (1H, s), 7.30 (4H, d), 7.39 (2H, d), 7.47 (2H, d), 7.87 (2H, d).

LCMS Spectrum: MH+ 570, 572, retention time 2.63 min.

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
72a		1-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutyl-urea	584, 586	2.86
72b		1-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	544, 546	2.46
72c		1-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	558, 560	2.63
72d		1-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	601, 603	2.51
72e		(S)-1-(4-(4-((4-chlorophenylsulfonyl)methyl)-6-(3-methylmorpholino)pyrimidin-2-yl)phenyl)-3-cyclobutylurea	556, 558	2.56
72f		1-[4-[4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethyl-urea	530, 532	2.38

Example 72a: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.72 (2H, m), 1.86 (2H, m), 1.86 (6H, s), 2.39 (2H, m), 3.32 (1H, ddd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.85 (1H, d), 4.06 (1H, dd), 4.14 (1H, d), 4.31 (1H, dtt), 4.49 (1H, br.d), 4.86 (1H, d), 6.29 (1H, s), 6.63 (1H, s), 7.27 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.86 (2H, d).

Example 72b: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.86 (6H, s), 2.86 (3H, d), 3.32 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.13 (1H, d), 4.48 (1H, br.d), 4.81 (1H, q), 6.52 (1H, s), 6.62 (1H, s), 7.28 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.87 (2H, d).

Example 72c: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.17 (3H, t), 1.34 (3H, d), 1.86 (6H, s), 3.32 (2H, dq), 3.32 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.13 (1H, d), 4.49 (1H, br.d), 4.78 (1H, t), 6.46 (1H, s), 6.62 (1H, s), 7.28 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.86 (2H, d).-

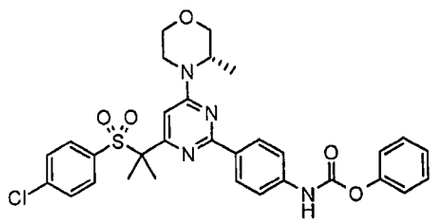
Example 72d: ^{1}H NMR (399.90 MHz, CDCl3) δ 1.34 (3H, d), 1.85 (6H, s), 2.32 (6H, s), 2.53 (2H, t), 3.31 (1H, ddd), 3.33 (2H, dt), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.14 (1H, d), 4.49 (1H, br.d), 5.29 (1H, br.s), 6.61 (1H, s), 7.29 (2H, d), 7.33 (2H, d), 7.47 (2H, d), 7.83 (2H, d), 8.41 (1H, v.br.s).

Example 72e: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 1.71 (2H, m), 1.84 (2H, m), 2.37 (2H, m), 3.30 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.14 (1H, d), 4.30 (2H, dtt), 4.38 (2H, s), 4.39 (1H, d), 4.97 (1H, d), 6.44 (1H, s), 6.49 (1H, s), 7.31 (2H, d), 7.43 (2H, d), 7.70 (2H, d), 7.87 (2H, d).

Example 72f: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.17 (3H, t), 1.33 (3H, d), 3.30 (1H, ddd), 3.32 (2H, dq), 3.60 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (1H, d), 4.38 (2H, s), 4.42 (1H, br.d), 4.77 (1H, t), 6.44 (1H, s), 6.47 (1H, s), 7.31 (2H, d), 7.43 (2H, d), 7.70 (2H, d), 7.88 (2H, d).

The preparation of phenyl *N*-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

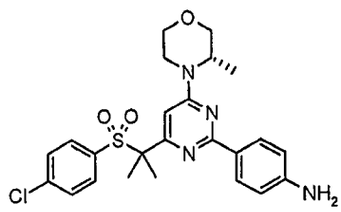


Phenyl chloroformate (0.256 mL, 2.04 mmol) was added dropwise to 4-[4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (850 mg, 1.85 mmol) and sodium hydrogencarbonate (233 mg, 2.78 mmol) in dioxane (20 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2 x 100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane. Pure fractions were evaporated to dryness to afford the desired material as a white solid (955 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 3.32 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, br.d), 4.38 (2H, s), 4.43 (1H, br.d), 6.46 (1H, s), 7.03 (1H, s), 7.21 (2H, d), 7.25 (1H, dd), 7.40 (2H, d), 7.43 (2H, dd), 7.45 (2H, d), 7.70 (2H, d), 7.92 (2H, d)

LCMS Spectrum: MH+ 579, 581, retention time 2.94 min.

4-[4-[2-(4-Chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



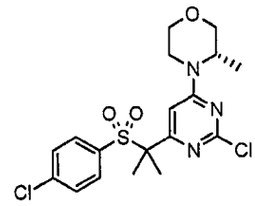
Sodium carbonate (2M in water, 6.69 mL, 13.38 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.815 g, 3.72 mmol) and 2-chloro-4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (1.60 g, 3.72 mmol) in a mixture of DME (10 mL), ethanol (10.00 mL), DMF (10.00 mL) and water (20 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen three times. Bis(triphenylphosphine)palladium(II) chloride (0.130 g, 0.19 mmol) was

added and the mixture was degassed and purged with nitrogen a further three times. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL) and washed with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 45% ethyl acetate in isohexane, to give the desired material as a white solid (1.502 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 1.84 (6H, s), 3.31 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 3.86 (2H, s), 4.05 (1H, dd), 4.13 (1H, br.d), 4.48 (1H, br.d), 6.57 (1H, s), 6.60 (2H, d), 7.30 (2H, d), 7.47 (2H, d), 7.72 (2H, d).

LCMS Spectrum: MH+ 487, 489, retention time 2.64 min.

2-Chloro-4-[2-(4-chlorophenyl)sulfonylpropan-2-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

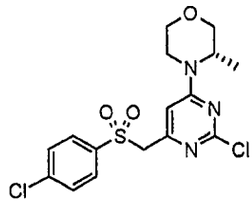


Methyl iodide (0.310 mL, 4.97 mmol) was added dropwise to 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.00 g, 4.97 mmol) and sodium *tert*-butoxide (0.478 g, 4.97 mmol) in DMF (50 mL) at 0°C over a period of 5 minutes under nitrogen. The resulting solution was stirred at 0°C for 15 minutes. Sodium tert-butoxide (0.478 g, 4.97 mmol) was added at 0°C, followed by methyl iodide (0.310 mL, 4.97 mmol) and the mixture stirred for a further 1 hour at 0°C. The mixture was poured into rapidly stirred water (700 mL); the resulting precipitate was collected by filtration, washed with water and dried *in vacuo* to give the desired material as a white solid (1.79 g)

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.74 (6H, s), 3.30 (1H, ddd), 3.57 (1H, ddd), 3.72 (dd, 1H), 3.81 (1H, d), 4.02 (2H, m), 4.33 (1H, br.s), 6.71 (1H, s), 7.45 (2H, d), 7.50 (2H, d).

LCMS Spectrum: MH+ 430, 432, retention time 2.68 min.

2-Chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



4-Chlorobenzenesulphinic acid sodium salt (5.39 g, 27.15 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (8.00 g, 22.63 mmol) in acetonitrile (400 mL) at RT. The resulting suspension was stirred at 85°C under reflux for 5 hours. The reaction mixture was concentrated and diluted with DCM (400 mL) and washed with water (400 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 25 to 40% ethyl acetate in isohexane, to give the desired material as a white solid (6.90 g).

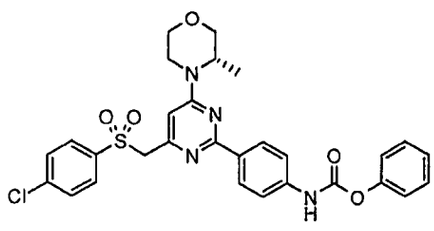
NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.55 (1H, ddd), 3.70 (1H, dd), 3.80 (1H, d), 4.02 (2H, m), 4.28 (1H, br.s), 4.29 (2H, s), 6.55 (1H, s), 7.51 (2H, d), 7.70 (2H, d).

LCMS Spectrum: MH+ 402, 404, retention time 2.26 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

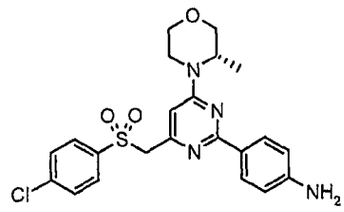


Phenyl chloroformate (0.256 mL, 2.04 mmol) was added dropwise to 4-[4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (850 mg, 1.85 mmol) and sodium hydrogen carbonate (233 mg, 2.78 mmol) in dioxane (20 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (955 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 3.32 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, br.d), 4.38 (2H, s), 4.43 (1H, br.d), 6.46 (1H, s), 7.03 (1H, s), 7.21 (2H, d), 7.25 (1H, dd), 7.40 (2H, d), 7.43 (2H, dd), 7.45 (2H, d), 7.70 (2H, d), 7.92 (2H, d).

LCMS Spectrum: MH+ 579, 581, retention time 2.94 min.

4-[4-[(4-Chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



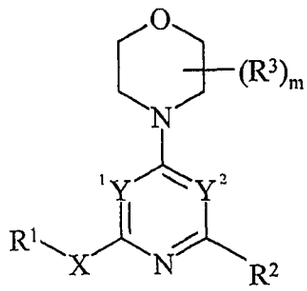
Sodium carbonate (2M in water, 4.47 mL, 8.95 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.572 g, 2.61 mmol) and 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.00 g, 2.49 mmol) in a mixture of DME (6.00 mL), DMF (6.00 mL), ethanol (6.00 mL) and water (14.00 mL) at RT. The mixture was degassed and purged with nitrogen three times. Bis(triphenylphosphine)palladium(II) chloride (0.087 g, 0.120 mmol) was added and the mixture was degassed and purged with nitrogen a further three times. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL) and washed with water (2 x 100 mL). The organic layer was dried over ($MgSO_4$), filtered and evaporated. The crude product was

purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a white solid (0.980 g).
NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.60 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 3.87 (2H, s), 4.04 (1H, dd), 4.15 (1H, m), 4.36 (2H, s), 4.42 (1H, br.s), 6.39 (1H, s), 6.62 (2H, d), 7.44 (2H, d), 7.69 (2H, d), 7.73 (2H, d).
LCMS Spectrum: MH+ 459, 461, retention time 2.34 min.

The preparation of 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

CLAIMS

1. A compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from -CR^4=CR^5-, -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡C-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7-, -S(O)$_2$NR^{4}CR^{6}R^7-, -C(O)NR^4-, -NR^{4}C(O)-, -NR^{4}C(O)NR^5-, -S(O)$_2$NR^4- and –NR^{4}S(O)$_2$-;

R^1 is a group selected from hydrogen, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, carbocyclyl, carbocyclylC$_{1-6}$alkyl, heterocyclyl and heterocyclylC$_{1-6}$alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, -OR^9, -SR^9, -SOR^9, -SO$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} and –NR^{9}SO$_2$R^{10};

R^2 is a group selected from C$_{1-6}$alkyl, carbocyclyl and heterocyclyl which group is substituted by –NR^{17}CONR^{18}R^{19} and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, and -NR^{11}COCONR^{12}R^{16};

each R^3, when present, is independently selected from halo, cyano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} and -NR^{13}SO$_2$R^{14};

R^4 and R^5 are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 are independently selected from hydrogen, halo, cyano, nitro and C_{1-6}alkyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

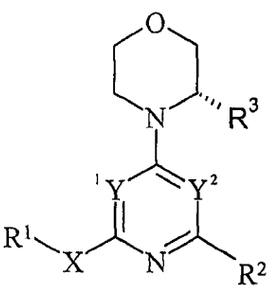
R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

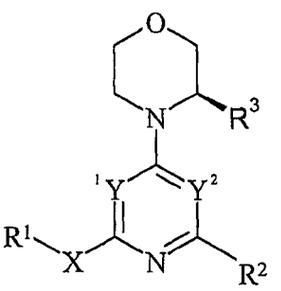
R^{13}, R^{14}, R^{15}, R^{16} and R^{19} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is

optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl; or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

2. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein the compound of formula (I) is a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, X, Y^1 and Y^2 are as defined for the compound of formula (I) as claimed in Claim 1.

3. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 1 or 2 wherein R^3 is methyl.

4. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 3 wherein Y^1 is CR^8 and Y^2 is N.

5. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 4 wherein Y^1 is CH and Y^2 is N.

6. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 5 wherein X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7$, $-C(O)NR^4-$ and $-NR^4C(O)-$.

7. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 6 wherein X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4-$, and $-NR^4C(O)-$.

8. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 6 wherein X is a linker group selected from $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NR^4-$ and $-NR^4C(O)-$.

9. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 6 wherein X is $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ or $-S(O)_2C(CH_3)_2-$.

10. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 6 wherein X is $-S(O)_2C(CH_3)_2-$.

11. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 10 wherein R^1 is a group selected from adamantyl, methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, oxetanyl, phenethyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl,

imidazolylethyl, pyrazolylmethyl, pyrazolylethyl, furanylmethyl, furanylethyl, thienylmethyl, thienylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrimidinylethyl, pyrazinylmethyl and pyrazinylethyl, which group is optionally substituted by 1, 2 or 3 substituent group selected from halo, cyano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} and –NR^9COR^{10}.

12. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 11 wherein R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, pyridinyl, pyrrolidinyl, pyrazolylethyl, furanylmethyl, oxetanyl, imidazolylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -NMe_2, -$NHCOCH_3$, -$CONH_2$ and –$CONHCH_3$.

13. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 11 wherein R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, -CH_2CH_2OH, -CH_2CH_2OMe, -$CH_2CH_2NMe_2$, -$CH_2CH_2NC(O)CH_3$, -CH_2CONH_2, phenyl, 3,5-difluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, oxetan-3-yl, 2-oxopyrolidin-3-yl, 1-methylimidazol-5-ylmethyl , 1-methylpyrrolidin-3-yl , thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

14. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 11 wherein R^1 is a group selected from methyl, isopropyl, cyclopropyl, cyclohexyl, -CH_2CH_2OH, -$CH_2CH_2NC(O)CH_3$, phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-methylphenyl, 4-acetamidophenyl, 4-aminophenyl, pyridin-4-yl, pyridin-2-yl, 2-oxopyrolidin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, and 3-methyl-1,3,4-thiadiazol-2-yl.

15. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 11 wherein R^1 is methyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, 3,5-difluorophenyl, pyridin-4-yl or cyclopropyl.

16. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 11 wherein R^1 is methyl, ethyl, isopropyl, tert-butyl, 4-fluorophenyl, pyridin-4-yl or cyclopropyl.

17. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16 wherein R^2 is selected from 5 or 6 membered carbocyclyl or heterocyclyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

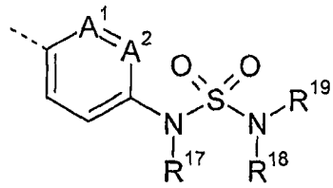
18. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 17 wherein R^2 is selected from a 6 membered aryl and 5 or 6 membered heteroaryl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

19. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 17 wherein R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ and $-NR^{11}COR^{12}$.

20. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 17 wherein R^2 is selected from phenyl, pyrrolyl, imidazolyl, pyrazolyl, furanyl, thienyl, pyridinyl, pyrimidinyl, pyridazinyl, thiazolyl which group is substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$.

21. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 17 wherein R^2 is phenyl or pyridyl substituted by $-NR^{17}CONR^{18}R^{19}$ and optionally substituted by one or more substituent group independently selected from fluoro, methyl, methoxy, hydroxymethyl, cyanomethyl, $-CONH_2$, $-CONHCH_3$ and $-CON(CH_3)_2$.

22. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 17 wherein R^2 is



wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH.

23. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 17 to 22 wherein R^{17} is hydrogen.

24. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 17 to 23 wherein R^{18} is hydrogen.

25. A compound, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 24 wherein R^{19} is hydrogen or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

26. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 25 wherein R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

27. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 25 wherein R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-methylphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, thien-2-yl, -CH_2(imidazol-2-yl), -CH_2(imidazol-3-yl), isoxazol-3-yl, 6-oxo-1H-pyridin-2-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 6-methoxypyridin-3-yl, 5-fluoropyridin-2-yl, pyridinyl-2-yl, pyrimidin-2-yl, and 1H-pyrazol-3-yl.

28. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 25 wherein R^{19} is a group selected from methyl, ethyl, propyl, cyclopropyl, cyclobutyl, -CH_2CH_2OH, -$CH_2CH_2NMe_2$, -$C(Me)_2CH_2OH$ and 1H-pyrazol-3-yl.

29. A compound, or a pharmaceutically acceptable salt thereof, according to Claim 1 selected from any one of the Examples, or a pharmaceutically acceptable salt thereof.

30. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of Claims 1 to 29 for use as a medicament in the treatment of proliferative disease.

31. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 29 in the manufacture of a medicament for use in the treatment of proliferative disease.

32. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 29 for the production of an anti-proliferative effect in a warm-blooded animal such as man.

33. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claim 1 to 29 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

34. A method for producing an anti-proliferative 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), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 29.

35. A method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 29.

36. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

37. A compound of formula (I) as defined in any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, for use as a medicament.

38. A method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in

need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 29 concurrently or sequentially or as a combined preparation with another treatment of use in the control of oncology disease.

Compuestos – 943

La presente invención se relaciona con derivados de morfolino pirimidina, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en terapia, por ejemplo en el tratamiento de una enfermedad proliferativa tal como el cáncer y particularmente en enfermedades mediadas por una quinasa mTOR y/o una o más enzimas PI3K.

Ahora se sabe con certeza que la desregulación de oncógenos y genes supresores de tumores contribuye a la formación de tumores malignos, por ejemplo por medio de una proliferación celular incrementada o supervivencia celular incrementada. También se sabe que las vías de señalización mediadas por las familias PI3K/mTOR tienen un rol central en un número de procesos celulares incluyendo la proliferación y la supervivencia, y la desregulación de estas vías es un factor causante de un amplio espectro de cánceres humanos y otras enfermedades.

El blanco en el mamífero del antibiótico macrólido Rapamicina (sirolimus) es la enzima mTOR. Esta enzima pertenece a la familia de la quinasa (PIKK) relacionada con la fosfatidilinositol (PI) quinasa de las proteínas quinasas, la cual también incluye ATM, ATR, DNA–PK y hSMG–1. La mTOR, como otros miembros de la familia PIKK, no posee actividad quinasa en lípidos detectable, sino que funciona como una serina/treonina quinasa. Mucho del conocimiento de la señalización de mTOR está basado en el uso de Rapamicina. La Rapamicina primero se une a la proteína de unión (FKBP12) de la inmunofilina FK506 de 12 kDa y este complejo inhibe la señalización de mTOR (Tee y Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29–37). La proteína mTOR consiste en un dominio catalítico de la quinasa, un dominio de unión (FRB) de FKBP12–Rapamicina, un dominio represor putativo próximo al *C*–terminal y hasta 20 motivos HEAT repetidos en tándem en el *N*–terminal, así como el dominio *C*–terminal de FAT y FRAP–ATM–TRRAP (FAT) (Huang y Houghton, Current Opinion in Pharmacology, 2003, 3, 371–377).

La mTOR quinasa es un regulador clave del crecimiento celular y ha sido demostrado que regula una gran variedad de funciones celulares incluyendo traducción, transcripción, rotación del ARNm, estabilidad de la proteína, reorganización citoesquelética de la actina y autofagia (Jacinto y Hall, Nature Reviews Molecular and Cell Biology, 2005, 4, 117–126). La quinasa mTOR integra las señales de los factores de crecimiento (tales como el factor de crecimiento tipo insulina o insulina) y nutrientes (tales como aminoácidos y glucosa) para

regular el crecimiento celular. La quinasa mTOR es activada por los factores de crecimiento a través de la vía PI3K–Akt. La función más característica de la quinasa mTOR en células de mamíferos es la regulación de la traducción a través de dos vías, a saber la activación de la S6K1 ribosomal para mejorar la traducción de los ARNm que portan un tracto terminal 5′ de oligopirimidina (TOP) y supresión de 4E–BP1 para permitir la traducción del ARNm dependiente de CAP.

Generalmente, los investigadores han explorado el rol fisiológico y patológico de la mTOR usando la inhibición con Rapamicina y análogos de la Rapamicina relacionados basados en su especificidad para la mTOR como un blanco intracelular. Sin embargo, datos recientes sugieren que la Rapamicina exhibe acciones inhibidoras variables en las funciones de señalización de la mTOR y sugieren que la inhibición directa del dominio quinasa mTOR puede exhibir actividades anticancerígenas sustancialmente más amplias que aquellas alcanzadas por la Rapamicina (Edinger y otros, Cancer Research, 2003, 63, 8451–8460). Por esta razón, inhibidores potentes y selectivos de la actividad quinasa mTOR serían útiles para permitir un entendimiento más completo de la función de la quinasa mTOR y proporcionar agentes terapéuticos útiles.

Existe ahora considerable evidencia que indica que las vías aguas arriba de la mTOR, tales como la vía PI3K, son frecuentemente activadas en el cáncer (Vivanco y Sawyers, Nature Reviews Cancer, 2002, 2, 489–501; Bjornsti y Houghton, Nature Reviews Cancer, 2004, 4, 335–348; Inoki y otros, Nature Genetics, 2005, 37, 19–24). Por ejemplo, los componentes de la vía PI3K que están mutados en los diferentes tumores humanos incluyen mutaciones activadoras de los receptores del factor de crecimiento y la amplificación y/o sobreexpresión de PI3K y Akt.

Además existe evidencia de que la proliferación celular endotelial puede también ser dependiente de la señalización de la mTOR. La proliferación celular endotelial es estimulada por la activación del factor de crecimiento celular endotelial vascular (VEGF) de la vía de señalización de PI3K–Akt–mTOR (Dancey, Expert Opinion on Investigational Drugs, 2005, 14, 313–328). Por otra parte, la señalización de la quinasa mTOR se cree que controla parcialmente la síntesis de VEGF a través de efectos en la expresión del factor 1–α inducible por la hipoxia (HIF–1α) (Hudson y otros, Molecular and Cellular Biology, 2002, 22, 7004–7014). Por lo tanto, la angiogénesis del tumor puede depender de la señalización de la quinasa mTOR de dos formas, a través de la síntesis de VEGF inducida por la hipoxia por las

células estromales y tumorales, y a través de la estimulación de la proliferación y supervivencia endotelial por VEGF a través de la señalización de PI3K–Akt–mTOR.

Estos descubrimientos sugieren que los inhibidores farmacológicos de la quinasa mTOR deberían ser de valor terapéutico para el tratamiento de varias formas de cáncer que comprenden tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides. En particular, los inhibidores de quinasa mTOR deberían ser de valor terapéutico para el tratamiento de, por ejemplo, cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata, y de cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias (incluyendo ALL y CML), mieloma múltiple y linfoma.

Además de la tumorigénesis, existe evidencia de que la quinasa mTOR desempeña un rol en una serie de síndromes de hamartoma. Estudios recientes han mostrado que las proteínas supresoras de tumores tales como TSC1, TSC2, PTEN y LKB1 controlan estrechamente la señalización de la quinasa mTOR. La pérdida de estas proteínas supresoras de tumor y conduce a una serie de hamartomas como resultado de la elevada señalización de la quinasa mTOR (Tee y Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29–37). Los síndromes con un enlace molecular establecido para la desregulación de la quinasa mTOR incluyen el síndrome de Peutz–Jeghers (PJS), enfermedad de Cowden, síndrome de Bannayan–Riley–Ruvalcaba (BRRS), síndrome de Proteus, enfermedad de Lhermitte–Duclos y esclerosis tuberosa (TSC) (Inoki y otros, Nature Genetics, 2005, 37, 19–24). Los pacientes con estos síndromes habitualmente desarrollan tumores hamartomatosos benignos en múltiples órganos.

Estudios recientes han revelado un rol de la quinasa mTOR en otras enfermedades (Easton & Houghton, Expert Opinion on Therapeutic Targets, 2004, 8, 551–564). Ha sido demostrado que la Rapamicina es un potente inmunosupresor al inhibir la proliferación inducida por antígenos de células T, células B y la producción de anticuerpos (Sehgal, Transplantation Proceedings, 2003, 35, 7S–14S) y de esta forma los inhibidores de quinasa mTOR pueden ser también inmunosupresores útiles. La inhibición de la actividad de la quinasa de mTOR puede ser también útil en la prevención de la 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 la vasculatura (Morice y otros, New England Journal of Medicine, 2002, 346, 1773–1780). Además, el análogo de la Rapamicina, everolimus, puede reducir la gravedad e incidencia de la vasculopatía del aloinjerto cardíaco (Eisen y otros, New England Journal of Medicine, 2003, 349, 847–858). La elevada actividad de la quinasa mTOR ha sido asociada con la hipertrofia cardiaca, la cual es de importancia clínica como un factor de riesgo mayor para la insuficiencia cardiaca y es una consecuencia del tamaño celular incrementado de los cardiomiocitos (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29–37). De esta forma los inhibidores de la quinasa mTOR se espera que sean útiles en la prevención y tratamiento de una gran variedad de enfermedades además del cáncer.

También se cree que un número de estos derivados de morfolino pirimidina pueden tener actividad inhibidora contra las fosfatidilinositol (PI) 3–quinasas familia de las quinasas.

Las fosfatidilinositol (PI) 3–quinasas (PI3K) son quinasas lipídicas ubicuas que funcionan tanto como transductores de la señal aguas abajo de los receptores de la superficie celular como en las vías del tráfico de proteínas y la membrana intracelular constitutiva. Todas las PI3K son enzimas con especificidad dual con una actividad quinasa lipídica que fosforila los fosfoinosítidos en la posición 3–hidroxi, y una actividad de la proteína quinasa no tan bien caracterizada. Los productos lipídicos de las reacciones catalizadas con PI3K que comprenden fosfatidilinositol 3,4,5–trisfosfato [PI(3,4,5)P_3], fosfatidilinositol 3,4–bifosfato [PI(3,4)P_2] y fosfatidilinositol 3–monofosfato [PI(3)P] constituyen los segundos mensajeros en una variedad de vías de transducción de la señal, incluyendo aquellas esenciales para la proliferación celular, adhesión, supervivencia, reorganización citoesquelética y tráfico vesicular. La PI(3)P está constitutivamente presente en todas las células y sus niveles no cambian dramáticamente a continuación de la estimulación agonista. Por el contrario, la PI(3,4)P_2 y PI(3,4,5)P_3 están nominalmente ausentes en la mayoría de las células pero éstas se acumulan rápidamente en la estimulación agonista.

Los efectos aguas abajo de los segundos mensajeros de la 3–fosfoinositida producidos por la PI3K son mediados por las moléculas blanco que contienen dominios de unión de la 3–fosfoinositida tales como el dominio de homología de pleckstrina (PH) y los dominios recientemente identificados FYVE y fox. Los blancos de las proteínas bien caracterizados para la PI3K incluyen la PDK1 y la proteína quinasa B (PKB). Además, las tirosina quinasas como Btk y Itk son dependientes de la actividad de la PI3K.

La familia de la PI3K de las quinasas lipídicas puede ser clasificada en tres grupos de acuerdo a su especificidad de substrato fisiológico (Vanhaesebroeck y otros, Trends in Biol. Sci., 1997, 22, 267). Las enzimas PI3K de la Clase III fosforilan la PI sola. En contraste, las enzimas PI3K de la Clase II fosforilan tanto la PI como la PI 4–fosfato [PI(4)P]. Las enzimas PI3K de la Clase I fosforilan la PI, PI(4)P y PI 4,5–bifosfato [$PI(4,5)P_2$], aunque solamente la $PI(4,5)P_2$ se cree que es el sustrato celular fisiológico. La fosforilación de la $PI(4,5)P_2$ produce el segundo mensajero lipídico $PI(3,4,5)P_3$. Miembros más distantes relacionados de la superfamilia de la quinasa lipídica son las quinasas de la Clase IV tales como mTOR (discutida anteriormente) y la quinasa dependiente del ADN que fosforilan los residuos de serina/treonina dentro de los sustratos de proteína. Las más estudiadas y comprendidas de las quinasas lipídicas PI3K son las enzimas PI3K de la Clase I.

Las PI3K de la Clase I son heterodímeros que consisten en una subunidad catalítica p110 y una subunidad regulatoria. La familia está dividida adicionalmente en enzimas de la Clase Ia y la Clase Ib sobre la base de los socios regulatorios y el mecanismo de regulación. Las enzimas de la Clase Ia consisten en tres subunidades catalíticas distintas (p110α, p110β y p110δ) que dimerizan con cinco subunidades regulatorias distintas (p85α, p55α, p50α, p85β y p55γ), con todas las subunidades catalíticas siendo capaces de interactuar con todas las subunidades regulatorias para formar una variedad de heterodímeros. Las PI3K de la Clase Ia son generalmente activadas en respuesta a la estimulación del factor de crecimiento del receptor tirosina quinasas a través de la interacción de sus dominios de subunidad regulatoria SH2 con residuos de fosfo–tirosina específicos del receptor activado o proteínas adaptadoras tales como IRS–1. Ambas p110α y p110β son constitutivamente expresadas en todos los tipos de células, mientras que la expresión de p110δ está más restringida a las poblaciones de leucocitos y algunas células epiteliales. En contraste, la enzima simple de la Clase Ib consiste en una subunidad catalítica p110γ que interactúa con una subunidad regulatoria p101. Además, la enzima de la Clase Ib es activada en respuesta a la proteína G acoplada a los sistemas receptores (GPCR) y su expresión parece estar limitada a los leucocitos y cardiomiocitos.

Existe ahora considerable evidencia que indica que las enzimas PI3K de la Clase Ia contribuyen a la tumorigénesis en una gran variedad de cánceres humanos, ya sea directa o indirectamente (Vivanco y Sawyers, Nature Reviews Cancer, 2002, 2, 489–501). Por ejemplo, la subunidad p110α es amplificada en algunos tumores tales como aquellos del

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ovario (Shayesteh y otros, Nature Genetics, 1999, 21, 99–102) y cérvix (Ma y otros, Oncogene, 2000, 19, 2739–2744). Más recientemente, mutaciones activadoras dentro del sitio catalítico de la subunidad catalítica p110α han sido asociadas con otros varios tumores tales como aquellos de la región colorrectal y de mama y pulmón (Samuels y otros, Science, 2004, 304, 554). Las mutaciones relacionadas con el tumor en la subunidad regulatoria p85α han sido también identificadas en cánceres tales como aquellos del ovario y colon (Philp y otros, Cancer Research, 2001, 61, 7426–7429). Además de los efectos directos, se cree que la activación de las PI3K de la Clase Ia contribuye a los eventos tumorigénicos que ocurren aguas arriba en las vías de señalización, por ejemplo por vía de la activación dependiente del ligando o independiente del ligando de los receptores tirosina quinasa, sistemas GPCR o integrinas (Vara y otros, Cancer Treatment Reviews, 2004, 30, 193–204). Ejemplos de tales vías de señalización aguas arriba incluyen la sobreexpresión del receptor tirosina quinasa erbB2 en una variedad de tumores que conducen a la activación de las vías mediadas por la PI3K (Harari y otros, Oncogene, 2000, 19, 6102–6114) y sobreexpresión del oncogén ras (Kauffmann–Zeh y otros, Nature, 1997, 385, 544–548). Además, las PI3K de la Clase Ia pueden contribuir indirectamente a la tumorigénesis causada por varios eventos de señalización aguas abajo. Por ejemplo, la pérdida del efecto de la fosfatasa supresora de tumores PTEN que cataliza la conversión de $PI(3,4,5)P_3$ de regreso a $PI(4,5)P_2$ está asociada con una gran variedad de tumores a través de la desregulación de la producción de $PI(3,4,5)P_3$ mediada por la PI3K (Simpson y Parsons, Exp. Cell Res., 2001, 264, 29–41). Además, el aumento de los efectos de otros eventos de señalización mediados por la PI3K se cree que contribuye a una variedad de cánceres, por ejemplo por activación de Akt (Nicholson y Anderson, Cellular Signalling, 2002, 14, 381–395).

Además de su rol en la mediación de la señalización proliferativa y la supervivencia en células tumorales, existe evidencia de que las enzimas PI3K de la Clase Ia contribuyen a la tumorigénesis en células estromales asociadas al tumor. Por ejemplo, se sabe que la señalización de la PI3K desempeña un importante rol en la mediación de eventos angiogénicos en células endoteliales en respuesta a factores proangiogénicos tales como VEGF (Abid y otros, Arterioscler. Thromb. Vasc. Biol., 2004, 24, 294–300). Ya que las enzimas PI3K de la Clase I están también involucradas en la motilidad y migración (Sawyer, Expert Opinion Investig. Drugs, 2004, 13, 1–19), los inhibidores de la enzima PI3K deberían proporcionar beneficio terapéutico a través de la inhibición de la invasión de células

tumorales y metástasis. Además, las enzimas PI3K de la Clase I desempeñan un importante rol en la regulación de células inmunes contribuyendo a los efectos protumorigénicos de las células inflamatorias (Coussens y Werb, Nature, 2002, 420, 860–867).

Estos descubrimientos sugieren que los inhibidores farmacológicos de las enzimas PI3K de la Clase I serán de valor terapéutico para el tratamiento de varias enfermedades incluyendo diferentes formas de la enfermedad de cáncer que comprenden tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides. En particular, los inhibidores de las enzimas PI3K de la Clase I deberían ser de valor terapéutico para el tratamiento de, por ejemplo, cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata, y del cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias (incluyendo ALL y CML), mieloma múltiple y linfoma.

La PI3Kγ, la PI3K de la Clase Ib, es activada por los GPCR, como fue finalmente demostrado en ratones carentes de la enzima. De esta forma, los neutrólifos y macrófagos derivados de los animales deficientes en PI3Kγ no produjeron $PI(3,4,5)P_3$ en respuesta a la estimulación con varias sustancias quimiostáticas (tales como IL–8, C5a, fMLP y MIP–1a), mientras que la señalización a través de los receptores acoplados a la proteína tirosina quinasa para las PI3K de la Clase Ia fue intacta (Hirsch y otros, Science, 2000, 287(5455), 1049–1053; Li y otros, Science, 2002, 287(5455), 1046–1049; Sasaki y otros, Science 2002, 287(5455), 1040–1046). Además, la fosforilación mediada por la $PI(3,4,5)P_3$ de PKB no fue iniciada por estos ligandos GPCR en células nulas de PI3Kγ. Tomados juntos, los resultados demostraron que, al menos en las células hematopoiéticas restantes, la PI3Kγ es la única isoforma de PI3K que es activada por los GPCR *in vivo*. Cuando los neutrólifos y macrófagos peritoneales derivados de la médula ósea murina de tipo salvaje y ratones $PI3K\gamma^{-/-}$ fueron probados *in vitro*, una ejecución reducida, pero no completamente suprimida, en ensayos de quimiotaxía y adherencia fue observada. Sin embargo, esto se tradujo en un deterioro drástico de la infiltración de neutrófilos inducida por IL–8 en los tejidos (Hirsch y otros, Science, 2000, 287(5455), 1049–1053). Datos recientes sugieren que la PI3Kγ está más bien involucrada en el proceso de búsqueda de encontrar el paso que en la generación de la fuerza mecánica para la motilidad, ya que no se produjo migración aleatoria en las células que

carecían de PI3Kγ (Hannigan y otros, Proc. Nat. Acad. of Sciences of U.S.A., 2002, 99(6), 3603–8). Los datos que vinculan a la PI3Kγ con la patología de la enfermedad respiratoria surgieron de la demostración que la PI3Kγ tiene un rol central en la regulación de la activación de neutrólifos e infiltración pulmonar inducida por endotoxinas conduciendo a la lesión aguda del pulmón (Yum y otros, J. Immunology, 2001, 167(11), 6601–8). El hecho de que aunque la PI3Kγ está altamente expresada en los leucocitos, su pérdida parece no interferir con la hematopoiesis, y el hecho de que los ratones nulos de PI3Kγ son viables y fértiles implica más a esta isoforma de la PI3K como un blanco potencial para el fármaco. El trabajo con ratones knockout también estableció que la PI3Kγ es un amplificador esencial de la activación de células de mastocitos (Laffargue y otros, Immunity, 2002, 16(3), 441–451).

De esta forma, además de la tumorigénesis, existe evidencia de que las enzimas PI3K de la Clase I desempeñan un rol en otras enfermedades (Wymann y otros, Trends in Pharmacological Science, 2003, 24, 366–376). Las enzimas PI3K de la Clase Ia y la enzima simple de la Clase Ib tienen roles importantes en las células del sistema inmune (Koyasu, Nature Immunology, 2003, 4, 313–319) y de esta forma son blancos terapéuticos para las indicaciones inflamatorias y alérgicas. Reportes recientes demuestran que los ratones deficientes en PI3Kγ y PI3Kδ son viables, pero tienen respuestas inflamatorias y alérgicas atenuadas (Ali y otros, Nature, 2004, 431(7011), 1007–11). La inhibición de la PI3K es también útil para tratar la enfermedad cardiovascular a través de los efectos antiinflamatorios o directamente afectando los miocitos cardíacos (Prasad y otros, Trends in Cardiovascular Medicine, 2003, 13, 206–212). De esta forma, los inhibidores de las enzimas PI3K de la Clase I se espera que sean útiles en la prevención y tratamiento de una gran variedad de enfermedades además de cáncer.

Muchos compuestos que inhiben las PI3K y la quinasa (PI3KK) relacionada con la fosfatidilinositol (PI) quinasa han sido identificados, incluyendo el derivado LY294002 de la wortmanina y la quercetina. Estos compuestos son inhibidores bastante específicos de las PI3K y PI3KK por encima de otras quinasas pero carecen de potencia y exhiben poca selectividad dentro de las familias de la PI3K.

Por consiguiente, sería deseable proporcionar inhibidores mTOR y/o PI3K efectivos adicionales para el uso en el tratamiento de cáncer, enfermedades inflamatorias u obstructivas de las vías respiratorias, enfermedades inmunes o cardiovasculares.

Los derivados de la morfolino pirimidina y los inhibidores de la PI3K son conocidos en el arte.

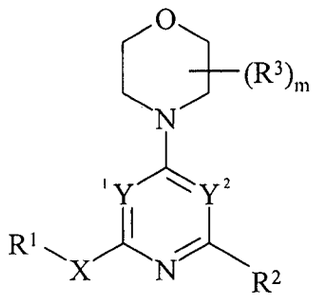
La Solicitud Internacional de Patente WO 2004/048365 divulga compuestos que poseen actividad inhibidora de la enzima PI3K y son útiles en el tratamiento de cáncer. Estos compuestos son pirimidinas sustituidas con arilamino y heteroarilamino las cuales difieren de los compuestos de la presente invención con respecto a sus sustituyentes arilamino y heteroarilamino. Estos sustituyentes no son equivalentes a los sustituyentes XR^1 de la presente invención. Los inhibidores de la actividad de la PI3K útiles en el tratamiento de cáncer también son divulgados en la Solicitud de Patente Europea 1 277 738 la cual menciona los compuestos heteroaril bicíclicos sustituidos con 4–morfolino tales como quinazolina y derivados de pirido[3,2–*d*]pirimidina y los compuestos heteroaril tricíclicos sustituidos con 4–morfolino pero no derivados de pirimidina monocíclica.

Un número de compuestos tales como 4–morfolin–4–il–6–(fenilsulfonilmetil)–2–piridin–4–il–pirimidina y 4–{6–[(fenilsulfonil)metil]–2–piridin–2–ilpirimidin–4–il}morfolina han sido registrados en la base de datos del Chemical Abstracts pero ninguna utilidad ha sido indicada y no hay sugerencia de que estos compuestos tengan actividad inhibidora mTOR y/o PI3K o propiedades terapéuticas útiles.

Sorprendentemente, hemos descubierto que ciertos derivados de la morfolino pirimidina poseen propiedades terapéuticas útiles. Sin querer ceñirnos a restricciones teóricas, se cree que la utilidad terapéutica de los derivados es derivada de su actividad inhibidora contra la quinasa mTOR y/o una o más enzimas PI3K (tales como la enzima de la Clase Ia y/o la enzima de la Clase Ib). Debido a que las vías de señalización mediadas por las familias PI3K/mTOR tienen un rol central en un número de procesos celulares incluyendo la proliferación y supervivencia, y debido a que la desregulación de estas vías es un factor causante en un amplio espectro de cánceres humanos y otras enfermedades, se espera que los derivados sean terapéuticamente útiles. En particular, se espera que los derivados tengan propiedades antiproliferativas y/o apoptóticas lo que significa que estos serán útiles en el tratamiento de una enfermedad proliferativa tal como el cáncer. Los compuestos de la presente invención también pueden ser útiles en la inhibición de la proliferación celular no controlada que surge a partir de varias enfermedades no malignas tales como enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares.

Generalmente, los compuestos de la presente invención poseen potente actividad inhibidora contra la quinasa mTOR pero el compuesto puede también poseer potente actividad inhibidora contra una o más enzimas PI3K (tales como la enzima de la Clase Ia y/o la enzima de la Clase Ib).

De acuerdo con un aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^1 es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y R^5 son independientemente hidrógeno o C_{1-6}alquil;

o R^1 y R^4 junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil,

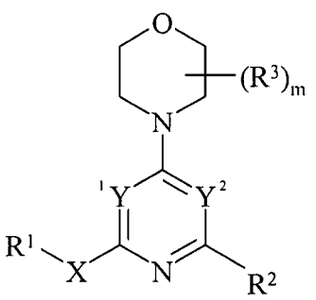
cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo seleccionado de C$_{1-6}$alquil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil

para el uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$,-$NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$,-$S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^{1} es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^{2} es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^{3}, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^{4} y **R**^{5} son independientemente hidrógeno o C_{1-6}alquil;

o **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{6} y **R**^{7} son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

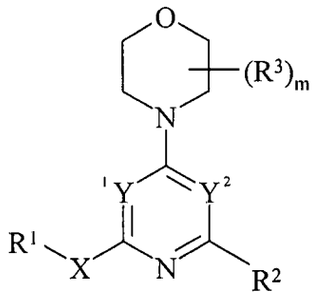
R^{13}, R^{14}, R^{15}, R^{16} y R^{19} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}-

$_{6}$alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

para el uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^{2}** son independientemente N o CR^{8} siempre que uno de ^{1}Y y Y^{2} es N y el otro es CR^{8};

X es un grupo de enlace seleccionado de $–CR^{4}=CR^{5}–$, $–CR^{4}=CR^{5}CR^{6}R^{7}–$, $–CR^{6}R^{7}CR^{5}=CR^{4}–$, $–C\equiv C–$, $–C\equiv CCR^{6}R^{7}–$, $–CR^{6}R^{7}C\equiv C–$, $–NR^{4}CR^{6}R^{7}–$, $–OCR^{6}R^{7}–$, $–SCR^{6}R^{7}–$, $–S(O)CR^{6}R^{7}–$, $–S(O)_{2}CR^{6}R^{7}–$, $–C(O)NR^{4}CR^{6}R^{7}–$, $–NR^{4}C(O)CR^{6}R^{7}–$, $–NR^{4}C(O)NR^{5}CR^{6}R^{7}–$, $–NR^{4}S(O)_{2}CR^{6}R^{7}–$, $–S(O)_{2}NR^{4}CR^{6}R^{7}–$, $–C(O)NR^{4}–$, $–NR^{4}C(O)–$, $–NR^{4}C(O)NR^{5}–$, $–S(O)_{2}NR^{4}–$ y $–NR^{4}S(O)_{2}–$;

R^{1} es un grupo seleccionado de C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^{9}, $–OR^{9}$, $–SR^{9}$, $–SOR^{9}$, $–SO_{2}R^{9}$, $–COR^{9}$, $–CO_{2}R^{9}$, $–CONR^{9}R^{10}$, $–NR^{9}R^{10}$, $–NR^{9}COR^{10}$, $–NR^{9}CO_{2}R^{10}$, $–NR^{9}CONR^{10}R^{15}$, $–NR^{9}COCONR^{10}R^{15}$ y $–NR^{9}SO_{2}R^{10}$;

o **$X–R^{1}$** es $–CR^{6}R^{7}OH$;

R^{2} es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $–R^{11}$, $–OR^{11}$, $–SR^{11}$, –

SOR^{11}, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y R^5 son independientemente hidrógeno o C_{1-6}alquil;

o R^1 y R^4 junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-}

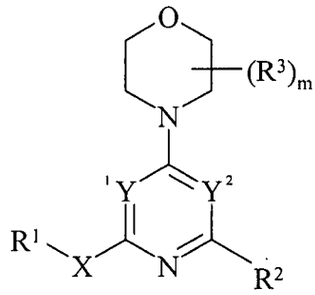
$_{6}$alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R}^{13}$, $\mathbf{R}^{14}$, $\mathbf{R}^{15}$, $\mathbf{R}^{16}$ y $\mathbf{R}^{19}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

para el uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de –CR^4=CR^5–, –CR^4=CR^{5}CR^{6}R^7–, –CR^{6}R^{7}CR^5=CR^4–, –C≡C–, –C≡CCR^{6}R^7–, –CR^{6}R^{7}C≡C–, –NR^{4}CR^{6}R^7–, –OCR^{6}R^7–, –SCR^{6}R^7–, –S(O)CR^{6}R^7–, –S(O)$_2$CR^{6}R^7–, –C(O)NR^{4}CR^{6}R^7–, –NR^{4}C(O)NR^{5}CR^{6}R^7–, –S(O)$_2$NR^{4}CR^{6}R^7–, –C(O)NR^4–, –NR^{4}C(O)–, –NR^{4}C(O)NR^5–, –S(O)$_2$NR^4– y –NR^{4}S(O)$_2$–;

R^1 es un grupo seleccionado de C$_{1-6}$alquil, C$_{2-6}$alquenil, C$_{2-6}$alquinil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, –OR^9, -SR^9, –SOR^9, –SO$_2$R^9, –COR^9, –CO$_2$R^9, –CONR^{9}R^{10}, –NR^{9}R^{10}, –NR^{9}COR^{10}, –NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, –NR^{9}COCONR^{10}R^{15} y –NR^{9}SO$_2$R^{10};

o **X**–**R**^{1} es –CR^{6}R^{7}OH;

R^2 es un grupo seleccionado de C$_{1-6}$alquil, carbociclil y heterociclil estando dicho grupo sustituido por –NR^{17}CONR^{18}R^{19} y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, –R^{11}, –OR^{11}, –SR^{11}, -SOR^{11}, –SO$_2$R^{11}, –COR^{11}, –CO$_2$R^{11}, –CONR^{11}R^{12}, –NR^{11}R^{12}, –NR^{11}COR^{12}, y -NR^{11}COCONR^{12}R^{16};

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, -R^{13}, –OR^{13}, –SR^{13}, –SOR^{13}, –SO$_2$R^{13}, –COR^{13}, –CO$_2$R^{13}, –CONR^{13}R^{14}, –NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^4 y **R**^{5} son independientemente hidrógeno o C$_{1-6}$alquil;

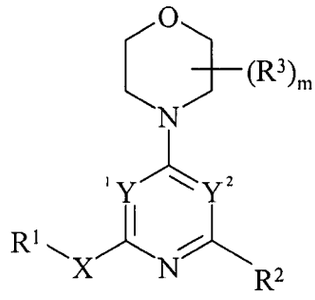
o **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;
R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;
R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;
R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;
R^{13}, R^{14}, R^{15}, R^{16} y R^{19} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;
o R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-}

$_{6}$alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

para el uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^{2}** son independientemente N o CR^{8} siempre que uno de ^{1}Y y Y^{2} es N y el otro es CR^{8};

X es un grupo de enlace seleccionado de $-CR^{4}=CR^{5}-$, $-CR^{4}=CR^{5}CR^{6}R^{7}-$, $-CR^{6}R^{7}CR^{5}=CR^{4}-$, $-C\equiv C-$, $-C\equiv CCR^{6}R^{7}-$, $-CR^{6}R^{7}C\equiv C-$, $-NR^{4}CR^{6}R^{7}-$, $-OCR^{6}R^{7}-$, $-SCR^{6}R^{7}-$, $-S(O)CR^{6}R^{7}-$, $-S(O)_{2}CR^{6}R^{7}-$, $-C(O)NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)CR^{6}R^{7}-$, $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$, $-NR^{4}S(O)_{2}CR^{6}R^{7}-$, $-S(O)_{2}NR^{4}CR^{6}R^{7}-$, $-C(O)NR^{4}-$, $-NR^{4}C(O)-$, $-NR^{4}C(O)NR^{5}-$, $-S(O)_{2}NR^{4}-$ y $-NR^{4}S(O)_{2}-$;

R^{1} es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^{9}$, $-OR^{9}$, $-SR^{9}$, $-SOR^{9}$, $-SO_{2}R^{9}$, $-COR^{9}$, $-CO_{2}R^{9}$, $-CONR^{9}R^{10}$, $-NR^{9}R^{10}$, $-NR^{9}COR^{10}$, $-NR^{9}CO_{2}R^{10}$, $-NR^{9}CONR^{10}R^{15}$, $-NR^{9}COCONR^{10}R^{15}$ y $-NR^{9}SO_{2}R^{10}$;

R^{2} es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$,

-SOR^{11}, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o C_{1-6}alquil;

o **R^1** y **R^4** junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y **R^7** son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}

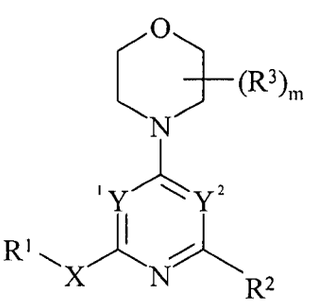
$_{6}$alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ y $\mathbf{R^{19}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

en la fabricación de un medicamento para el uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^1 es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o C_{1-6}alquil;

o **R^1** y **R^4** junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-}

$_{6}$alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R}^6$ y $\mathbf{R}^7$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R}^8$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R}^9$ y $\mathbf{R}^{10}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R}^{11}$, $\mathbf{R}^{12}$, $\mathbf{R}^{17}$ y $\mathbf{R}^{18}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

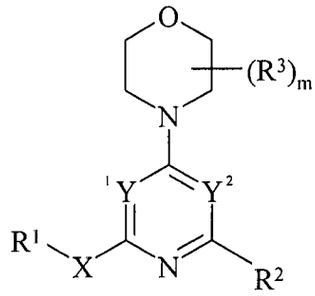
$\mathbf{R}^{13}$, $\mathbf{R}^{14}$, $\mathbf{R}^{15}$, $\mathbf{R}^{16}$ y $\mathbf{R}^{19}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son

opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

en la fabricación de un medicamento para el uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^1 es un grupo seleccionado de C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

o **X–R**^{1} es –CR^{6}R^{7}OH;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por –NR^{17}CONR^{18}R^{19} y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, –R^{11}, –OR^{11}, – SR^{11}, -SOR^{11}, –SO$_2$R^{11}, –COR^{11}, –CO$_2$R^{11}, –CONR^{11}R^{12}, –NR^{11}R^{12}, –NR^{11}COR^{12}, y -NR^{11}COCONR^{12}R^{16};

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, -R^{13}, –OR^{13}, –SR^{13}, –SOR^{13}, –SO$_2$R^{13}, –COR^{13}, –CO$_2$R^{13}, –CONR^{13}R^{14}, –NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^4 y **R**^{5} son independientemente hidrógeno o C_{1-6}alquil;

o **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y **R**^{7} son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y **R**^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

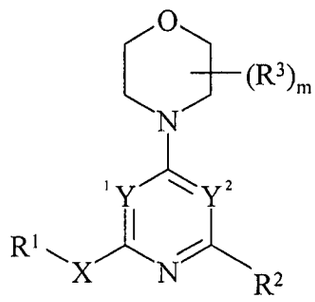
R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{13}, R^{14}, R^{15}, R^{16} y R^{19} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil

en la fabricación de un medicamento para el uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable; donde

m es 0, 1, 2, 3 ó 4;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de –CR^4=CR^5–, –CR^4=CR^{5}CR^{6}R^7–, –CR^{6}R^{7}CR^5=CR^4–, –C≡C–, –C≡CCR^{6}R^7–, –CR^{6}R^{7}C≡C–, –NR^{4}CR^{6}R^7–, –OCR^{6}R^7–, –SCR^{6}R^7–, –S(O)CR^{6}R^7–, –S(O)$_2$CR^{6}R^7–, –C(O)NR^{4}CR^{6}R^7–, –NR^{4}C(O)NR^{5}CR^{6}R^7–, –S(O)$_2$NR^{4}CR^{6}R^7–, –C(O)NR^4–, –NR^{4}C(O)–, –NR^{4}C(O)NR^5–, –S(O)$_2$NR^4– y –NR^{4}S(O)$_2$–;

R^1 es un grupo seleccionado de C$_{1-6}$alquil, C$_{2-6}$alquenil, C$_{2-6}$alquinil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, –R^9, –OR^9, –SR^9, –SOR^9, –SO$_2$R^9, –COR^9, –CO$_2$R^9, –CONR^{9}R^{10}, –NR^{9}R^{10}, –NR^{9}COR^{10}, –NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, –NR^{9}COCONR^{10}R^{15} y –NR^{9}SO$_2$R^{10};

o **X**–**R**^{1} es –CR^{6}R^{7}OH

R^2 es un grupo seleccionado de C$_{1-6}$alquil, carbociclil y heterociclil estando dicho grupo sustituido por –NR^{17}CONR^{18}R^{19} y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, –R^{11}, –OR^{11}, – SR^{11}, -SOR^{11}, –SO$_2$R^{11}, –COR^{11}, –CO$_2$R^{11}, –CONR^{11}R^{12}, –NR^{11}R^{12}, –NR^{11}COR^{12}, y -NR^{11}COCONR^{12}R^{16};

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, -R^{13}, –OR^{13}, –SR^{13}, –SOR^{13}, –SO$_2$R^{13}, –COR^{13}, –CO$_2$R^{13}, –CONR^{13}R^{14}, –NR^{13}R^{14}, –NR^{13}COR^{14}, -R^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^4 y **R**^{5} son independientemente hidrógeno o C$_{1-6}$alquil;

o **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido

por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^6}$ y $\mathbf{R^7}$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

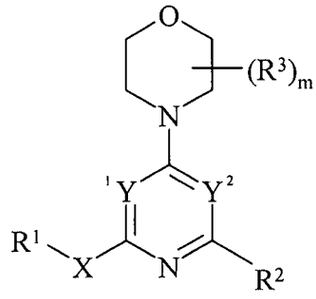
$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ y $\mathbf{R^{19}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil,

cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil

en la fabricación de un medicamento para el uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con un aspecto adicional de la presente invención, también se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^{2}** son independientemente N o CR^{8} siempre que uno de ^{1}Y y Y^{2} es N y el otro es CR^{8};

X es un grupo de enlace seleccionado de –CR^{4}=CR^{5}–, –CR^{4}=CR^{5}CR^{6}R^{7}–, –CR^{6}R^{7}CR^{5}=CR^{4}–, –C≡C–, –C≡CCR^{6}R^{7}–, –CR^{6}R^{7}C≡C–, –NR^{4}CR^{6}R^{7}–, –OCR^{6}R^{7}–, –SCR^{6}R^{7}–, –S(O)CR^{6}R^{7}–, –S(O)$_{2}$CR^{6}R^{7}–, –C(O)NR^{4}CR^{6}R^{7}–, –NR^{4}C(O)CR^{6}R^{7}–, –NR^{4}C(O)NR^{5}CR^{6}R^{7}–, -NR^{4}S(O)$_{2}$CR^{6}R^{7}–, –S(O)$_{2}$NR^{4}CR^{6}R^{7}–, –C(O)NR^{4}–, –NR^{4}C(O)–, –NR^{4}C(O)NR^{5}–, -(O)$_{2}$NR^{4}– y –NR^{4}S(O)$_{2}$–;

$\mathbf{R^1}$ es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $NR^9SO_2R^{10}$;

$\mathbf{R^2}$ es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada $\mathbf{R^3}$, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son independientemente hidrógeno o C_{1-6}alquil;

o $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^6}$ y $\mathbf{R^7}$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil,

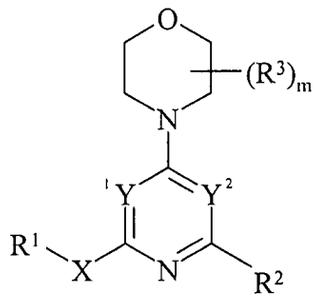
cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo seleccionado de C$_{1-6}$alquil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo seleccionado de C$_{1-6}$alquil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil.

De acuerdo con un aspecto adicional de la presente invención, también se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^1 es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $NR^9SO_2R^{10}$;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o C_{1-6}alquil;

o **R^1** y **R^4** junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido

por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^6}$ y $\mathbf{R^7}$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

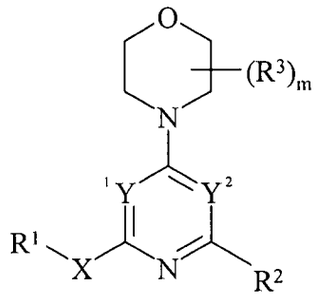
$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ y $\mathbf{R^{19}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil,

cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

o **R**^{18} y **R**^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil.

De acuerdo con un aspecto adicional de la presente invención, también se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de –CR^4=CR^5–, –CR^4=CR^{5}CR^{6}R^7–, –CR^{6}R^{7}CR^5=CR^4–, –C≡C–, –C≡CCR^{6}R^7–, –CR^{6}R^{7}C≡C–, –NR^{4}CR^{6}R^7–, –OCR^{6}R^7–, –SCR^{6}R^7–, –S(O)CR^{6}R^7–, –S(O)$_2$CR^{6}R^7–, –C(O)NR^{4}CR^{6}R^7–, –NR^{4}C(O)CR^{6}R^7–, –NR^{4}C(O)NR^{5}CR^{6}R^7–, -NR^{4}S(O)$_2$CR^{6}R^7–, –S(O)$_2$NR^{4}CR^{6}R^7–, –C(O)NR^4–, –NR^{4}C(O)–, –NR^{4}C(O)NR^5–, -(O)$_2$NR^4– y –NR^{4}S(O)$_2$–;

R^1 es un grupo seleccionado de C$_{1-6}$alquil, C$_{2-6}$alquenil, C$_{2-6}$alquinil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil, estando dicho grupo opcionalmente

sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $NR^9SO_2R^{10}$;

o **X–R¹** es $-CR^6R^7OH$;

R² es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R³, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R⁴ y **R⁵** son independientemente hidrógeno o C_{1-6}alquil;

o **R¹** y **R⁴** junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R⁶ y **R⁷** son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R⁸ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R⁹ y **R¹⁰** son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-

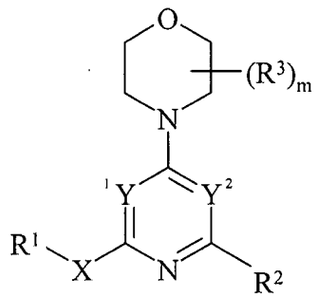
$_{6}$alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{13}, R^{14}, R^{15}, R^{16} y **R^{19}** son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

De acuerdo con un aspecto adicional de la presente invención, también se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^1Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-CR^4=CR^5-$, $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv C-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-C(O)NR^4-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

R^1 es un grupo seleccionado de C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $NR^9SO_2R^{10}$;

o **X**–**R**^{1} es $-CR^6R^7OH$;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, y $-NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R**^{5} son independientemente hidrógeno o C_{1-6}alquil;

o **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido

por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^6}$ y $\mathbf{R^7}$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{16}}$ y $\mathbf{R^{19}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil,

cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil;

o **R**^{18} y **R**^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-6}$alquilsulfonilamino, C$_{1-6}$alquilsulfonil(C$_{1-6}$alquil)amino, sulfamoil, C$_{1-6}$alquilsulfamoil, bis(C$_{1-6}$alquil)sulfamoil, C$_{1-6}$alcanoilamino, C$_{1-6}$alcanoil(C$_{1-6}$alquil)amino, carbamoil, C$_{1-6}$alquilcarbamoil y bis(C$_{1-6}$alquil)carbamoil.

Ciertos compuestos de fórmula (I) son capaces de existir en formas estereoisoméricas. Se entenderá que la invención abarca todos los isómeros geométricos y ópticos de los compuestos de fórmula (I) y las mezclas de los mismos incluyendo los racematos. Los tautómeros y las mezclas de los mismos también forman un aspecto de la presente invención. Los solvatos y las mezclas de los mismos también forman un aspecto de la presente invención. Por ejemplo, un solvato adecuado de un compuesto de fórmula (I) es, por ejemplo, un hidrato tal como un hemihidrato, un monohidrato, un dihidrato o un trihidrato o una cantidad alternativa de los mismos.

La presente invención se relaciona con los compuestos de fórmula (I) como se definió aquí, así como con las sales de los mismos. Las sales para el uso en composiciones farmacéuticas serán sales farmacéuticamente aceptables, pero otras sales pueden ser útiles en la producción de los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables de la invención pueden, por ejemplo, incluir las sales de adición ácida de los compuestos de fórmula (I) como se definió aquí las cuales son lo suficientemente básicas para formar tales sales. Tales sales de adición ácida incluyen, pero no están limitadas a, las sales fumarato, metanosulfonato, hidrocloruro, hidrobromuro, citrato y maleato y sales formadas con ácido sulfúrico y fosfórico. Además donde los compuestos de fórmula (I) son suficientemente ácidos, las sales son sales básicas y ejemplos incluyen, pero no están limitados a, una sal de metal alcalino por ejemplo sodio o potasio, una sal de metal

alcalino térreo por ejemplo calcio o magnesio, o sal de amina orgánica por ejemplo trietilamina, etanolamina, dietanolamina, trietanolamina, morfolina, *N*–metilpiperidina, *N*–etilpiperidina, dibencilamina o aminoácidos tales como lisina.

Los compuestos de fórmula (I) también pueden ser proporcionados como ésteres hidrolizables *in vivo*. Un éster hidrolizable *in vivo* de un compuesto de fórmula (I) que contiene un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable el cual es escindido en el cuerpo humano o animal para producir el alcohol ó ácido madre. Tales ésteres pueden ser identificados administrando, por ejemplo, intravenosamente a un animal de prueba, el compuesto bajo prueba y posteriormente examinando el fluido corporal del animal de prueba.

Ésteres farmacéuticamente aceptables adecuados para el carboxi incluyen C_{1-6}alcoximetil ésteres por ejemplo metoximetil, C_{1-6}alcanoiloximetil ésteres por ejemplo pivaloiloximetil, ftalidil ésteres, C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquil ésteres por ejemplo 1–ciclohexilcarboniloxietil, 1,3–dioxolen–2–onilmetil ésteres por ejemplo 5–metil–1,3–dioxolen–2–onilmetil, y C_{1-6}alcoxicarboniloxietil ésteres por ejemplo 1–metoxicarboniloxietil; y pueden ser formados en cualquier grupo carboxi en los compuestos de esta invención.

Ésteres farmacéuticamente aceptables adecuados para el hidroxi incluyen ésteres inorgánicos tales como los fosfato ésteres (incluyendo ésteres fosforamídicos cíclicos) y α–aciloxialquil éteres y compuestos relacionados los cuales como resultado de la hidrólisis *in vivo* del éster se descomponen para dar el/los grupo/s hidroxi madre. Ejemplos de α–aciloxialquil éteres incluyen acetoximetoxi y 2,2–dimetilpropioniloximetoxi. Una selección de ésteres hidrolizables *in vivo* que forman grupos para el hidroxi incluyen C_{1-10}alcanoil, por ejemplo formil, acetil, benzoil, fenilacetil, benzoil y fenilacetil sustituidos; C_{1-10}alcoxicarbonil (para dar ésteres de alquil carbonato), por ejemplo etoxicarbonil; di–C_{1-4}alquilcarbamoil y *N*–(di–C_{1-4}alquilaminoetil)–*N*–C_{1-4}alquilcarbamoil (para dar carbamatos); di–C_{1-4}alquilaminoacetil y carboxiacetil. Ejemplos de sustituyentes del anillo en fenilacetil y benzoil incluyen aminometil, C_{1-4}alquilaminometil y di–(C_{1-4}alquil)aminometil, y morfolino o piperazino enlazado a partir de un átomo de nitrógeno del anillo a través de un grupo de enlace metileno a la posición 3 ó 4 del anillo benzoil. Otros ésteres hidrolizables *in vivo* de interés incluyen, por ejemplo, $R^AC(O)OC_{1-6}$alquil–CO–, donde R^A es por ejemplo, benciloxi–

C_{1-4}alquil, o fenil. Sustituyentes adecuados en un grupo fenil en tales ésteres incluyen, por ejemplo, 4–C_{1-4}piperazino–C_{1-4}alquil, piperazino–C_{1-4}alquil y morfolino–C_{1-4}alquil.

Los compuestos de fórmula (I) también pueden ser administrados en forma de un profármaco el cual se descompone en el cuerpo humano o animal para dar un compuesto de fórmula (I). Varias formas de profármacos son conocidas en el arte. Para ejemplos de tales derivados de profármacos véase:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology, Vol. 42, p. 309–396, editado por K. Widder, y otros (Academic Press, 1985);

b) A Textbook of Drug Design and Development, editado por Krogsgaard–Larsen y H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", de H. Bundgaard p. 113–191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1–38 (1992);

d) H. Bundgaard, y otros, Journal of Pharmaceutical Sciences, 77, 285 (1988); y

e) N. Kakeya, y otros, Chem Pharm Bull, 32, 692 (1984).

En esta descripción el término genérico "C_{p-q}alquil" incluye tanto grupos alquil de cadena lineal como de cadena ramificada. Sin embargo referencias a grupos alquil individuales tales como "propil" son específicas para la versión de cadena lineal solamente (es decir *n*–propil e isopropil) y referencias a grupos alquil individuales de cadena ramificada tales como "*tert*–butil" son específicas para la versión de cadena ramificada solamente.

El prefijo C_{p-q} en C_{p-q}alquil y otros términos (donde p y q son números enteros) indica el rango de átomos de carbono que están presentes en el grupo, por ejemplo C_{1-4}alquil incluye C_1alquil (metil), C_2alquil (etil), C_3alquil (propil como *n*–propil e isopropil) y C_4alquil (n–butil, sec–butil, isobutil y *tert*–butil).

El término C_{p-q}alcoxi comprende grupos alquil –O–C_{p-q}.

El término C_{p-q}alcanoil comprende grupos alquil –C(O).

El término halo incluye fluoro, cloro, bromo y yodo.

"Carbociclil" es un sistema de anillo monocíclico, bicíclico o tricíclico saturado, insaturado o parcialmente saturado que contiene de 3 a 14 átomos en el anillo, donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O. "Carbociclil" incluye "aril", "C_{p-q}cicloalquil" y "C_{p-q}cicloalquenil".

"Aril" es un sistema de anillo carbociclil monocíclico, bicíclico o tricíclico, aromático.

"C_{p-q}cicloalquenil" es un sistema de anillo carbociclil monocíclico, bicíclico o tricíclico insaturado o parcialmente saturado que contiene al menos 1 enlace C=C y donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O.

"C_{p-q}cicloalquil" es un sistema de anillo carbociclil monocíclico, bicíclico o tricíclico, saturado y donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O.

"Heterociclil" es un sistema de anillo monocíclico, bicíclico o tricíclico, saturado, insaturado o parcialmente saturado que contiene de 3 a 14 átomos en el anillo de los cuales 1, 2, 3 ó 4 átomos del anillo son escogidos de nitrógeno, azufre u oxígeno, dicho anillo puede ser carbono o nitrógeno enlazado y donde un átomo de nitrógeno o azufre del anillo puede ser oxidado y donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O. "Heterociclil" incluye "heteroaril", "cicloheteroalquil" y "cicloheteroalquenil".

"Heteroaril" es un heterociclil monocíclico, bicíclico o tricíclico, aromático que tiene particularmente de 5 a 10 átomos en el anillo, de los cuales 1, 2, 3 ó 4 átomos del anillo son escogidos de nitrógeno, azufre u oxígeno donde un nitrógeno o azufre del anillo puede ser oxidado.

"Cicloheteroalquenil" es un sistema de anillo heterociclil monocíclico, bicíclico o tricíclico, insaturado o parcialmente saturado, que tiene particularmente de 5 a 10 átomos en el anillo, de los cuales 1, 2, 3 ó 4 átomos del anillo son escogidos de nitrógeno, azufre u oxígeno, dicho anillo puede ser carbono o nitrógeno enlazado y donde un átomo de nitrógeno o azufre del anillo puede ser oxidado y donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O.

"Cicloheteroalquil" es un sistema de anillo monocíclico, bicíclico o tricíclico heterocíclico, saturado que tiene particularmente de 5 a 10 átomos en el anillo, de los cuales 1, 2, 3 ó 4 átomos del anillo son escogidos de nitrógeno, azufre u oxígeno, dicho anillo puede ser carbono o nitrógeno enlazado y donde un átomo de nitrógeno o azufre del anillo puede ser oxidado y donde un grupo CH_2 del anillo puede ser reemplazado con un grupo C=O.

Esta descripción puede hacer uso de términos compuestos para describir grupos que comprenden más de una funcionalidad. A menos que otra cosa sea descrita aquí, tales términos son interpretados como se entienden en el arte. Por ejemplo carbociclilC_{p-q}alquil comprende C_{p-q}alquil sustituido por carbociclil, heterociclilC_{p-q}alquil comprende C_{p-q}alquil sustituido por heterociclil, y bis(C_{p-q}alquil)amino comprende amino sustituido por 2 grupos C_{p-q} alquil los cuales pueden ser iguales o diferentes.

HaloC$_{p-q}$alquil es un grupo C$_{p-q}$alquil que es sustituido por 1 o más sustituyentes halo y particularmente 1, 2 ó 3 sustituyentes halo. De manera similar, otros términos genéricos que contienen halo tales como haloC$_{p-q}$alcoxi pueden contener 1 o más sustituyentes halo y particularmente 1, 2 ó 3 sustituyentes halo.

HidroxiC$_{p-q}$alquil es un grupo C$_{p-q}$alquil que es sustituido por 1 o más sustituyentes hidroxil y particularmente por 1, 2 ó 3 sustituyentes hidroxi. De manera similar otros términos genéricos que contienen hidroxi tales como hidroxiC$_{p-q}$alcoxi pueden contener 1 o más y particularmente 1, 2 ó 3 sustituyentes hidroxi.

C$_{p-q}$alcoxiC$_{p-q}$alquil es un grupo C$_{p-q}$alquil que es sustituido por 1 o más sustituyentes C$_{p-q}$alcoxi y particularmente 1, 2 ó 3 sustituyentes C$_{p-q}$alcoxi. De manera similar otros términos genéricos que contienen C$_{p-q}$alcoxi tales como C$_{p-q}$alcoxiC$_{p-q}$alcoxi pueden contener 1 o más sustituyentes C$_{p-q}$alcoxi y particularmente 1, 2 ó 3 sustituyentes C$_{p-q}$alcoxi.

Donde sustituyentes opcionales son escogidos de "1 ó 2", de "1, 2 ó 3" o de "1, 2, 3 ó 4" grupos o sustituyentes se entiende que esta definición incluye todos los sustituyentes que son escogidos de uno de los grupos especificados, es decir, todos los sustituyentes que son iguales o los sustituyentes que son escogidos de dos o más de los grupos especificados, es decir, los sustituyentes que no son iguales.

"Una enfermedad proliferativa" incluye enfermedades malignas tales como el cáncer así como enfermedades no maligna(s) tales como enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares.

Los valores adecuados para cualquier grupo R o cualquier parte o sustituyente para tales grupos incluyen:

para C$_{1-4}$alquil:	metil, etil, propil, butil, 2–metilpropil y *tert*–butil;
para C$_{1-6}$alquil:	C$_{1-4}$alquil, pentil, 2,2–dimetilpropil, 3–metilbutil y hexil;
para C$_{3-6}$cicloalquil:	ciclopropil, ciclobutil, ciclopentil y ciclohexil;
para C$_{3-6}$cicloalquilC$_{1-4}$alquil:	ciclopropilmetil, ciclopropiletil, ciclobutilmetil, ciclopentilmetil y ciclohexilmetil;
para aril:	fenil y naftil;
para arilC$_{1-4}$alquil:	bencil, fenetil, naftilmetil y naftiletil;
para Carbocilil:	aril, ciclohexenil y C$_{3-6}$cicloalquil;
para halo:	fluoro, cloro, bromo y yodo;

para C_{1-4}alcoxi:	metoxi, etoxi, propoxi e isopropoxi;
para C_{1-6}alcoxi:	C_{1-4}alcoxi, pentiloxi, 1–etilpropoxi y hexiloxi;
para C_{1-6}alcanoil:	acetil, propanoil y 2–metilpropanoil;
para heteroaril:	piridil, imidazolil, quinolinil, cinnolil, pirimidinil, tienil, pirrolil, pirazolil, tiazolil, triazolil, oxazolil, isoxazolil, furanil, piridazinil, pirazinil, indolil, benzofuranil, dibenzofuranil y benzotienil;
para heteroarilC_{1-4}alquil:	pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, theiniletil, piridilmetil, piridiletil, pirazinilmetil, piraziniletil, pirimidinilmetil, pirimidiniletil, pirimidinilpropil, pirimidinilbutil, imidazolilpropil, imidazolilbutil, quinolinilpropil, 1,3,4–triazolilpropil y oxazolilmetil;
para heterociclil:	heteroaril, pirrolidinil, isoquinolinil, quinoxalinil, benzotiazolil, benzoxazolil, piperidinil, piperazinil, azetidinil, morfolinil, tetrahidroisoquinolinil, tetrahidroquinolinil, indolinil, dihidro–*2H*–piranil y tetrahidrofuranil.

Debe ser notado que los ejemplos dados para los términos usados en la descripción no están limitados.

Los valores particulares de m, X, ^{1}Y y Y^2, R^1, R^2 y R^3 son los siguientes. Tales valores pueden ser usados cuando sea apropiado, en relación con cualquier aspecto de la invención, o parte de la misma, y con cualquiera de las definiciones, reivindicaciones o realizaciones definidas aquí.

m

En un aspecto de la invención m es 0, 1, 2 ó 3.

En otro aspecto m es 0, 1 ó 2.

En un aspecto adicional m es 0 ó 1.

En aún otro aspecto m es 0 de manera que R^3 está ausente.

En aún otro aspecto m es 1 y R^3 es metil.

^{1}Y y Y^2

En un aspecto de la invención ^{1}Y es N y Y^2 es CR^8.

En otro aspecto ^{1}Y es N y Y^2 es CH.

En aún otro aspecto ^{1}Y es CR^8 y Y^2 es N.

En un aspecto adicional ^{1}Y es CH o CF y Y^2 es N.

En aún un aspecto adicional ^{1}Y es CH y Y^2 es N.

X

En un aspecto de la invención X es un grupo de enlace seleccionado de $–NR^4CR^6R^7–$, $–OCR^6R^7–$, $–SCR^6R^7–$, $–S(O)CR^6R^7–$, $–S(O)_2CR^6R^7–$, $–C(O)NR^4CR^6R^7–$, $–NR^4C(O)NR^5CR^6R^7–$, $–S(O)_2NR^4CR^6R^7–$, $–NR^4C(O)–$, $–C(O)NR^4–$, $–S(O)_2NR^4–$ y $-NR^4S(O)_2–$.

En otro aspecto **X** es un grupo de enlace seleccionado de $–NR^4CR^6R^7–$, $–OCR^6R^7–$, $-SCR^6R^7–$, $–S(O)CR^6R^7–$, $–S(O)_2CR^6R^7–$, $–C(O)NR^4CR^6R^7–$, $–NR^4C(O)NR^5CR^6R^7–$, $-S(O)_2NR^4CR^6R^7$, $–C(O)NR^4–$ y $–NR^4C(O)–$.

En un aspecto adicional X es un grupo de enlace seleccionado de $–NR^4CR^6R^7–$, $-OCR^6R^7–$, $–SCR^6R^7–$, $–S(O)CR^6R^7–$, $–S(O)_2CR^6R^7–$, $–C(O)NR^4–$, y $–NR^4C(O)–$.

En un aspecto adicional X es un grupo de enlace seleccionado de $–NR^4CR^6R^7–$, $-OCR^6R^7–$, $–SCR^6R^7–$, $–S(O)CR^6R^7–$ y $–S(O)_2CR^6R^7–$.

En aún otro aspecto X es un grupo de enlace seleccionado de $–SCR^6R^7–$, $-S(O)CR^6R^7–$ y $–S(O)_2CR^6R^7–$.

En otro aspecto X es un grupo de enlace seleccionado de $–NR^4CH_2–$, $–OCH_2–$, $-OCH(CH_3)–$, $–OC(CH_3)_2–$, $–SCH_2–$, $–SCH(CH_3)–$, $–SC(CH_3)_2–$, $–S(O)CH_2–$, $-S(O)CH(CH_3)–$, $–S(O)C(CH_3)_2–$, $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$, $–S(O)_2C(CH_3)_2–$, $-C(O)NR^4–$ y $–NR^4C(O)–$.

En otro aspecto X es un grupo de enlace seleccionado de $–NR^4CH_2–$, $–OCH_2–$, $-SCH_2–$, $–S(O)CH_2–$, $–S(O)_2CH_2–$, $–C(O)NR^4–$, y $–NR^4C(O)–$.

En otro aspecto X es un grupo de enlace seleccionado de $–NR^4CH_2–$, $–OCH_2–$, $-OCH(CH_3)–$, $–OC(CH_3)_2–$, $–SCH_2–$, $–SCH(CH_3)–$, $–SC(CH_3)_2–$, $–S(O)CH_2–$, $-S(O)CH(CH_3)–$, $–S(O)C(CH_3)_2–$, $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$ y $–S(O)_2C(CH_3)_2–$.

En otro aspecto X es un grupo de enlace seleccionado de $–NR^4CH_2–$, $–OCH_2–$, $-SCH_2–$, $–S(O)CH_2–$ y $–S(O)_2CH_2–$.

En un aspecto adicional X es un grupo de enlace seleccionado de $–NHCH_2–$, $-N(CH_3)CH_2–$, $–OCH_2–$, $–OCH(CH_3)–$, $–OC(CH_3)_2–$, $–SCH_2–$, $–SCH(CH_3)–$, $–SC(CH_3)_2–$, $-S(O)CH_2–$, $–S(O)CH(CH_3)–$, $–S(O)C(CH_3)_2–$, $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$, $-S(O)_2C(CH_3)_2–$, $–C(O)NH–$, $–C(O)N(CH_3)–$, $–NHC(O)–$ y $–N(CH_3)C(O)–$.

En un aspecto adicional X es un grupo de enlace seleccionado de $–NHCH_2–$, $-N(CH_3)CH_2–$, $–OCH_2–$, $–SCH_2–$, $–S(O)CH_2–$, $–S(O)_2CH_2–$, $–C(O)NH–$, $–C(O)N(CH_3)–$, $-NHC(O)–$ y $–N(CH_3)C(O)–$.

En aún un aspecto adicional X es un grupo de enlace seleccionado de $–NHCH_2–$, $-N(CH_3)CH_2–$, $–OCH_2–$, $–OCH(CH_3)–$, $–OC(CH_3)_2–$, $–SCH_2–$, $–SCH(CH_3)–$, $–SC(CH_3)_2–$, $-S(O)CH_2–$, $–S(O)CH(CH_3)–$, $–S(O)C(CH_3)_2–$, $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$ y $–S(O)_2C(CH_3)_2–$.

En aún un aspecto adicional X es un grupo de enlace seleccionado de $–NHCH_2–$, $-N(CH_3)CH_2–$, $–OCH_2–$, $–SCH_2–$ y $–S(O)_2CH_2–$.

En otro aspecto X es $–SCH_2–$ o $–S(O)_2CH_2–$.

En otro aspecto X es $–SCH_2–$, $–SCH(CH_3)–$ o $–SC(CH_3)_2–$.

En otro aspecto X es $–S(O)CH_2–$, $–S(O)CH(CH_3)–$ o $–S(O)C(CH_3)_2–$.

En otro aspecto X es $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$ o $–S(O)_2C(CH_3)_2–$.

En otro aspecto X es $–S(O)_2CH_2–$.

En otro aspecto X es $–S(O)_2C(CH_3)_2–$.

R^1

En un aspecto de la invención R^1 es un grupo seleccionado de C_{1-4}alquil, C_{3-10}cicloalquil, aril, C_{3-10}cicloalquilC_{1-4}alquil, arilC_{1-4}alquil, cicloheteroalquil, heteroaril, cicloheteroalquilC_{1-4}alquil, heteroarilC_{1-4}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $–OR^9$, $-COR^9$, $–CONR^9R^{10}$, $–NR^9R^{10}$ y $–NR^9COR^{10}$.

En otro aspecto, R^1 es un grupo seleccionado de adamantil, metil, etil, propil, butil, isobutil, tert–butil, ciclopentil, ciclohexil, fenil, bencil, oxetanil, fenetil, pirrolidinil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, pirazinil, pirrolidinilmetil, pirrolidiniletil, pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, tieniletil, piridinilmetil, piridiniletil, pirimidinilmetil, pirimidiniletil, pirazinilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $–OR^9$, $–COR^9$, $–CONR^9R^{10}$, $–NR^9R^{10}$ y $–NR^9COR^{10}$.

En otro aspecto, R^1 es un grupo seleccionado de adamantil, metil, etil, propil, butil, isobutil, tert–butil, ciclopentil, ciclohexil, fenil, bencil, fenetil, pirrolidinil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, pirazinil, pirrolidinilmetil, pirrolidiniletil,

pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, tieniletil, piridinilmetil, piridiniletil, pirimidinilmetil, pirimidiniletil, pirazinilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $–OR^9$, $–COR^9$, $-CONR^9R^{10}$, $–NR^9R^{10}$ y $–NR^9COR^{10}$.

En un aspecto adicional, R^1 es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $–NMe_2$, $–NHCOCH_3$, $–CONH_2$ y $–CONHCH_3$.

En un aspecto adicional, R^1 es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirazoliletil, furanilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $–NHCOCH_3$, $–CONH_2$ y $–CONHCH_3$.

En otro aspecto R^1 es un grupo seleccionado de metil, etil, isopropil, ciclopropil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2NC(O)CH_3$, fenil, 4–fluorofenil, 2–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, 2–oxopirolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il.

En aún otro aspecto R^1 es un grupo seleccionado de metil, isopropil, ciclopropil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2NC(O)CH_3$, $–CH_2CONH_2$, fenil, 4–fluorofenil, 2–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, 2–oxopirolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il.

En aún otro aspecto R^1 es un grupo seleccionado de metil, etil, isopropil, tert–butil, ciclopropil, ciclopentil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2OMe$, $–CH_2CH_2NMe_2$, $–CH_2CH_2NC(O)CH_3$, $–CH_2CONH_2$, fenil, 3,5–difluorofenil, 4–fluorofenil, 2–clorofenil, 4–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil,

piridin–4–il, piridin–2–il, oxetan–3–il, 2–oxopirolidin–3–il, 1–metilimidazol–5–ilmetil , 1–metilpirrolidin–3–il , tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il.

En otro aspecto R^1 es metil, etil, isopropil, *tert*–butil, 4–fluorofenil, 3,5–difluorofenil, piridin–4–il o ciclopropil.

En otro aspecto R^1 es metil, etil, isopropil, *tert*–butil, 4–fluorofenil, piridin–4–il o ciclopropil.

En otro aspecto R^1 es metil o ciclopropil.

En otro aspecto R^1 es metil.

X–R¹

En una realización X–R^1 es $-C(CH_3)_2OH$ o $-CH_2OH$.

En una realización X–R^1 es $-CH_2OH$.

R^2

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil de 5 ó 6 miembros estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por

uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de carbociclil o heterociclil de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de un aril de 6 miembros y heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de un aril de 6 miembros y heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es seleccionado de un aril de 6 miembros y heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes

independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenil o piridil sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenil o piridil sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

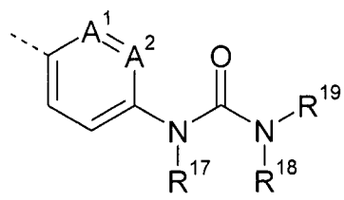
En otro aspecto R^2 es fenil o piridil sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenil o piridil opcionalmente sustituido por $-NR^{17}CONR^{18}R^{19}$.

En otro aspecto R^2 es fenil o piridil opcionalmente sustituido por $-NHCONR^{18}R^{19}$.

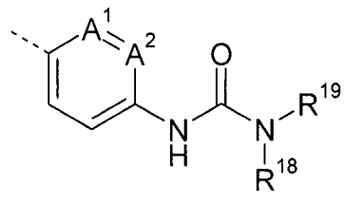
En otro aspecto R^2 es fenil o piridil opcionalmente sustituido por $-NHCONHR^{19}$.

En otro aspecto R^2 es



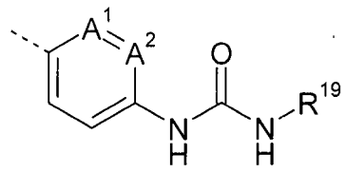
donde A^1 y A^2 son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH.

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R^4

En un aspecto de la invención R^4 es hidrógeno o metil.

En otro aspecto R^4 es hidrógeno.

R^4 y R^1

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ o $-NR^4S(O)_2-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-}

$_{6}$alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ o $-NR^4S(O)_2-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4, 5, 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ o $-NR^4S(O)_2-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 5 ó 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ o $-NR^4S(O)_2-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y

estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, $-NR^4C(O)-$, $-NR^4C(O)NR^5-$ o $-NR^4S(O)_2-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo de piperidina, morfolina, azetidina, azepina, diazepán y tiomorfolina estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, hidroxi, oxo y C_{1-6}alquil.

En otro aspecto de la invención, cuando **X** es $-NR^4C(O)-$ $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo de piperidina, morfolina, azetidina, azepina, diazepán y tiomorfolina estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, hidroxi, oxo y C_{1-6}alquil.

En otro aspecto de la invención, cuando **X** es $-NR^4C(O)-$ $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo de 1–metil–piperidina, 4–hidroxi–piperidina, morfolina, 3–metilmorfolina, 3–hidroxiazetidina, azepina, 1,4–diazepán y tiomorfolina–1,1–dióxido.

R^5

En un aspecto de la invención R^5 es hidrógeno o metil.

En otro aspecto R^5 es hidrógeno.

En otro aspecto R^5 es metil.

R^6

En un aspecto de la invención R^6 es hidrógeno o metil.

En otro aspecto R^6 es hidrógeno.

En otro aspecto R^6 es metil.

R^7

En un aspecto de la invención R^7 es hidrógeno o metil.

En otro aspecto R^7 es hidrógeno.

En otro aspecto R^7 es metil.

R^8

En un aspecto de la invención R^8 es hidrógeno o halo.

En otro aspecto R^8 es hidrógeno o fluoro.

En un aspecto adicional R^8 es hidrógeno.

R^9

En un aspecto de la invención R^9 es hidrógeno o C_{1-4}alquil opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-4}alcoxi, amino, C_{1-4}alquilamino y bis(C_{1-4}alquil)amino.

En otro aspecto R^9 es hidrógeno o C_{1-4}alquil opcionalmente sustituido por 1, 2 ó 3 sustituyentes halo.

En un aspecto adicional R^9 es hidrógeno, metil o trifluorometil.

R^{10}

En un aspecto de la invención R^{10} es hidrógeno.

R^{11}

En un aspecto de la invención R^{11} es hidrógeno o un grupo seleccionado de C_{1-4}alquil, aril y cicloheteroalquil estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos seleccionados de halo, hidroxi y ciano.

En otro aspecto R^{11} es hidrógeno, metil opcionalmente sustituido con hidroxi o ciano, fenil o pirrolidinil.

En otro aspecto R^{11} es hidrógeno o metil.

R^{12}

En un aspecto de la invención R^{12} es hidrógeno o metil.

R^{17}

En un aspecto de la invención R^{17} es hidrógeno o un grupo seleccionado de C_{1-4}alquil, aril y cicloheteroalquil estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos seleccionados de halo, hidroxi y ciano.

En otro aspecto R^{17} es hidrógeno, metil opcionalmente sustituido con hidroxi o ciano, fenil o pirrolidinil.

En otro aspecto R^{17} es hidrógeno o metil.

En otro aspecto R^{17} es hidrógeno.

R^{18}

En un aspecto de la invención R^{18} es hidrógeno o metil.

En un aspecto de la invención R^{18} es hidrógeno.

R^{19}

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, fenil, naftil, pirrolil, imidazolil, isoxazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil, azaindolil, indolil, quinolinil, bencimidazolil, benzofuranil, dibenzofuranil, benzotienil, fenilC_{1-6}alquil, naftilC_{1-6}alquil, pirrolilC_{1-6}alquil, imidazolilC_{1-6}alquil, isoxazolilC_{1-6}alquil, pirazolilC_{1-6}alquil, furanilC_{1-6}alquil, tienilC_{1-6}alquil, piridinilC_{1-6}alquil, pirimidinilC_{1-6}alquil, piridazinilC_{1-6}alquil, azaindolilC_{1-6}alquil, indolilC_{1-6}alquil, quinolinilC_{1-6}alquil, bencimidazolilC_{1-6}alquil, benzofuranilC_{1-6}alquil, dibenzofuranilC_{1-6}alquil, benzotienilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-

$_{6}$alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, fenil, naftil, pirrolil, imidazolil, isoxazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil, azaindolil, indolil, quinolinil, bencimidazolil, benzofuranil, dibenzofuranil, benzotienil, fenilC_{1-6}alquil, naftilC_{1-6}alquil, pirrolilC_{1-6}alquil, imidazolilC_{1-6}alquil, isoxazolilC_{1-6}alquil, pirazolilC_{1-6}alquil, furanilC_{1-6}alquil, tienilC_{1-6}alquil, piridinilC_{1-6}alquil, pirimidinilC_{1-6}alquil, piridazinilC_{1-6}alquil, azaindolilC_{1-6}alquil, indolilC_{1-6}alquil, quinolinilC_{1-6}alquil, bencimidazolilC_{1-6}alquil, benzofuranilC_{1-6}alquil, dibenzofuranilC_{1-6}alquil, benzotienilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil,

fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, –CH_2(ciclopropil), –$CH_2CH_2NMe_2$, –$CH(CH_3)CH_2OH$, –$C(CH_3)_2CH_2OH$, –CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, –CH_2(imidazol–2–il), –CH_2(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, –CH_2(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, piridinil–2–il, pirimidin–2–il, y 1H–pirazol–3–il.

En un aspecto de la invención R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, -CH_2(ciclopropil), –$CH_2CH_2NMe_2$, –$CH(CH_3)CH_2OH$, –$C(CH_3)_2CH_2OH$, –CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, –CH_2(imidazol–2–il), –CH_2(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, –CH_2(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, pirimidin–2–il, y 1H–pirazol–3–il.

En otro aspecto de la invención R^{19} es un grupo seleccionado de metil, etil, propil, ciclopropil, ciclobutil, –CH_2CH_2OH, –$CH_2CH_2NMe_2$, –$C(Me)_2CH_2OH$ y 1H–pirazol–3–il.

R^{18} y R^{19}

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-}

$_{6}$alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al cual están unidos forman un anillo de morfolina.

En un aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos;

m es 0, 1 ó 2;

^{1}Y y **Y^{2}** son independientemente N o CR^{8} siempre que uno de ^{1}Y y Y^{2} es N y el otro es CR^{8};

X es un grupo de enlace seleccionado de $-NR^{4}CR^{6}R^{7}-$, $-OCR^{6}R^{7}-$, $-SCR^{6}R^{7}-$, $-S(O)CR^{6}R^{7}-$, $-S(O)_{2}CR^{6}R^{7}-$, $-C(O)NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)NR^{5}CR^{6}R^{7}-$, $-S(O)_{2}NR^{4}CR^{6}R^{7}-$, $-NR^{4}C(O)-$, $-S(O)_{2}NR^{4}-$ y $-NR^{4}S(O)_{2}-$;

R^{1} es un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^{9}, $-OR^{9}$, $-COR^{9}$, $-CONR^{9}R^{10}$, $-NR^{9}R^{10}$ y $-NR^{9}COR^{10}$;

o **X–R^{1}** es $-C(CH_{3})_{2}OH$ o $-CH_{2}OH$;

R^{2} es seleccionado de aril y heteroaril estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente

seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

cada R^3, cuando está presente, es metil;

R^4 y R^5 son independientemente hidrógeno o C_{1-6}alquil;

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ o $-NR^4S(O)_2-$, R^1 y R^4 junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4, 5, 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil,

(C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos;

m es 0, 1 ó 2;

$^{1}\mathbf{Y}$ y $\mathbf{Y^{2}}$ son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

$\mathbf{R^1}$ es un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X**–$\mathbf{R^1}$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R^2}$ es seleccionado de aril y heteroaril estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

cada $\mathbf{R^3}$, cuando está presente, es metil;

R^4 y R^5 son independientemente hidrógeno o C_{1-6}alquil;

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ o $-NR^4S(O)_2-$, R^1 y R^4 junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4, 5, 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil,

bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos;

m es 0, 1 ó 2;

$^{1}\mathbf{Y}$ y $\mathbf{Y}^{2}$ son independientemente N o CR^{8} siempre que uno de ^{1}Y y Y^{2} es N y el otro es CR^{8};

X es un grupo de enlace seleccionado de $-NR^{4}CH_{2}-$, $-OCH_{2}-$, $-OCH(CH_{3})-$, $-OC(CH_{3})_{2}-$, $-SCH_{2}-$, $-SCH(CH_{3})-$, $-SC(CH_{3})_{2}-$, $-S(O)CH_{2}-$, $-S(O)CH(CH_{3})-$, $-S(O)C(CH_{3})_{2}-$, $-S(O)_{2}CH_{2}-$, $-S(O)_{2}CH(CH_{3})-$, $-S(O)_{2}C(CH_{3})_{2}-$, $-C(O)NR^{4}-$ y $-NR^{4}C(O)-$;

$\mathbf{R}^{1}$ es un grupo seleccionado de adamantil, metil, etil, propil, butil, isobutil, tert–butil, ciclopentil, ciclohexil, fenil, bencil, fenetil, pirrolidinil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, pirazinil, pirrolidinilmetil, pirrolidiniletil, pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, tieniletil, piridinilmetil, piridiniletil, pirimidinilmetil, pirimidiniletil, pirazinilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, R^{9}, $-OR^{9}$, $-COR^{9}$, $-CONR^{9}R^{10}$, $-NR^{9}R^{10}$ y $-NR^{9}COR^{10}$;

o $\mathbf{X}-\mathbf{R}^{1}$ es $-C(CH_{3})_{2}OH$ o $-CH_{2}OH$;

$\mathbf{R}^{2}$ es seleccionado de aril y heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

cada $\mathbf{R}^{3}$, cuando está presente, es metil;

$\mathbf{R^4}$ es hidrógeno o C_{1-6}alquil;

o, cuando **X** es $-NR^4CH_2-$ o $-NR^4C(O)-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 5 ó 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otra clase particular del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0 ó 1;

$^{1}\mathbf{Y}$ es CH y $\mathbf{Y}^{2}$ es N;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

$\mathbf{R}^{1}$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-\mathbf{XR}^{1}$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R}^{2}$ es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R}^{3}$, cuando está presente, es metil;

$\mathbf{R}^{11}$, $\mathbf{R}^{12}$ y $\mathbf{R}^{18}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otra clase particular del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0 ó 1;

^{1}**Y** es CH y $\mathbf{Y^2}$ es N;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

$\mathbf{R^1}$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirazoliletil, furanilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-\mathbf{XR^1}$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R^2}$ es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R^3}$, cuando está presente, es metil;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o

más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 1;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y $\mathbf{Y}^2$ es N.

$\mathbf{R}^1$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

$\mathbf{R}^2$ es fenil o piridil sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

$\mathbf{R}^3$ es metil; y

$\mathbf{R}^{19}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 1;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirazoliletil, furanilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

$\mathbf{R^2}$ es fenil o piridil sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

$\mathbf{R^3}$ es metil; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 1;

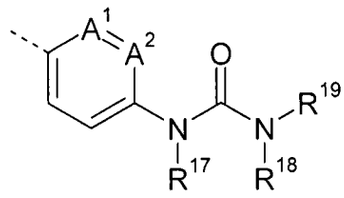
X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo seleccionado de metil, etil, isopropil, tert–butil, ciclopropil, ciclopentil, ciclohexil, $-CH_2CH_2OH$, $-CH_2CH_2OMe$, $-CH_2CH_2NMe_2$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, fenil, 3,5–difluorofenil, 4–fluorofenil, 2–clorofenil, 4–clorofenil, 2–

trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, oxetan–3–il, 2–oxopirolidin–3–il, 1–metilimidazol–5–ilmetil , 1–metilpirrolidin–3–il , tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il;

R^2 es



donde **A**^{1} y **A**^{2} son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno;

R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, –CH_2(ciclopropil), –$CH_2CH_2NMe_2$, –$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, –CH_2CH_2OH, –$CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, –CH_2(imidazol–2–il), –CH_2(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, –CH_2(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, piridinil–2–il, pirimidin–2–il, y 1H–pirazol–3–il;

y, **R**^{3} es metil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

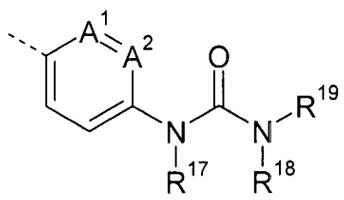
m es 1;

X es un grupo de enlace seleccionado de –$S(O)_2CH_2$–, –$S(O)_2CH(CH_3)$– y –$S(O)_2C(CH_3)_2$–;

^{1}**Y** es CH y **Y**^{2} es N.

R^1 es un grupo seleccionado de metil, isopropil, ciclopropil, ciclohexil, –CH_2CH_2OH, –$CH_2CH_2NC(O)CH_3$, –CH_2CONH_2, fenil, 4–fluorofenil, 2–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, 2–oxopirolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il;

R^2 es



donde **A**^{1} y **A**^{2} son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno;

R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, –CH_2(ciclopropil), –$CH_2CH_2NMe_2$, –$CH(CH_3)CH_2OH$, –$C(CH_3)_2CH_2OH$, –CH_2CH_2OH, –$CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, –CH_2(imidazol–2–il), –CH_2(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, –CH_2(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, pirimidin–2–il, y 1H–pirazol–3–il;

y, **R**^{3} es metil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

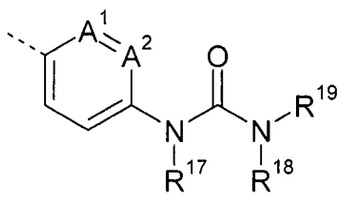
m es 1;

X es un grupo de enlace seleccionado de –$S(O)_2CH_2$–, –$S(O)_2CH(CH_3)$– y –$S(O)_2C(CH_3)_2$–;

^{1}**Y** es CH y **Y**^{2} es N.

R^1 es metil o ciclopropil;

R^2 es



donde **A**^{1} y **A**^{2} son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

$\mathbf{R}^{18}$ es hidrógeno;

$\mathbf{R}^{19}$ es metil, etil, propil, ciclopropil, ciclobutil, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ y 1H–pirazol–3–il;

y, $\mathbf{R}^3$ es metil.

En una clase particular adicional del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

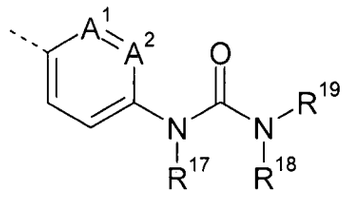
m es 1;

X es un grupo de enlace $-S(O)_2C(CH_3)_2-$;

$^1\mathbf{Y}$ es CH y $\mathbf{Y}^2$ es N.

$\mathbf{R}^1$ es etil, isopropil, tert–butil, 4–fluorofenil, piridin–4–il o ciclopropil;

$\mathbf{R}^2$ es



donde $\mathbf{A}^1$ y $\mathbf{A}^2$ son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

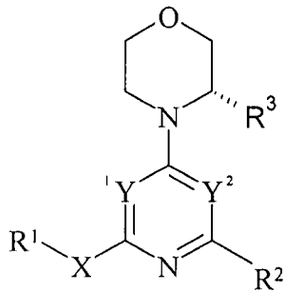
$\mathbf{R}^{17}$ es hidrógeno;

$\mathbf{R}^{18}$ es hidrógeno;

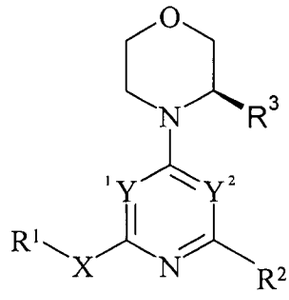
$\mathbf{R}^{19}$ es metil, etil, propil, ciclopropil, ciclobutil, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ y 1H–pirazol–3–il;

y, $\mathbf{R}^3$ es metil.

En un aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I) donde el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-S(O)_2NR^4CR^6R^7-$, $-NR^4C(O)-$, $-S(O)_2NR^4-$ y $-NR^4S(O)_2-$;

$\mathbf{R}^1$ es un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X**–$\mathbf{R}^1$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R}^2$ es seleccionado de aril y heteroaril estando dicho grupo sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R}^3$ es metil;

$\mathbf{R}^4$ y $\mathbf{R}^5$ son independientemente hidrógeno o C_{1-6}alquil;

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4C(O)-$ o $-NR^4S(O)_2-$, $\mathbf{R}^1$ y $\mathbf{R}^4$ junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4, 5, 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R}^6$ y $\mathbf{R}^7$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R}^8$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R}^9$ y $\mathbf{R}^{10}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-}

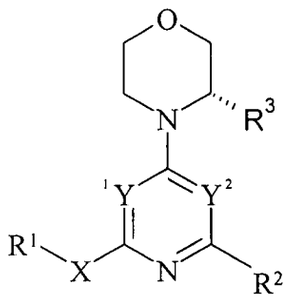
$_{6}$alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

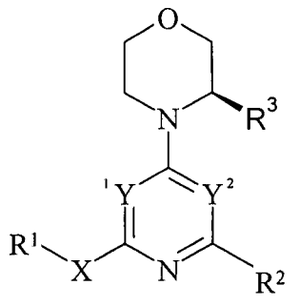
$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I) donde el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de –NR^{4}CR^{6}R^7–, –OCR^{6}R^7–, –SCR^{6}R^7–, –S(O)CR^{6}R^7–, –S(O)$_2$CR^{6}R^7–, –C(O)NR^{4}CR^{6}R^7–, –NR^{4}C(O)NR^{5}CR^{6}R^7–, –S(O)$_2$NR^{4}CR^{6}R^7–, –NR^{4}C(O)–, –S(O)$_2$NR^4– y –NR^{4}S(O)$_2$–;

R^1 es un grupo seleccionado de C$_{1-6}$alquil, carbociclil, carbociclilC$_{1-6}$alquil, heterociclil y heterociclilC$_{1-6}$alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, –OR^9, –COR^9, –CONR^{9}R^{10}, –NR^{9}R^{10} y –NR^{9}COR^{10};

o **X**–**R**^{1} es –C(CH$_3$)$_2$OH o –CH$_2$OH;

R^2 es seleccionado de aril y heteroaril estando dicho grupo sustituido por –NR^{17}CONR^{18}R^{19} y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, –R^{11}, –OR^{11}, –COR^{11}, –CONR^{11}R^{12}, –NR^{11}R^{12} y –NR^{11}COR^{12};

R^3 es metil;

R^4 y **R**^{5} son independientemente hidrógeno o C$_{1-6}$alquil;

o, cuando **X** es –NR^{4}CR^{6}R^7–, –NR^{4}C(O)NR^{5}CR^{6}R^7–, –NR^{4}C(O)– o –NR^{4}S(O)$_2$–, **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 4, 5, 6 ó 7 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C$_{1-6}$alquil, C$_{1-6}$alcoxi, haloC$_{1-6}$alquil, haloC$_{1-6}$alcoxi, hidroxiC$_{1-6}$alquil, hidroxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alquil, C$_{1-6}$alcoxiC$_{1-6}$alcoxi, amino, C$_{1-6}$alquilamino, bis(C$_{1-6}$alquil)amino, aminoC$_{1-6}$alquil, (C$_{1-6}$alquil)aminoC$_{1-6}$alquil, bis(C$_{1-6}$alquil)aminoC$_{1-6}$alquil, cianoC$_{1-6}$alquil, C$_{1-6}$alquilsulfonil, C$_{1-}$

$_{6}$alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R}^{6}$ y $\mathbf{R}^{7}$ son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

$\mathbf{R}^{8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R}^{9}$ y $\mathbf{R}^{10}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

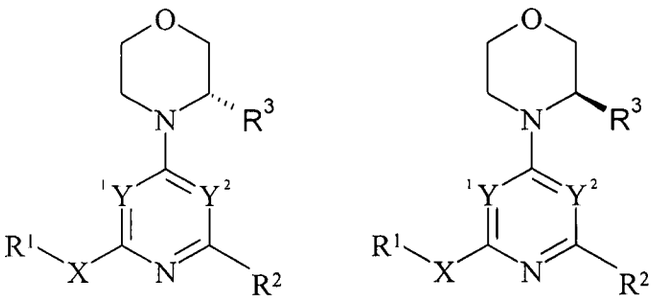
$\mathbf{R}^{11}$, $\mathbf{R}^{12}$, $\mathbf{R}^{17}$ y $\mathbf{R}^{18}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R}^{19}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil,

C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otro aspecto de la invención se proporciona un subconjunto de los compuestos de fórmula (I) donde el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia) (Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}**Y** y **Y**^{2} son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $-NR^4CH_2-$, $-OCH_2-$, $-OCH(CH_3)-$, $-OC(CH_3)_2-$, $-SCH_2-$, $-SCH(CH_3)-$, $-SC(CH_3)_2-$, $-S(O)CH_2-$, $-S(O)CH(CH_3)-$, $-S(O)C(CH_3)_2-$, $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$, $-S(O)_2C(CH_3)_2-$, $-C(O)NR^4-$ y $-NR^4C(O)-$;

R^1 es un grupo seleccionado de adamantil, metil, etil, propil, butil, isobutil, tert–butil, ciclopentil, ciclohexil, fenil, bencil, fenetil, pirrolidinil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, pirazinil, pirrolidinilmetil, pirrolidiniletil, pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, tieniletil, piridinilmetil, piridiniletil, pirimidinilmetil, pirimidiniletil, pirazinilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X**–**R**^{1} es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 es seleccionado de aril y heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $-NHCONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

R^3 es metil;

R^4 es hidrógeno o C_{1-6}alquil;

o, cuando **X** es $-NR^4CH_2-$ o $-NR^4C(O)-$, **R**^{1} y **R**^{4} junto con el átomo o átomos a los cuales están unidos forman un anillo heterocíclico de 5 ó 6 miembros donde 1 átomo de carbono del

anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

$\mathbf{R^8}$ es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino;

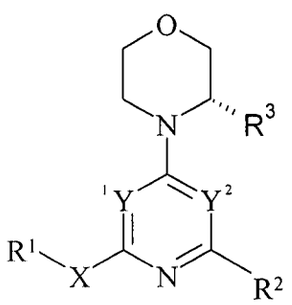
$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

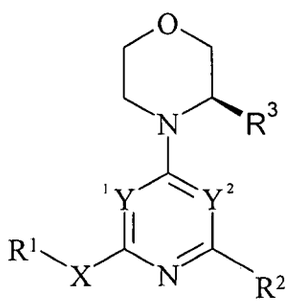
o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 6 miembros donde 1 átomo de carbono del anillo es opcionalmente reemplazado con N u O y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-}

$_{6}$alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otra clase particular del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib),



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}**Y** es CH y **Y**^{2} es N;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

R^{1} es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ y $.CONHCH_3$;

o **–XR**^{1} es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^{2} es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

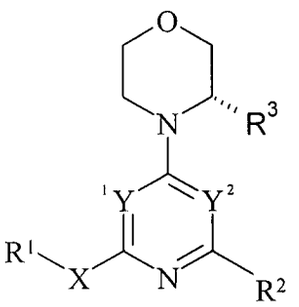
R^{3} es metil;

R^{11}, **R**^{12} y **R**^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos

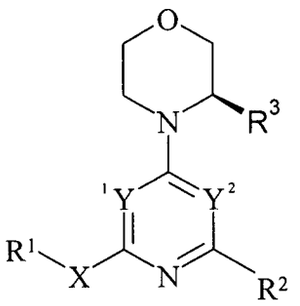
sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R}^{19}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En otra clase particular del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib),



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

$^1\mathbf{Y}$ es CH y $\mathbf{Y}^2$ es N;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

$\mathbf{R}^1$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirazoliletil, furanilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-\mathbf{XR}^1$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R}^2$ es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil y tiazolil estando dicho grupo sustituido por $-NHCONHR^{19}$ y opcionalmente

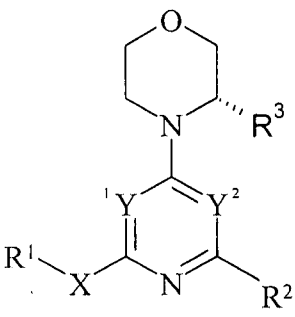
sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ es metil;

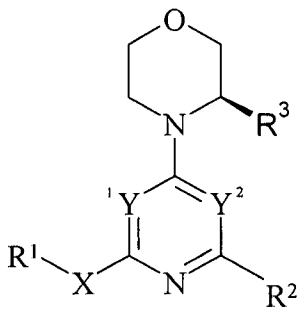
$\mathbf{R^{11}}$, $\mathbf{R^{12}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino y bis(C_{1-6}alquil)amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

$^1\mathbf{Y}$ es CH y $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando

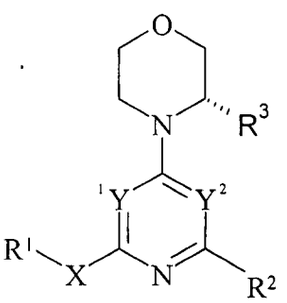
dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $-NMe_2$, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

$\mathbf{R^2}$ es fenil o piridil sustituido por $-NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

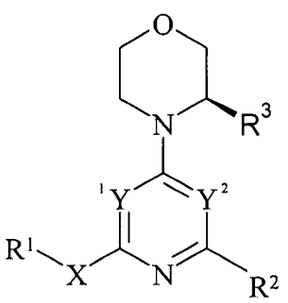
$\mathbf{R^3}$ es metil; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

$\mathbf{X}$ es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

$^{1}\mathbf{Y}$ es CH y $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo seleccionado de metil, etil, propil, butil, isobutil, tert–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirazoliletil, furanilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por

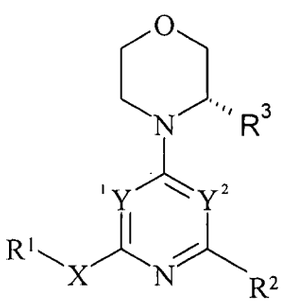
1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $–NHCOCH_3$, $–CONH_2$ y $–CONHCH_3$;

R^2 es fenil o piridil sustituido por $–NHCONHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $–CONH_2$, $–CONHCH_3$ y $–CON(CH_3)_2$;

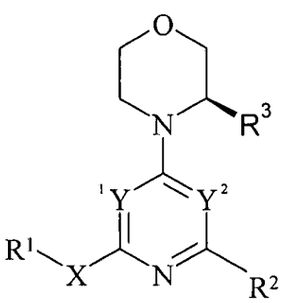
R^3 es metil; y

R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

m es 1;

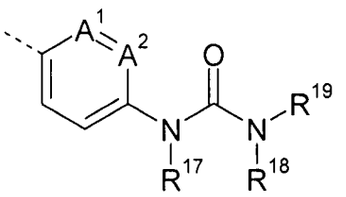
X es un grupo de enlace seleccionado de $–S(O)_2CH_2–$, $–S(O)_2CH(CH_3)–$ y $–S(O)_2C(CH_3)_2–$;

^1Y es CH y **Y^2** es N.

R^1 es un grupo seleccionado de metil, etil, isopropil, tert–butil, ciclopropil, ciclopentil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2OMe$, $–CH_2CH_2NMe_2$, $–CH_2CH_2NC(O)CH_3$, $–CH_2CONH_2$, fenil, 3,5–difluorofenil, 4–fluorofenil, 2–clorofenil, 4–clorofenil, 2–

trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, oxetan–3–il, 2–oxopirolidin–3–il, 1–metilimidazol–5–ilmetil, 1–metilpirrolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il;

$\mathbf{R^2}$ es



donde $\mathbf{A^1}$ y $\mathbf{A^2}$ son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

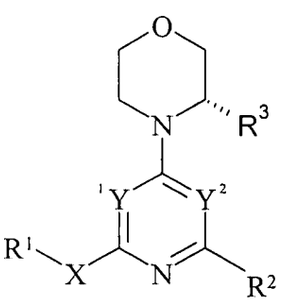
$\mathbf{R^{17}}$ es hidrógeno;

$\mathbf{R^{18}}$ es hidrógeno; y

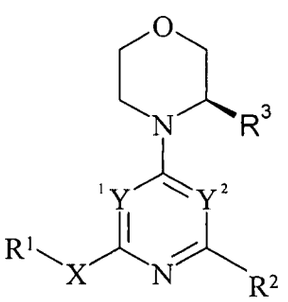
$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, $–CH_2$(ciclopropil), $–CH_2CH_2NMe_2$, $–CH(CH_3)CH_2OH$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2OH$, $–CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, $–CH_2$(imidazol–2–il), $–CH_2$(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, $–CH_2$(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, piridinil–2–il, pirimidin–2–il, y 1H–pirazol–3–il;

y, $\mathbf{R^3}$ es metil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

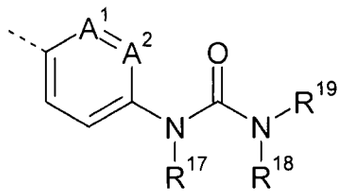
m es 1;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo seleccionado de metil, isopropil, ciclopropil, ciclohexil, $-CH_2CH_2OH$, $-CH_2CH_2NC(O)CH_3$, $-CH_2CONH_2$, fenil, 4–fluorofenil, 2–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, 2–oxopirolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il;

$\mathbf{R^2}$ es



donde $\mathbf{A^1}$ y $\mathbf{A^2}$ son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

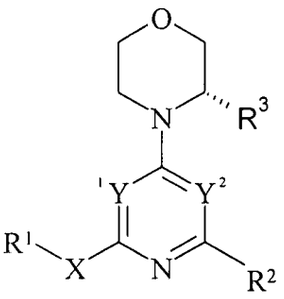
$\mathbf{R^{17}}$ es hidrógeno;

$\mathbf{R^{18}}$ es hidrógeno; y

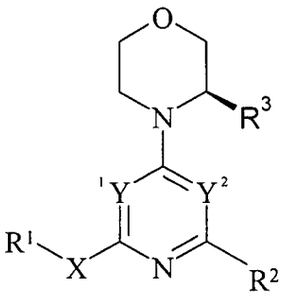
$\mathbf{R^{19}}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, $-CH_2$(ciclopropil), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, $-CH_2$(imidazol–2–il), $-CH_2$(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, $-CH_2$(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, pirimidin–2–il, y 1H–pirazol–3–il;

y, $\mathbf{R^3}$ es metil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

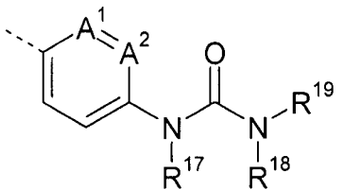
m es 1;

X es un grupo de enlace seleccionado de $-S(O)_2CH_2-$, $-S(O)_2CH(CH_3)-$ y $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y $\mathbf{Y}^2$ es N.

$\mathbf{R}^1$ es metil o ciclopropil;

$\mathbf{R}^2$ es



donde $\mathbf{A}^1$ y $\mathbf{A}^2$ son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

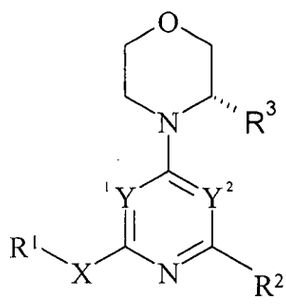
$\mathbf{R}^{17}$ es hidrógeno;

$\mathbf{R}^{18}$ es hidrógeno; y

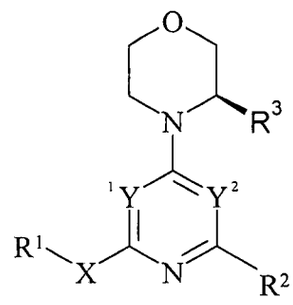
$\mathbf{R}^{19}$ es hidrógeno o un grupo seleccionado de metil, etil, propil, ciclopropil, ciclobutil, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ y 1H–pirazol–3–il;

y, $\mathbf{R}^3$ es metil.

En una clase particular adicional del compuesto de fórmula (I), el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

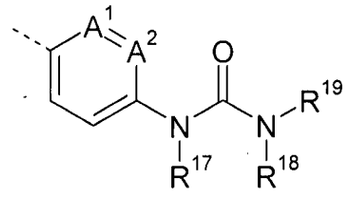
m es 1;

X es un grupo de enlace $-S(O)_2C(CH_3)_2-$;

^{1}**Y** es CH y **Y^2** es N.

R^1 es metil, etil, isopropil, tert–butil, 4–fluorofenil, piridin–4–il o ciclopropil;

R^2 es



donde **A^1** y **A^2** son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

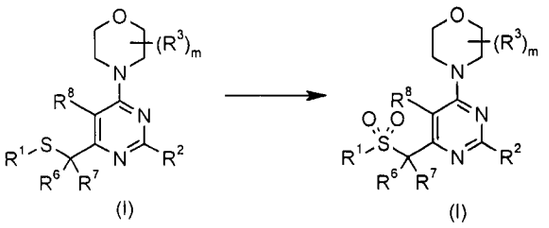
R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, ciclopropil, ciclobutil, $-CH_2CH_2OH$, $-CH_2CH_2NMe_2$, $-C(Me)_2CH_2OH$ y 1H–pirazol–3–il;

y, **R^3** es metil.

Otro aspecto de la invención proporciona un compuesto, o una combinación de compuestos, seleccionado de cualquiera de los Ejemplos o una sal farmacéuticamente aceptable del mismo.

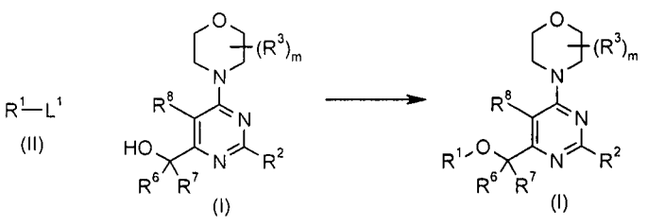
La invención también proporciona procesos para la preparación de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Un compuesto de fórmula (I), donde X = $-S(O)_2CR^6R^7-$, puede ser preparado oxidando un compuesto de fórmula (I), donde X = SCR^6R^7-, por ejemplo usando Oxone® a temperatura ambiente en un sistema solvente mezclado de agua y etanol.



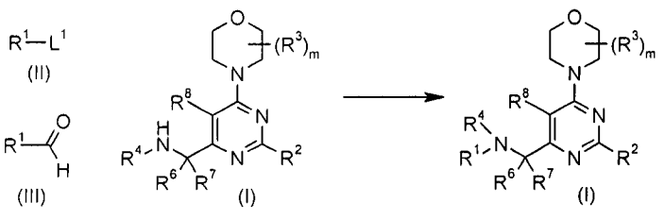
(I) (I)

Un compuesto de fórmula (I), donde $R^1X = R^1OCR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (I), donde $R^1X = HOCR^6R^7-$, con un compuesto de fórmula (II), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) opcionalmente en presencia de una base adecuada tal como trietilamina y un solvente tal como tetrahidrofurano o *N,N*–dimetilformamida.



(II) (I) (I)

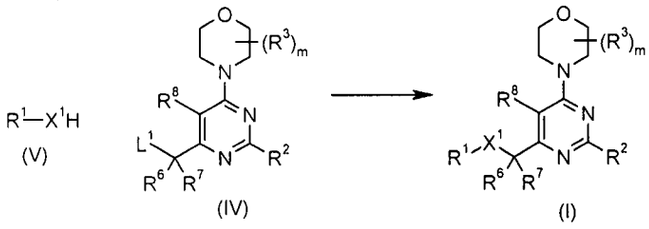
Un compuesto de fórmula (I), donde $R^1X = R^1R^4NCR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (I), donde $R^1X = HR^4NCR^6R^7-$, con un compuesto de fórmula (II), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) opcionalmente en presencia de una base adecuada tal como trietilamina y un solvente tal como tetrahidrofurano o *N,N*–dimetilformamida; o por la reacción de un compuesto de fórmula (I), donde $R^1X = HR^4NCR^6R^7-$, con un compuesto de fórmula (III) en presencia de un agente reductor adecuado tal como $NaCNBH_3$.



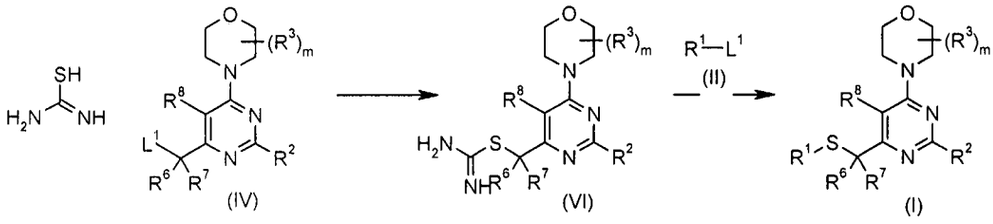
(II) (III) (I) (I)

Un compuesto de fórmula (I), donde $X^1 = -S(O)_2CR^6R^7-$, $-SCR^6R^7-$, $-OCR^6R^7-$, $-R^4NCR^6R^7-$, $-S(O)CR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (IV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), con un compuesto de

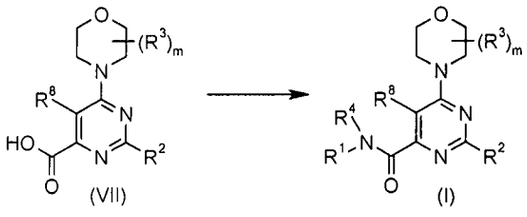
fórmula (V) opcionalmente en presencia de una base adecuada tal como trietilamina y un solvente tal como tetrahidrofurano o *N,N*–dimetilformamida.



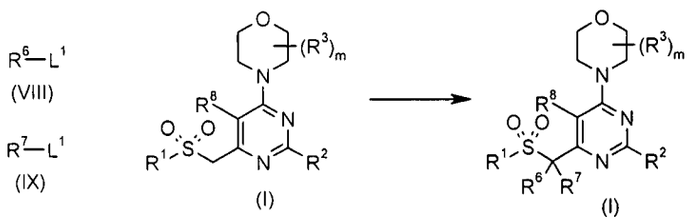
Un compuesto de fórmula (I), donde X = $-SCR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (IV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), con tiourea en un solvente adecuado tal como etanol para generar un compuesto de fórmula (VI) el cual es posteriormente reaccionado con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un solvente tal como *N,N*–dimetilformamida.



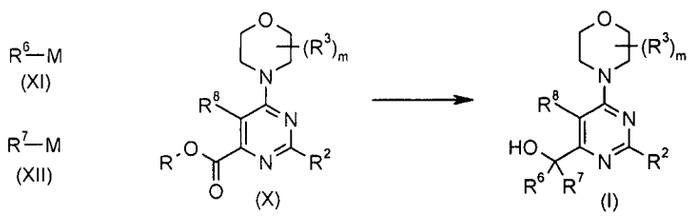
Un compuesto de fórmula (I), donde X = $-R^4NC(O)-$, puede ser preparado por la reacción de un compuesto de fórmula (VII) con una amina de fórmula R^1R^4NH seguido por la activación adecuada del ácido carboxílico por métodos conocidos en la literatura tales como el uso de un agente de acoplamiento tal como HATU o la conversión a un acil cloruro.



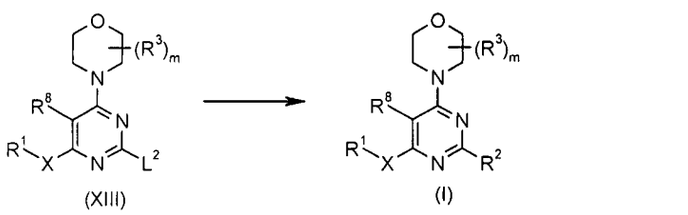
Un compuesto de fórmula (I), donde X = $-S(O)_2CR^6R^7-$, puede ser preparado por la reacción secuencial de un compuesto de fórmula (I), donde X = $-S(O)_2CH_2-$, con un compuesto de fórmula (VIII) seguido por la reacción con un compuesto de fórmula (IX), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), en presencia de una base adecuada tal como hidruro de sodio o *tert*–butóxido de potasio en un solvente adecuado tal como tetrahidrofurano o *N,N*–dimetilformamida.



Un compuesto de fórmula (I), donde $R^1X = HOCR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (X), con reactivos organometálicos adecuados de fórmula (XI) y fórmula (XII) tales como el reactivo de Grignard en un solvente adecuado. Cuando R^6 y R^7 son diferentes entonces puede ser posible usar técnicas conocidas en la literatura tales como la conversión de un compuesto de fórmula (X) a la amida Weinreb y la reacción con un reactivo organometálico de fórmula (XI) y luego la reacción con un reactivo organometálico de fórmula (XII) en un paso posterior.

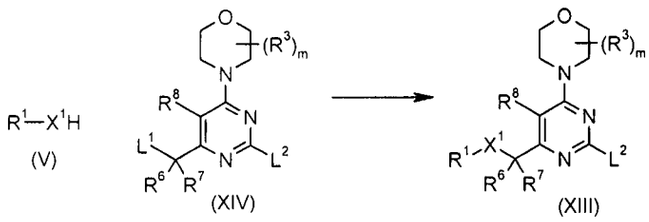


Un compuesto de fórmula (I) puede ser preparado a partir de un compuesto de fórmula (XIII), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(OR)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un solvente adecuado tal como 1,4–dioxano. Como alternativa cuando R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre un compuesto de fórmula (I) puede ser preparado a partir de un compuesto de fórmula (XIII), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), por la reacción con la amina, alcohol o tiol requeridos en presencia de una base adecuada tal como carbonato de potasio en un solvente adecuado tal como *N,N*–dimetilformamida.

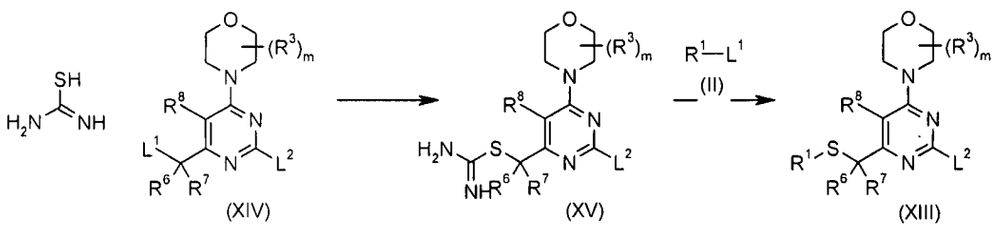


Será apreciado que un compuesto de fórmula (XIII) puede ser transformado en otro compuesto de fórmula (XIII) por técnicas tales como oxidación, alquilación, aminación reductiva, etc., enumeradas anteriormente o de otra forma conocida en la literatura.

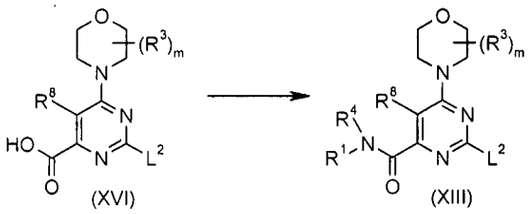
Un compuesto de fórmula (XIII), donde $X^1 = –S(O)_2CR^6R^7–$, $–SCR^6R^7–$, $–OCR^6R^7–$, $–R^4NCR^6R^7–$, $–S(O)CR^6R^7–$, puede ser preparado por la reacción de un compuesto de fórmula (XIV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), con un compuesto de fórmula (V) opcionalmente en presencia de una base adecuada tal como trietilamina y un solvente tal como tetrahidrofurano o *N,N*–dimetilformamida.



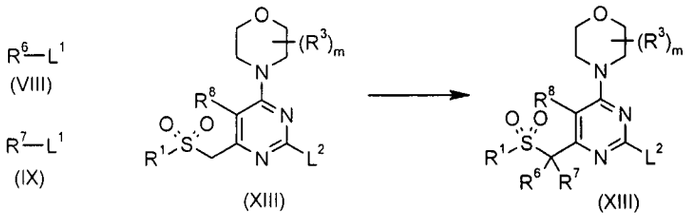
Un compuesto de fórmula (XIII), donde X = $–SCR^6R^7–$, puede ser preparado por la reacción de un compuesto de fórmula (XIV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), con tiourea en un solvente adecuado tal como etanol para generar un compuesto de fórmula (XV) el cual es posteriormente reaccionado con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un solvente tal como *N,N*–dimetilformamida.



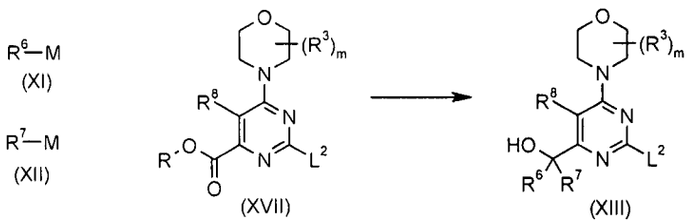
Un compuesto de fórmula (XIII), donde X = $–R^4NC(O)–$, puede ser preparado por la reacción de un compuesto de fórmula (XVI) con una amina de fórmula R^1R^4NH seguido por la activación adecuada del ácido carboxílico por métodos conocidos en la literatura tales como el uso de un agente de acoplamiento tal como HATU o la conversión a un acil cloruro.



Un compuesto de fórmula (XIII), donde X = $-S(O)_2CR^6R^7-$, puede ser preparado por la reacción secuencial de un compuesto de fórmula (XIII), donde X = $-S(O)_2CH_2-$, con un compuesto de fórmula (VIII) seguido por la reacción con un compuesto de fórmula (IX), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), en presencia de una base adecuada tal como hidruro de sodio o tert–butóxido de potasio en un solvente adecuado tal como tetrahidrofurano o *N,N*–dimetilformamida.

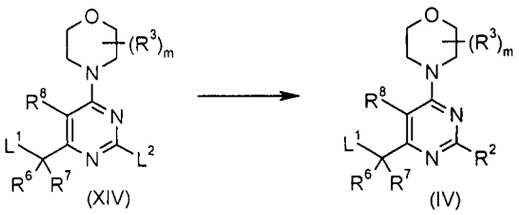


Un compuesto de fórmula (XIII), donde $R^1X = HOCR^6R^7-$, puede ser preparado por la reacción de un compuesto de fórmula (XVII), con un reactivo organometálico adecuado de fórmula (XI) y fórmula (XII) tal como el reactivo de Grignard en un solvente adecuado. Cuando R^6 y R^7 son diferentes entonces puede ser posible usar técnicas conocidas en la literatura tales como la conversión de un compuesto de fórmula (XVII) a la amida Weinreb y la reacción con un reactivo organometálico de fórmula (XI) y luego la reacción con un reactivo organometálico de fórmula (XII) en un paso posterior.



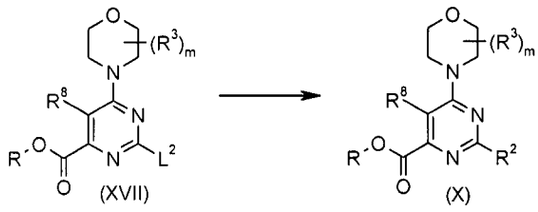
Un compuesto de fórmula (IV) puede ser preparado a partir de un compuesto de fórmula (XIV), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.) y L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(OR)_2$ etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un solvente adecuado tal como 1,4–dioxano. Como alternativa cuando R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre un compuesto de fórmula (IV) puede ser preparado a partir de un compuesto de fórmula (XIV), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), por la reacción con la

amina, alcohol o tiol requeridos en presencia de una base adecuada tal como carbonato de potasio en un solvente adecuado tal como *N,N*–dimetilformamida.



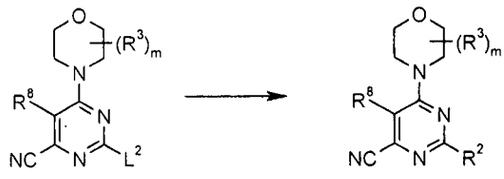
(XIV) (IV)

Un compuesto de fórmula (X) puede ser preparado a partir de un compuesto de fórmula (XVII), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.) y R es un hidrógeno o grupo C_{1-4} alquil, con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(OR)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un solvente adecuado tal como 1,4–dioxano. Como alternativa cuando R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre un compuesto de fórmula (X) puede ser preparado a partir de un compuesto de fórmula (XVII), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), por la reacción con la amina, alcohol o tiol requeridos en presencia de una base adecuada tal como carbonato de potasio en un solvente adecuado tal como *N,N*–dimetilformamida.



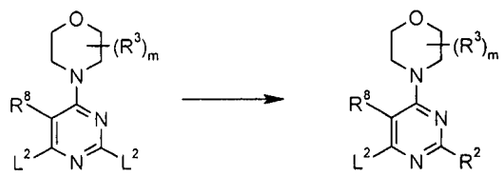
(XVII) (X)

Un compuesto de fórmula (XVIII) puede ser preparado a partir de un compuesto de fórmula (XIX), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(OR)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un solvente adecuado tal como 1,4–dioxano. Como alternativa cuando R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre un compuesto de fórmula (XVIII) puede ser preparado a partir de un compuesto de fórmula (XIX), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), por la reacción con la amina, alcohol o tiol requeridos en presencia de una base adecuada tal como carbonato de potasio en un solvente adecuado tal como *N,N*–dimetilformamida.



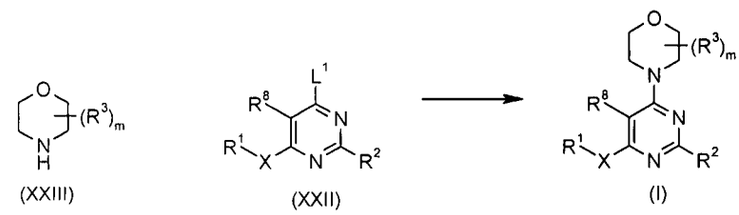
(XIX) (XVIII)

Un compuesto de fórmula (XX) puede ser preparado a partir de un compuesto de fórmula (XXI), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(OR)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un solvente adecuado tal como 1,4–dioxano. Como alternativa cuando R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre un compuesto de fórmula (XX) puede ser preparado a partir de un compuesto de fórmula (XXI), donde L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.), por la reacción con la amina, alcohol o tiol requeridos en presencia de una base adecuada tal como carbonato de potasio en un solvente adecuado tal como *N,N*–dimetilformamida.



(XXI) (XX)

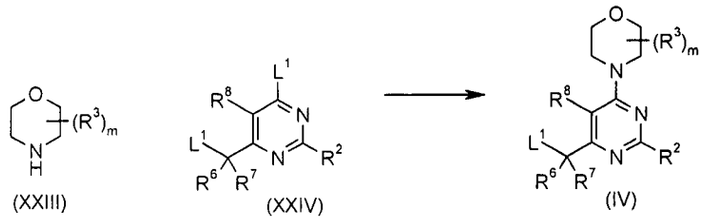
Un compuesto de fórmula (I), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXII) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



(XXIII) (XXII) (I)

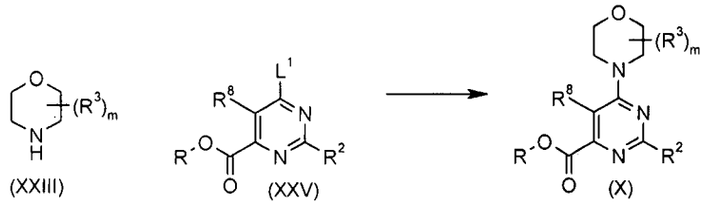
Será apreciado que un compuesto de fórmula (XXII) puede ser transformado en otro compuesto de fórmula (XXII) por técnicas tales como oxidación, alquilación, aminación reductiva, etc., enumeradas anteriormente o de otra forma conocida en la literatura.

Un compuesto de fórmula (IV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXIV) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



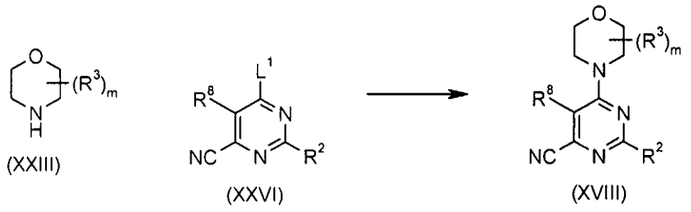
(XXIII) (XXIV) (IV)

Un compuesto de fórmula (X), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y R es un hidrógeno o un grupo C_{1-4} alquil, puede ser preparado por la reacción de un compuesto de fórmula (XXV) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



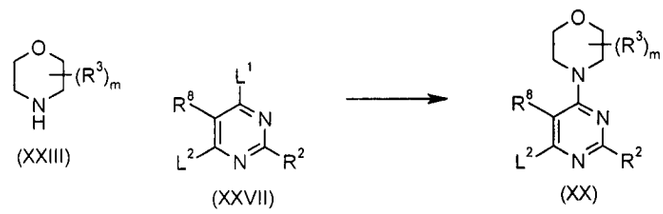
(XXIII) (XXV) (X)

Un compuesto de fórmula (XVIII), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXVI) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



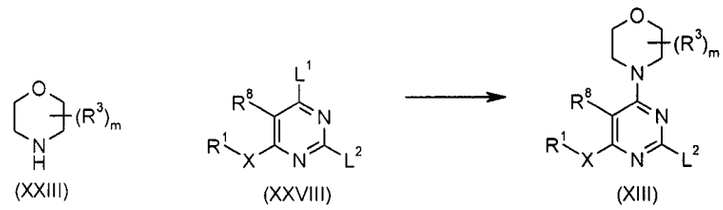
(XXIII) (XXVI) (XVIII)

Un compuesto de fórmula (XX), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXVII) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



(XXIII) (XXVII) (XX)

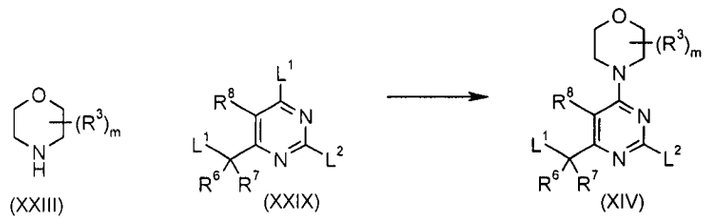
Un compuesto de fórmula (XIII), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXVIII) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



(XXIII) (XXVIII) (XIII)

Será apreciado que un compuesto de fórmula (XIII) puede ser transformado en otro compuesto de fórmula (XIII) por técnicas tales como oxidación, alquilación, aminación reductiva, etc., enumeradas anteriormente o de otra forma conocida en la literatura.

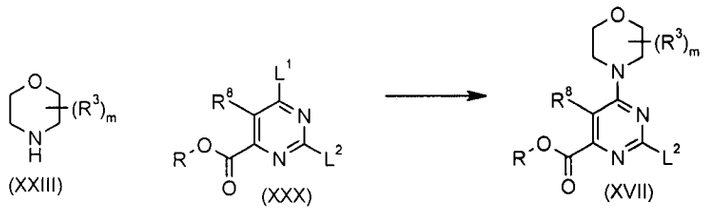
Un compuesto de fórmula (XIV), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXIX) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



(XXIII) (XXIX) (XIV)

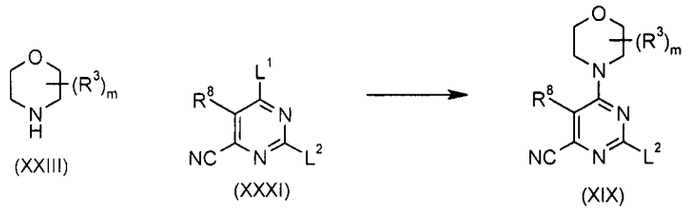
Un compuesto de fórmula (XVII), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $–S(O)_2Me$, etc.) y R es un hidrógeno o un grupo C_{1-4} alquil, puede ser preparado por la reacción de un compuesto de fórmula (XXX) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una

base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



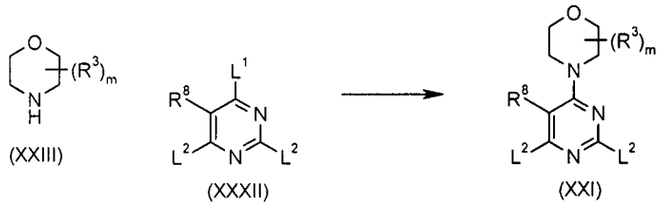
(XXIII) (XXX) (XVII)

Un compuesto de fórmula (XIX), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXXI) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



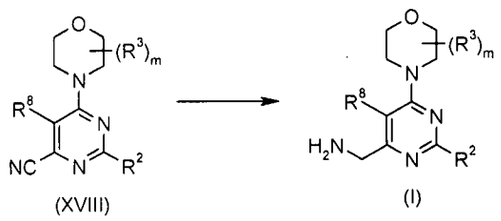
(XXIII) (XXXI) (XIX)

Un compuesto de fórmula (XXI), donde L^1 es un grupo de salida (tal como halo, tosil, mesil, etc.) y L^2 es un grupo de salida (tal como halo, tosil, mesil, –SMe, $-S(O)_2Me$, etc.), puede ser preparado por la reacción de un compuesto de fórmula (XXXII) con un compuesto de fórmula (XXIII) opcionalmente en presencia de una base adecuada tal como trietilamina en un solvente adecuado tal como *N,N*–dimetilformamida.



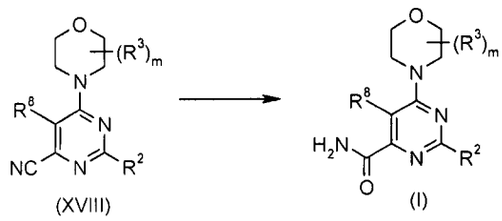
(XXIII) (XXXII) (XXI)

Un compuesto de fórmula (I), donde $R^1X = H_2NCH_2-$, puede ser preparado a partir de un compuesto de fórmula (XVIII) por una reducción tal como hidrogenación con gas hidrógeno y un catalizador adecuado tal como paladio sobre carbono en un solvente adecuado tal como etanol.



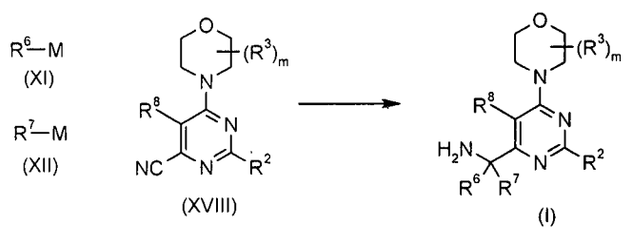
(XVIII) (I)

Un compuesto de fórmula (I), donde $R^1X = H_2NC(O)–$, puede ser preparado a partir de un compuesto de fórmula (XVIII) por hidrólisis con, por ejemplo, hidróxido de sodio en un solvente adecuado tal como una mezcla de agua y etanol.



(XVIII) (I)

Un compuesto de fórmula (I), donde $R^1X = H_2NCR^6R^7–$, puede ser preparado a partir de un compuesto de fórmula (XVIII) por la reacción con reactivos organometálicos (XI) y (XII).

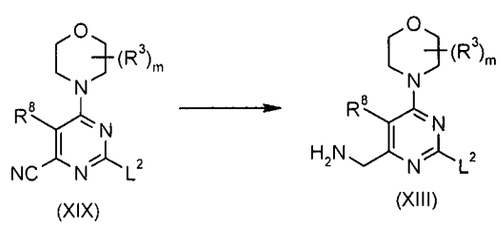


(XI)

(XII)

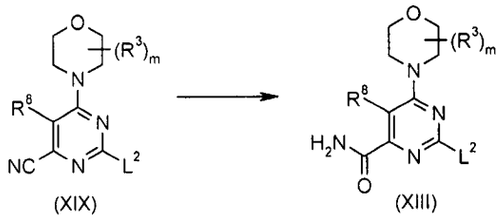
(XVIII) (I)

Un compuesto de fórmula (XIII), donde $R^1X = H_2NCH_2–$, puede ser preparado a partir de un compuesto de fórmula (XIX) por una reducción tal como hidrogenación con gas hidrógeno y un catalizador adecuado tal como paladio sobre carbono en un solvente adecuado tal como etanol.



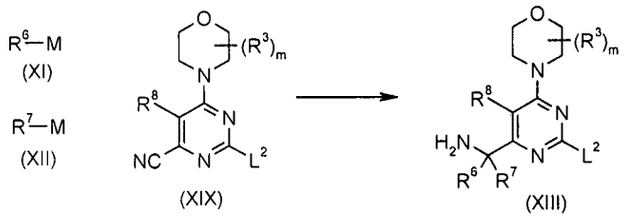
(XIX) (XIII)

Un compuesto de fórmula (XIII), donde $R^1X = H_2NC(O)–$, puede ser preparado a partir de un compuesto de fórmula (XIX) por hidrólisis con, por ejemplo, hidróxido de sodio en un solvente adecuado tal como una mezcla de agua y etanol.



(XIX) (XIII)

Un compuesto de fórmula (XIII), donde $R^1X = H_2NCR^6R^7-$, puede ser preparado a partir de un compuesto de fórmula (XIX) por la reacción con reactivos organometálicos (XI) y (XII).



(XIX) (XIII)

Será apreciado que el grupo R^2 puede ser introducido inicialmente en cualquier etapa como una amina carbocíclica o heterocíclica (opcionalmente con el nitrógeno protegido, tales grupos de protección incluyen pero no están limitados a nitro, *tert*–butoxi carbamato, etc.) la que puede ser transformada en una etapa posterior en la síntesis (después de una desprotección apropiada) en una urea por la reacción directa con un isocianato (o un grupo de otra manera activado tal como un fenoxi carbamato, etc.) o por la activación de la amina (tal como con fosgeno o la formación de un fenoxi carbamato, etc.) y la reacción posterior con una amina apropiada, u otros métodos de formación de una urea conocidos en la literatura.

Será apreciado que algunos de los varios sustituyentes del anillo en los compuestos de la presente invención pueden ser introducidos por reacciones de sustitución aromáticas estándares o generados por modificaciones del grupo funcionales convencionales antes de o inmediatamente a continuación de los procesos mencionados anteriormente, y como tal son incluidos en el aspecto de procesos de la invención. Por ejemplo los compuestos de fórmula (I) pueden ser convertidos en compuestos adicionales de fórmula (I) por reacciones de sustitución aromáticas estándares o por modificaciones del grupo funcionales convencionales. Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reacción de sustitución aromática, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes. Los reactivos y las condiciones de reacción de tales procedimientos son bien conocidos en el arte de la química. Ejemplos particulares de reacciones de sustitución aromáticas incluyen la introducción de un grupo nitro usando ácido

nítrico concentrado, la introducción de un grupo acil usando, por ejemplo, un acil haluro y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquil usando un alquil haluro y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro a un grupo amino mediante, por ejemplo, hidrogenación catalítica con un catalizador de níquel o tratamiento con hierro en presencia de ácido clorhídrico con calentamiento; oxidación de alquiltio a alquilsulfinil o alquilsulfonil.

Será también apreciado que en algunas de las reacciones mencionadas aquí puede ser necesario/deseable proteger cualquier grupo sensible en los compuestos. Los casos en los que la protección es necesaria o deseable y métodos adecuados para la protección son conocidos por aquellos versados en el arte. Los grupos de protección convencionales pueden ser usados de acuerdo con la práctica estándar (para ejemplos véase T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). De esta forma, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aquí.

Un grupo de protección adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acil, por ejemplo un grupo alcanoil tal como acetil, un grupo alcoxicarbonil, por ejemplo un grupo metoxicarbonil, etoxicarbonil o *tert*–butoxicarbonil, un grupo arilmetoxicarbonil, por ejemplo benciloxicarbonil, o un grupo aroil, por ejemplo benzoil. Las condiciones de desprotección para los grupos de protección anteriores necesariamente varían con la elección del grupo de protección. De esta forma, por ejemplo, un grupo acil tal como un grupo alcanoil o alcoxicarbonil o un grupo aroil puede ser eliminado por ejemplo, por hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo litio o hidróxido de sodio. Como alternativa, un grupo acil tal como un grupo *tert*–butoxicarbonil puede ser eliminado, por ejemplo, por tratamiento con un ácido adecuado como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonil tal como un grupo benciloxicarbonil puede ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono, o por tratamiento con un ácido de Lewis por ejemplo boro tris(trifluoroacetato). Un grupo de protección alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloil el cual puede ser eliminado por tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina, o con hidrazina.

Un grupo de protección adecuado para un grupo hidroxi es, por ejemplo, un grupo acil, por ejemplo un grupo alcanoil tal como acetil, un grupo aroil, por ejemplo benzoil, o un grupo arilmetil, por ejemplo bencil. Las condiciones de desprotección para los grupos de protección anteriores necesariamente variarán con la elección del grupo de protección. De esta forma, por ejemplo, un grupo acil tal como un grupo alcanoil o aroil puede ser eliminado, por ejemplo, por hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo litio o hidróxido de sodio. Como alternativa, un grupo arilmetil tal como un grupo bencil puede ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono.

Un grupo de protección adecuado para un grupo carboxi es, por ejemplo, un grupo de esterificación, por ejemplo un grupo metil o etil el cual puede ser eliminado, por ejemplo, por hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *tert*–butil el cual puede ser eliminado, por ejemplo, por tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencil el cual puede ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono.

Los grupos de protección pueden ser eliminados en cualquier etapa conveniente en la síntesis usando técnicas convencionales bien conocidas en el arte de la química.

Muchos de los productos intermedios definidos aquí son nuevos y son proporcionados como una característica adicional de la invención.

Ensayos biológicos

Los siguientes ensayos pueden ser usados para medir los efectos de los compuestos de la presente invención como inhibidores de la quinasa mTOR, como inhibidores de la quinasa PI3, como inhibidores *in vitro* de la activación de las vías de señalización de la quinasa PI3 y como inhibidores *in vitro* de la proliferación de células humanas de adenocarcinoma de mama MDA–MB–468.

(a) Ensayo de la quinasa mTOR *in vitro*

El ensayo usó la tecnología AlphaScreen (Gray y otros, Analytical Biochemistry, 2003, 313: 234–245) para determinar la capacidad de los compuestos de prueba para inhibir la fosforilación por mTOR recombinante.

Un truncamiento *C*-terminal de mTOR que abarca los residuos aminoácido 1362 al 2549 de mTOR (EMBL Acceso No. L34075) fue establemente expresado como una fusión etiquetada FLAG en células HEK293 como es descrito por Vilella-Bach y otros, Journal of Biochemistry, 1999, 274, 4266-4272. La línea celular estable HEK293 (1362-2549) de mTOR etiquetada FLAG fue rutinariamente mantenida a 37°C con 5% CO_2 hasta una confluencia de 70-90% en medio de crecimiento Eagle modificado de Dulbecco (DMEM; Invitrogen Limited, Paisley, Reino Unido, Catálogo No. 41966-029) conteniendo 10% suero fetal de ternero inactivado por calor (FCS; Sigma, Poole, Dorset, Reino Unido Catálogo, No. F0392), 1% L-glutamina (Gibco, Catálogo No. 25030-024) y 2 mg/ml Geneticina (G418 sulfato; Invitrogen Limited, Reino Unido, Catálogo No. 10131-027). A continuación de la expresión en la línea celular HEK293 de mamífero, la proteína expresada fue purificada usando la etiqueta del epítopo FLAG usando técnicas de purificación estándares.

Los compuestos de prueba fueron preparados como 10 mM de soluciones madre en DMSO y diluidos en agua como se requirió para dar un rango de concentraciones finales del ensayo. Alícuotas (2 µl) de cada dilución del compuesto fueron colocadas en un pocillo de una placa Greiner de poliestireno blanco de bajo volumen (LV) de 384 pocillos (Greiner Bio-one). 30 µl de una mezcla de la enzima mTOR purificada recombinante, 1 µM de sustrato peptídico biotinilado (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 Reino Unido Ltd), ATP (20 µM) y una solución tampón [que comprende tampón 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)] fue agitada a temperatura ambiente durante 90 minutos.

Los pocillos control que produjeron una señal máxima correspondiente a la máxima actividad de la enzima fueron creados usando 5% DMSO en lugar del compuesto de prueba. Los pocillos control que produjeron una señal mínima correspondiente a la enzima completamente inhibida fueron creados añadiendo EDTA (83 mM) en lugar del compuesto de prueba. Estas soluciones de ensayo fueron incubadas durante 2 horas a temperatura ambiente.

Cada reacción fue detenida por la adición de 10 µl de una mezcla de EDTA (50 mM), albúmina de suero bovino (BSA; 0.5 mg/mL) y tampón Tris-HCl pH7.4 (50 mM) conteniendo Anticuerpo Monoclonal 1A5 p70 S6 Quinasa (T389) (Cell Signalling Technology, Catálogo No. 9206B) y perlas donantes de Estreptavidina de AlphaScreen y aceptoras de Proteína A (200 ng; Perkin Elmer, Catálogo No. 6760002B y 6760137R

respectivamente) fueron añadidas y las placas de ensayo fueron dejadas durante alrededor de 20 horas a temperatura ambiente en la oscuridad. Las señales resultantes que se derivan de la excitación con luz láser a 680 nm fueron leídas usando un instrumento Packard Envision.

El péptido biotinilado fosforilado es formado *in situ* como resultado de la fosforilación mediada por la mTOR. El péptido biotinilado fosforilado que está asociado con las perlas donantes de Estreptavidina de AlphaScreen forma un complejo con el Anticuerpo Monoclonal 1A5 p70 S6 Quinasa (T389) que está asociado con las perlas aceptoras de Proteína A de AlphaScreen. Tras la excitación con luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede ser medida. Por consiguiente, la presencia de la actividad de la quinasa mTOR resulta en una señal del ensayo. En presencia de un inhibidor de la quinasa mTOR, la intensidad de la señal es reducida.

La inhibición de la enzima mTOR para un compuesto de prueba dado fue expresada como un valor IC_{50}.

(b) Ensayo de la enzima PI3K *in vitro*

El ensayo usó la tecnología AlphaScreen (Gray y otros, Analytical Biochemistry, 2003, 313: 234–245) para determinar la capacidad de los compuestos de prueba para inhibir la fosforilación por las enzimas PI3K recombinantes Tipo I del lípido PI(4,5)P2.

Los fragmentos de ADN que codifican las subunidades regulatorias y catalíticas de la PI3K humana fueron aislados a partir de librerías de ADNc usando técnicas de clonación por PCR y de biología molecular estándares. Los fragmentos de ADN seleccionados fueron usados para generar vectores de expresión de baculovirus. En particular, el ADN de longitud completa de cada una de las isoformas p110 de la PI3K humana de Tipo Ia, p110α, p110β y p110δ (EMBL Nos. de Acceso. HSU79143, S67334, Y10055 para p110α, p110β y p110δ respectivamente) fue subclonado en un vector pDEST10 (Invitrogen Limited, Fountain Drive, Paisley, Reino Unido). El vector es una versión adaptada de Gateway de Fastbac1 que contiene una etiqueta del epítopo 6–His. Una forma truncada de la isoforma p110γ de la PI3K humana de Tipo Ib que corresponde a los residuos de aminoácido 144–1102 (EMBL No. de Acceso. X8336A) y la subunidad regulatoria de p85α humana de longitud completa (EMBL No. de Acceso. HSP13KIN) fueron también subclonadas en el vector pFastBac1 que contiene una etiqueta del epítopo 6–His. Los constructos p110 de Tipo Ia fueron coexpresados con la subunidad regulatoria p85α. A continuación de la expresión en el sistema de baculovirus

usando técnicas de expresión de baculovirus estándares, las proteínas expresadas fueron purificadas usando la etiqueta del epítopo His usando técnicas de purificación estándares.

El ADN correspondiente a los aminoácidos 263 al 380 del receptor humano general para el dominio PH de fosfoinosítidos (Grp1) fue aislado de una librería de ADNc usando técnicas de clonación por PCR y de biología molecular estándares. El fragmento de ADN resultante fue subclonado en un vector de expresión pGEX 4T1 de *E. coli* conteniendo una etiqueta del epítopo GST (Amersham Pharmacia Biotech, Rainham, Essex, Reino Unido) como es descrito por Gray y otros, Analytical Biochemistry, 2003, 313: 234–245). El dominio PH Grp1 etiquetado GST fue expresado y purificado usando técnicas estándares.

Los compuestos de prueba fueron preparados como 10 mM de soluciones madre en DMSO y diluidos en agua como se requirió para dar un rango de concentraciones finales del ensayo. Alícuotas (2 µl) de cada dilución del compuesto fueron colocadas en un pocillo de una placa Greiner de poliestireno blanco de bajo volumen (LV) de 384 pocillos (Greiner Bio–one, Brunel Way, Stonehouse, Gloucestershire, Reino Unido, Catálogo No. 784075). Una mezcla de cada enzima PI3K purificada recombinante seleccionada (15 ng), sustrato DiC8–PI(4,5)P2 (40 µM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catálogo No. 901), adenosina trifosfato (ATP; 4 µM) y una solución tampón [que comprende tampón Tris–HCl pH7.6 (40 mM, 10 µl), 3–[(3–colamidopropil)dimetilamonio]–1–propanosulfonato (CHAPS; 0.04%), ditiotreitol (DTT; 2 mM) y cloruro de magnesio (10 mM)] fue agitada a temperatura ambiente durante 20 minutos.

Los pocillos control que produjeron una señal mínima correspondiente a la máxima actividad de la enzima fueron creados usando 5% DMSO en lugar del compuesto de prueba. Los pocillos control que produjeron una señal máxima correspondiente a la enzima completamente inhibida fueron creados añadiendo wortmanina (6 µM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, Reino Unido, Catálogo No. 681675) en lugar del compuesto de prueba. Estas soluciones de ensayo fueron también agitadas durante 20 minutos a temperatura ambiente.

Cada reacción fue detenida por la adición de 10 µl de una mezcla de EDTA (100 mM), albúmina de suero bovino (BSA, 0.045 %) y tampón Tris–HCl pH7.6 (40 mM).

DiC8–PI(3,4,5)P3 biotinilada (50 nM; Cell Signals Inc., Catálogo No. 107), proteína PH GST–Grp1 purificada recombinante (2.5 nM) y perlas donantes y aceptoras Anti–GST de

AlphaScreen (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, Reino Unido, Catálogo No. 6760603M) fueron añadidas y las placas de ensayo fueron dejadas durante alrededor de 5 a 20 horas a temperatura ambiente en la oscuridad. Las señales resultantes que se derivan de la excitación con luz láser a 680 nm fueron leídas usando un instrumento Packard AlphaQuest.

PI(3,4,5)P3 es formada *in situ* como resultado de la fosforilación de PI(4,5)P2 mediada por PI3K. La proteína del dominio PH GST–Grp1 que está asociada con las perlas donantes Anti–GST de AlphaScreen forma un complejo con la PI(3,4,5)P3 biotinilada que está asociada con las perlas aceptoras de Estreptavidina de AlphaScreen. La PI(3,4,5)P3 enzimáticamente producida compite con la PI(3,4,5)P3 biotinilada para unirse a la proteína del dominio PH. Tras la excitación con luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede ser medida. Por consiguiente, la actividad de la enzima PI3K para formar la PI(3,4,5)P3 y la posterior competencia con la PI(3,4,5)P3 biotinilada resulta en una señal reducida. En presencia de un inhibidor de la enzima PI3K, la intensidad de la señal es recuperada.

La inhibición de la enzima PI3K para un compuesto de prueba dado fue expresada como un valor IC_{50}.

(c) Ensayo Akt de fosfo–Ser473 *in vitro*

Esto ensayo determina la capacidad de los compuestos de prueba para inhibir la fosforilación de Serina 473 en Akt como se evaluó usando la tecnología Acumen Explorer (Acumen Bioscience Limited), un lector de placa que puede ser usado para rápidamente cuantificar características de imágenes generadas por la exploración láser.

Una línea celular de adenocarcinoma de mama humana MDA–MB–468 (LGC Promochem, Teddington, Middlesex, Reino Unido, Catálogo No. HTB–132) fue rutinariamente mantenida a 37°C con 5% CO_2 hasta una confluencia de 70–90% en DMEM conteniendo 10% de FCS inactivadas por calor y 1% L–glutamina.

Para el ensayo, las células fueron separadas del frasco de cultivo usando 'Accutase' (Innovative Cell Technologies Inc., San Diego, CA, USA; Catálogo No. AT104) usando métodos de cultivo de tejidos estándares y resuspendidas en medios para dar $1.7x10^5$ células por mL. Alícuotas (90 µl) fueron sembradas en cada uno de los 60 pocillos internos de una placa de 96 pocillos Packard negra (PerkinElmer, Boston, MA, USA; Catálogo No. 6005182) para dar una densidad de ~15000 células por pocillo. Alícuotas (90 µl) de los medios de

cultivo fueron colocadas en los pocillos externos para prevenir los efectos de borde. Las células fueron incubadas toda la noche a 37°C con 5% CO_2 para permitirles adherirse.

El día 2, las células fueron tratadas con compuestos de prueba e incubadas durante 2 horas a 37°C con 5% CO_2. Los compuestos de prueba fueron preparados como 10 mM de soluciones madre en DMSO y diluidos de manera seriada como se requirió con medios de crecimiento para dar un rango de concentraciones que fueron 10 veces las concentraciones finales de prueba requeridas. Alícuotas (10 µl) de cada dilución del compuesto fueron colocadas en un pocillo (por triplicado) para dar las concentraciones finales requeridas. Como un control de respuesta mínima, cada placa contenía pocillos con una concentración final de 100 µM LY294002 (Calbiochem, Beeston, Reino Unido, Catálogo No. 440202). Como un control de respuesta máxima, los pocillos contenían 1% DMSO en lugar del compuesto de prueba. A continuación de la incubación, el contenido de las placas fue fijado por tratamiento con 1.6% de una solución de formaldehído acuosa (Sigma, Poole, Dorset, Reino Unido, Catálogo No. F1635) a temperatura ambiente durante 1 hora.

Todos los pasos de aspiración y lavado posteriores fueron llevados a cabo usando un lavador de placas de 96 pocillos Tecan (velocidad de aspiración 10 mm/seg). La solución de fijación fue eliminada y el contenido de las placas fue lavado con solución salina tamponada con fosfato (PBS; 50 µl; Gibco, Catálogo No. 10010015). El contenido de las placas fue tratado durante 10 minutos a temperatura ambiente con una alícuota (50 µl) de un tampón de permeabilización celular que consiste en una mezcla de PBS y 0.5% de Tween–20. El tampón de 'permeabilización' fue eliminado y sitios de unión no específicos fueron bloqueados por tratamiento durante 1 hora a temperatura ambiente de una alícuota (50 µl) de un tampón de bloqueo que consiste en 5% de leche descremada seca ['Marvel' (marca registrada); Premier Beverages, Stafford, GB] en una mezcla de PBS y 0.05% de Tween–20. El tampón de 'bloqueo' fue eliminado y las células fueron incubadas durante 1 hora a temperatura ambiente con solución de anticuerpo de conejo anti fosfo–Akt (Ser473) (50 µl por pocillo; Cell Signalling, Hitchin, Herts, Reino Unido, Catálogo No. 9277) que había sido diluida 1:500 en el tampón de "bloqueo". Las células fueron lavadas tres veces en una mezcla de PBS y 0.05% de Tween–20. Posteriormente, las células fueron incubadas durante 1 hora a temperatura ambiente con IgG de cabra anticonejo marcada Alexafluor488 (50 µl por pocillo; Molecular Probes, Invitrogen Limited, Paisley, Reino Unido, Catálogo No. A11008) que

había sido diluida 1:500 en el tampón de "bloqueo". Las células fueron lavadas 3 veces con una mezcla de PBS y 0.05% de Tween–20. Una alícuota de PBS (50 µl) fue añadida a cada pocillo y las placas fueron selladas con selladores de placa negros y la señal de fluorescencia fue detectada y analizada.

Los datos de la respuesta a la dosis de fluorescencia obtenidos con cada compuesto fueron analizados y el grado de inhibición de la Serina 473 en Akt fue expresado como un valor IC_{50}.

(d) Ensayo de proliferación de adenocarcinoma de mama humano MDA–MB–468 *in vitro*

Este ensayo determina la capacidad de los compuestos de prueba para inhibir la proliferación celular como se evaluó usando la tecnología Cellomics Arrayscan. Una línea celular de adenocarcinoma de mama humano MDA–MB–468 (LGC Promochem, Catálogo No. HTB–132) fue rutinariamente mantenida como se describió en el Ensayo Biológico (b) aquí.

Para el ensayo de proliferación, las células fueron separadas del frasco de cultivo usando Accutase y sembradas en 60 pocillos interiores de una placa de 96 pocillos Packard negra a una densidad de 8000 células por pocillo en 100 µl de los medios de crecimiento completos. Los pocillos externos contenían 100 µl de PBS estéril. Las células fueron incubadas toda la noche a 37°C con 5% de CO_2 para permitirles adherirse.

El día 2, las células fueron tratadas con los compuestos de prueba e incubadas durante 48 horas a 37°C con 5% de CO_2. Los compuestos de prueba fueron preparados como 10 mM de soluciones madre en DMSO y diluidos de manera seriada como se requirió con los medios de crecimiento para dar un rango de concentraciones de prueba. Alícuotas (50 µl) de cada dilución del compuesto fueron colocadas en un pocillo y las células fueron incubadas durante 2 días a 37°C con 5% de CO_2. Cada placa contenía pocillos control sin compuesto de prueba.

El día 4, reactivo marcado BrdU (Sigma, Catálogo No. B9285) a una dilución final de 1:1000 fue añadido y las células fueron incubadas durante 2 horas a 37°C. El medio fue eliminado y las células en cada pocillo fueron fijadas por tratamiento con 100 µl de una mezcla de etanol y ácido acético glacial (90% etanol, 5% ácido acético glacial y 5% agua) durante 30 minutos a temperatura ambiente. Las células en cada pocillo fueron lavadas dos veces con PBS (100 µl). Ácido clorhídrico acuoso (2M, 100 µl) fue añadido a cada pocillo. Después de 20 minutos a temperatura ambiente, las células fueron lavadas dos veces con PBS.

Peróxido de hidrógeno (3%, 50 µl; Sigma, Catálogo No. H1009) fue añadido a cada pocillo. Después de 10 minutos a temperatura ambiente, los pocillos fueron lavados nuevamente con PBS.

La incorporación de BrdU fue detectada por incubación durante 1 hora a temperatura ambiente con anticuerpo anti–BrdU de ratón (50 µl; Caltag, Burlingame, CA, US; Catálogo No. MD5200) que fue diluido 1:40 en PBS con 1% BSA y 0.05% de Tween–20. El anticuerpo no unido fue eliminado con dos lavados de PBS. Para la visualización del BrdU incorporado, las células fueron tratadas durante 1 hora a temperatura ambiente con PBS (50 µl) y 0.05% de tampón Tween–20 con una dilución 1:1000 de IgG de cabra anti–ratón marcada Alexa fluo 488. Para la visualización de los núcleos celulares, una dilución 1:1000 de tinte Hoechst (Molecular Probes, Catálogo No. H3570) fue añadida. Cada placa fue lavada a su vez con PBS. Posteriormente, PBS (100 µl) fue añadido a cada pocillo y las placas fueron analizadas usando un ArrayScan de Cellomics para evaluar el número total de células y el número de células positivas BrdU.

Los datos de la respuesta a la dosis de fluorescencia obtenidos con cada compuesto fueron analizados y el grado de inhibición del crecimiento celular con MDA–MB–468 fue expresado como un valor IC_{50}.

Aunque las propiedades farmacológicas de los compuestos de fórmula (I) varían con el cambio estructural como se esperaba, en general, se cree que la actividad que los compuestos de fórmula (I) poseen puede ser demostrada a las siguientes concentraciones o dosis en una o más de las siguientes pruebas (a) a (d) :

Prueba (a):– IC_{50} contra quinasa mTOR de al menos 10 µM, en particular 0.001 – 0.5 µM para muchos compuestos; por ejemplo 34b el IC_{50} fue medido en dos ocasiones, los valores fueron 0.155 y 0.093µM.

Prueba (b):– IC_{50} contra PI3K humana Tipo Ib p110γ de al menos 10 µM, en particular 0.001 – 0.5 µM para muchos compuestos; y IC_{50} contra PI3K humana Tipo Ia p110α de al menos 10 µM, en particular 0.001 – 0.5 µM para muchos compuestos;
por ejemplo 34b el IC_{50} fue medido en dos ocasiones, los valores fueron 91.2 y 57.8 µM.

Prueba (c):– IC_{50} contra Serina 473 en Akt de al menos 10 μM, en particular 0.1 – 20 μM para muchos compuestos); por ejemplo 34b el IC_{50} fue medido en dos ocasiones, los valores fueron 1.361 y 0.654μM.

Prueba (d):– IC_{50} de al menos 20 μM;

Los compuestos de la presente invención son ventajosos ya que poseen actividad farmacológica. En particular, los compuestos de la presente invención modulan (en particular, inhiben) las enzimas quinasa mTOR y/o fosfatidilinositol–3–quinasa (PI3K), tales como las enzimas PI3K de la Clase Ia (por ejemplo PI3Kalfa, PI3Kbeta y PI3Kdelta) y la enzima PI3K de la Clase Ib (PI3Kgamma). Más particularmente los compuestos de la presente invención modulan (en particular, inhiben) la quinasa mTOR. Más particularmente los compuestos de la presente invención modulan (en particular, inhiben) una o más enzimas PI3K. Las propiedades inhibidoras de los compuestos de fórmula (I) pueden ser demostradas usando el procedimiento de prueba establecido aquí y en la sección experimental. Por consiguiente, los compuestos de fórmula (I) pueden ser usados en el tratamiento (terapéutico o profiláctico) de afecciones/enfermedades en animales no humanos y humanos las cuales son mediadas por la quinasa mTOR y/o una o más enzima(s) PI3K, y en particular por la quinasa mTOR.

La invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en asociación con un diluyente o portador farmacéuticamente aceptable.

Las composiciones de la invención pueden estar en una forma adecuada para uso oral (por ejemplo como tabletas, pastillas, cápsulas duras o blandas, suspensiones aceitosas o acuosas, emulsiones, polvos o gránulos dispersables, siropes o elixires), para uso tópico (por ejemplo como cremas, ungüentos, geles, o soluciones o suspensiones aceitosas o acuosas), para la administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para la administración por insuflación (por ejemplo como un polvo finamente dividido) o para la administración parenteral (por ejemplo como una solución aceitosa o acuosa estéril para dosificación intravenosa, subcutánea, intraperitoneal o intramuscular o como un supositorio para dosificación rectal).

Las composiciones de la invención pueden ser obtenidas por procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en el arte. De esta forma, las composiciones para uso oral pueden contener, por ejemplo, uno o más

agentes de coloración, edulcorantes, saborizantes y/o preservantes.

La cantidad de ingrediente activo que es combinada con uno o más excipientes para producir una forma de dosificación única variará necesariamente dependiendo del hospedero tratado y la vía particular de administración. Por ejemplo, una formulación para administración oral a humanos generalmente contendrá, por ejemplo, de 1 mg a 1 g de agente activo (más adecuadamente de 1 a 250 mg, por ejemplo de 1 a 100 mg) compuesto de una cantidad apropiada y conveniente de excipientes la cual puede variar desde alrededor de 5 a alrededor de 98 por ciento por peso de la composición total.

El tamaño de la dosis para propósitos profilácticos o terapéuticos de un compuesto de fórmula I variará naturalmente de acuerdo a la naturaleza y gravedad del estado de la enfermedad, la edad y sexo del animal o paciente y la vía de administración, de acuerdo a principios de medicina bien conocidos.

Cuando se use un compuesto de fórmula (I) para propósitos profilácticos o terapéuticos será generalmente administrado de manera que una dosis diaria en el rango, por ejemplo, de 1 mg/kg a 100 mg/kg de peso corporal es recibida, dada si es requerido en dosis divididas. En general, dosis inferiores serán administradas cuando una vía parenteral es empleada. De esta forma, por ejemplo, para la administración intravenosa, una dosis en el de rango, por ejemplo, de 1 mg/kg a 25 mg/kg de peso corporal será generalmente usada. De manera similar, para administración por inhalación, una dosis en el rango, por ejemplo, de 1 mg/kg a 25 mg/kg de peso corporal será usada. Típicamente, las formas de dosificación unitaria contendrán alrededor de 10 mg a 0.5 g de un compuesto de esta invención.

Como se declaró aquí, se sabe que la quinasa mTOR y las enzimas PI3K tienen roles tanto en la tumorigénesis así como en otras numerosas enfermedades. Hemos descubierto que los compuestos de fórmula (I) poseen actividad antitumoral potente la cual se cree que es obtenida por medio de la inhibición de la quinasa mTOR y/o una o más de las enzimas PI3K.

Por consiguiente, los compuestos de la presente invención son útiles como agentes antitumorales. Particularmente, los compuestos de la presente invención son útiles como agentes antiproliferativos, apoptóticos y/o antiinvasivos en la contención y/o tratamiento de enfermedad de tumor sólido y/o líquido. Particularmente, los compuestos de la presente invención se espera que sean útiles en la prevención o el tratamiento de aquellos tumores que son sensibles a la inhibición de mTOR y/o una o más de las enzimas PI3K tales como las enzimas PI3K de la Clase Ia y la enzima PI3K de la Clase Ib. Además, los compuestos de la

presente invención se espera que sean útiles en la prevención o el tratamiento de aquellos tumores que son mediados solo o en parte por mTOR y/o una o más de las enzimas PI3K tales como las enzimas PI3K de la Clase Ia y la enzima PI3K de la Clase Ib. Los compuestos pueden de esta forma ser usados para producir un efecto inhibidor de la enzima mTOR en un animal de sangre caliente necesitado de tal tratamiento. Ciertos compuestos pueden ser usados para producir un efecto inhibidor de la enzima PI3K en un animal de sangre caliente necesitado de tal tratamiento.

Como se declaró aquí, los inhibidores de la quinasa mTOR y/o una o más enzimas PI3K deberían ser de valor terapéutico para el tratamiento de una enfermedad proliferativa tal como el cáncer y en particular tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides y en particular para el tratamiento de, por ejemplo, cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata, y de cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias [incluyendo la leucemia linfótica aguda (ALL) y leucemia mielógena crónica (CML)], mieloma múltiple y linfoma.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso como un medicamento en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en un animal de sangre caliente tal como el hombre como un agente

antiinvasivo en la contención y/o tratamiento de una enfermedad proliferativa tal como el cáncer.

De acuerdo con un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en un animal de sangre caliente tal como el hombre como un agente antiinvasivo en la contención y/o tratamiento de una enfermedad proliferativa tal como el cáncer.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto antiproliferativo en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto antiinvasivo mediante la contención y/o tratamiento de la enfermedad de tumor sólido en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad

efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con un aspecto adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en la prevención o el tratamiento de una enfermedad proliferativa tal como el cáncer en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para la prevención o el tratamiento de una enfermedad proliferativa tal como el cáncer en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en la prevención o el tratamiento de aquellos tumores que son sensibles a la inhibición de la quinasa mTOR y/o una o más enzimas PI3K (tales como las enzimas de la Clase Ia y/o la enzima PI3K de la Clase Ib) que están involucradas en los pasos de transducción de la señal, los que conducen a la proliferación, supervivencia, invasividad y capacidad migratoria de las células tumorales.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en la prevención o el tratamiento de aquellos tumores que son sensibles a la inhibición de la quinasa mTOR y/o una o más enzimas PI3K (tales como las enzimas de la Clase Ia y/o la enzima PI3K de la Clase Ib) que están involucradas en los pasos de transducción de la señal, los que conducen a la proliferación, supervivencia, invasividad y capacidad migratoria de las células tumorales.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para la prevención o el tratamiento de aquellos tumores que son sensibles a la inhibición de la quinasa mTOR y/o una o más enzimas PI3K (tales como las enzimas de la Clase Ia y/o la enzima PI3K de la Clase Ib) que están involucradas en los pasos de transducción de la señal, los que conducen a la proliferación, supervivencia, invasividad y

capacidad migratoria de las células tumorales, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para proporcionar un efecto inhibidor de la quinasa mTOR y/o un efecto inhibidor de la enzima PI3K (tal como un efecto inhibidor de la enzima PI3K de la Clase Ia o la enzima PI3K de la Clase Ib).

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para proporcionar un efecto inhibidor de la quinasa mTOR y/o un efecto inhibidor de la enzima PI3K (tal como un efecto inhibidor de la enzima PI3K de la Clase Ia o la enzima PI3K de la Clase Ib).

De acuerdo con un aspecto adicional de la invención también se proporciona un método para proporcionar un efecto inhibidor de la quinasa mTOR y/o un efecto inhibidor de la enzima PI3K (tal como un efecto inhibidor de la enzima PI3K de la Clase Ia o la enzima PI3K de la Clase Ib) que comprende administrar una cantidad efectiva de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en el tratamiento de cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en el tratamiento de tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en el tratamiento de cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí para el uso en el tratamiento de cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias (incluyendo ALL y CML), mieloma múltiple y linfoma.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en el tratamiento de cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en el tratamiento de tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en el tratamiento de cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí en la fabricación de un medicamento para el uso en el tratamiento de cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias (incluyendo ALL y CML), mieloma múltiple y linfoma.

De acuerdo con una característica adicional de la invención se proporciona un método para tratar cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con una característica adicional de la invención se proporciona un método para tratar tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con una característica adicional de la invención se proporciona un método para tratar el cáncer de mama, colorrectal, pulmón (incluyendo cáncer de pulmón de células pequeñas, cáncer de pulmón de células no pequeñas y cáncer broncoalveolar) y próstata en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

De acuerdo con una característica adicional de la invención se proporciona un método para tratar el cáncer del conducto biliar, hueso, vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículos, tiroides, útero, cérvix y vulva, y de leucemias (incluyendo ALL y CML), mieloma múltiple y linfoma en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí.

Como se declaró aquí, los efectos *in vivo* de un compuesto de fórmula (I) pueden ser ejercidos en parte por uno o más metabolitos que son formados dentro del cuerpo humano o animal después de la administración de un compuesto de fórmula (I).

La invención se relaciona adicionalmente con terapias de combinación donde un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, o una composición farmacéutica o formulación que comprende un compuesto de fórmula (I) es administrado concurrentemente o secuencialmente o como una preparación combinada con otro tratamiento usado en el control de la enfermedad oncológica.

En particular, el tratamiento definido aquí puede ser aplicado como una sola terapia o puede incluir, además de a los compuestos de la invención, cirugía convencional o radioterapia o quimioterapia. Por consiguiente, los compuestos de la invención también pueden ser usados en combinación con agentes terapéuticos existentes para el tratamiento de cáncer.

Los agentes adecuados para ser usados en combinación incluyen :

(i) fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, como se usan en oncología médica, tales como agentes alquilatantes (por ejemplo cisplatino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfán y nitrosoureas); antimetabolitos (por ejemplo antifolatos tales como fluoropirimidinas como el 5– fluorouracilo y tegafur, raltitrexed, metotrexato, citosina arabinosida, hidroxiurea y gemcitabina); antibióticos antitumorales (por ejemplo antraciclinas como adriamicina, bleomicina, doxorrubicina, daunomicina, epirrubicina, idarrubicina, mitomicina C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo alcaloides vinca como vincristina, vinblastina, vindesina y vinorelbina y taxoides como paclitaxel y taxotere); e inhibidores de la topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y teniposida, amsacrina, topotecan y camptotecinas);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo, tamoxifeno, toremifeno, raloxifeno, droloxifeno y yodoxifeno), reguladores hacia abajo del receptor de estrógenos (por ejemplo fulvestrant), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo, acetato de megestrol), inhibidores de la aromatasa (por ejemplo como anastrozol, letrozol, vorazol y exemestano) y los inhibidores de la 5α–reductasa como finasterida;

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

(iv) inhibidores de la función del factor de crecimiento: por ejemplo tales inhibidores incluyen los anticuerpos del factor de crecimiento y los anticuerpos del receptor del factor de crecimiento (por ejemplo, el anticuerpo anti–erbB2 trastuzumab [Herceptin™] y el anticuerpo anti–erbB1 cetuximab [C225], tales inhibidores también incluyen, por ejemplo, los inhibidores de la tirosina quinasa, por ejemplo inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo inhibidores de la tirosina quinasa de la familia de 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, OSI-774) y 6-acrilamido-*N*-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033) y los inhibidores de la tirosina quinasa erbB2 (tales como lapatinib), los inhibidores de la familia del factor de crecimiento de hepatocitos, los inhibidores de la familia del factor de crecimiento derivado de las plaquetas tales como imatinib, inhibidores de las serina/treonina quinasas (por ejemplo inhibidores de señales Ras/Raf tales como los inhibidores de la farnesil transferasa, por ejemplo sorafenib (BAY 43-9006) y los inhibidores de señales celulares a través de quinasas MEK y/o AKT;

(v) agentes antiangiogénicos tales como los que inhiben los efectos del factor de crecimiento endotelial vascular, [por ejemplo el anticuerpo del factor de crecimiento de células endoteliales antivascular bevacizumab (Avastin™) e inhibidores de la tirosina quinasa del receptor del VEGF tales como 4-(4-bromo-2-fluoroanilino)-6-metoxi-7-(1-metilpiperidin-4-ilmetoxi)quinazolina (ZD6474; Ejemplo 2 dentro de WO 01/32651), 4-(4-fluoro-2-metilindol-5-iloxi)-6-metoxi-7-(3-pirrolidin-1-ilpropoxi)quinazolina (AZD2171; Ejemplo 240 dentro de WO 00/47212), vatalanib (PTK787; WO 98/35985) y SU11248 (sunitinib; WO 01/60814), y compuestos que funcionan por otros mecanismos (por ejemplo linomida, inhibidores de la función de la integrina $\alpha v\beta 3$ y angiostatina)];

(vi) agentes perjudiciales vasculares tales como combretastatina A4 y compuestos divulgados en las Solicitudes Internacionales de Patente WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias antisentido, por ejemplo aquellas que son dirigidas a los blancos mencionados anteriormente, tales como ISIS 2503, un agente antisentido anti-ras;

(viii) aproximaciones a la terapia génica, incluyendo aproximaciones para reemplazar los genes aberrantes tales como las aproximaciones aberrantes p53 o la BRCA1 o BRCA2, GDEPT aberrantes (terapia con profármacos de enzimas dirigidas a los genes) tales como aquellas que usan citosina deaminasa, timidina quinasa o una enzima nitroreductasa bacteriana y aproximaciones para aumentar la tolerancia del paciente a la quimioterapia o la radioterapia tales como la terapia génica resistente a múltiples fármacos; y

(ix) aproximaciones de inmunoterapia, incluyendo por ejemplo aproximaciones *ex vivo* e *in vivo* para aumentar la inmunogenicidad de las células tumorales del paciente, tales como la transfección con citocinas como la interleucina 2, interleucina 4 o el factor estimulador de colonias de granulocitos macrófagos, aproximaciones para disminuir la anergia de células T,

aproximaciones usando células inmunes transfectadas tales como las células dendríticas transfectadas de citoquinas, aproximaciones usando líneas celulares tumorales transfectadas de citoquinas y aproximaciones usando anticuerpos antiidiotípicos.

La invención será ahora adicionalmente explicada con referencia a los siguientes ejemplos ilustrativos.

A menos que se declare lo contrario, los materiales de partida estaban comercialmente disponibles. Todos los solventes y reactivos comerciales fueron de grado de laboratorio y fueron usados tal y como fueron recibidos.

En los ejemplos los espectros ^{1}H NMR fueron registrados en un instrumento Bruker DPX 300 (300 MHz), Bruker DRX 400 (400 MHz) o un instrumento Bruker DRX 500 (500 MHz). Los picos centrales de cloroformo–d (δ_H 7.27 ppm), dimetilsulfóxido–d_6 (δ_H 2.50 ppm) o acetona–d_6 (δ_H 2.05 ppm) fueron usados como referencias internas. Las siguientes abreviaturas han sido usadas: s, singlete; d, doblete; t, triplete; q, cuartete; m, multiplete; br, amplio.

La cromatografía en columna fue llevada a cabo usando gel de sílice (0.04–0.063 mm, Merck). En general, una columna Kromasil KR–100–5–C18 de fase inversa (250 x 20 mm, Akzo Nobel) fue usada para la HPLC preparativa con mezclas de acetonitrilo y agua [conteniendo 0.1% de ácido trifluoroacético (TFA)] usadas como eluente a una tasa de flujo de 10 mL/min.

Los siguientes métodos fueron usados para la cromatografía líquida (LC) / análisis espectral de masa (MS):

HPLC:	Agilent 1100 o Waters Alliance HT (2790 & 2795)
Espectrómetro de Masa:	Waters ZQ ESCi

Columna HPLC

La columna HPLC estándar usada es la Phemonenex Gemini C18 5µm, 50 x 2 mm.

Métodos HPLC Ácida

Las fases móviles usadas son:	Fase móvil A:	Agua
	Fase móvil B:	Acetonitrilo
	Fase móvil C:	1% Ácido Fórmico en Agua:MeCN (v/v) 50:50

Cada método es seguido por un rápido equilibrado usando una tasa de flujo de 5 mL durante 0.45 min.

Cuatro métodos HPLC genéricos están disponibles:

Método Ácido Monitor 5 Minutos

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil C:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Método Ácido temprano para los compuestos de elución temprana

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil C:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Método Ácido medio para los compuestos de elución media

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil C:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Método Ácido tardío para los compuestos de elución tardía

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil C:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

Métodos HPLC Básica

En algunos casos los métodos ácidos estándares pueden ser inadecuados para la ionización del compuesto o la separación cromatográfica requerida. En tales casos cuatro métodos HPLC Básica comparables están disponibles.

Las fases móviles usadas son: Fase móvil A: Agua

Fase móvil B: Acetonitrilo

Fase móvil D: 0.1% 880 Amoniaco en acetonitrilo

Cada método es seguido por un rápido equilibrado usando una tasa de flujo de 5 mL durante 0.45 min.

Método Básico Monitor Minuto

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil D:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Método Básico temprano para los compuestos de elución temprana

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil D:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1

4.5	57.5	37.5	5	6	1.1

Método Básico medio para los compuestos de elución media

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil D:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Método Básico tardío para los compuestos de elución tardía

Tiempo /min	Fase móvil A:	Fase móvil B:	Fase móvil C:	Curva	Tasa de Flujo /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

El siguiente método fue usado para la cromatografía líquida (LC) / análisis espectral de masa (MS):

Instrumento: Agilent 1100; Columna: Waters 'Symmetry' 2.1 x 30 mm; análisis espectral de masa usando ionización química (APCI); Tasa de flujo: 0.7 mL/min; Absorción Longitud de Onda: 254 nm; Solvente A: agua + 0.1% TFA; Solvente B: acetonitrilo + 0.1% TFA; Gradiente de Solvente: 15–95% Solvente B durante 2.7 minutos seguido por 95% Solvente B durante 0.3 minutos.

Los siguientes métodos fueron usados para el análisis LC :

Método A : Instrumento: Agilent 1100; Columna: Kromasil C18 sílice de fase inversa, 100 x 3 mm, 5μm tamaño de partículas; Solvente A: 0.1% TFA/agua, Solvente B: 0.08% TFA/acetonitrilo; Tasa de flujo: 1 mL/min; Gradiente de solvente: 10–100% Solvente B durante 20 minutos seguido por 100% Solvente B durante 1 minuto; Absorción Longitud de Ondas: 220, 254 y 280 nm. En general, el tiempo de retención del producto fue notado.

Método B : Instrumento: Agilent 1100; Columna: Waters 'Xterra' C8 sílice fase inversa, 100 x 3 mm, 5μm tamaño de partículas; Solvente A: 0.015M amoniaco en agua, Solvente B: acetonitrilo; Tasa de flujo: 1 ml/min, Gradiente de Solvente: 10–100% Solvente B durante 20 minutos seguido por 100% Solvente B durante 1 minuto; Absorción Longitud de Onda: 220, 254 y 280 nm. En general, el tiempo de retención del producto fue notado.

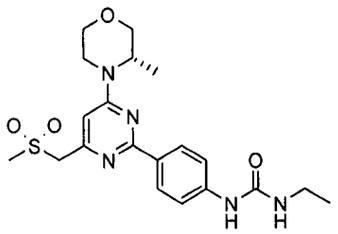
Las siguientes abreviaturas son usadas aquí o dentro de los siguientes ejemplos ilustrativos :

HPLC	Cromatografía Líquida de Alto Rendimiento
HBTU	*O*–(benzotriazol–1–il)–*N*,*N*,*N*',*N*'–tetrametiluronio hexafluorofosfato;
HATU	*O*–(7–azabenzotriazol–1–il)–*N*,*N*,*N*',*N*'–tetrametiluronio hexafluorofosfato;
HOBT	1–hidroxibenzotriazol;
HOAT	1–hidroxi–7–azabenzotriazol;
NMP	*N*–metilpirrolidin–2–ona;
DMSO	dimetilsulfóxido;
DMF	*N*,*N*–dimetilformamida;
DMA	*N*,*N*–dimetilacetamida;
THF	tetrahidrofurano;
DME	1,2–dimetoxietano;
DCCI	diciclohexilcarbodiimida;
MeOH	metanol;
MeCN	acetonitrilo;
DCM	diclorometano;
DIPEA	*N*,*N*–diisopropiletilamina;
DBU	1,8–diazabiciclo[5.4.0]undec–7–eno;
RT	temperatura ambiente (aproximadamente 17 a 25°C);
tR	tiempo de retención;
m/z	proporción masa/carga.

Los nombres químicos fueron generados por un programa el cual usó Lexichem Toolkit (v. 1.40) de OpenEye Scientific Software (www.eyesopen.com) para generar nombres IUPAC conformados.

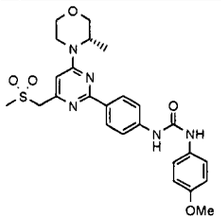
Ejemplo 1:

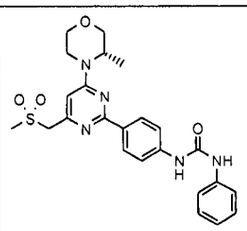
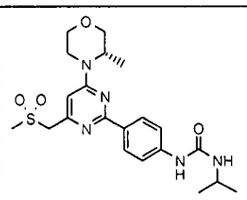
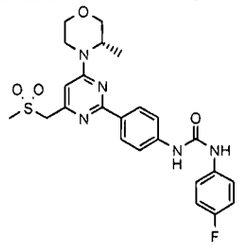
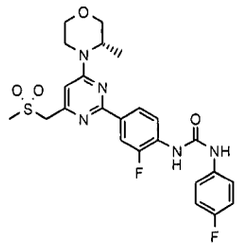
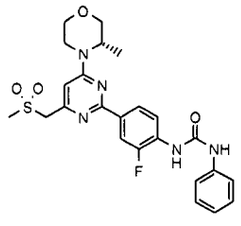
1–Etil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea

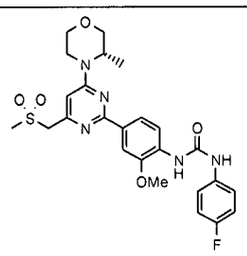
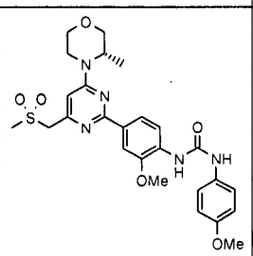
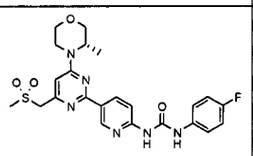
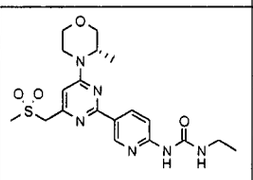


4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina (100 mg, 0.28 mmol) fue disuelta en dioxano (4 mL). Etilisocianato (0.109 mL, 1.38 mmol) fue añadido y la reacción calentada a 70°C durante 4 horas. La reacción se completó y fue evaporada hasta secarse. El aceite resultante fue purificado por cromatografía, eluyendo con 10 – 50% etil acetato en isohexano, para dar 3–etil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea como un aceite amarillo pálido (113 mg, 94%).
Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ0.99 (t, 3H), 1.25 (d, 3H), 3.11 (q, 2H), 3.20 (s, 3H), 3.29 (m, 2H), 3.5 (m, 1H), 3.67 (m, 1H), 3.78 (m, 1H), 3.99 (m, 1H), 4.16 (m, 1H), 4.47 (s, 2H), 6.18 (t, 1H), 6.78 (s, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.68 (s, 1H)
Espectro LCMS: MH+ 434, tiempo de retención 1.37 min, Método Ácido 5 Min

Los compuestos mostrados en la tabla fueron preparados de una manera análoga al 3–etil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea reaccionando el isocianato apropiado con la anilina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
1a		1–(4–metoxifenil)–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	512	2.19	Purificado por una lechada de etil acetado y luego cromatografía

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
1b		1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-fenil-urea	482	2.26	Cromatografía eluida con 0-8% MeOH/ DCM
1c		3-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-propan-2-il-urea	448	1.90	Cromatografía eluida con 0-8% MeOH/ DCM
1e		3-(4-fluorofenil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	500	2.05	Triturado con etil acetato
1f		1-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(4-fluorofenil)urea	518	2.38	Purificado por cromatografía en fase inversa
1g		1-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-fenil-urea	500	2.36	Purificado por cromatografía en fase inversa

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
1h		3–(4–fluorofenil)–1–[2–metoxi–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	529	2.22	Cristalizado a partir de NMP/agua luego triturado con EtOAc
1i		3–[2–metoxi–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1–(4–metoxifenil)urea	542	2.06	Cristalizado a partir de NMP/agua luego triturado con EtOAc
1j		3–(4–fluorofenil)–1–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piridin–2–il]urea	501	2.26	Cristalizado a partir de dimetilformamida/ agua
1k		1–etil–3–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piridin–2–il]urea	435	1.51	Purificado por cromatografía en fase inversa

Ejemplo 1a: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.28 (d, 3H), 3.21 (s, 3H), 3.4 (m, 2H), 3.5 (m, 1H), 3.65 (m, 1H), 3.71 (s, 3H), 3.8 (d, 1H), 3.99 (m, 1H), 4.2 (m, 1H), 4.50 (s, 2H), 6.79 (s, 1H), 6.89 (d, 2H), 7.38 (d, 2H), 7.55 (d, 2H), 8.25 (d, 2H), 8.50 (s, 1H), 8.83 (s, 1H)

Ejemplo 1b: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 (d, 3H), 3.21 (s, 2H), 3.28–3.38 (m, 2H), 3.35 (t, 1H), 3.67 (d, 1H), 3.69 (d, 1H), 4.18–4.22 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.00 (m, 1H), 7.31 (m, 2H) 7.47 (d, 2H), 7.59 (d, 2H), 8.27 (d, 2H), 8.71 (s, 1H), 8.91 (s, 1H)

Ejemplo 1c: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.10 (d, 6H), 1.24 (d, 3H), 3.29 (s, 3H), 3.49 (m, 1H), 3.64–3.66 (m, 1H), 3.77 (m, 2H), 4.18–4.21 (m, 1H), 4.49 (s, 3H), 6.08 (d, 1H), 6.79, (s, 1H), 7.48 (d, 2H), 8.22 (d, 2H), 8.51 (s, 1H)

Ejemplo 1d: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 – 1.27 (m, 3H), 3.22 (s, 3H), 3.35 – 3.36 (m, 1H), 3.41 (s, 1H), 3.51 (d, 2H), 3.65 – 3.68 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.18 (s, 1H), 4.50 (s, 2H), 6.80 (s, 1H), 7.12 – 7.16 (m, 2H), 7.47 – 7.50 (m, 2H), 7.57 (d, 2H), 8.27 (d, 2H), 8.75 (s, 1H), 8.92 (s, 1H)

Ejemplo 1e: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 – 1.27 (m, 3H), 3.21 (s, 3H), 3.25 (t, 1H), 3.48 – 3.54 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.19 (s, 1H), 4.50 (m, 1H), 4.51 (s, 2H), 6.84 (s, 1H), 7.16 (d, 2H), 7.47 – 7.51 (m, 2H), 8.08 – 8.12 (m, 1H), 8.13 – 8.15 (m, 1H), 8.31 (t, 1H), 8.77 (d, 1H), 9.17 (s, 1H)

Ejemplo 1f: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.26 (d, 3H), 3.21 (s, 3H), 3.24–3.26 (m, 1H), 3.52 (t, 1H), 3.66 (t, 1H), 3.79 (d, 1H), 3.99 – 4.02 (m, 2H), 4.18 (m, 1H), 4.52 (s, 3H), 6.84 (s, 1H), 7.02 (t, 1H), 7.30 – 7.34 (m, 2H), 7.48 (d, 2H), 8.08 – 8.15 (m, 2H), 8.34 (t, 1H), 8.79 (d, 1H), 9.15 (s, 1H)

Ejemplo 1g: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 – 1.27 (m, 3H), 3.24 (s, 3H), 3.30 (m, 1H), 3.49 – 3.53 (m, 1H), 3.65 – 3.69 (m, 1H), 3.80 (d, 1H), 3.98 (s, 3H), 4.00 (m, 1H), 4.02 (m, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 6.82 (s, 1H), 7.12 – 7.17 (m, 2H), 7.47 – 7.51 (m, 2H), 7.96 (s, 2H), 8.27 (s, 1H), 8.42 (s, 1H), 9.45 (d, 1H)

Ejemplo 1h: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.26 (d, 3H), 3.24 (s, 3H), 3.30 (m, 1H), 3.49 – 3.55 (m, 1H), 3.65 – 3.69 (m, 1H), 3.74 (s, 3H), 3.80 (d, 1H), 3.97 (s, 3H), 4.00 (m, 1H), 4.02 (m, 1H), 4.18 – 4.22 (m, 1H), 4.47 – 4.49 (m, 1H), 4.52 (s, 2H), 6.81 (s, 1H), 6.88 – 6.91 (m, 2H, 7.36 – 7.40 (m, 2H), 7.95 (s, 2H), 8.28 (d, 1H), 8.36 (s, 1H), 9.23 (s, 1H)

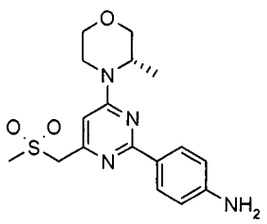
Ejemplo 1i: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.27 (d, 3H), 3.21 (s, 3H), 3.25 (m, 1H), 3.48 – 3.55 (m, 1H), 3.65 – 3.69 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.20 (s, 1H), 4.52 (s, 3H), 6.87 (s, 1H), 7.14 – 7.21 (m, 2H), 7.56 – 7.60 (m, 2H), 7.61 – 7.64 (m, 1H), 8.57 – 8.59 (m, 1H), 9.21 – 9.21 (m, 1H), 9.70 (s, 1H), 10.52 (s, 1H)

Ejemplo 1j: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.12 (t, 3H), 1.25 – 1.26 (m, 3H), 3.20 (s, 3H), 3.22 – 3.24 (m, 2H), 3.26 (m, 1H), 3.47 – 3.54 (m, 1H), 3.64 – 3.67 (m, 1H), 3.78 (d, 1H), 3.97 – 4.01 (m, 1H), 4.18 (s, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.48 (d, 1H), 8.10 (d, 1H), 8.48 – 8.51 (m, 1H), 9.11 (m, 1H), 9.41 (s, 1H)

Prueba (a): Ejemplo (1) 0.0062 μM; Ejemplo (1a) 0.062 μM; Ejemplo (1b) 0.013 μM; Ejemplo (1c) 0.078 μM; Ejemplo (1d) 0.042 μM; Ejemplo (1e) 0.32 μM; Ejemplo (1f) 0.36 μM; Ejemplo (1g) 0.96 μM; Ejemplo (1h) 1.2 μM; Ejemplo (1i) 0.55 μM; Ejemplo (1j) 0.043 μM.

La preparación de las anilinas 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina y 2–fluoro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina es descrita a continuación.

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina

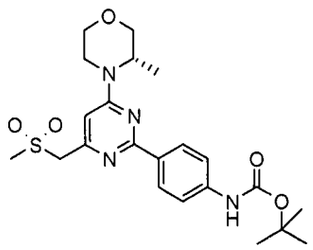


tert–Butil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato (1.09 g, 2.35 mmol) fue disuelto en metanol (5 mL) e hidrógeno cloruro en dioxano 4M (5 mL) fue añadido. La solución fue agitada a temperatura ambiente toda la noche, luego la mezcla fue evaporada hasta obtener un aceite marrón oscuro y disuelta en etil acetato (10 mL). Agua (5 mL) fue añadida seguido por la adición de solución de bicarbonato de sodio hasta que un pH neutro fue logrado (~2 mL). Las fases fueron separadas y la fase orgánica lavada con agua (10 mL). La capa orgánica fue secada sobre sulfato de magnesio y evaporada hasta obtener una espuma amarilla pálida (805 mg).

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.23 (3H, d), 3.31 (3H, s), 3.5 (1H, m), 3.64 (1H, m), 3.78 (1H, m), 4.13 (1H, m), 4.49 (2H, m), 5.57 (2H, s), 6.61 (2H, d), 6.68 (1H, s), 8.08 (1H, d)

Espectro LCMS: MH+ 363, tiempo de retención 1.02 min, Método Ácido 5 Min

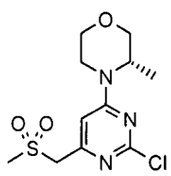
tert–Butil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato



2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.0 g, 3.27 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (7 mL). Ácido [4–[(2–metilpropan–2–il)oxicarbonilamino]fenil]borónico (1.165 g, 4.91 mmol), solución de carbonato de sodio 2M (4 mL) y catalizador de diclorobis(trifenilfosfina) paladio (115 mg, 0.16 mmol) fueron luego añadidos a la solución y refluidos a 90°C durante 5 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente luego particionada entre etil acetato y agua. Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados hasta secarse. El aceite crudo fue disuelto en diclorometano y filtrado para eliminar el material insoluble. Un sólido beige se precipitó de los filtrados y los filtrados fueron filtrados nuevamente. El sólido fue analizado y resultó ser el exceso de ácido borónico y los filtrados contenían el producto y algunas impurezas. Los filtrados fueron purificados por cromatografía en sílice, eluyendo con 0–40% etil acetato en isohexano, para dar el compuesto deseado como un aceite naranja (530 mg).

Espectro LCMS: MH+ 463, tiempo de retención 2.23 min, Método Ácido 5 Min

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina



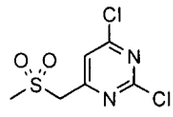
2,4–Dicloro–6–(metilsulfonilmetil)pirimidina (30 g, 0.13 mol) fue disuelta en diclorometano y agitada (bajo nitrógeno) a –5°C. Trietilamina (17.4 mL, 0.13 mol) fue añadida para dar una solución marrón clara. (3*S*)–3–Metilmorfolina fue disuelta en diclorometano y añadida en forma de gotas manteniendo la reacción por debajo de –5°C. El baño de enfriamiento fue luego eliminado y la mezcla agitada durante 1 hora. La mezcla de reacción fue calentada a reflujo durante 2 horas, luego la mezcla de reacción fue lavada con agua, secada y luego

evaporada. El material crudo fue purificado por HPLC preparativa para dar el material deseado como un sólido (19.3 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.21 – 1.23 (m, 3H), 3.11 (s, 3H), 3.19 – 3.26 (m, 1H), 3.42 – 3.49 (m, 1H), 3.58 – 3.62 (1H, m), 3.73 (d, 1H), 3.92 – 3.96 (m, 2H), 4.27 – 4.31 (m, 1H), 4.45 (s, 2H), 6.92 (s, 1H)

Espectro LCMS: MH+ 306, tiempo de retención 1.42 min, Método Ácido 5 Min

2,4–Dicloro–6–(metilsulfonilmetil)pirimidina

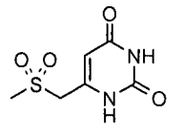


6–(Metilsulfonilmetil)–1*H*–pirimidina–2,4–diona (132 g, 0.65 mol) fue añadida a oxicloruro de fósforo (1.2 L) y la mezcla calentada hasta reflujo durante 16 horas, luego enfriada hasta temperatura ambiente. El exceso de oxicloruro de fósforo fue eliminado al vacío, el residuo azeotropizado con tolueno (2 x 500 mL) y disuelto en diclorometano. Esta mezcla fue luego vertida lentamente sobre hielo (4 L) y agitada durante 20 minutos, luego extraída con diclorometano (3 x 1 L) (el material negro insoluble fue filtrado y desechado) y etil acetato (2 x 1 L). Los extractos fueron combinados, secados, luego evaporados para dejar el material deseado como un sólido marrón oscuro (51 g). El material fue usado sin purificación adicional.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)

Espectro LCMS: MH+ 239, tiempo de retención 1.21 min, Método Ácido 5 Min

6–(Metilsulfonilmetil)–1*H*–pirimidina–2,4–diona

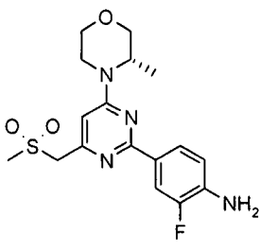


6–(Clorometil)–1*H*–pirimidina–2,4–diona (175 g, 1.09 mol) fue disuelta en DMF (2 L) y sal sódica del ácido metanosulfínico (133.5 g, 1.31 mol) fue añadida. La reacción fue calentada hasta 125°C durante 2 horas luego se dejó enfriar y la suspensión filtrada y concentrada al vacío para dar un sólido amarillo. El material crudo fue lavado con agua, filtrado, luego triturado con tolueno. El sólido fue filtrado luego triturado con isohexano para dejar el

compuesto deseado como un sólido amarillo (250 g). El material fue usado sin purificación adicional.

6-(Clorometil)-1*H*-pirimidina-2,4-diona es un material comercialmente disponible.

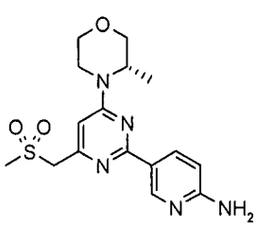
2-Fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]anilina



2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (860 mg) fue disuelta en 18% DMF en 7:3:2 DME:agua:etanol (21 mL volumen total del solvente). 4-Pinacolato boro-2-fluoroanilina (1.005 g), carbonato de sodio 2M (4 mL) y diclorobis(trifenilfosfina) paladio (99 mg) fueron luego añadidos a la solución y calentados bajo reflujo a 90°C durante 5 horas bajo una atmósfera de nitrógeno. La reacción fue particionada entre DCM (50 mL) y agua (50 mL). El extracto orgánico fue secado sobre sulfato de magnesio, filtrado y concentrado al vacío. El aceite marrón fue disuelto en diclorometano, filtrado para eliminar el material fino y cargado en un Companion para la purificación usando 0-50% etil acetato en gradiente de isohexano durante 20 minutos. El producto purificado fue obtenido como un aceite amarillo pálido.

Espectro LCMS: MH+ 381, tiempo de retención 1.32 min, Método Ácido 5 Min

5-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]piridin-2-amina

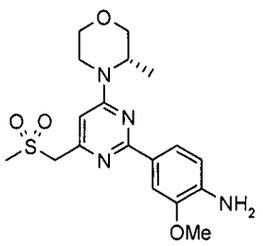


2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (363 mg, 1.19 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 DME:agua:etanol

(7mL). 5-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-amina (496 mg, 2.25 mmol), solución de carbonato de sodio 2M (2 mL) y diclorobis(trifenilfosfina) paladio (42 mg) fueron añadidos a la solución y esta fue calentada bajo reflujo a 90°C durante 90 minutos bajo una atmósfera de nitrógeno. La reacción fue particionada entre etil acetato (50 mL) y agua (50 mL), los productos orgánicos secados sobre sulfato de magnesio, filtrados y concentrados al vacío para dar el producto deseado como un aceite amarillo (410 mg) el cual fue usado sin purificación adicional.

Espectro LCMS: MH+ 364, tiempo de retención 0.89 min, Método Ácido 5 Min

2-Metoxi-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]anilina



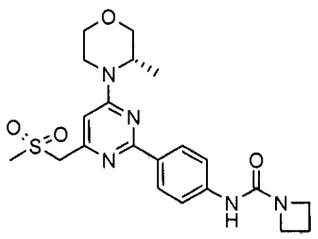
2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (700 mg, 2.29 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (7mL). Ácido (4-Amino-3-metoxi-fenil)borónico (574 mg, 3.43 mmol), solución de carbonato de sodio 2M (4 mL) y diclorobis(trifenilfosfina) paladio (81 mg) fueron luego añadidos a la solución y refluidos a 90°C durante 1 hora. La reacción se dejó enfriar hasta la temp. ambiente luego fue particionada entre etil acetato (50 mL) y agua (50 mL), los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El residuo fue disuelto en diclorometano y filtrado para eliminar el material insoluble. Los filtrados fueron purificados usando un companion.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.24 (d, 3H), 3.17 – 3.21 (m, 1H), 3.23 (s, 3H), 3.47 – 3.54 (m, 1H), 3.64 – 3.67 (m, 1H), 3.78 (d, 1H), 3.83 (s, 3H), 3.97 – 4.01 (m, 1H), 4.16 (d, 1H), 4.46 (s, 3H), 5.23 (s, 2H), 6.68 – 6.70 (m, 1H), 6.69 (s, 1H), 7.77 (m, 1H), 7.97 (s, 1H)

Espectro LCMS: MH+ 393, tiempo de retención 1.17min, método ácido 5 min

Ejemplo 2:

N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]azetidina–1–carboxamida

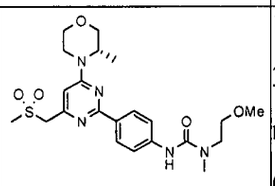
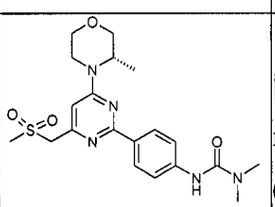
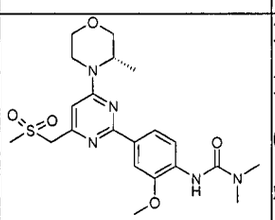
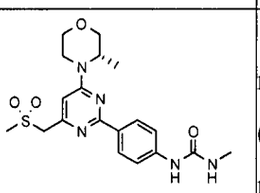
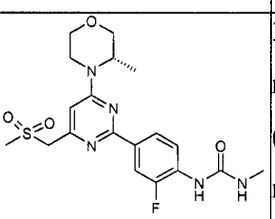


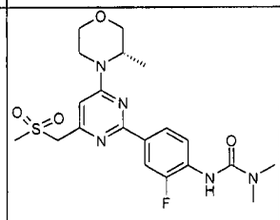
Solución de fosgeno 20% en tolueno (0.245 ml, 0.50 mmol) fue diluida con diclorometano (0.5 mL). 4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina (150 mg, 0.41 mmol) fue disuelta en diclorometano (2 mL) y piridina (0.5 mL). Esto fue añadido a la solución de fosgeno en forma de gotas durante 2 minutos. La reacción fue agitada a temp. ambiente durante 1 hora. Luego azetidina (0.034 mL, 0.50 mmol) fue añadida y la mezcla agitada a temp. ambiente durante 1 hora. La reacción fue particionada entre agua y etil acetato (25 mL de cada uno). La capa orgánica fue secada sobre sulfato de magnesio y evaporada hasta secarse. El aceite amarillo fue purificado por cromatografía, eluyendo con 10–70% etil acetato en isohexano, para dar el material deseado como una espuma amarilla (50 mg, 25%).

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 (d, 3H), 2.16 – 2.24 (m, 2H), 3.19 – 3.23 (m, 4H), 3.47 – 3.54 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.99 (t, 5H), 4.17 (s, 1H), 4.49 (s, 3H), 6.79 (s, 1H), 7.62 – 7.64 (m, 2H), 8.20 – 8.23 (m, 2H), 8.57 (s, 1H)

Espectro LCMS: MH+ 446, tiempo de retención 1.37 min, Método Ácido 5 Min

Los siguientes compuestos fueron preparados de una manera análoga a *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]azetidina–1–carboxamida a partir de 4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
2a		1–(2–metoxietil)–1–metil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	478	1.46	N/a
2b		1,1–dimetil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	434	1.28	Purificado por cromatografía en fase inversa
2c		3–[2–metoxi–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1,1–dimetil–urea	464	1.54	Purificado por cromatografía en fase inversa
2d		1–metil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	420	1.19	Purificado por cromatografía en fase inversa
2e		3–[2–fluoro–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1–metil–urea	438	1.44	Purificado por cromatografía en fase inversa

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
2f		3–[2–fluoro–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1,1–dimetil–urea	452	1.55	Purificado por cromatografía en fase inversa

Ejemplo 2a: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 (d, 3H), 3.00 (s, 3H), 3.21 (s, 3H), 3.23 – 3.27 (m, 2H), 3.45 (m, 2H), 3.51 (s, 4H), 3.53 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.17 – 4.21 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.58 (s, 2H), 8.21 – 8.23 (m, 2H), 8.47 (s, 1H)

Ejemplo 2b: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.24 – 1.26 (m, 3H), 2.96 (s, 6H), 3.21 (s, 3H), 3.25 (d, 1H), 3.48 – 3.54 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.19 (d, 1H), 4.49 (s, 3H), 6.79 (s, 1H), 7.58 – 7.62 (m, 2H), 8.20 – 8.23 (m, 2H), 8.50 (s, 1H)

Ejemplo 2c: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 – 1.27 (m, 3H), 2.97 (s, 6H), 3.18 (m, 1H), 3.23 (s, 3H), 3.48 – 3.55 (m, 1H), 3.65 – 3.69 (m, 1H), 3.79 (d, 1H), 3.93 (s, 3H), 3.98 – 4.02 (m, 1H), 4.20 (d, 1H), 4.47 (s, 1H), 4.51 (s, 2H), 6.82 (s, 1H), 7.52 (s, 1H), 7.91 – 7.94 (m, 2H), 8.00 (s, 1H)

Ejemplo 2d: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 (d, 3H), 2.66 – 2.67 (d, 3H), 3.21 (s, 3H), 3.23 (d, 1H), 3.47 – 3.54 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.97 – 4.01 (m, 1H), 4.18 (d, 1H), 4.48 (m, 1H), 4.49 (s, 2H), 6.08 (q, 1H), 6.78 (s, 1H), 7.49 – 7.53 (m, 2H), 8.20 – 8.22 (m, 2H), 8.76 (s, 1H)

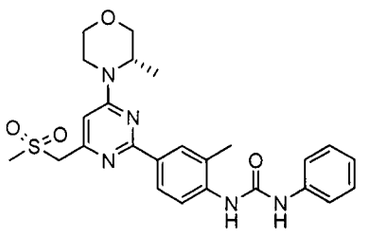
Ejemplo 2e: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.24 – 1.26 (m, 3H), 2.69 (d, 3H), 3.23 – 3.24 (m, 1H), 3.26 – 3.27 (m, 1H), 3.20 (s, 3H), 3.47 – 3.54 (m, 1H), 3.64 – 3.67 (m, 1H), 3.79 (d, 1H), 3.97 – 4.01 (m, 1H), 4.16 – 4.20 (m, 1H), 4.50 (s, 2H), 6.57 (q, 1H), 6.82 (s, 1H), 8.02 – 8.09 (m, 1H), 8.05 – 8.07 (m, 1H), 8.29 (m, 1H), 8.55 (d, 1H)

Ejemplo 2f: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 – 1.27 (m, 3H), 2.96 (s, 6H), 3.20 (s, 3H), 3.48 – 3.55 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 3.98 – 4.02 (m, 1H), 4.21 (t, 1H), 4.40 (m, 1H), 4.51 (s, 2H), 6.85 (s, 1H), 7.68 (t, 1H), 8.02 – 8.11 (m, 2H), 8.15 (s, 1H)

Prueba (a): Ejemplo (2) 0.31 μM; Ejemplo (2a) 2.3 μM; Ejemplo (2b) 0.29 μM; Ejemplo (2c) 1.2 μM; Ejemplo (2d) 0.0068 μM; Ejemplo (2e) 0.038 μM; Ejemplo (2f) 1.7 μM.

Ejemplo 3:

1-[2-Metil-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-fenil-urea

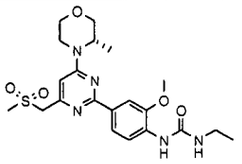
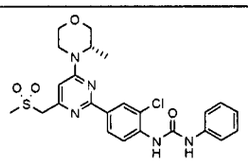
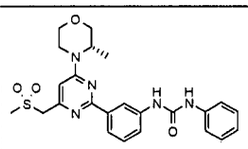
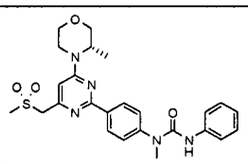


2-Metil-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]anilina (130 mg, 0.34 mmol) fue disuelta en 1,4-dioxano (4 mL). Fenilisocianato (0.038 mL, 0.34 mmol) fue añadido y la reacción calentada a 75°C durante 3 horas. La mezcla de reacción fue evaporada hasta secarse y el residuo resultante triturado con etil acetato para dar el compuesto deseado como un sólido color crema (42 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.25 (s, 3H), 2.34 (s, 3H), 3.21 (s, 3H), 3.23 – 3.26 (m, 1H), 3.48 – 3.55 (m, 1H), 3.64 – 3.68 (m, 1H), 3.79 (d, 1H), 4.00 (d, 1H), 4.20 (d, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 6.97 – 7.01 (m, 1H), 7.31 (d, 2H), 7.47 – 7.50 (m, 2H), 8.08 (s, 2H), 8.13 (d, 2H), 9.13 (s, 1H)

Espectro LCMS: MH+ 496, tiempo de retención 2.08 minutos, Método Ácido 5 Min

El siguiente compuesto fue preparado de una forma análoga a partir de la anilina e isocianato apropiados.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
3a		1–etil–3–[2–metoxi–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	464	1.54	Purificado por cromatografía en fase inversa seguido por cromatografía en fase normal
3b		1–[2–Cloro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–fenil–urea	515	2.51	Purificado en sílice eluyendo con 0–4% metanol en DCM
3c		1–[3–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–fenil–urea	481	2.30	Purificado por recristalización a partir de DMF/agua (dos veces) seguido por trituración con acetonitrilo
3d		1–Metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–fenil–urea	496	2.18	

Ejemplo 3a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.07 (t, 3H), 1.25 (d, 3H), 3.09 – 3.14 (m, 2H), 3.19–3.24 (m, 1H), 3.25 (s, 3H), 3.47 – 3.54 (m, 1H), 3.64 – 3.68 (m, 1H), 3.78 (d, 1H),

3.92 (s, 3H), 3.97 – 4.01 (m, H), 4.17 – 4.20 (m, 1H), 4.50 (s, 3H), 6.78 (s, 1H), 6.95 (t, 1H), 7.87 – 7.90 (m, 2H), 8.06 (s, 1H), 8.21 – 8.24 (m, 1H)

Ejemplo 3b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.26 (d, 3H), 3.20 (s, 3H), 3.25 (d, 1H), 3.48–3.54 (m, 1H), 3.64–3.68 (m, 1H), 3.79 (d, 1H), 3.98–4.02 (m, 1H), 4.20 (d, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 6.84 (s, 1H), 7.02 (t, 1H), 7.32 (d, 2H), 7.49 (d, 2H), 8.24–8.27 (m, 1H), 8.34 (d, 1H), 8.34–8.37 (m, 1H), 8.49 (s, 1H), 9.52 (s, 1H)

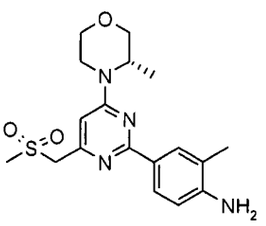
Ejemplo 3c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.27 (d, 3H), 3.23 (s, 3H), 3.26 (m, 1H), 3.49–3.56 (m, 1H), 3.65–3.69 (m, 1H), 3.80 (d, 1H), 3.99–4.03 (m, 1H), 4.20 (d, 1H), 4.53 (s, 3H), 6.87 (s, 1H), 6.98 (t, 1H), 7.29 (t, 2H), 7.40 (t, 1H), 7.47 (d, 2H), 7.71–7.74 (m, 1H), 7.95 (d, 1H), 8.31 (s, 1H), 8.65 (s, 1H), 8.82 (s, 1H)

Ejemplo 3d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.25 (d, 3H), 3.21 (s, 3H), 3.34 (s, 3H), 3.39 (m, 1H), 3.50 (d, 1H), 3.66 (d, 1H), 3.79 (d, 1H), 4.00 (d, 1H), 4.17 (d, 1H), 4.52 (s, 3H), 6.85 (s, 1H), 6.96 (t, 1H), 7.24 (t, 2H), 7.44 (m, 4H), 8.33 (s, 1H), 8.35 (s, 2H)

Prueba (a): Ejemplo (3) 1.5 μM; Ejemplo (3a) 0.1 μM; Ejemplo (3b) 0.44 μM; Ejemplo (3c) 3.3 μM; Ejemplo (3d) 2.9 μM.

La preparación de 2–metil–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina es descrita a continuación.

2–Metil–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina



4–Bromo–2–metilanilina (1.00 g, 5.37 mmol), acetato de potasio (1.59 g, 16.1 mmol) y 4,4,5,5–tetrametil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1,3,2–dioxaborolano (1.64 g, 6.45 mmol) fueron disueltos en 1,4–dioxano (20 mL) y la solución desgasificada durante 5 minutos. Diclorobis(trifenilfosfina)paladio (264 mg, 0.32 mmol) fue añadido y la reacción agitada a 90°C durante 4 horas. 2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.65 g, 5.37 mmol), etanol (1.5 mL), solución acuosa de

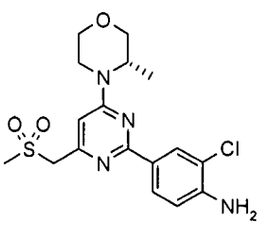
carbonato de sodio 2M (3 mL) y diclorobis(trifenilfosfina)paladio (264 mg) fueron añadidos. La reacción fue mantenida a 90°C durante 18 horas luego se dejó enfriar hasta la temperatura ambiente. Agua (15 mL) y etil acetato (15 mL) fueron añadidos y la mezcla fue filtrada para eliminar las impurezas insolubles. Las fases fueron separadas y la capa acuosa extraída con una segunda porción de etil acetato (15 mL). Los productos orgánicos combinados fueron secados ($MgSO_4$) y concentrados al vacío. El residuo fue cromatografiado en sílice, eluyendo con 0–3% metanol en DCM, para dar el compuesto deseado como una espuma beige (290 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.22 – 1.24 (m, 3H), 3.16 – 3.19 (m, 1H), 3.20 (s, 3H), 3.46 – 3.52 (m, 1H), 3.62 – 3.66 (m, 1H), 3.77 (d, 1H), 3.90 (s, 1H), 3.96 – 4.00 (m, 1H), 4.14 – 4.18 (m, 1H), 4.43 (s, 2H), 4.45 (s, 1H), 5.32 (s, 2H), 6.63 (s, 1H), 6.66 (s, 1H), 7.91 – 7.94 (m, 2H)

Espectro LCMS: MH+ 377, tiempo de retención 1.21 min, Método Ácido 5 Min

La preparación de 2–cloro–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina es descrita a continuación.

2–Cloro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina



4–Bromo–2–cloroanilina (1.00 g, 4.84 mmol), acetato de potasio (1.58 g, 14.5 mmol) y bis(pinacolato)diboro (1.64 g, 5.81 mmol) fueron disueltos en 1,4–dioxano (20 mL). La solución fue desgasificada bajo nitrógeno durante 5min. [1,1'–Bis(difenilfosfino)ferroceno] (213 mg, 0.29 mmol) fue añadido. La reacción fue agitada a 90°C durante 4 horas. Etanol (1.5 mL), 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.49 g, 4.84 mmol), solución de carbonato de sodio 2M (5.4 mL) y [1,1'–bis(difenilfosfino)ferroceno] (213 mg) fueron añadidos y el calentamiento se continuó durante 18 horas. La reacción fue evaporada hasta secarse y el residuo particionado entre agua (15 mL) y etil acetato (15 mL). La mezcla fue filtrada para eliminar el material insoluble, las fases fueron separadas y la capa

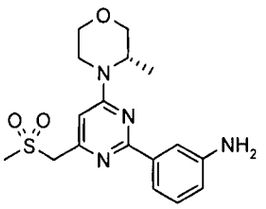
acuosa fue lavada con etil acetato (15 mL). Los productos orgánicos combinados fueron secados sobre sulfato de magnesio y evaporados hasta obtener un aceite amarillo. El producto crudo fue purificado por cromatografía en sílice, eluyendo con 0–4% metanol en DCM, para dar el material deseado como una espuma color crema (1.1 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.22–1.24 (m, 3H), 3.18 (s, 3H), 3.19–3.21 (m, 1H), 3.45–3.52 (m, 1H), 3.62–3.65 (m, 1H), 3.77 (d, 1H), 3.96–4.00 (m, 1H), 4.13–4.17 (m, 1H), 4.46 (s, 3H), 5.82 (s, 2H), 6.72 (s, 1H), 6.85 (d, 1H), 8.00–8.03 (m, 1H), 8.14 (d, 1H)

Espectro LCMS: MH+397, tiempo de retención 1.64 min, Método Ácido 5 Min

La preparación de 3–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina es descrita a continuación.

3–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina



2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.50 g, 4.91 mmol) fue disuelta en 18% DMF en 7:3:2 dimetoxietano:agua:etanol (15 mL). Ácido (3–Aminofenil)borónico (1.01 g, 7.36 mmol), carbonato de sodio 2M (5 mL) y diclorobis(trifenilfosfina) paladio (173 mg, 0.25 mmol) fueron añadidos a la solución. La reacción fue refluida a 90°C durante 18 horas bajo una atmósfera de nitrógeno luego la reacción se dejó enfriar y fue particionada entre etil acetato (50 mL) y agua (50 mL). La capa orgánica fue secada sobre sulfato de magnesio, filtrada y sometida a vacío hasta secarse. El aceite marrón resultante fue disuelto en DCM y filtrado para eliminar el material insoluble luego el filtrado fue cromatografiado en sílice, eluyendo con 0–4% metanol en DCM, para dar el producto deseado como un aceite amarillo (1.61 g).

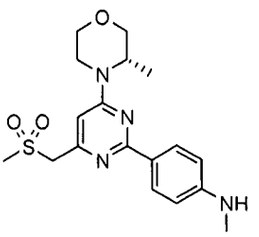
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.24–1.26 (m, 3H), 2.90 (s, 3H), 3.19–3.26 (m, 1H), 3.47–3.54 (m, 1H), 3.64–3.68 (m, 1H), 3.77–3.80 (m, 1H), 3.99 (d, 1H), 4.17 (s,

1H), 4.49 (s, 3H), 6.67–6.70 (m, 1H), 6.81 (s, 1H), 7.11 (d, 1H), 7.50–7.52 (m, 1H), 7.57–7.58 (m, 1H), 7.96 (s, 1H)

Espectro LCMS: MH+364, tiempo de retención 0.93 min, Método Ácido 5 Min

La preparación de *N*–metil–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina es descrita a continuación.

N–Metil–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]anilina



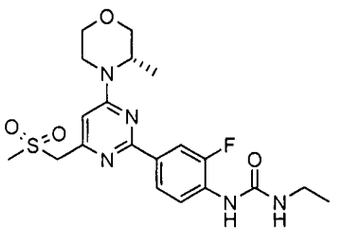
2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.01 g, 3.30 mmol) fue disuelta en 18% DMF en 7:3:2 dimetoxi etano:agua:etanol (7 mL). *N*–Metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (1.00 g, 4.29 mmol), solución de carbonato de sodio 2M (4 mL) y diclorobis(trifenilfosfina) paladio (116 mg, 0.16 mmol) fueron añadidos a la solución. La reacción fue refluida a 90°C durante 3 horas bajo una atmósfera de nitrógeno luego la mezcla se dejó enfriar y fue particionada entre etil acetato (30 mL) y agua (30 mL). La capa orgánica fue secada sobre sulfato de magnesio, filtrada y evaporada hasta secarse. El aceite marrón fue disuelto en DCM y filtrado para eliminar el material insoluble luego el filtrado fue cromatografiado en sílice, eluyendo con 0–4% metanol en DCM, para dar el producto deseado como una espuma amarilla (1.12 g, 90%).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.23 (d, 3H), 2.74 (d, 3H), 3.06–3.17 (m, 1H), 3.21 (s, 3H), 3.46–3.52 (m, 1H), 3.62–3.66 (m, 1H), 3.77 (d, 1H), 3.96–4.00 (m, 1H), 4.14 (d, 1H), 4.44 (s, 2H), 4.46 (s, 1H), 6.14 (q, 1H), 6.57–6.61 (m, 2H), 6.67 (s, 1H), 8.10–8.13 (m, 2H)

Espectro LCMS: MH+377, tiempo de retención 1.33 min, Método Ácido 5 Min

Ejemplo 4:

1–Etil–3–[2–fluoro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea

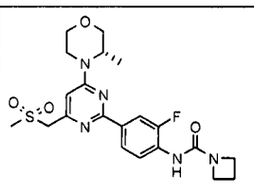


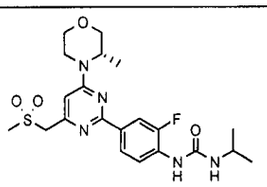
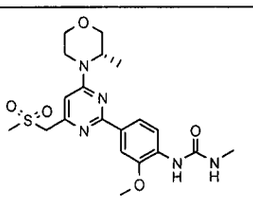
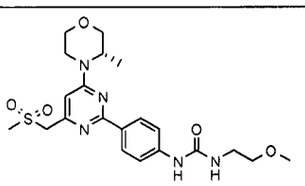
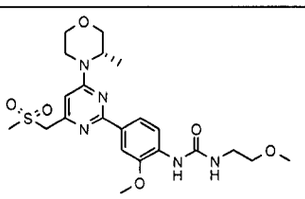
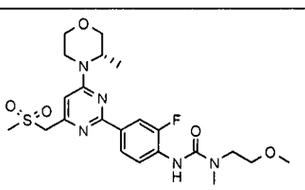
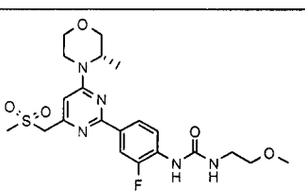
Bis(triclorometil) carbonato (44 mg, 0.16 mmol) fue disuelto en DCM (0.25 mL) para dar una solución incolora. 2-Fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]anilina (140 mg, 0.39 mmol) fue disuelta en DCM (2.0 mL) y piridina (0.2 mL). La solución resultante fue añadida en forma de gotas a la solución de bis(triclorometil) carbonato a 0°C y la mezcla se dejó calentar hasta la temperatura ambiente luego fue agitada durante 10 minutos. Etilamina (2M en THF, 0.5 mL, 1.0 mmol) fue añadida y la mezcla agitada a temperatura ambiente durante 1 hora. Agua (5 mL) fue añadida y la capa acuosa fue extraída con DCM (5 mL). Las capas orgánicas combinadas fueron secadas ($MgSO_4$) y concentradas al vacío. El aceite crudo fue purificado por HPLC prep. para dar el material deseado como un sólido blanco (149 mg, 84%).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.08 (t, 3H), 1.25 (d, 3H), 3.13 – 3.18 (m, 2H), 3.20 (s, 3H), 3.22 – 3.27 (m, 1H), 3.47 – 3.53 (m, 1H) 3.63 – 3.67 (m, 1H), 3.78 (d, 1H), 3.97 – 4.01 (m, 1H), 4.16 – 4.20 (m, 1H), 4.49 (m, 3H), 6.68 (t, 1H), 6.81 (s, 1H), 8.01 – 8.08 (m, 2H), 8.29 (t, 1H), 8.47 (d, 1H)

Espectro de masa:

Los siguientes compuestos fueron preparados de una forma análoga usando la anilina y aminas apropiadas.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
4a		*N*-[2-Fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]azetidina-1-carboxamida	463	1.61

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
4b		3-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-propan-2-il-urea	465	1.83
4c		3-[2-metoxi-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-metil-urea	450	1.36
4d*		1-(2-metoxietil)-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	464	1.32
4e*		1-(2-metoxietil)-3-[2-metoxi-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	440	1.47
4f*		3-[2-Fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-(2-metoxietil)-1-metil-urea	495	1.74
4g*		3-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-(2-	482	1.87

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metoxietil)urea		

* Cromatografiado en sílice, eluyendo con 0 – 5% metanol en DCM

Ejemplo 4a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.25 (d, 3H), 2.16 – 2.24 (m, 2H), 3.20 (s, 3H), 3.23 – 3.26 (m, 1H), 3.47 – 3.54 (m, 1H), 3.63 – 3.67 (m, 1H), 3.78 (d, 1H), 4.00 (t, 5H), 4.19 (d, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.83 – 7.87 (m, 1H, 8.04 (d, 1H6), 8.08 – 8.10 (m, 1H), 8.18 (s, 1H)

Ejemplo 4b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.12 (d, 6H), 1.25 (d, 3H), 3.20 (s, 3H), 3.24 (d, 1H), 3.47 – 3.53 (m, 1H), 3.63 – 3.67 (m, 1H), 3.74 – 3.82 (m, 2H), 3.97 – 4.01 (m, 1H), 4.18 (d, 1H), 4.49 (s, 3H), 6.63 (d, 1H), 6.81 (s, 1H), 8.01 – 8.08 (m, 2H), 8.29 (t, 1H), 8.37 (d, 1H)

Ejemplo 4c: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 – 1.26 (m, 3H), 2.66 – 2.67 (m, 3H), 3.18 (d, 1H), 3.23 (s, 3H), 3.48 – 3.55 (m, 1H), 3.65 – 3.68 (m, 1H), 3.79 (d, 1H), 3.92 (s, 3H), 3.98 – 4.02 (m, 1H) 4.19 (s, 1H), 4.50 (s, 2H), 6.79 (s, H.), 6.85 (d, 1H), 7.90 (s, 1H), 8.11 (s, 1H), 8.22 – 8.24 (m, 1H)

Ejemplo 4d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.24 (d, 3H), 3.19 – 3.24 (m, 2H), 3.21 (s, 3H), 3.27 (s, 3H), 3.40 (t, 2H), 3.47 – 3.53 (m, 1H), 3.63 – 3.67 (m, 1H), 3.78 (d, 1H), 3.97 – 4.01 (m, 1H), 4.17 (s, 1H), 4.49 (s, 3H), 6.27 (t, 1H), 6.77 (s, 1H), 7.47 – 7.51 (m, 2H), 8.19 – 8.23 (m, 2H), 8.78 (s, 1H)

Ejemplo 4e: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 – 1.26 (m, 3H), 3.23 (s, 3H), 3.27 (s, 1H), 3.28–3.21 (m, 2H), 3.38 – 3.40 (m, 2H), 3.51 (d, 1H), 3.66 (d, 1H), 3.77 (s, 1H), 3.92 (s, 3H), 4.00 (d, 1H), 4.17 – 4.21 (m, 1H), 4.50 (s, 3H), 6.79 (s, 1H), 7.12 (s, 1H), 7.88 – 7.90 (m, 2H), 8.22 – 8.24 (m, 1H), 8.26 (1s, H)

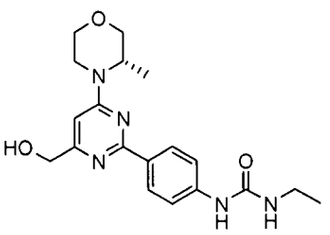
Ejemplo 4f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.24 – 1.26 (m, 3H.), 2.97 (s, 3H), 3.20 (s, 3H), 3.23 – 3.26 (m, 1H), 3.47 – 3.56 (m, 5H), 3.64 – 3.67 (m, 1H), 3.78 (d, 1H), 3.97 – 4.01 (m, 1H), 4.17 – 4.21 (m, 1H), 4.50 (s, 3H), 6.84 (s, 1H), 7.82 (t, 1H), 8.02 – 8.10 (m, 2H), 8.41 (s, 1H)

Ejemplo 4g: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 (d, 3H), 3.20 (s, 3H), 3.23 (m, 1H), 3.29 (m, 2H), 3.30 (s, 3H), 3.41 (t, 2H), 3.51 (d, 1H), 3.65 (d, 1H), 3.78 (d, 1H), 3.97 – 4.01 (m, 1H), 4.19 (d, 1H), 4.50 (s, 3H), 6.82 (s, 1H), 6.87 (t, 1H), 8.02 – 8.09 (m, 2H), 8.29 (t, 1H), 8.63 (d, 1H)

Prueba (a): Ejemplo (4) 0.031 μM; Ejemplo (4a) 1 μM; Ejemplo (4b) 0.14 μM; Ejemplo (4c) 0.8 μM; Ejemplo (4d) 0.17 μM; Ejemplo (4e) 0.6 μM; Ejemplo (4f) 0.68 μM; Ejemplo (4g) 0.83 μM.

Ejemplo 5:

1–Etil–3–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



1–[4–[4–[(Dimetil–*tert*–butil–silil)oximetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea (104 mg) fue disuelta en THF (10 mL) y TBAF (solución 1.0 M, 0.22 mL) fue añadido. La reacción se dejó agitar durante 1 hora a temperatura ambiente y luego se pasó por una columna SCX–2. La columna fue lavada con metanol y el material deseado eluido con amoniaco 7N en metanol. Las fracciones fueron concentradas al vacío para dar el compuesto deseado (76 mg) como un sólido blanco.

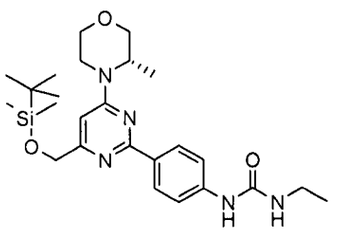
Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.07 (3H, t), 1.23 (3H, d), 3.11 – 3.16 (2H, m), 3.19 – 3.23 (1H, m), 3.49 (1H, d), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.95 – 3.99 (1H, m), 4.16 (1H, d), 4.45 (2H, d), 4.48 (1H, s), 5.38 (1H, s), 6.14 (1H, t), 6.66 (1H, s), 7.46 (2H, d), 8.19 (2H, d), 8.62 (1H, s)

Espectro de masa: $M+H^+$ 372.

Prueba (a): 0.063 μM.

La preparación de 1–[4–[4–[(dimetil–*tert*–butil–silil)oximetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea es descrita a continuación.

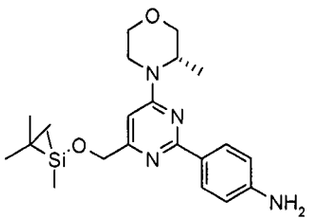
1-[4-[4-[(Dimetil-*tert*-butil-silil)oximetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etil-urea



4-[4-[(Dimetil-*tert*-butil-silil)oximetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (250 mg) fue disuelta en 1,4-dioxano (4 mL) y etil isocianato (0.144 mL) fue añadido. La reacción fue calentada hasta 120°C durante 1 hora en un reactor de microondas. La reacción fue concentrada al vacío luego el residuo cromatografiado en sílice, eluyendo con 2.5% metanol en DCM, para dar el compuesto deseado (106 mg) como un sólido blanco.

Espectro de masa: $M+H^+$ 486.

4-[4-[(Dimetil-*tert*-butil-silil)oximetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

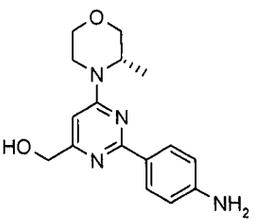


[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (1.54 g) fue disuelto en DCM (60 mL) y *tert*-butildiemetilsililcloruro (928 mg) e imidozol fue añadido. La mezcla fue agitada a temperatura ambiente durante 0.5 horas antes de ser filtrada y concentrada al vacío. El residuo fue cromatografiado en sílice, eluyendo con 1% metanol en DCM, para dar el compuesto deseado (1.61 g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.12 – 0.13 (6H, m), 0.94 – 0.95 (9H, m), 1.21 (3H, d), 3.13 – 3.20 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.13 (1H, d), 4.37 – 4.39 (1H, m), 4.60 (2H, s), 5.48 (2H, d), 6.50 (1H, s), 6.57 – 6.59 (2H, m), 8.02 – 8.04 (2H, m)

Espectro de masa: $M+H^+$ 415.

[2–(4–Aminofenil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol

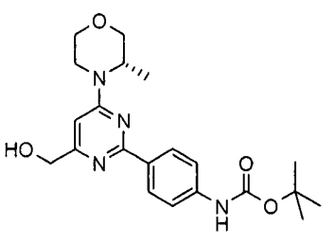


tert–Butil *N*–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (1.20 g) fue disuelto en hidrógeno cloruro 4M en dioxano (5 mL) y dioxano (5 mL). La reacción fue agitada durante 18 horas, luego DCM (10 mL) fue añadido para ayudar a solubilizar el material. La reacción fue agitada a 40°C durante unas 18 horas adicionales, luego evaporada hasta secarse. El sólido fue suspendido en DCM (20 mL) y una mezcla de una solución saturada acuosa de hidrógeno carbonato de sodio (6 mL) y agua (4 mL) fue añadida. Los productos orgánicos fueron separados, secados ($MgSO_4$) y concentrados al vacío para dar el compuesto deseado (648 mg) como un sólido amarillo pálido.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.21 (3H, d), 3.16 (1H, d), 3.48 (1H, d), 3.61 – 3.65 (1H, m), 3.75 (1H, d), 3.95 (1H, d), 4.13 (1H, d), 4.41 (2H, d), 4.45 (1H, s), 5.32 (1H, t), 5.47 (2H, s), 6.57 – 6.59 (3H, m), 8.02 – 8.04 (2H, m)

Espectro de masa: $M+H^+$ 301.

tert–Butil *N*–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

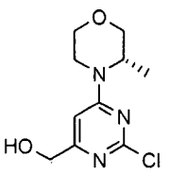


Una mezcla de [2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (2.44 g), ácido (4–Boc–aminofenil)borónico (4.76 g), solución 2M de carbonato de sodio (10 mL) y una mezcla de solventes (18% DMF en 7:3:2 DME: Agua: Etanol) (35 mL) fue desgasificada. Diclorobis(trifenilfosfina) paladio (300 mg) fue añadido y la reacción calentada a 80°C durante 3 horas. La reacción se dejó enfriar y fue concentrada al vacío. El residuo fue particionado entre etil acetato (200 mL) y agua (200 mL), los productos orgánicos lavados

con salmuera (100 mL) y secados ($MgSO_4$). El material crudo fue cromatografiado en sílice, eluyendo con 2.5% metanol en DCM, para dar el compuesto deseado (4.00 g) como un sólido blanco.

Espectro de masa: $M+H^+$ 401.

[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol

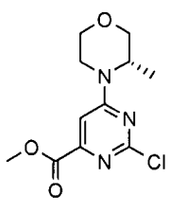


Metil 2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato (3.15 g) fue disuelto en THF seco (20 mL) y enfriado hasta 0°C bajo nitrógeno. A esto es añadida en forma de gotas una solución de borohidruro de litio (2.0M en THF, 6.09 mL). La solución se dejó calentar hasta la temperatura ambiente y agitada durante 1 hora. La reacción fue apagada con agua (20 mL) y luego evaporada hasta secarse. El residuo fue disuelto en etil acetato (150 mL) y lavado con agua (150 mL) seguido por salmuera (50 mL). Los productos orgánicos fueron concentrados al vacío para dar el compuesto deseado (2.44 g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.20 – 1.21 (3H, m), 3.18 – 3.22 (1H, m), 3.40 – 3.47 (1H, m), 3.56 – 3.60 (1H, m), 3.71 (1H, d), 3.91 – 3.94 (1H, m), 3.98 (1H, d), 4.35 (3H, d), 5.51 (1H, t), 6.74 (1H, s)

Espectro de masa: $M+H^+$ 244.

Metil 2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato



Metil 2,6–dicloropirimidina–4–carboxilato (5.00 g) fue disuelto en DCM (120 mL). (3*S*)–3–Metilmorfolina (2.49 g) disuelta en trietilamina (3.70 mL) y DCM (10 mL) fue añadida en forma de gotas a la solución durante 10 minutos. La reacción se dejó agitar a temperatura ambiente durante 1 hora, luego la mezcla fue concentrada al vacío y disuelta en DCM (300 mL). Los productos orgánicos fueron lavados con agua (150 mL) y secados ($MgSO_4$). El

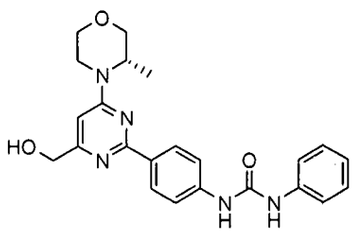
material crudo fue cromatografiado en sílice, eluyendo con 2.5% metanol en DCM, para dar el compuesto deseado (3.15 g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.22 – 1.24 (3H, m), 3.25 (1H, d), 3.41 – 3.48 (1H, m), 3.57 – 3.61 (1H, m), 3.71 (1H, d), 3.87 (3H, s), 3.91 – 3.95 (1H, m), 4.25 (1H, s), 4.45 (1H, s), 7.29 (1H, s)

Espectro de masa: M+H$^+$ 272.

Ejemplo 6:

1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea



1–(4–Bromo–fenil)–3–fenil–urea (960 mg), acetato de potasio (969 mg), bis(pinacolato)diboro (1.01 g) fueron disueltos en 1,4 dioxano (50 mL). La solución fue desgasificada durante 5 minutos, luego aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano fue añadido (162 mg) y la reacción fue calentada hasta 80°C durante 3 horas. Más aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano fue añadido (162 mg) y la reacción fue agitada a 80°C durante otras 3 horas. [2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (803 mg), etanol (3.75 mL), solución de carbonato de sodio 2M (6.9 mL) y aducto 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (162 mg) fueron añadidos y el calentamiento se continuó durante 16 horas. Más etanol (5 mL) y aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (162 mg) fueron añadidos y la reacción se dejó agitar durante otras 5 horas antes de dejarse enfriar y ser neutralizada con ácido clorhídrico 2M. La mezcla de reacción fue pasada a través de tres columnas SCX–2, cada vez cargando la muestra y lavando con metanol, luego eliminando el material deseado con amoniaco 7N en metanol. La solución fue concentrada al vacío, y el residuo cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (398 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.24 (3H, d), 3.20 – 3.24 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.18 (1H, d), 4.47 (2H, d), 4.50 (1H, s), 5.39 (1H, t), 6.68 (1H, s), 6.97 – 7.01 (1H, m), 7.28 – 7.31 (1H, m), 7.30 (1H, s), 7.46 – 7.48 (2H, m), 7.52 – 7.56 (2H, m), 8.25 – 8.27 (2H, m), 8.68 (1H, s), 8.87 (1H, s)

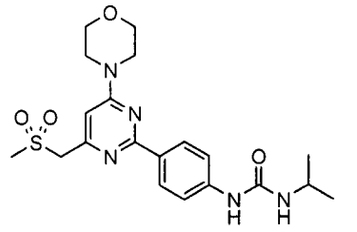
Espectro de masa: M+H$^+$ 419.

Prueba (a): 0.56 μM.

La preparación de [2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol fue descrita anteriormente.

Ejemplo 7:

3–[4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–propan–2–il–urea

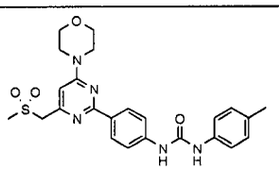
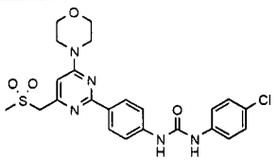
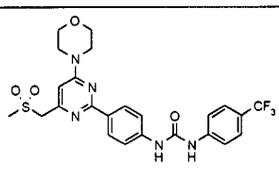
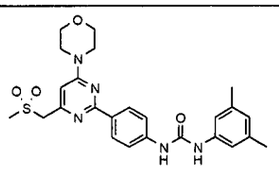
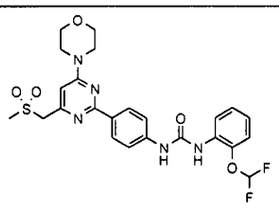
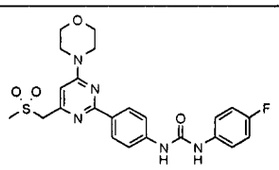
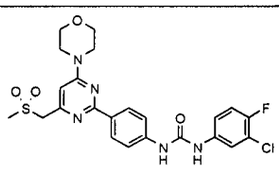


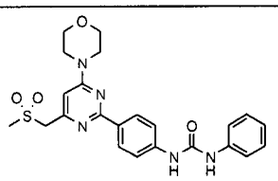
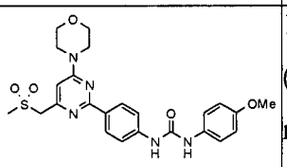
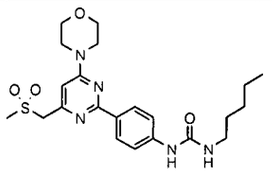
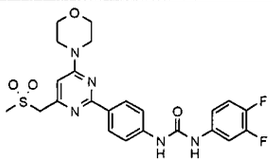
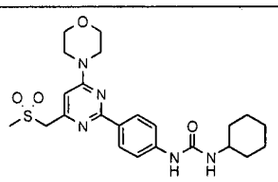
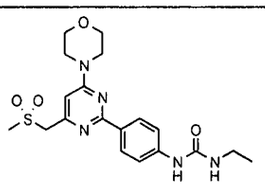
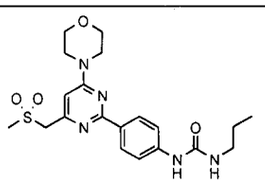
4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]anilina (70 mg, 0.2 mmol) e isoproilisocianato (0.1 mL, 1 mmol) fueron calentados en dioxano (2 mL) a 70°C durante 4 horas. La mezcla de reacción fue evaporada y el residuo triturado con etil acetato. La suspensión fue filtrada y el sólido blanco lavado con etil acetato y dietil éter, luego secado al vacío a 60°C toda la noche para producir el compuesto del título (38 mg).

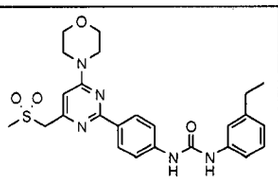
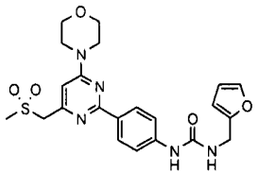
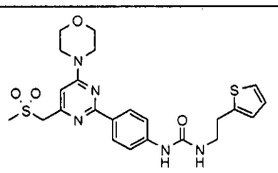
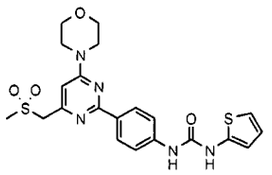
Espectro LCMS: MH+ 434, Tiempo de retención 1.66 min, Método: Básico Monitor

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.11 (d, 6H), 3.2 (s, 3H), 3.7 (m, 8H), 3.76 (m, 1H), 4.48 (s, 2H), 6.05 (d, 1H), 6.8 (s, 1H), 7.48 (d, 2H), 8.2 (d, 2H), 8.54 (s, 1H)

Los siguientes compuestos fueron preparados de una forma análoga a partir de XXX usando el isocianato apropiado.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7a		1–(4–metilfenil)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	482.03	2.15
7b		3–(4–clorofenil)–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	501.95	2.26
7c		1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–3–[4–(trifluorometil)fenil]urea	536.00	2.39
7d		1–(3,5–dimetilfenil)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	496.05	2.29
7e		3–[2–(difluorometoxi)fenil]–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	533.97	2.25
7f		3–(4–fluorofenil)–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	485.97	2.07
7g		3–(3–cloro–4–fluoro–fenil)–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	519.96	2.29

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7h*		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-fenil-urea	468.56	3.00
7i*		1-(4-metoxifenil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	498.60	2.93
7j*		3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-1-pentil-urea	462.64	3.02
7k*		3-(3,4-difluorofenil)-1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	504.59	
7l*		3-ciclohexil-1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	474.63	3.02
7m*		1-etil-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	420.60	2.49
7n*		3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-1-propil-urea	434.61	2.66

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7o*		1-(3-etilfenil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	496.62	3.29
7p*		3-(2-furilmetil)-1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	472.58	2.76
7q*		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-(2-tiofen-2-iletil)urea	502.58	2.96
7r*		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-tiofen-2-il-urea	474.54	2.92

* Los compuestos fueron purificados adicionalmente por HPLC prep.

Ejemplo 7a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.25 (s, 3H), 3.21 (s, 3H), 3.71 (s, 8H), 4.49 (s, 2H), 6.83 (s, 1H), 7.09 (d, 2H), 7.34 (d, 2H), 7.56 (d, 2H), 8.26 (d, 2H), 8.6 (s, 1H), 8.88 (s, 1H)

Ejemplo 7b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.22 (s, 3H), 3.70 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (d, 2H), 7.50 (d, 2H), 7.56 (d, 2H), 8.28 (d, 2H), 8.84 (s, 1H), 8.95 (s, 1H)

Ejemplo 7c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.59 (d, 2H), 7.65 (m, 4H), 8.3 (d, 2H), 9.40 (s, 1H), 9.13 (s, 1H)

Ejemplo 7d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ2.23 (s, 6H), 3.21 (s, 3H), 3.72 (bs, 8H), 4.49 (s, 2H), 6.64 (s, 1H), 6.85 (s, 1H), 7.08 (s, 2H), 7.55 (d, 2H), 8.28 (d, 2H), 8.58 (s, 1H), 8.92 (s, 1H)

Ejemplo 7e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.05 (m, 1H), 7.22 (m, 2H), 7.59 (d, 2H), 8.24 (d, 1H), 8.3 (d, 2H), 8.38 (s, 1H), 9.60 (s, 1H)

Ejemplo 7f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.22 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.12 (m, 2H), 7.48 (m, 2H), 7.55 (d, 2H), 8.26 (d, 2H), 8.73 (s, 1H), 8.90 (s, 1H)

Ejemplo 7g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.21 (s, 3H), 3.72 (s, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (m, 2H), 7.56 (m, 2H), 7.8 (m, 1H), 8.28 (m, 2H), 8.95 (s, 1H), 9.05 (s, 1H)

Ejemplo 7i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.22 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.84 (s, 1H), 7.34 (d, 2H), 7.50 (d, 2H), 7.56 (d, 2H), 8.28 (d, 2H), 8.84 (s, 1H), 8.95 (s, 1H)

Ejemplo 7j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.88 (m, 3H), 1.39 (m, 4H), 1.43 (m, 2H), 3.08 (m, 2H), 3.21 (s, 3H), 3.70 (bs, 8H), 4.47 (s, 2H), 6.2 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.66 (s, 1H)

Ejemplo 7m: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.05 (t, 3H), 3.12 (q, 2H), 3.21 (s, 3H), 3.7 (bs, 8H), 4.46 (s, 2H), 6.19 (t, 1H), 6.8 (s, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.69 (s, 1H)

Ejemplo 7n: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.87 (m, 3H), 1.45 (m, 2H), 3.05 (m, 2H), 3.20 (s, 3H), 3.70 (bs, 8H), 4.45 (s, 2H), 6.14 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.69 (s, 1H)

Ejemplo 7o: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.19 (t, 3H), 2.55 (q, 2H), 3.21 (s, 3H), 3.70 (bs, 8H), 4.49 (s, 2H), 6.85 (m, 2H), 7.19 (t, 2H), 7.27 (d, 1H), 7.33 (s, 1H), 7.56 (d, 2H), 8.26 (d, 2H), 8.68 (s, 1H), 8.92 (s, 1H)

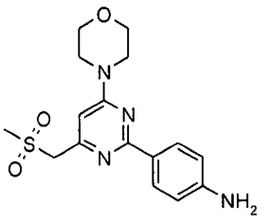
Ejemplo 7p: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.20 (s, 3H), 3.70 (bs, 8H), 4.31 (d, 1H), 4.47 (s, 2H), 6.28 (d, 1h), 6.40 (d, 1H), 6.61 (t, 1H), 6.82 (s, 1H), 7.51 (d, 2H), 7.59 (s, 1H), 8.22 (d, 2H), 8.77 (s, 1H)

Ejemplo 7q: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ2.98 (t, 2H), 3.21 (s, 3H), 3.38 (m, 2H), 3.70 (bs, 8H), 4.47 (s, 2H), 6.29 (t, 1H), 6.81 (s, 1H), 6.93 (d, 1H), 6.97 (m, 1H), 7.36 (m, 1H), 7.50 (d, 2H), 8.21 (d, 2H), 8.80 (s, 1H)

Prueba (a): Ejemplo (7) 0.17 μM; Ejemplo (7a) 0.28 μM; Ejemplo (7b) 0.42 μM; Ejemplo (7c) 1.7 μM; Ejemplo (7d) 2.6 μM; Ejemplo (7e) 2.6 μM; Ejemplo (7f) 0.029 μM; Ejemplo (7g) 1.3 μM; Ejemplo (7h) 0.24 μM; Ejemplo (7i) 0.032 μM; Ejemplo (7j) 1.9 μM; Ejemplo (7k) 0.72 μM; Ejemplo (7l) 7 μM; Ejemplo (7m) 0.081 μM; Ejemplo (7n) 0.2 μM; Ejemplo (7o) 1.7 μM; Ejemplo (7p) 3.8 μM; Ejemplo (7q) 1.7 μM; Ejemplo (7r) 0.19 μM.

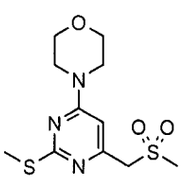
La preparación de 4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]anilina es descrita a continuación:

4-[4-(Metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]anilina



2-Metilsulfanil-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina (1.00g, 3.3 mmol), ácido 4-aminofenilborónico (904 mg, 6.60 mmol), Cobre(I)tiofeno-2-carboxilato (1.64 g, 8.58 mmol), $Pd(PPh_3)_4$ (153 mg, 0.04 equiv., 0.13 mmol) fueron añadidos a un frasco de microondas y 1,4-Dioxano (20 mL) fue añadido. El sistema fue desgasificado con N_2, sellado y calentado en un reactor de microondas a 130° C durante 1 hora. Después de enfriar la reacción fue vertida en agua y el precipitado resultante fue recogido por filtración y secado al vacío para proporcionar el compuesto del título como un sólido blanco hueso. (988 mg)
Espectro LCMS: MH+ 349.41, Tiempo de retención 1.43 Método: Ácido Monitor
Espectro NMR: ^{1}H NMR (300.132 MHz, DMSO) δ3.20 (3H, s), 3.61 – 3.83 (8H, m), 4.43 (2H, s), 5.57 (1H, s), 6.60 (2H, d), 6.70 (1H, s), 8.04 (2H, d)

2-Metilsulfanil-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina



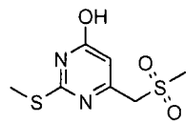
2-Metilsulfanil-6-(metilsulfonilmetil)pirimidin-4-ol (15 g, 63.97 mmol) fue calentado a reflujo en oxicloruro de fósforo (100 ml) durante aproximadamente 1 hora. El oxicloruro de fósforo fue evaporado y el residuo fue neutralizado con solución de hidróxido de sodio y extraído en etil acetato. La mezcla resultante fue luego secada sobre sulfato de magnesio, filtrada y evaporada hasta secarse para proporcionar el producto de cloro crudo. Esto fue luego disuelto en DCM, morfolina (319 mmol, 28 ml) fue añadida y la reacción agitada a

temperatura ambiente. Una vez completado, el precipitado resultante fue recogido como un sólido blanco. La concentración del filtrado proporcionó más sólido, dando un rendimiento combinado de 13.7g.

Espectro NMR: ^{1}H NMR (300.132 MHz, DMSO) δ2.45 (s, 3H), 3.49 – 3.74 (m, 8H), 4.37 (s, 2H), 6.66 (s, 1H) ppm.

Espectro LCMS: MH+ 304.50, Tiempo de retención 1.49min, Método: Básico Monitor

2–Metilsulfanil–6–(metilsulfonilmetil)pirimidin–4–ol

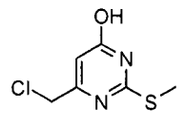


6–(Clorometil)–2–metilsulfanil–pirimidin–4–ol (19.07 g, 100 mmol) fue suspendido en acetonitrilo (400 ml). A esta suspensión en agitación fueron añadidos sal sódica del ácido metanosulfínico (12.255g, 120 mmol) y DMF (100 ml). La reacción fue luego calentada hasta 100° C para dar una suspensión oscura y monitoreada por LCMS. Una vez completada, los solventes fueron eliminados y el producto resultante añadido a 1:1 MeOH:DCM (200 ml) y acidificada con ácido acético (10 ml). El precipitado resultante fue recogido, lavado con agua (200 ml) y MeOH (100 ml) y secado toda la noche al vacío para proporcionar el compuesto del título como un sólido blanco, 16.45g.

Espectro NMR: ^{1}H NMR (300.132 MHz, DMSO) δ2.50 (s, 3H), 3.12 (s, 3H), 4.39 (s, 2H), 6.25 (s, 1H), 13.09 (s, 1H) ppm.

Espectro LCMS: MH+ 235.2, Tiempo de retención 0.5 minutos, Método: Básico Temprano 5min

6–(Clorometil)–2–metilsulfanil–pirimidin–4–ol



S–Metil–2–tiopseudourea sulfato (20 g, 71.85 mmol), etil 4–cloroacetoacetato (10.755 ml, 79.04 mmol) y carbonato de sodio (13.925 g, 107.78 mmol) fueron disueltos en agua (100 ml) y agitados a temperatura ambiente toda la noche. La reacción fue monitoreada por TLC, y una vez completada, el precipitado de la reacción fue recogido y el sobrenadante fue neutralizado con ácido clorhídrico 6N para producir más precipitado de la reacción el cual también fue

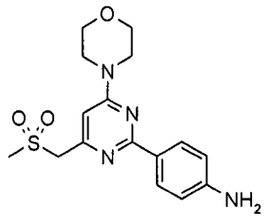
recogido. El precipitado acumulado fue luego lavado con agua (x3) y un sólido blanco hueso fue obtenido. Esto fue secado al vacío a 60° C durante 48 horas para producir el compuesto deseado como un sólido blanco/amarillo pálido, 43.2g.

Espectro NMR: ^{1}H NMR (300.132 MHz, $CDCl_3$) δ2.59 (s, 3H), 4.35 (s, 2H), 6.41 (s, 1H), 12.70 (s, 1H) ppm

Espectro de masa: M^+ 190

4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]anilina puede también ser preparada a partir de 2,4–dicloro–6–(metilsulfonilmetil)pirimidina como es descrito a continuación

4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]anilina

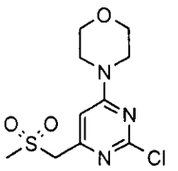


2–Cloro–4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidina (5 g, 17.1 mmol), fue disuelta en una mezcla de DMF:DME:agua:etanol (16.5 mL:41 mL:18 mL:12 mL). 4–(4,4,5,5–Tetrametil–1,3,2–dioxaborolan–2–il)anilina (5.62 g, 25.6 mmol), una solución acuosa 2M de carbonato de sodio (25 mL), y diclorobis(trifenilfosfina) paladio (600 mg) fueron añadidos y la mezcla refluida durante 5 horas bajo una atmósfera de nitrógeno. La mezcla fue enfriada, diluida con agua y extraída en DCM. La capa orgánica fue secada sobre Na_2SO_4, filtrada y evaporada. El material crudo fue disuelto en un mínimo de DCM caliente, luego hexano fue añadido y el precipitado filtrado para dar el material deseado (1.6 g).

Espectro LCMS: MH+349, Tiempo de retención 1.48min, Método : Básico Monitor

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.20 (3H, s), 3.67 – 3.72 (8H, m), 4.43 (2H, s), 5.55 – 5.56 (2H, m), 6.59 (2H, d), 6.70 (1H, s), 8.03 (2H, d)

2–Cloro–4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidina



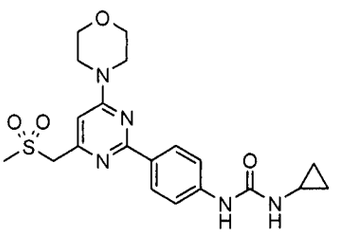
Una suspensión de 2,4–dicloro–6–(metilsulfonilmetil)pirimidina (10.56 g) en DCM (230 mL) fue agitada magnéticamente (bajo nitrógeno) y enfriada hasta –5°C. Trietilamina (6.78 mL) fue añadida seguido por la adición en forma de gotas de una solución de morfolina (3.85 mL) en DCM (30 mL) manteniendo la temperatura de la reacción por debajo de –5°C. La reacción fue agitada a temperatura ambiente durante 1 hora y luego la mezcla orgánica fue lavada con agua (300 mL). La fase orgánica fue secada ($MgSO_4$), filtrada y evaporada hasta obtener un sólido marrón el cual fue cromatografiado en sílice, eluyendo con 50% etil acetato en DCM, para dar el material deseado (6.81g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ3.12 (3H, s), 3.63 (4H, s), 3.68 – 3.70 (4H, m), 4.45 (2H, s), 6.96 (1H, s)

Espectro de masa: MH+ 292.

Ejemplo 8:

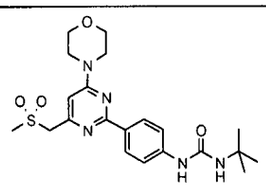
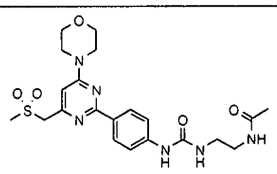
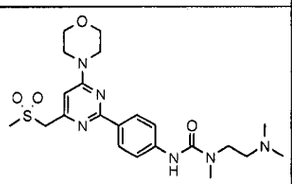
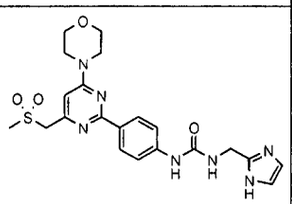
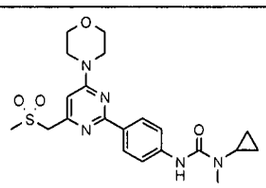
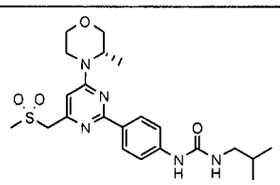
3–Ciclopropil–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea



Una mezcla de fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato (94 mg,0.2 mmol), ciclopropilamina (0.069 mL, 1 mmol), y trietilamina (0.090 mL, 0.65 mmol), en NMP (1 – 2 mL) fue calentada a 50–70°C durante 2 horas. La mezcla fue luego purificada directamente usando HPLC prep. (método Básico Monitor) para dar el material deseado.

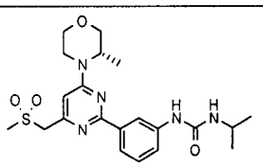
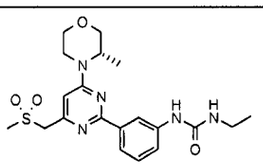
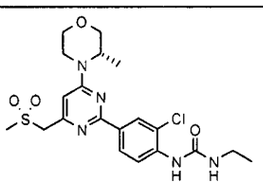
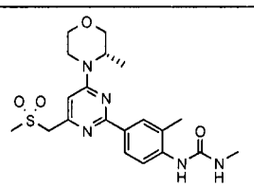
Espectro LCMS : MH+432, Tiempo de retención 2.42 min, Método Básico

Los siguientes compuestos fueron preparados de una forma análoga a partir del fenil carbamato requerido y la amina apropiada, usando NMP o DMF como el solvente.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
8a		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-tert-butil-urea	448	2.82	
8b		N-[2-[[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]carbamoilamino]etil]acetamida	478	2.24	
8c		1-(2-dimetilaminoetil)-1-metil-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	478	2.6	
8d		3-(1H-imidazol-2-ilmetil)-1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	472	2.11	
8e		1-ciclopropil-1-metil-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	446	2.45	
8f		1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(2-	462	2.84	

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
		metilpropil)urea			
8g		1–[3–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–propan–2–il–urea	448	1.71	Purificado por trituración con metanol
8h		3–Etil–1–[3–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	434	1.71	Purificado por recristalización a partir de metanol
8i		1–[2–Cloro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–etil– urea	468	1.78	
8j		3–Metil–1–[2–metil–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	434	1.28	

Ejemplo 8g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.11 (d, 6H), 1.26 (d, 3H), 3.23 (s, 3H), 3.25 (d, 1H), 3.48–3.55 (m, 1H), 3.65–3.68 (m, 1H), 3.76 (d, 1H), 3.80 (t, 1H), 3.98–4.02 (m, 1H), 4.18 (d, 1H), 4.48 (m, 1H), 4.52 (s, 2H), 5.98 (d, 1H), 6.85 (s, 1H), 7.32 (t, 1H), 7.65–7.68 (m, 1H), 7.86–7.88 (m, 1H), 8.20 (t, 1H), 8.43 (s, 1H)

Ejemplo 8h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.07 (t, 3H), 1.26 (d, 3H), 3.09–3.14 (m, 2H), 3.22 (s, 3H), 3.24 (m, 1H), 3.48–3.55 (m, 1H), 3.65–3.68 (m, 1H), 3.79 (d, 1H), 3.98–4.02 (m, 1H), 4.18 (s, 1H), 4.51 (s, 3H), 6.08 (t, 1H), 6.85 (s, 1H), 7.32 (t, 1H), 7.64–7.67 (m, 1H), 7.86–7.88 (m, 1H), 8.23 (t, 1H), 8.55 (s, 1H)

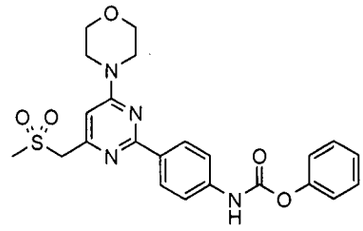
Ejemplo 8i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.09 (t, 3H), 1.25 (d, 3H), 3.15 (m, 2H), 3.19 (s, 3H), 3.20–3.26 (m, 1H), 3.47–3.53 (m, 1H), 3.63–3.67 (m, 1H), 3.78 (d, 1H), 3.97–4.01 (m, 1H), 4.18 (d, 1H), 4.46 (s, 1H), 4.50 (s, 2H), 6.82 (s, 1H), 7.13 (t, 1H), 8.14 (s, 1H), 8.17–8.20 (m, 1H), 8.28 (d, 1H), 8.33 (d, 1H)

Ejemplo 8j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (d, 3H), 2.26 (s, 3H), 2.68 (d, 3H), 3.20 (s, 3H), 3.22–3.26 (m, 1H), 3.47–3.54 (m, 1H), 3.63–3.67 (m, 1H), 3.78 (d, 1H), 3.97–4.01 (m, 1H), 4.19 (d, 1H), 4.49 (s, 3H), 6.56 (q, 1H), 6.77 (s, 1H), 7.79 (s, 1H), 8.02 (s, 1H), 8.06–8.09 (m, 2H)

Prueba (a): Ejemplo (8) 0.031 μM; Ejemplo (8a) 0.47 μM; Ejemplo (8b) 0.42 μM; Ejemplo (8c) 2.2 μM; Ejemplo (8d) 0.57 μM; Ejemplo (8e) 0.28 μM; Ejemplo (8f) 0.3 μM; Ejemplo (8g) 0.96 μM; Ejemplo (8h) 0.92 μM; Ejemplo (8i) 1.4 μM; Ejemplo (8j) 0.16 μM.

La preparación de fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato



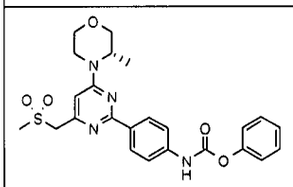
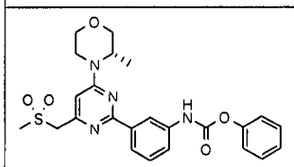
Fenil cloroformato (1.33 mL, 10.6 mmol) fue añadido a 0–5°C a una mezcla de hidrógeno carbonato de sodio (1.34 g, 15.9 mmol) y 4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]anilina (3.7 g, 10.6 mmol) en dioxano (150 mL). La reacción fue agitada a RT durante 3 horas, evaporada, y luego disuelta en DCM. La mezcla orgánica fue lavada con agua, secada sobre Na_2SO_4, filtrada y evaporada hasta obtener una espuma amarilla pálida la

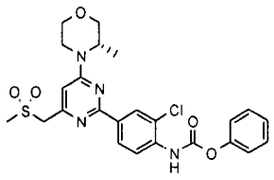
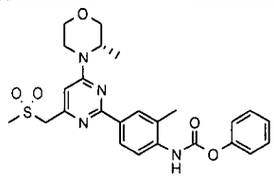
cual fue triturada con hexano/éter, luego filtrada produciendo el material deseado como un sólido blanco (5.4 g).

Espectro LCMS MH+470, Tiempo de retención 2.18 Método: Básico Monitor

Espectro NMR ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.22 (3H, s), 3.58 (4H, s), 3.73 (4H, s), 4.50 (2H, s), 6.88 (1H,s), 7.24 – 7.30 (3H, m), 7.43 – 7.47 (2H, m), 7.63 (2H, d), 8.30 (2H, d), 10.45(1H,s).

Los siguientes fenil carbamatos fueron preparados de una forma análoga a partir de la anilina apropiada.

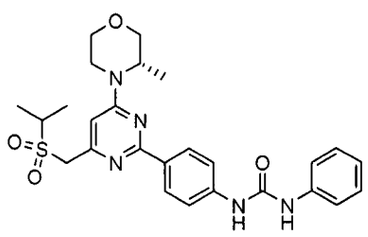
Estructura	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**	**NMR ^{1}H NMR (400.13 MHz, DMSO–d_6)**
	Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato	483	2.37	
	Fenil *N*–[3–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato	482	2.36	δ1.26 (d, 3H), 3.23 (s, 3H), 3.21–3.29 (m, 1H), 3.49–3.54 (m, 1H), 3.58 (s, 1H), 3.64–3.68 (m, 1H), 3.79 (d, 1H), 3.98–4.06 (m, 1H), 4.19 (d, 1H), 4.53 (s, 2H), 6.87 (s, 1H), 7.23–7.31 (m, 2H), 7.42 (d, 1H), 7.44–7.47 (m, 2H), 7.61–7.66 (m, 1H), 7.71 (d, 1H), 8.02–8.05 (m, 1H), 8.50 (t, 1H), 10.36 (s, 1H)

Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	NMR ^{1}H NMR (400.13 MHz, DMSO–d_6)
	Fenil *N*–[2–cloro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato	517	2.40	δ 1.26 (s, 3H), 3.20 (s, 3H), 3.24–3.25 (m, 1H), 3.48–3.54 (m, 1H), 3.64–3.68 (m, 1H), 3.79 (d, 1H), 3.98–4.02 (m, 1H), 4.18–4.23 (m, 1H), 4.51 (m, 1H), 4.55 (s, 2H), 6.90 (s, 1H), 7.14–7.18 (m, 1H), 7.24–7.28 (m, 2H), 7.42–7.45 (m, 2H), 7.84 (d, 1H), 8.29–8.31 (m,1H), 8.39 (d, 1H), 9.83 (s, 1H)
	Fenil *N*–[2–metil–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato	496	1.61	

Las preparaciones de las anilinas requeridas arriba fueron descritas anteriormente.

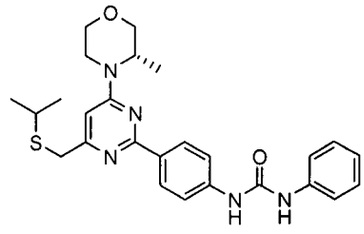
Ejemplo 9:

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]–3–fenil–urea



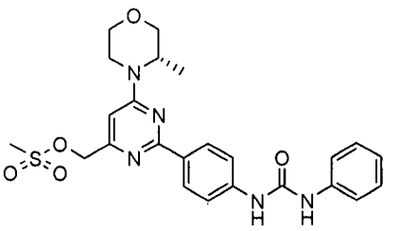
1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(propan–2–ilsulfanilmetil)pirimidin–2–il]fenil]–3–fenil–urea (78 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperoxibenzoico (75%) (34 mg) añadido seguido inmediatamente por permanganato de sodio (40 mg). La reacción se dejó agitar a temperatura ambiente durante 2 horas. La reacción fue cargada en una columna SCX–2, la columna lavada con metanol y el material deseado eluido con amoniaco 7N en metanol. Las fracciones fueron concentradas al vacío para dar el compuesto deseado como un sólido amarillo pálido (77 mg).
Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ1.25 (3H, d), 1.31 – 1.38 (6H, m), 3.18 – 3.24 (1H, m), 3.48 – 3.58 (2H, m), 3.64 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.01 (1H, m), 4.18 (1H, d), 4.48 (3H, s), 6.79 (1H, s), 6.97 – 7.01 (1H, m), 7.28 – 7.31 (1H, m), 7.31 (1H, d), 7.46 – 7.49 (2H, m), 7.56 – 7.58 (2H, m), 8.25 (2H, d), 8.73 (1H, s), 8.92 (1H, s)
Espectro de masa: $M+H^+$ 510.
Prueba (a): 0.59 μM.

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(propan–2–ilsulfanilmetil)pirimidin–2–il]fenil]–3–fenil–urea



Isopropil mercaptano (0.075 mL) fue disuelto en acetonitrilo (5 mL) y 1,8–diazabiciclo[5.4.0]undec–7–eno (0.12 mL). La reacción se dejó agitar a temperatura ambiente durante 15 minutos, luego 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea (228 mg) en acetonitrilo (5 mL) fue añadida. La reacción fue agitada durante 30 minutos, luego concentrada al vacío. El residuo fue cromatografiado en sílice, eluyendo con 2.5% metanol en DCM, para dar el compuesto deseado (78 mg) como una goma.
Espectro de masa: $M+H^+$ 478.

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea

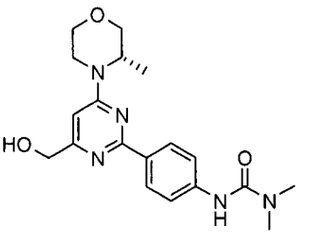


1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea (388 mg) fue disuelta en DCM (15 mL) y trietilamina (0.194 mL) y la solución fue enfriada hasta 0°C. Metanosulfonil cloruro (0.108 mL) fue añadido y la reacción agitada durante 90 min a 0°C. La mezcla de reacción fue concentrada al vacío y particionada entre DCM (20 mL) y agua (10 mL). La fase orgánica fue lavada con salmuera (10 mL), secada ($MgSO_4$) y concentrada al vacío para dar el compuesto deseado (273 mg) como un sólido.

La preparación de 1–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 10:

3–[4–[4–(Hidroximetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea



3–(4–Bromofenil)–1,1–dimetil–urea (825 mg), acetato de potasio (998 mg), y bis(pinacolato)diboro (1.03 g) fueron disueltos en 1,4 dioxano (45 mL). La solución fue desgasificada durante 5 minutos, luego aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano fue añadido (167 mg) y la reacción fue calentada hasta 85°C durante 3 horas. [2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (828 mg), etanol (3.75 mL), solución de carbonato de sodio 2M (8.53 mL) y aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (167 mg) fueron añadidos y el calentamiento se continuó durante 16 horas. La reacción fue enfriada y evaporada hasta secarse y el residuo particionado entre etil acetato (125 mL) y agua

(100 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (737 mg) como un sólido blanco.

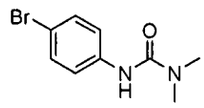
Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.22 – 1.24 (3H, m), 2.95 (6H, s), 3.16 – 3.23 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.18 (1H, d), 4.45 – 4.50 (3H, m), 5.38 (1H, t), 6.66 (1H, s), 7.55 – 7.59 (2H, m), 8.18 – 8.22 (2H, m), 8.45 (1H, s)

Espectro de masa: M+H$^+$ 372.

Prueba (a): 19 μM.

La preparación de 3–(4–bromofenil)–1,1–dimetil–urea es descrita a continuación.

3–(4–Bromofenil)–1,1–dimetil–urea



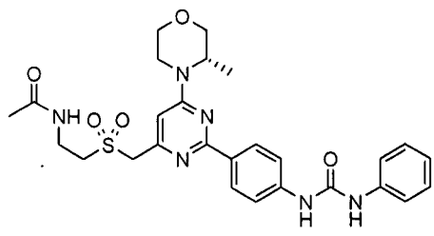
4–Bromofenil isocianato (1.00 g) fue disuelto en THF (30 mL). Dimetilamina (2.0M en THF, 2.78 mL) fue añadida a la solución y la reacción agitada a RT durante 2 horas. La reacción fue filtrada, concentrada al vacío y el residuo cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (830 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ2.90 (6H, s), 7.37 – 7.40 (2H, m), 7.45 – 7.47 (2H, m), 8.37 (1H, s)

Espectro de masa: M+H$^+$ 244.

Ejemplo 11:

***N*–[2–[[6–[(3*S*)–3–metilmorfolin–4–il]–2–[4–(fenilcarbamoilamino)fenil]pirimidin–4–il]metilsulfonil]etil]acetamida**



N-[2-[[6-[(3*S*)-3-Metilmorfolin-4-il]-2-[4-(fenilcarbamoilamino)fenil]pirimidin-4-il]metilsulfanil]etil]acetamida (100 mg) fue disuelta en 1,4-dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3-cloroperbenzoico (75%) (40 mg) añadido seguido inmediatamente por permanganato de sodio (47 mg). La reacción se dejó agitar a RT durante 2 horas. Ácido 3-cloroperbenzoico (4 mg) y permanganato de sodio (4 mg) adicionales fueron añadidos y la reacción agitada durante una hora extra. La reacción fue cargada en una columna SCX-2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado fue aislado como un sólido blanco (102 mg).

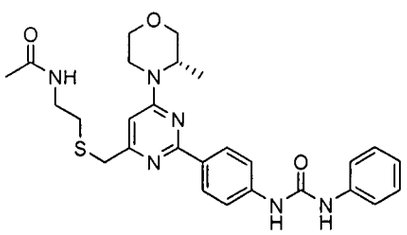
Espectro NMR: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 1.84 (3H, s), 3.18 – 3.24 (1H, m), 3.48 – 3.54 (2H, m), 3.52 (1H, s), 3.58 (2H, q), 3.64 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.01 (1H, m), 4.18 (1H, d), 4.49 (1H, s), 4.53 (2H, s), 6.80 (1H, s), 6.99 (1H, t), 7.31 (2H, d), 7.46 – 7.49 (2H, m), 7.57 (2H, d), 8.16 (1H, t), 8.27 (2H, d), 8.70 (1H, s), 8.92 (1H, s)

Espectro de masa: M+H$^+$ 553.

Prueba (a): 0.14 μM.

La preparación de *N*-[2-[[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenilcarbamoilamino)fenil]pirimidin-4-il]metilsulfanil]etil]acetamida es descrita a continuación.

N-[2-[[6-[(3*S*)-3-Metilmorfolin-4-il]-2-[4-(fenilcarbamoilamino)fenil]pirimidin-4-il]metilsulfanil]etil]acetamida



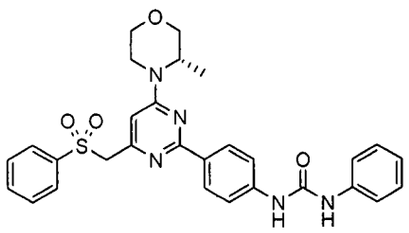
N- Acetilcisteamina (0.086 mL) fue disuelta en acetonitrilo (5 mL). DBU (0.120 mL) fue luego añadido a la solución y se dejó agitar a RT durante 15 minutos. 1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-fenil-urea (228 mg) en acetonitrilo (5 mL) fue añadida a la reacción y agitada durante 30 minutos. La reacción fue concentrada al vacío y el residuo crudo purificado en sílice, eluyendo con 5% metanol en DCM, para dar el compuesto deseado (100 mg) como un sólido blanco.

Espectro de masa: $M+H^+$ 521.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 12:

1–[4–[4–(Bencenosulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]–3–fenil–urea (62 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperbenzoico (75%) (26 mg) fue añadido seguido inmediatamente por permanganato de sodio (30 mg). La reacción se dejó agitar a RT durante 2 horas, luego ácido 3–cloroperbenzoico (4 mg) y permanganato de sodio (4 mg) adicionales fueron añadidos. La reacción fue agitada durante 1 hora extra, luego la reacción fue cargada en una columna SCX–2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado fue aislado como un sólido amarillo pálido (64 mg).

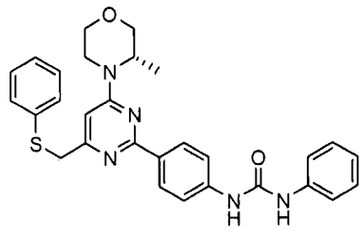
Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.20 (3H, d), 3.14 – 3.21 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.10 (1H, d), 4.38 (1H, s), 4.71 (2H, s), 6.63 (1H, s), 6.99 (1H, m), 7.31 (2H, d), 7.46 (4H, t), 7.63 (2H, t), 7.73 – 7.78 (1H, m), 7.82 (1H, d), 7.82 – 7.84 (1H, m), 7.87 (2H, d), 8.69 (1H, s), 8.87 (1H, s).

Espectro de masa: $M+H^+$ 544.

Prueba (a): 0.23 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]–3–fenil–urea es descrita a continuación.

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]–3–fenil–urea

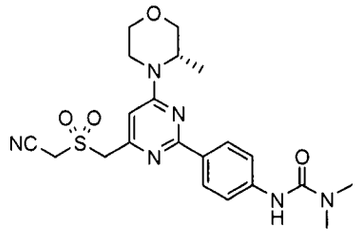


Tiofenol (0.029 mL) fue disuelto en Acetonitrilo (3 mL). DBU (0.043 mL) fue luego añadido a la solución y se dejó agitar a RT durante 15 minutos. 1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea (80 mg) fue añadida a la reacción y agitada durante 30 minutos. La reacción fue concentrada al vacío y el residuo cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (62 mg) como un sólido blanco.

Espectro de masa: $M+H^+$ 512.

Ejemplo 13:

3–[4–[4–(Cianometilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea



3–[4–[4–(Cianometilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea (162 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperbenzoico (75%) (79 mg) fue añadido seguido inmediatamente por permanganato de sodio (92 mg). La reacción se dejó agitar a RT durante 2 horas. Ácido 3–cloroperbenzoico (40 mg) y permanganato de sodio (45 mg) adicionales fueron añadidos y la reacción agitada durante 1 hora, luego ácido 3–cloroperbenzoico (40 mg) y permanganato de sodio (45 mg) adicionales fueron añadidos y la reacción agitada durante 1 hora. La reacción fue cargada en una columna SCX–2, lavada con metanol y el material

deseado eliminado con amoniaco 7N en metanol. El material deseado fue aislado como un sólido blanco (17 mg).

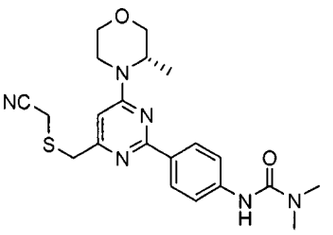
Espectro NMR: ^{1}H NMR (DMSO-d_6) δ1.25 (3H, d), 2.96 (6H, s), 3.18 (1H, d), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.79 (1H, d), 3.98 – 4.01 (1H, m), 4.17 (1H, s), 4.46 (1H, d), 4.74 (2H, s), 5.10 (2H, d), 6.82 (1H, s), 7.59 – 7.61 (2H, m), 8.21 – 8.23 (2H, m), 8.49 (1H, s)

Espectro de masa: M+H$^+$ 459.

Prueba (a): 2.1 μM.

La preparación de 3-[4-[4-(cianometilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1,1-dimetil-urea es descrita a continuación.

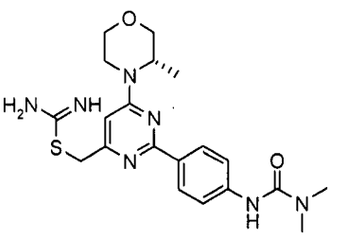
3-[4-[4-(Cianometilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1,1-dimetil-urea



3-[4-[4-(Carbamimidoilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1,1-dimetil-urea (0.38 mmol) fue disuelta en DMF (2 mL). Esto fue tratado con bromoacetonitrilo (0.030 mL) y luego el hidróxido de sodio (61 mg) en agua (1 mL) y agitado a RT durante 15 minutos. La mezcla de reacción fue concentrada al vacío y el residuo cargado en una columna SCX-2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado fue aislado y usado sin cromatografía adicional.

Espectro de masa: M+H$^+$ 427.

3-[4-[4-(Carbamimidoilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1,1-dimetil-urea

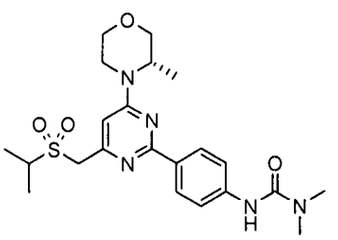


3–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea (140 mg) fue disuelta en DCM (5 mL) y trietilamina (0.079 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.044 mL) y la reacción fue agitada durante 15 minutos a RT. El solvente fue eliminado a presión reducida y reemplazado con etanol (5 mL), luego tiourea (32 mg) fue añadida. La reacción fue luego calentada hasta 70°C durante 30 minutos, luego se dejó enfriar y fue concentrada al vacío para dar el material deseado el cual fue usado sin purificación adicional.

Espectro de masa: $M+H^+$ 430.

Ejemplo 14:

1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea



1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfanilmetil)pirimidin–2–il]fenil]urea (163 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperbenzoico (75%) (79 mg) fue añadido seguido inmediatamente por permanganato de sodio (92 mg). La reacción se dejó agitar a RT durante 2 horas luego ácido 3–cloroperbenzoico (20 mg) y permanganato de sodio (25 mg) adicionales fueron añadidos. La reacción se dejó agitar durante 1 hora, luego cargada en una columna SCX–2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado (90 mg) fue aislado como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.25 (3H, d), 1.35 – 1.37 (6H, m), 2.95 (6H, s), 3.21 – 3.26 (2H, m), 3.47 – 3.54 (2H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m),

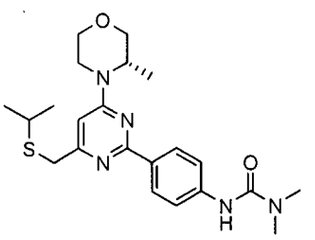
4.24 (1H, m) 4.45 – 4.47 (2H, m), 6.78 (1H, s), 7.58 – 7.61 (2H, m), 8.17 – 8.20 (2H, m), 8.48 (1H, s)

Espectro de masa: $M+H^+$ 462.

Prueba (a): 0.42 μM.

La preparación de 1,1–dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfanilmetil)pirimidin–2–il]fenil]urea es descrita a continuación.

1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfanilmetil)pirimidin–2–il]fenil]urea

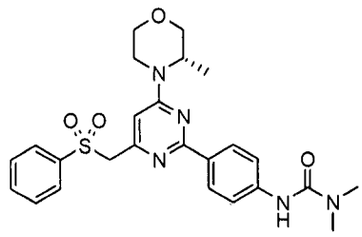


3–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea (140 mg) fue disuelta en DCM (5 mL) y trietilamina (0.079 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.044 mL) y la reacción fue agitada durante 15 minutos a RT antes de ser concentrada al vacío para dar el mesilato el cual fue usado sin purificación adicional. Isopropil mercaptano (0.062 mL) fue disuelto en acetonitrilo (5 mL). DBU (0.099 mL) fue luego añadido a la solución y se dejó agitar a RT durante 5 minutos. El mesilato crudo de arriba fue suspendido en acetonitrilo (5 mL) y añadido a la solución de tiol. La reacción se dejó agitar a RT durante 1 hora, luego DBU adicional (0.099 mL) fue añadido y la reacción fue agitada a RT durante 30 minutos. La mezcla de reacción fue concentrada al vacío para dar el material deseado el cual fue usado sin purificación adicional.

Espectro de masa: $M+H^+$ 430.

Ejemplo 15:

3–[4–[4–(Bencenosulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1,1–dimetil–urea



1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]urea (158 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperbenzoico (75%) (89 mg) fue añadido seguido inmediatamente por permanganato de sodio (96 mg). La reacción se dejó agitar a RT durante 16 horas, luego ácido 3–cloroperbenzoico (20 mg) y permanganato de sodio (25 mg) adicionales fueron añadidos. La reacción se dejó agitar durante 1 hora, luego fue cargada en una columna SCX–2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado fue aislado como un sólido blanco (90 mg).

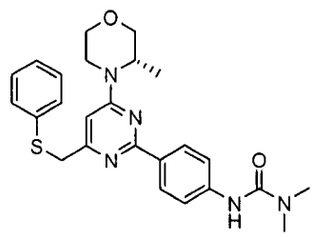
Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.20 (3H, d), 2.95 (6H, s), 3.13 – 3.20 (1H, m), 3.44 – 3.51 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.07 (1H, t), 4.36 (1H, s), 4.70 (2H, s), 6.62 (1H, s), 7.47 – 7.49 (2H, m), 7.62 (2H, t), 7.72 – 7.75 (1H, m), 7.79 – 7.84 (4H, m), 8.43 (1H, s)

Espectro de masa: M+H$^+$ 496.

Prueba (a): 1 μM.

La preparación de 1,1–dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]urea es descrita a continuación.

1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(fenilsulfanilmetil)pirimidin–2–il]fenil]urea

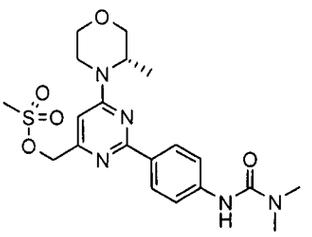


Tiofenol (0.062 mL) fue disuelto en acetonitrilo (5 mL). DBU (0.141 mL) fue luego añadido a la solución y se dejó agitar a RT durante 5 minutos. 1,1–Dimetil–3–[4–[4–[(3*S*)–3–

metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (154 mg) fue suspendida en acetonitrilo (5 mL) y añadida al tiol. La reacción se dejó agitar a RT 1 hora, luego fue concentrada al vacío para dar el material deseado el cual fue usado sin purificación adicional.

Espectro de masa: $M+H^+$ 464.

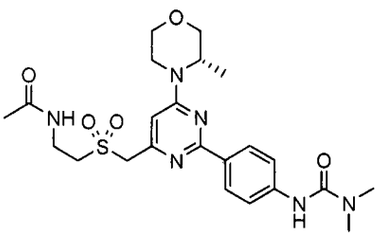
1,1-Dimetil-3-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea



3-[4-[4-(Hidroximetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1,1-dimetil-urea (384 mg) fue disuelta en DCM (12 mL) y trietilamina (0.216 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.121 mL) y la reacción fue agitada durante 15 minutos a RT antes de ser concentrada al vacío para dar el material deseado.
Espectro de masa: $M+H^+$ 450.

Ejemplo 16:

***N*-[2-[[2-[4-(Dimetilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etil]acetamida**



N-[2-[[2-[4-(Dimetilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]etil]acetamida (158 mg) fue disuelta en 1,4-dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3-cloroperbenzoico (75%) (116 mg) fue añadido seguido inmediatamente por permanganato de sodio (134 mg). La reacción se dejó agitar a RT durante 1 hora, luego cargada en una columna SCX-2, lavada con metanol y el material

deseado eliminado con amoniaco 7N en metanol. El material deseado (84 mg) fue aislado como un sólido blanco.

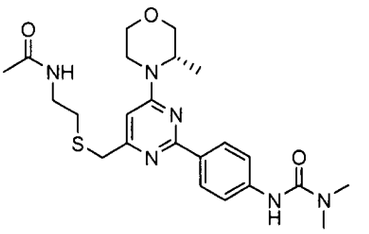
Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.25 (3H, d), 1.83 (3H, s), 2.96 (6H, s), 3.20 – 3.25 (1H, m), 3.47 – 3.50 (1H, m), 3.52 (2H, d), 3.57 (2H, q), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.51 (3H, m), 6.78 (1H, s), 7.58 – 7.61 (2H, m), 8.16 – 8.19 (1H, m), 8.19 – 8.22 (2H, m), 8.49 (1H, s)

Espectro de masa: M+H$^+$ 505.

Prueba (a): 4 μM.

La preparación de *N*–[2–[[2–[4–(Dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]etil]acetamida es descrita a continuación.

N–[2–[[2–[4–(Dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]etil]acetamida

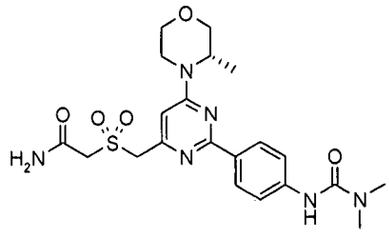


N–Acetilcisteamina (0.064 mL) fue disuelta en acetonitrilo (5 mL). DBU (0.141 mL) fue luego añadido a la solución y se dejó agitar a RT durante 5 minutos. 1,1–Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea (154 mg) fue suspendida en acetonitrilo (5 mL) y añadida al tiol. La reacción se dejó agitar a RT 1 hora, luego fue concentrada al vacío para dar el material deseado.

Espectro de masa: M+H$^+$ 473.

Ejemplo 17:

2–[[2–[4–(Dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]acetamida



2–[[2–[4–(Dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida (158 mg) fue disuelta en 1,4–dioxano (6 mL) y agua (1 mL). La solución fue enfriada hasta 0°C y ácido 3–cloroperbenzoico (75%) (123 mg) fue añadido seguido inmediatamente por permanganato de sodio (143 mg). La reacción se dejó agitar a RT durante 1 hora, luego fue cargada en una columna SCX–2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado (55 mg) fue aislado como un sólido blanco.

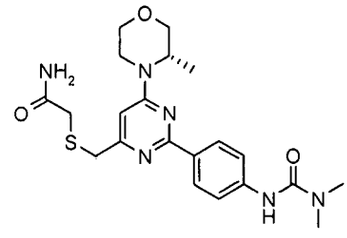
Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.25 (3H, d), 2.96 (6H, s), 3.22 – 3.26 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.27 (2H, s), 4.47 (1H, s), 4.67 (2H, s), 6.77 (1H, s), 7.53 (1H, s), 7.58 – 7.61 (2H, m), 7.79 (1H, s), 8.17 – 8.21 (2H, m), 8.49 (1H, s)

Espectro de masa: M+H^+ 477.

Prueba (a): 1.1 μM.

La preparación de 2–[[2–[4–(dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida es descrita a continuación.

2–[[2–[4–(Dimetilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida



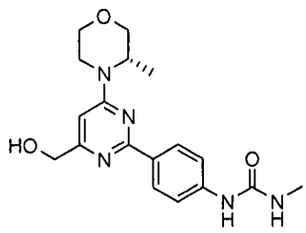
Dimetil–3–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea (154 mg) fue disuelta en etanol (5 mL) y tiourea (29 mg) fue añadida. La reacción fue luego calentada hasta 70°C durante 30 minutos antes de ser concentrada al vacío.

El residuo fue disuelto en DMF (2 mL) y tratado con 2–bromoacetamida (52 mg) seguido por hidróxido de sodio (55 mg) en agua (1 mL) y agitado a RT durante 30 minutos. La mezcla de reacción fue concentrada al vacío luego cargada en una columna SCX–2, lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material deseado fue usado sin purificación adicional.

Espectro de masa: $M+H^+$ 445.

Ejemplo 18:

1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea



1–(4–Bromofenil)–3–metil–urea (2.50 g), acetato de potasio (3.21 g), y bis(pinacolato)diboro (3.33 g) fueron disueltos en 1,4 dioxano (120 mL). La solución fue desgasificada durante 5 minutos, luego aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano fue añadido (535 mg) y la reacción fue calentada hasta 90°C durante 3 horas. Aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (250 mg) adicional fue añadido y el calentamiento se continuó durante 1 hora. Aducto de 1,1'–bis(difenilfosfino) ferrocenodicloropaladio(II) diclorometano (250 mg) adicional fue añadido y el calentamiento se continuó durante 1 hora adicional. [2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (2.66 mg), etanol (9.5 mL), solución de carbonato de sodio 2M (27.3 mL) y aducto de 1,1'–bis(difenilfosfino)ferrocenodicloropaladio(II) diclorometano (535 mg) fueron añadidos y el calentamiento se continuó durante 16 horas. La reacción fue enfriada y evaporada hasta secarse, luego el residuo fue particionado entre etil acetato (250 mL) y agua (100 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (1.25 g) como un sólido marrón.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.23 (3H, d), 2.66 (3H, d), 3.18 – 3.23 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.76 (1H, d), 3.96 – 3.99 (1H, m), 4.16 (1H, d), 4.45 (2H,

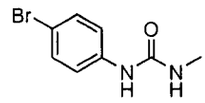
d), 4.49 (1H, d), 5.38 (1H, t), 6.05 (1H, q), 6.66 (1H, s), 7.46 – 7.48 (2H, m), 8.18 – 8.21 (2H, m), 8.69 (1H, s)

Espectro de masa: $M+H^+$ 358.

Prueba (a): 0.12 μM.

La preparación de 1–(4–bromofenil)–3–metil–urea es descrita a continuación.

1–(4–Bromofenil)–3–metil–urea



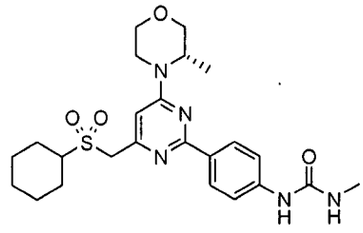
4–Bromofenil isocianato (2.50 g) fue disuelto en THF (75 mL). Metilamina (2.0M en THF, 75 mL) fue añadida a la solución y agitada a RT durante 1 hora. La reacción fue filtrada y sometida a vacío hasta secarse. El material crudo fue cromatografiado en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (2.65 g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ2.64 (3H, d), 6.03 (1H, d), 7.37 (4H, s), 8.61 (1H, s)

Espectro de masa: $M+H^+$ 229.

Ejemplo 19:

1–[4–[4–(Ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea



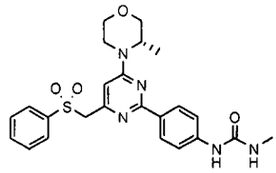
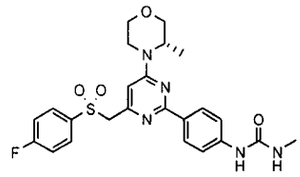
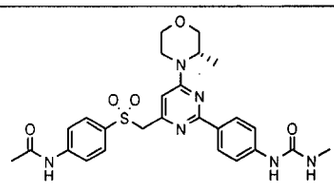
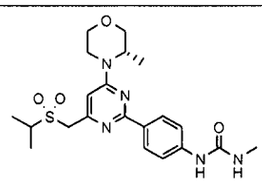
1–[4–[4–(Ciclohexilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea (0.35 mmol) fue disuelta en 1,4–dioxano (5 mL) y agua (1 mL). Ácido 3–cloroperbenzoico (75%) (121 mg) fue añadido a la solución seguido inmediatamente por permanganato de sodio (140 mg) y las reacciones agitadas a RT durante 1 hora. Ácido 3–cloroperbenzoico (75%) (121 mg) y permanganato de sodio (140 mg) adicionales fueron añadidos y las reacciones se dejaron agitar a RT durante 1 hora. Ácido 3–cloroperbenzoico (75%) (121 mg) y permanganato de sodio (140 mg) adicionales fueron añadidos y las

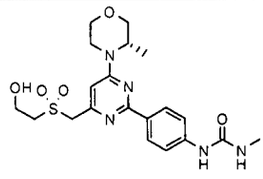
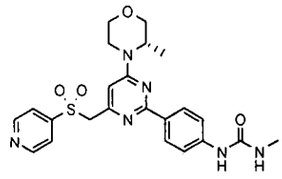
reacciones se dejaron agitar a RT durante otra hora, luego fueron cargadas en una columna SCX–3. La columna fue lavada con metanol y el material deseado eliminado con amoniaco 7N en metanol. El material crudo fue purificado por HPLC prep. (básica) para dar el material deseado (74 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (DMSO–d_6) δ1.18 – 1.32 (7H, m), 1.42 (1H, d), 1.48 (1H, d), 1.68 (1H, d), 1.89 (2H, d), 2.25 (3H, d), 2.32 – 2.34 (1H, m), 2.66 (3H, d), 3.46 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.43 (3H, s), 6.08 (1H, t), 6.77 (1H, s), 7.50 – 7.52 (2H, m), 8.19 – 8.21 (2H, m)

Espectro de masa: M+H$^+$ 488.

Los siguientes compuestos fueron preparados de una forma análoga a partir de los sulfuros apropiados.

Ejemplo	Estructura	NOMBRE	LCMS MH+
19a		1–[4–[4–(bencenosulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	482
19b		1–[4–[4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	500
19c		*N*–[4–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]fenil]acetamida	539
19d		3–metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	448

Ejemplo	Estructura	NOMBRE	LCMS MH+
19e		1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	450
19f		3–metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]urea	483

Ejemplo 19a: ^{1}H NMR (DMSO–d_6) δ1.18 (3H, d), 2.66 (3H, q), 3.11 – 3.19 (1H, m), 3.43 – 3.50 (1H, m), 3.60 – 3.63 (1H, m), 3.75 (1H, d), 3.94 – 3.98 (1H, m), 4.08 (1H, d), 4.35 (1H, s), 4.69 (2H, s), 6.04 (1H, q), 6.59 (1H, s), 7.36 – 7.38 (2H, m), 7.61 (2H, t), 7.71 – 7.75 (1H, m), 7.79 – 7.81 (3H, m), 7.82 (1H, s), 8.69 (1H, s)

Ejemplo 19b: ^{1}H NMR (DMSO–d_6) δ1.20 (3H, d), 2.66 (3H, d), 3.14 – 3.21 (1H, m), 3.45 – 3.51 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.11 (1H, d), 4.37 (1H, s), 4.71 (2H, s), 6.04 (1H, q), 6.64 (1H, s), 7.37 – 7.41 (2H, m), 7.43 – 7.48 (2H, m), 7.77 – 7.80 (2H, m), 7.85 – 7.89 (2H, m), 8.71 (1H, s)

Ejemplo 19c: ^{1}H NMR (DMSO–d_6) δ1.18 (3H, d), 2.13 (3H, s), 2.60 – 2.61 (3H, m), 2.67 (3H, q), 2.68 (1H, s), 3.44 – 3.49 (1H, m), 4.08 (1H, d), 4.35 (1H, s), 4.60 (2H, s), 6.05 (1H, q), 6.54 (1H, s), 7.37 – 7.39 (2H, m), 7.70 (2H, d), 7.77 (2H, d), 7.82 (2H, d), 8.68 (1H, s), 10.37 (1H, s)

Ejemplo 19d: ^{1}H NMR (DMSO–d_6) δ1.24 (3H, d), 1.35 – 1.37 (7H, m), 2.66 – 2.69 (3H, m), 3.21 – 3.25 (1H, m), 3.47 – 3.54 (2H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.46 (3H, s), 6.08 (1H, q), 6.77 (1H, s), 7.49 – 7.51 (2H, m), 8.17 – 8.19 (2H, m), 8.73 (1H, s)

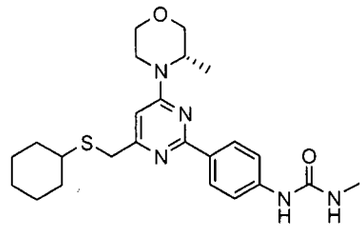
Ejemplo 19e: ^{1}H NMR (DMSO–d_6) δ1.24 (3H, d), 2.66 (2H, s), 2.68 (2H, q), 3.21 – 3.26 (1H, m), 3.51 (3H, t), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.89 – 3.94 (2H, m), 3.97 – 4.01 (1H, m), 4.50 (3H, s), 5.18 (1H, t), 6.07 (1H, d), 6.76 (1H, s), 7.49 – 7.51 (2H, m), 8.20 – 8.22 (2H, m), 8.74 (1H, s)

Ejemplo 19f: ^{1}H NMR (DMSO-d_6) δ1.20 – 1.25 (3H, m), 2.66 (3H, t), 3.15 – 3.21 (1H, m), 3.45 – 3.51 (1H, m), 3.61 – 3.65 (1H, m), 3.77 (1H, t), 3.95 – 3.99 (1H, m), 4.11 (1H, d), 4.39 (1H, s), 4.87 (2H, s), 6.05 (1H, q), 6.71 (1H, s), 7.35 – 7.37 (2H, m), 7.64 – 7.66 (2H, m), 7.81 – 7.82 (2H, m), 8.70 (1H, d), 8.90 (1H, d), 8.91 (1H, s)

Prueba (a): Ejemplo (19) 0.25 μM; Ejemplo (19a) 0.0047 μM; Ejemplo (19b) 0.033 μM; Ejemplo (19c) 0.022 μM; Ejemplo (19d) 0.066 μM; Ejemplo (19e) 0.011 μM; Ejemplo (19f) 0.027 μM.

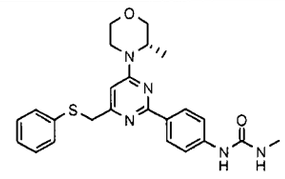
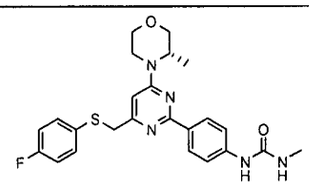
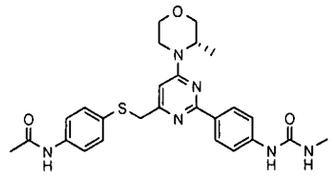
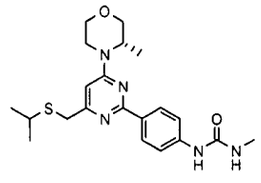
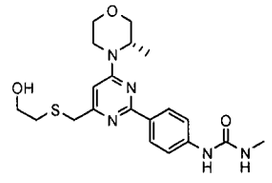
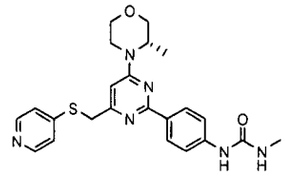
La preparación de 1-[4-[4-(ciclohexilsulfanilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea es descrita a continuación.

1-[4-[4-(Ciclohexilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea



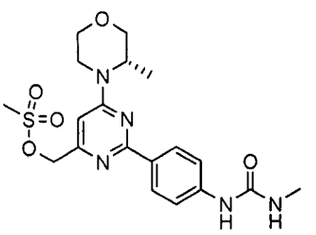
Ciclohexanotiol (0.61 mmol) fue disuelto en acetonitrilo (4 mL). DBU (0.050 mL) fue luego añadido y la solución se dejó agitar a RT durante 5 minutos. 3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (151 mg) disuelta en acetonitrilo (2 mL) y DBU (0.054 mL) fue añadida y las reacciones agitadas a RT durante 2 horas. La mezcla de reacción fue concentrada al vacío para dar el material deseado el cual fue usado sin purificación adicional.

Los siguientes sulfuros fueron hechos de una manera análoga a partir de 3-metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea y el tiol apropiado.

Estructura	NOMBRE
	3-metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(fenilsulfanilmetil)pirimidin-2-il]fenil]urea
	1-[4-[4-[(4-fluorofenil)sulfanilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea
	*N*-[4-[[2-[4-(metilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]fenil]acetamida
	3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfanilmetil)pirimidin-2-il]fenil]urea
	1-[4-[4-(2-hidroxietilsulfanilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea
	3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfanilmetil)pirimidin-2-il]fenil]urea

La preparación de 3-metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea es descrita a continuación.

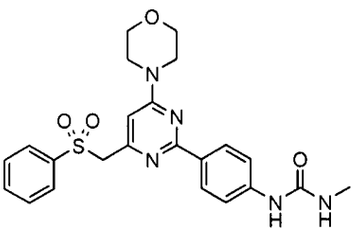
3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea



1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea (1.24 g) fue parcialmente disuelta en DCM (30 mL) y trietilamina (0.724 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.405 mL) y la reacción fue agitada durante 15 minutos a RT, luego concentrada al vacío para dar el material deseado.
Espectro de masa: $M+H^+$ 436.

Ejemplo 20:

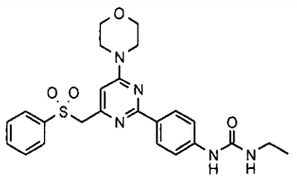
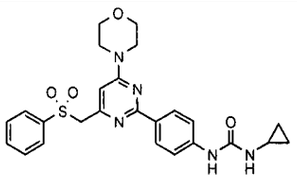
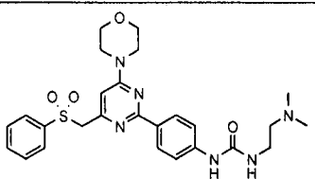
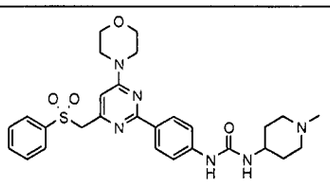
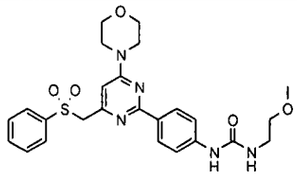
3–[4–[4–(Bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–metil–urea

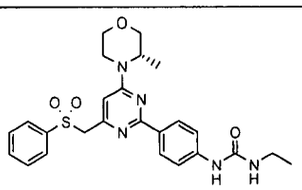
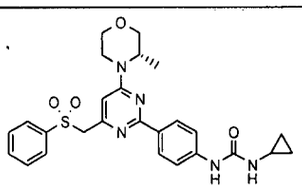
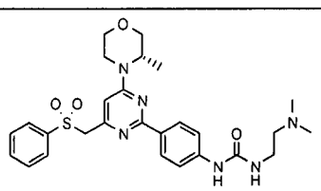
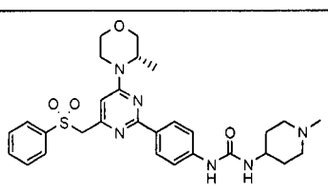
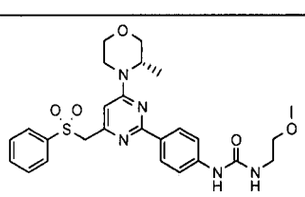


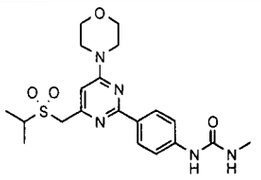
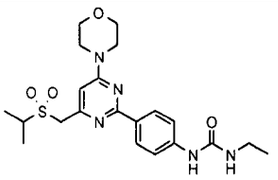
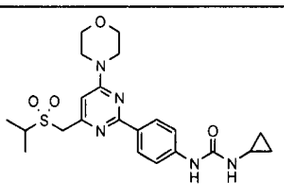
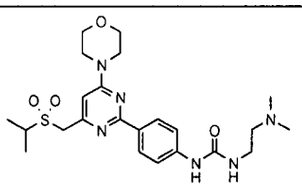
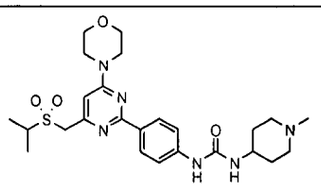
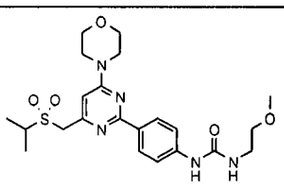
Fenil (4–{4–morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)carbamato (250 mg, 0.45 mmol) fue disuelto en DMF (5 mL). Trietilamina (0.188 mL, 1.35 mmol) fue añadida seguido por metilamina (2M en THF, 1.1 mL) y la solución calentada a 50°C durante 1 hora. La reacción fue enfriada hasta temperatura ambiente y concentrada al vacío. El aceite resultante fue purificado por cromatografía en sílice, eluyendo con 0–5% metanol en DCM para dar el material deseado como un sólido blanco (120 mg).
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ2.66 (d, 3H), 3.63 (m, 4H), 3.70 (m, 4H), 4.69 (s, 2H), 6.05 (m, 1H), 6.65 (s, 1H), 7.38 (d, 2H), 7.63 (t, 2H), 7.74 (d, 1H), 7.80 (m, 3H), 8.69 (s, 1H)
Espectro LCMS: MH+ 468, tiempo de retención 1.76 min, Método Básico 5 Min

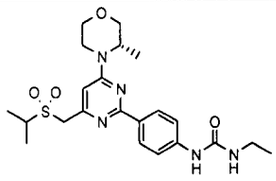
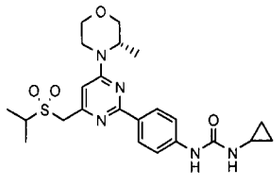
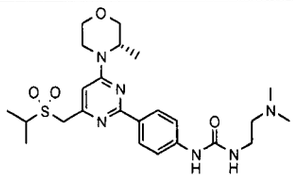
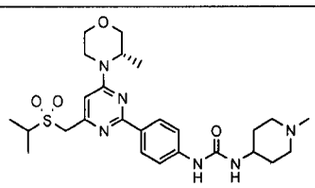
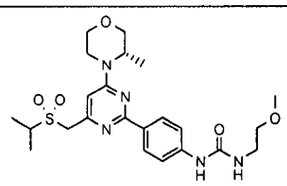
Los compuestos mostrados en la tabla fueron preparados de una manera análoga a *N*'–(4–{4–morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)urea reaccionando la amina

apropiada con el carbamato apropiado y mediante purificación por cromatografía en sílice o por HPLC preparativa.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
20a		3–[4–[4–(bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–etil–urea	482	1.98
20b		1–[4–[4–(bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–3–ciclopropil–urea	494	1.92
20c		3–[4–[4–(bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–(2–dimetilaminoetil)urea	525	1.98
20d		3–[4–[4–(bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–(1–metil–4–piperidil)urea	551	1.93
20e		3–[4–[4–(bencenosulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–1–(2–metoxietil)urea	512	1.77

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
20f		3-[4-[4-(bencenosulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etil-urea	496	2.06
20g		1-[4-[4-(bencenosulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropil-urea	508	2.08
20h		1-[4-[4-(bencenosulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	539	1.94
20i		1-[4-[4-(bencenosulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metil-4-piperidil)urea	565	1.94
20j		1-[4-[4-(bencenosulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metoxietil)urea	526	1.98

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
20k		3-metil-1-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	434	1.47
20l		1-etil-3-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	448	1.61
20m		3-ciclopropil-1-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	460	1.63
20n		3-(2-dimetilaminoetil)-1-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	491	1.59
20o		3-(1-metil-4-piperidil)-1-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	517	1.61
20p		3-(2-metoxietil)-1-[4-[4-morfolin-4-il-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	478	1.53

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
20q		1–etil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	462	1.75
20r		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	474	1.77
20s		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	505	1.76
20t		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]–3–(1–metil–4–piperidil)urea	531	1.77
20u		3–(2–metoxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	492	1.67

Ejemplo 20a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.00 (t, 3H), 3.05 (m, 2H), 3.56 (s, 4H), 3.63 (m, 4H), 4.62 (s, 2H), 6.07 (t, 1H), 6.59 (s, 1H), 7.30 (d, 2H), 7.55 (t, 2H), 7.71 (m, 5H), 8.54 (s, 1H)

Ejemplo 20b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 2.55 (m, 1H), 3.64 (m, 4H), 3.71 (m, 4H), 4.69 (s, 2H), 6.41 (d, 1H), 6.66 (s, 1H), 7.38 (d, 2H), 7.63 (t, 2H), 7.75 (m, 1H), 7.81 (m, 4H), 8.49 (s, 1H)

Ejemplo 20c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ2.20 (s, 6H), 2.38 (t, 2H), 3.20 (m, 2H), 3.63 (s, 4H), 3.70 (s, 4H), 4.69 (s, 2H), 6.17 (s, 1H), 6.65 (s, 1H), 7.37 (d, 2H), 7.62 (t, 2H), 7.75 (t, 1H), 7.81 (t, 4H), 8.87 (s, 1H)

Ejemplo 20d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.49 (m, 2H), 1.86 (m, 2H), 2.32 (s, 3H), 2.84 (m, 2H), 3.54 (m, 2H), 3.63 (s, 4H), 3.70 (m, 4H), 4.69 (s, 2H), 6.46 (d, 1H), 6.65 (s, 1H), 7.35 (d, 2H), 7.63 (t, 2H), 7.74 (t, 2H), 7.81 (m, 3H), 8.76 (s, 1H)

Ejemplo 20e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.27 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.63 (s, 4H), 3.71 (m, 4H), 4.69 (s, 2H), 6.25 (t, 1H), 6.66 (s, 1H), 7.35 (d, 2H), 7.62 (t, 1H), 7.75 (m, 2H), 7.81 (m, 4H), 8.73 (s, 1H)

Ejemplo 20f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.15 (t, 3H), 1.25 (d, 3H), 3.12 (m, 3H), 3.47 (t, 1H), 3.62 (d, 1H), 3.76 (d, 1H), 3.96 (d, 1H), 4.08 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.14 (t, 1H), 6.60 (s, 1H), 7.38 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.81 (m, 4H), 8.62 (s, 1H)

Ejemplo 20g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.20 (d, 3H), 2.55 (m, 1H), 3.16 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.97 (m, 1H), 4.09 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.42 (d, 1H), 6.60 (s, 1H), 7.39 (d, 2H), 7.63 (t, 2H), 7.75 (t, 1H), 7.82 (m, 4H), 8.49 (s, 1H)

Ejemplo 20h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.19 (d, 3H), 2.23 (s, 6H), 2.40 (t, 2H), 3.21 (m, 3H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.96 (m, 1H), 4.08 (d, 1H), 4.36 (s, 1H), 4.70 (s, 2H), 6.21 (t, 1H), 6.60 (s, 1H), 7.40 (d, 2H), 7.62 (t, 2H), 7.75 (t, 1H), 7.82 (m, 3H), 7.96 (s, 1H), 8.90 (s, 1H)

Ejemplo 20i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.19 (d, 3H), 1.40 (m, 2H), 1.79 (m, 2H), 2.02 (t, 2H), 2.16 (s, 3H), 2.64 (m, 2H), 3.16 (m, 1H), 3.47 (m, 2H), 3.62 (m, 1H), 3.75 (d, 1H), 3.96 (m, 1H), 4.08 (d, 1H), 4.35 (s, 1H), 4.69 (s, 2H), 6.16 (d, 1H), 6.60 (s, 1H), 7.35 (d, 2H), 7.65 (t, 2H), 7.74 (t, 1H), 7.81 (m, 4H), 8.52 (s, 1H)

Ejemplo 20j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.20 (d, 3H), 3.15 (t, 1H), 3.29 (m, 5H), 3.40 (t, 2H), 3.47 (t, 1H), 3.62 (d, 1H), 3.75 (d, 1H), 3.96 (d, 1H), 4.08 (d, 1H), 4.36 (s, 1H),

4.70 (s, 2H), 6.25 (t, 1H), 6.60 (s, 1H), 7.37 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 4H), 8.73 (s, 1H)

Ejemplo 20k: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.36 (d, 6H), 2.66 (s, 3H), 3.51 (m, 1H), 3.72 (s, 8H), 4.47 (s, 2H), 6.09 (s, 1H), 6.83 (s, 1H), 7.51 (d, 2H), 8.18 (d, 2H), 8.76 (s, 1H)

Ejemplo 20l: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.07 (t, 3H), 1.35 (d, 6H), 3.12 (m, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.47 (s, 2H), 6.18 (s, 1H), 6.83 (s, 1H), 7.51 (d, 2H), 8.18 (d, 2H), 8.68 (s, 1H)

Ejemplo 20m: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.38 (d, 6H), 2.56 (m, 1H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.45 (s, 1H), 6.82 (s, 1H), 7.51 (d, 2H), 8.19 (d, 2H), 8.55 (s, 1H)

Ejemplo 20n: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.36 (d, 6H), 2.85 (d, 6H), 3.20 (m, 2H), 3.46 (m, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.56 (t, 1H), 6.83 (s, 1H), 7.55 (d, 2H), 8.21 (d, 2H), 9.10 (s, 1H)

Ejemplo 20o: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.36 (d, 6H), 1.57 (m, 2H), 1.97 (d, 2H), 2.59 (s, 1H), 2.78 (s, 2H), 3.16 (d, 2H), 3.29 (s, 3H), 3.50 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.44 (d, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.65 (s, 1H)

Ejemplo 20p: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.38 (d, 6H), 3.28 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.51 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.28 (t, 1H), 6.81 (s, 1H), 7.49 (d, 2H), 8.20 (d, 2H), 8.77 (s, 1H)

Ejemplo 20q: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.07 (t, 3H), 1.24 (d, 3H), 1.36 (m, 6H), 3.13 (m, 2H), 3.23 (m, 1H), 3.51 (m, 2H), 3.65 (m, 1H), 3.72 (d, 1H), 3.99 (m, 1H), 4.17 (d, 1H), 4.46 (s, 3H), 6.17 (t, 1H), 6.77 (s, 1H), 7.50 (d, 2H), 8.18 (d, 2H), 8.65 (s, 1H)

Ejemplo 20r: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.25 (d, 3H), 1.37 (d, 6H), 2.57 (m, 2H), 3.23 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.44 (d, 1H), 6.77 (s, 1H), 7.51 (d, 2H), 8.19 (d, 2H), 8.53 (s, 1H)

Ejemplo 20s: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.22 (d, 3H), 1.36 (m, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.21 (m, 2H), 3.50 (m, 2H), 3.65 (m, 1H), 3.76 (d, 1H), 3.99 (m, 1H), 4.06 (q, 2H), 4.17 (d, 1H), 4.46 (s, 2H), 6.17 (t, 1H), 6.77 (s, 1H), 7.49 (d, 2H), 8.18 (d, 2H), 8.89 (s, 1H)

Ejemplo 20t: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.22 (d, 3H), 1.36 (m, 6H), 1.42 (m, 2H), 1.80 (m, 2H), 2.03 (t, 2H), 2.17 (s, 3H), 2.65 (d, 2H), 3.18 (d, 1H), 3.23 (m, 1H), 3.50 (m,

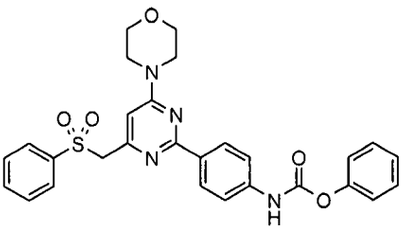
2H), 3.65 (m, 1H), 3.76 (d, 1H), 3.98 (m, 1H), 4.06 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.19 (d, 1H), 6.77 (s, 1H), 7.48 (d, 2H), 8.18 (d, 2H), 8.56 (s, 1H)

Ejemplo 20u: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.24 (d, 4H), 1.36 (m, 6H), 3.18 (d, 3H), 3.24 (m, 2H), 3.40 (t, 2H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.06 (m, 1H), 4.17 (d, 1H), 4.46 (s, 2H), 6.28 (t, 1H), 6.77 (s, 1H), 7.49 (d, 2H), 8.19 (d, 2H), 8.77 (s, 1H)

Prueba (a): Ejemplo (20) 0.043 μM; Ejemplo (20a) 0.15 μM; Ejemplo (20b) 0.17 μM; Ejemplo (20c) 1 μM; Ejemplo (20d) 1.6 μM; Ejemplo (20e) 2.1 μM; Ejemplo (20f) 0.035 μM; Ejemplo (20g) 0.039 μM; Ejemplo (20h) 0.44 μM; Ejemplo (20i) 0.7 μM; Ejemplo (20j) 0.75 μM; Ejemplo (20k) 0.036 μM; Ejemplo (20l) 0.074 μM; Ejemplo (20m) 0.081 μM; Ejemplo (20n) 0.86 μM; Ejemplo (20o) 1.3 μM; Ejemplo (20p) 0.91 μM; Ejemplo (20q) 0.039 μM; Ejemplo (20r) 0.094 μM; Ejemplo (20s) 0.62 μM; Ejemplo (20t) 0.6 μM; Ejemplo (20u) 0.27 μM.

Las preparaciones de los fenil carbamatos (4–{4–morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)carbamato, fenil (4–{4–[(3*S*)–3–metilmorfolin–4–il]–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)carbamato, fenil (4–{4–[(isopropilsulfonil)metil]–6–morfolin–4–ilpirimidin–2–il}fenil)carbamato, fenil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato son descritas a continuación.

Fenil (4–{4–morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)carbamato



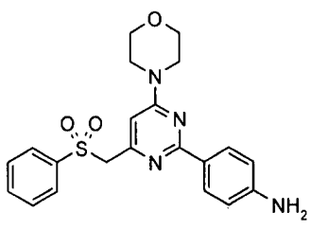
(4–{4–Morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)amina (1 g, 2.44 mmol) fue disuelta en dioxano (10 mL). Bicarbonato de sodio (307 mg, 3.65 mmol) fue añadido, seguido por fenil cloroformato (0.307 mL, 2.44 mmol) y la reacción agitada a temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre

10 mL DCM y 10 mL agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM, para dar el material deseado como un sólido blanco (790 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.64 (s, 4H), 3.70 (m, 4H), 4.71 (s, 2H), 6.70 (s, 1H), 7.27 (m, 3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (m, 1H), 7.85 (m, 4H), 10.38 (s, 1H)

Espectro LCMS: MH+ 531, tiempo de retención 2.61 min, Método Básico 5 Min

(4–{4–Morfolin–4–il–6–[(fenilsulfonil)metil]pirimidin–2–il}fenil)amina

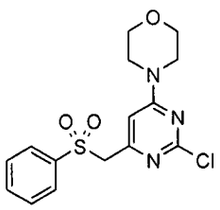


4–{2–Cloro–6–[(fenilsulfonil)metil]pirimidin–4–il}morfolina (3.3 g, 9.33 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 dimetoxietano:agua:etanol (36 mL). [4–(4,4,5,5–Tetrametil–1,3,2–dioxaborolan–2–il)fenil]amina (3.07 g, 13.99 mmol), solución de carbonato de sodio 2M (12 mL) y catalizador de diclorobis(trifenilfosfina) paladio (328 mg, 0.47 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El aceite crudo fue disuelto en DCM y filtrado para eliminar el material insoluble. Un sólido beige se precipitó de los filtrados y los filtrados fueron filtrados nuevamente. El sólido fue analizado y resultó ser el material deseado (2.2 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ3.60 (m, 4H), 3.69 (m, 4H), 4.64 (s, 2H), 5.50 (s, 2H), 6.48 (d, 2H), 6.54 (s, 1H), 7.63 (m, 4H), 7.74 (t, 1H), 7.82 (m, 2H)

Espectro LCMS: MH+ 411, tiempo de retención 1.70 min, Método Básico 5 Min

4–{2–Cloro–6–[(fenilsulfonil)metil]pirimidin–4–il}morfolina

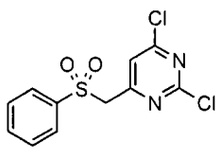


2,4-dicloro-6-[(fenilsulfonil)metil]pirimidina (6 g, 19.8 mmol) fue disuelta en DCM (50 mL) y agitada (bajo nitrógeno) a -5°C. Trietilamina (3.06 mL, 21.8 mmol) fue añadida para dar una solución marrón clara. Morfolina (1.65 mL, 19.8 mmol) fue disuelta en DCM y añadida en forma de gotas manteniendo la reacción por debajo de -5°C. El baño de enfriamiento fue luego eliminado y la mezcla de reacción agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue luego lavada con agua (50 mL), secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 0-50% etil acetato en DCM para dar el material deseado como un sólido blanco (4 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.53 (s, 4H), 3.65 (t, 4H), 4.61 (s, 2H), 6.71 (s, 1H), 7.64 (t, 2H), 7.77 (m, 3H)

Espectro LCMS: MH+ 354, tiempo de retención 1.50 min, Método Básico 5 Min

2,4-dicloro-6-[(fenilsulfonil)metil]pirimidina

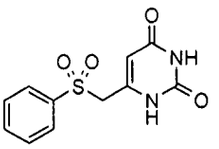


6-[(Fenilsulfonil)metil]pirimidina-2,4(1*H*,3*H*)-diona (13.3 g, 49 mmol) fue añadida a oxicloruro de fósforo (100 mL) y la mezcla calentada hasta reflujo durante 16 horas. La reacción fue luego enfriada hasta temperatura ambiente y el exceso de oxicloruro de fósforo fue eliminado al vacío. El residuo fue azeotropizado con tolueno (2 x 100 mL) y disuelto en DCM. Esta mezcla fue luego vertida lentamente sobre hielo (1 L) y agitada durante 20 minutos, luego extraída con DCM (3 x 500 mL). Los extractos fueron combinados, secados sobre sulfato de magnesio, luego concentrados al vacío para dar el material deseado como un sólido marrón (12 g). El material fue usado sin purificación adicional.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ4.97 (s, 2H), 7.65 (t, 2H), 7.72 (s, 1H), 7.79 (m, 3H)

Espectro LCMS: M-H 301, tiempo de retención 2.08 min, Método Básico 5 Min

6-[(Fenilsulfonil)metil]pirimidina-2,4(1*H*,3*H*)-diona

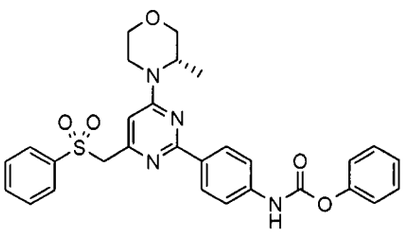


6-(Clorometil)-1*H*-pirimidina-2,4-diona (8 g, 50 mmol) fue disuelta en DMF (200 mL) y sal sódica del ácido bencenosulfínico (9.8 g, 60 mmol) fue añadida. La reacción fue calentada hasta 125°C durante 2 horas luego se dejó enfriar y la suspensión fue filtrada y concentrada al vacío para dar un sólido amarillo. El material crudo fue lavado con agua (100 mL), filtrado, luego triturado con acetonitrilo para dar el material deseado como un sólido color crema (13.2 g). El material fue usado sin purificación adicional.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ4.46 (s, 2H), 7.69 (t, 2H), 7.81 (m, 1H), 7.87 (m, 3H), 10.85 (s, 1H), 11.11 (s, 1H)

6-(Clorometil)-1*H*-pirimidina-2,4-diona es un material comercialmente disponible.

Fenil (4-{4-[(3*S*)-3-metilmorfolin-4-il]-6-[(fenilsulfonil)metil]pirimidin-2-il}fenil)carbamato

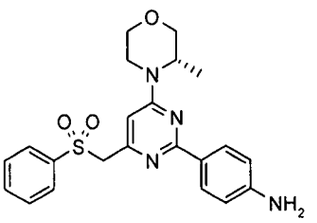


(4-{4-[(3*S*)-3-Metilmorfolin-4-il]-6-[(fenilsulfonil)metil]pirimidin-2-il}fenil)amina (2 g, 4.71 mmol) fue disuelta en dioxano (20 mL). Bicarbonato de sodio (594 mg, 7.07 mmol) fue añadido, seguido por fenil cloroformato (0.593 mL, 4.71 mmol) y la reacción agitada a temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre 20 mL DCM y 20 mL agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0-50% etil acetato en DCM, para dar el material deseado como un sólido blanco (1.1 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.20 (d, 3H), 3.17 (m, 1H), 3.48 (m, 1H), 3.63 (m, 1H), 3.76 (d, 1H), 3.97 (m ,1H), 4.11 (d, 1H), 4.37 (s, 1H), 4.72 (s, 2H), 6.65 (s, 1H), 7.27 (m, 3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 2H), 7.90 (d, 2H), 10.38 (s, 1H)

Espectro LCMS: MH+ 545, tiempo de retención 2.7 min, Método Básico 5 Min

(4-{4-[(3*S*)-3-Metilmorfolin-4-il]-6-[(fenilsulfonil)metil]pirimidin-2-il}fenil)amina

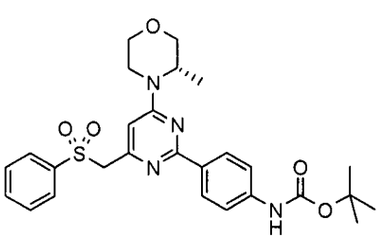


tert-Butil (4-{4-[(3*S*)-3-metilmorfolin-4-il]-6-[(fenilsulfonil)metil]pirimidin-2-il}fenil)carbamato (3.1 g, 5.91 mmol) fue disuelto en DCM (20 mL) y ácido trifluoroacético (10 mL) fue añadido. La mezcla de reacción fue agitada a temperatura ambiente durante 2 horas, luego diluida con DCM (20 mL) y lavada con bicarbonato de sodio saturado acuoso (20 mL). La fase orgánica fue recogida, secada sobre sulfato de magnesio, filtrada y concentrada al vacío para dar el material deseado como un sólido beige (2.5 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 3.24 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.78 (d, 1H), 3.98 (m, 1H), 4.14 (s, 1H), 4.37 (s, 1H), 4.75 (s, 2H), 6.56 (s, 1H), 6.67 (d, 3H), 7.65 (m, 2H), 7.78 (m, 3H), 7.84 (m, 3H)

Espectro LCMS: MH+ 425, tiempo de retención 2.03 min, Método Básico 5 Min

tert-Butil (4-{4-[(3*S*)-3-metilmorfolin-4-il]-6-[(fenilsulfonil)metil]pirimidin-2-il}fenil)carbamato



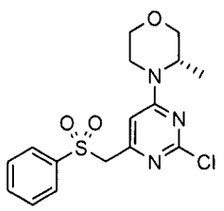
(3*S*)-4-{2-Cloro-6-[(fenilsulfonil)metil]pirimidin-4-il}-3-metilmorfolina (3.2 g, 8.70 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2

dimetoxietano:agua:etanol (36 mL). *tert*-Butil [4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]carbamato (4.16 g, 13.05 mmol), solución de carbonato de sodio 2M (8 mL) y catalizador de diclorobis(trifenilfosfina) paladio (306 mg, 0.43 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente, luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El sólido crudo fue cromatografiado en sílice, eluyendo con 0-30% etil acetato en DCM para dar el material deseado como un sólido beige (3.1 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.19 (d, 3H), 1.49 (s, 9H), 3.16 (m, 1H), 3.47 (m, 1H), 3.62 (m, 1H), 3.75 (d, 1H), 3.97 (m, 1H), 4.10 (d, 1H), 4.35 (s, 1H), 4.70 (s, 2H), 6.62 (s, 1H), 7.44 (d, 2H), 7.63 (d, 2H), 7.74 (m, 1H), 7.82 (m, 4H), 9.49 (s, 1H)

Espectro LCMS: MH+ 525, tiempo de retención 2.80 min, Método Básico 5 Min

(3*S*)-4-{2-cloro-6-[(fenilsulfonil)metil]pirimidin-4-il}-3-metilmorfolina

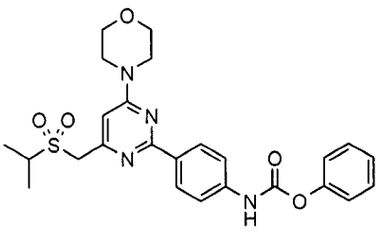


2,4-dicloro-6-[(fenilsulfonil)metil]pirimidina (2.8 g, 9.24 mmol) fue disuelta en DCM (20 mL) y agitada (bajo nitrógeno) a -5°C. Trietilamina (1.42 mL, 10.17 mmol) fue añadida para dar una solución marrón clara. (3*S*)-3-metilmorfolina (935 mg, 9.24 mmol) fue disuelta en DCM y añadida en forma de gotas manteniendo la reacción por debajo de -5°C. El baño de enfriamiento fue luego eliminado y la mezcla de reacción agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue luego lavada con agua (50 mL), secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 0-50% etil acetato en DCM para dar el material deseado como un sólido blanco (2.6 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.15 (d, 3H), 3.15 (m, 1H), 3.42 (m, 1H), 3.56 (m, 1H), 3.72 (d, 1H), 3.92 (m, 2H), 4.15 (s, 1H), 4.62 (s, 2H), 6.66 (s, 1H), 7.74 (t, 1H), 7.76 (t, 1H), 7.78 (d, 1H), 7.80 (m, 2H)

Espectro LCMS: MH+ 368, tiempo de retención 1.95 min, Método Básico 5 Min

Fenil (4-{4-[(isopropilsulfonil)metil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato

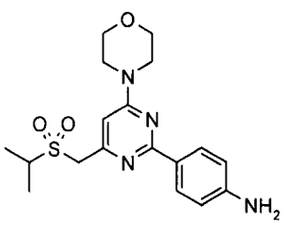


(4-{4-[(Isopropilsulfonil)metil]-6-morfolin-4-ilpirimidin-2-il}fenil)amina (1.5 g, 3.98 mmol) fue disuelta en dioxano(10 mL). Bicarbonato de sodio (503 mg, 5.98 mmol) fue añadido, seguido por fenil cloroformato (0.502 mL, 3.98 mmol) y la reacción agitada a temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre 10 mL DCM y 10 mL agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0-50% etil acetato en DCM, para dar el material deseado como un sólido blanco (1.5 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.30 (d, 6H), 3.45 (m, 1H), 3.65 (s, 8H), 4.40 (s, 2H), 6.78 (s, 1H), 7.20 (m, 3H), 7.38 (t, 2H), 7.56 (d, 2H), 8.22 (d, 2H), 10.37 (s, 1H)

Espectro LCMS: MH+ 497, tiempo de retención 2.54 min, Método Básico 5 Min

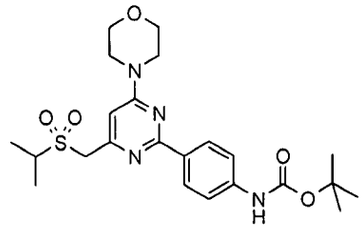
(4-{4-[(Isopropilsulfonil)metil]-6-morfolin-4-ilpirimidin-2-il}fenil)amina



tert-Butil (4-{4-[(isopropilsulfonil)metil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato (2.7 g, 5.67 mmol) fue disuelto en DCM (20 mL) y ácido trifluoroacético (10 mL) fue añadido. La mezcla de reacción fue agitada a temperatura ambiente durante 2 horas, luego diluida con DCM (20 mL) y lavada con bicarbonato de sodio saturado acuoso (20 mL). La fase orgánica fue recogida, secada sobre sulfato de magnesio, filtrada y concentrada al vacío para dar el material deseado como un sólido color crema (2.1 g).

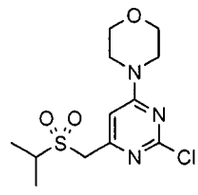
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.35 (d, 6H), 3.50 (m, 1H), 3.67 (m, 4H), 3.72 (m, 4H), 4.41 (s, 2H), 5.57 (s, 2H), 6.60 (d, 2H), 6.70 (s, 1H), 8.03 (d, 2H)
Espectro LCMS: MH+ 377, tiempo de retención 1.61 min, Método Básico 5 Min

tert–Butil (4–{4–[(isopropilsulfonil)metil]–6–morfolin–4–ilpirimidin–2–il}fenil)carbamato



4–{2–Cloro–6–[(isopropilsulfonil)metil]pirimidin–4–il}morfolina (1.5 g, 4.69 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 dimetoxietano:agua:etanol (36 mL). Ácido {4–[(*tert*–butoxicarbonil)amino]fenil}borónico (1.67 g, 7.04 mmol), solución de carbonato de sodio 2M (12 mL) y catalizador de diclorobis(trifenilfosfina) paladio (165 mg, 0.23 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente, luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El aceite crudo fue disuelto en DCM y filtrado para eliminar el material insoluble. Un sólido marrón se precipitó de los filtrados y los filtrados fueron filtrados nuevamente. El sólido fue analizado y resultó ser que era el material deseado (1.9 g).
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.36 (d, 6H), 1.50 (s, 9H), 3.52 (m, 1H), 3.72 (s, 8H), 4.46 (s, 2H), 6.83 (s, 1H), 7.57 (d, 2H), 8.22 (d, 2H), 9.56 (s, 1H)
Espectro LCMS: MH+ 477, tiempo de retención 2.50 min, Método Básico 5 Min

4–{2–Cloro–6–[(fenilsulfonil)metil]pirimidin–4–il}morfolina

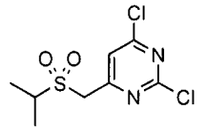


2,4–Dicloro–6–[(isopropilsulfonil)metil]pirimidina (2.65 g, 9.85 mmol) fue disuelta en DCM (50 mL) y agitada (bajo nitrógeno) a –5°C. Trietilamina (1.5 mL, 10.84 mmol) fue añadida

para dar una solución marrón clara. Morfolina (0.86 mL, 9.85 mmol) fue disuelta en DCM y añadida en forma de gotas manteniendo la reacción por debajo de –5°C. El baño de enfriamiento fue luego eliminado y la mezcla de reacción agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue luego lavada con agua (50 mL), secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM para dar el material deseado (2.5 g).
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.30 (d, 6H), 3.42 (m, 1H), 3.62 (s, 4H), 3.68 (m, 4H), 4.42 (s, 2H), 6.95 (s, 1H)

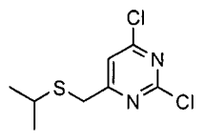
Espectro LCMS: MH+ 320, tiempo de retención 1.51 min, Método Básico 5 Min

2,4–Dicloro–6–[(isopropilsulfonil)metil]pirimidina



2,4–Dicloro–6–[(isopropiltio)metil]pirimidina (6.2 g, 26.16 mmol) fue disuelta en DCM (100 mL) y ácido 3,5–diclorobencenocarboperoxoico (13.5 g, 78.4 mmol) fue añadido en forma de porciones durante 10 minutos. La reacción fue agitada a temperatura ambiente durante 4 horas. La mezcla de reacción fue luego lavada con bicarbonato de sodio saturado acuoso (50 mL), secada sobre sulfato de magnesio, filtrada y concentrada al vacío para dar un sólido color crema. La purificación por cromatografía en fase normal, eluyendo con 0–50% etil acetato en iso–hexano dio el material deseado como un sólido color crema (5.3 g).
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.25 (d, 6H), 3.43 (m, 1H), 4.77 (s, 2H), 7.87 (s, 1H)
Espectro LCMS: M–H 267, tiempo de retención 1.64 min, Método Básico 5 Min

2,4–Dicloro–6–[(isopropiltio)metil]pirimidina



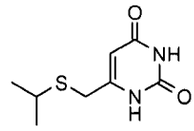
6–[(Isopropiltio)metil]pirimidina–2,4(1*H*,3*H*)–diona (8 g, 40 mmol) fue añadida a oxicloruro de fósforo (100 mL) y la mezcla calentada hasta reflujo durante 16 horas. La reacción fue

luego enfriada hasta temperatura ambiente y el exceso de oxicloruro de fósforo fue eliminado al vacío. El residuo fue azeotropizado con tolueno (2 x 100 mL) y disuelto en DCM. Esta mezcla fue luego vertida lentamente sobre hielo (1 L) y agitada durante 20 minutos, luego extraída con DCM (3 x 500 mL). Los extractos fueron combinados, secados sobre sulfato de magnesio, luego concentrados al vacío para dar el material deseado como un aceite marrón (6.5 g). El material fue usado sin purificación adicional.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.21 (d, 6H), 2.96 (m, 1H), 3.85 (s, 2H), 7.82 (s, 1H)

Espectro LCMS: Tiempo de retención 2.51 min, Método Básico 5 Min

6–[(Isopropiltio)metil]pirimidina–2,4(1*H*,3*H*)–diona



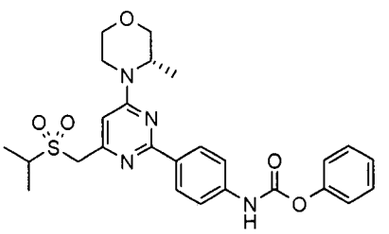
6–(Clorometil)–1*H*–pirimidina–2,4–diona (8 g, 50 mmol) fue disuelta en acetonitrilo (200 mL) y 1,8–Diazabiciclo[5.4.0]undec–7–eno (13 mL, 87.19 mmol) fue añadido y la reacción agitada a temperatura ambiente durante 15 minutos. Isopropil mercaptano (8.1 mL, 87.19 mmol) fue luego añadido y la reacción agitada a temperatura ambiente durante unas 2 horas adicionales. El solvente fue eliminado al vacío y el aceite marrón resultante fue disuelto en DCM y lavado con agua. La fase orgánica secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El aceite resultante fue cromatografiado en sílice, eluyendo con 0–10% metanol en DCM para dar el material deseado como un sólido blanco (8 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.21 (d, 6H), 2.90 (m, 1H), 3.42 (s, 2H), 5.49 (s, 1H), 10.82 (s, 1H), 10.94 (s, 1H)

Espectro LCMS: M–H 199, tiempo de retención 0.63 min, Método Básico 5 Min

6–(Clorometil)–1*H*–pirimidina–2,4–diona es un material comercialmente disponible.

Fenil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato

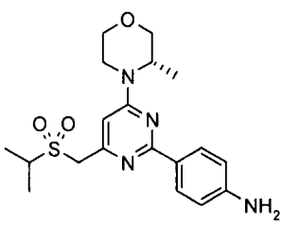


(4–{4–[(Isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)amina (1.5g, 3.84 mmol) fue disuelta en dioxano (10 mL). Bicarbonato de sodio (485 mg, 5.76 mmol) fue añadido, seguido por fenil cloroformato (0.484 mL, 3.84 mmol) y la reacción agitada a temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre 10 mL de DCM y 10 mL de agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM, para dar el material deseado como un sólido blanco (1.8 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.18 (d, 3H), 1.30 (m, 6H), 3.17 (m, 2H), 3.44 (m, 2H), 3.58 (m, 1H), 3.70 (d, 1H), 3.92 (m, 1H), 4.12 (d, 1H), 4.41 (s, 2H), 6.74 (s, 1H), 7.20 (m, 3H), 7.38 (t, 2H), 7.56 (d, 2H), 8.22 (d, 2H), 10.37 (s, 1H)

Espectro LCMS: MH+ 511, tiempo de retención 2.67 min, Método Básico 5 Min

(4–{4–[(Isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)amina

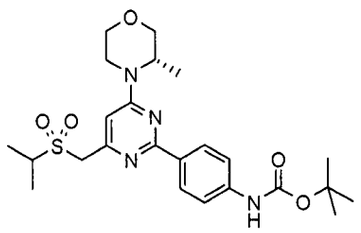


tert–Butil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato (3.2 g, 6.52 mmol) fue disuelto en DCM (20 mL) y ácido trifluoroacético (10 mL) fue añadido. La mezcla de reacción fue agitada a temperatura ambiente durante 2 horas, luego diluida con DCM (20 mL) y lavada con bicarbonato de sodio saturado acuoso (20 mL). La fase orgánica fue recogida, secada sobre sulfato de magnesio, filtrada y concentrada al vacío para dar el material deseado como un sólido color crema (2.4 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.22 (d, 3H), 1.35 (m, 6H), 3.19 (m, 1H), 3.49 (m, 2H), 3.64 (m, 1H), 3.77 (d, 1H), 3.97 (m, 1H), 4.14 (d, 1H), 4.41 (s, 2H), 4.45 (m, 1H), 5.56 (s, 2H), 6.60 (d, 2H), 6.66 (s, 1H), 8.02 (d, 2H)

Espectro LCMS: MH+ 391, tiempo de retención 1.84 min, Método Básico 5 Min

tert–Butil (4–{4–[(isopropilsulfonil)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato

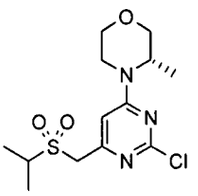


(3*S*)–4–{2–Cloro–6–[(isopropilsulfonil)metil]pirimidin–4–il}–3–metilmorfolina (2.0 g, 5.99 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 dimetoxietano:agua:etanol (16 mL). Ácido {4–[(*tert*–butoxicarbonil)amino]fenil}borónico (2.13 g, 8.99 mmol), solución de carbonato de sodio 2M (8 mL) y catalizador de diclorobis(trifenilfosfina) paladio (211 mg, 0.30 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente, luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM, para dar el material deseado como un sólido marrón (3.2 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.36 (m, 6H), 1.50 (s, 9H), 3.24 (m, 4H), 3.51 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.99 (m, 1H), 4.18 (d, 1H), 4.47 (s, 2H), 6.79 (s, 1H), 7.57 (d, 2H), 8.21 (d, 2H), 9.55 (s, 1H)

Espectro LCMS: MH+ 491, tiempo de retención 2.67 min, Método Básico 5 Min

(3*S*)–4–{2–Cloro–6–[(isopropilsulfonil)metil]pirimidin–4–il}–3–metilmorfolina



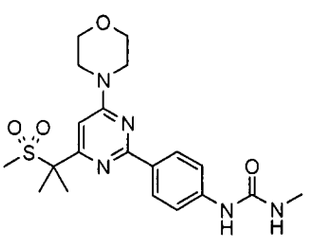
2,4-Dicloro-6-[(isopropilsulfonil)metil]pirimidina (2.65 g, 9.85 mmol) fue disuelta en DCM (50 mL) y agitada (bajo nitrógeno) a -5°C. Trietilamina (1.5 mL, 10.84 mmol) fue añadida para dar una solución marrón clara. 3S-3-Metil morfolina (997 mg, 9.85 mmol) fue disuelta en DCM y añadida en forma de gotas manteniendo la reacción por debajo de -5°C. El baño de enfriamiento fue luego eliminado y la mezcla de reacción agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue luego lavada con agua (50 mL), secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El material crudo fue cromatografiado en sílice, eluyendo con 0-50% etil acetato en DCM para dar el material deseado como un sólido blanco (2 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.22 (d, 3H), 1.31 (d, 6H), 3.22 (m, 1H), 3.43 (m, 2H), 3.60 (m, 1H), 3.74 (d, 1H), 3.98 (m, 1H), 4.30 (s, 1H), 4.43 (s, 2H), 6.91 (s, 1H)

Espectro LCMS: MH+ 332, tiempo de retención 1.70 min, Método Básico 5 Min

Ejemplo 21:

3-Metil-1-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea

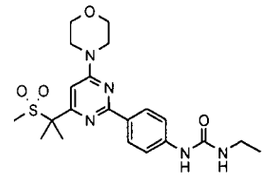
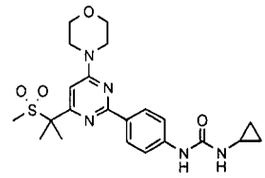
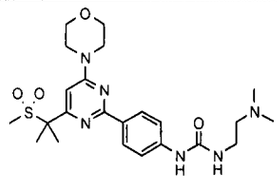
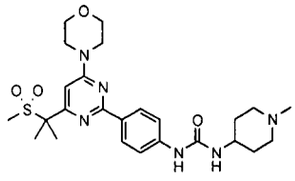


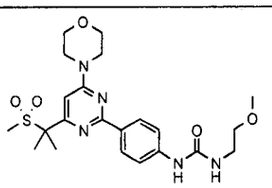
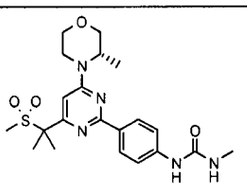
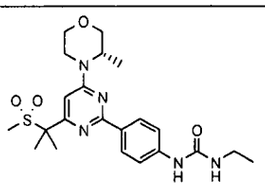
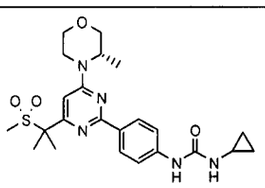
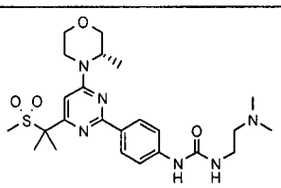
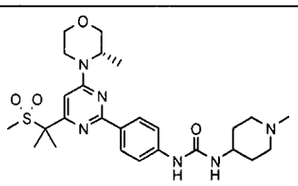
Fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato (116 mg, 0.22 mmol) fue disuelto en DMF (3 mL). Trietilamina (0.098 mL, 0.7 mmol) fue añadido seguido por metilamina (2M en THF, 0.6 mL, 1.17 mmol). La mezcla fue agitada a 50°C durante 1 hora. La reacción fue concentrada y purificada por HPLC preparativa para dar el material deseado como un sólido blanco (54 mg).

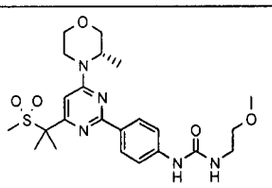
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.77 (s, 6H), 2.66 (d, 3H), 3.04 (s, 3H), 3.73 (s, 8H), 6.06 (m, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.74 (s, 1H)

Espectro LCMS: MH+ 434, tiempo de retención 1.64 min, Método Básico 5 Min

Los siguientes compuestos fueron preparados de una manera análoga a partir de fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato o fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il}fenil)carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
21a		1-etil-3-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	448	1.78
21b		3-ciclopropil-1-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	460	1.91
21c		3-(2-dimetilaminoetil)-1-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	491	1.71
21d		3-(1-metil-4-piperidil)-1-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	517	1.75

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
21e		3-(2-metoxietil)-1-[4-[4-(2-metilsulfonilpropan-2-il)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	478	1.72
21f		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	448	1.76
21g		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	462	1.92
21h		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	474	1.93
21i		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	505	1.83
21j		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1-metil-4-piperidil)urea	531	1.86

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
21k		3–(2–metoxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	492	1.84

Ejemplo 21a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.07 (t, 3H), 1.77 (s, 6H), 3.04 (s, 3H), 3.13 (m, 2H), 3.73 (s, 8H), 6.15 (t, 1H), 6.79 (s, 1H), 7.50 (d, 2H), 8.24 (d, 2H), 8.66 (s, 1H)

Ejemplo 21b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.77 (s, 6H), 2.57 (m, 1H), 3.04 (s, 3H), 3.73 (s, 8H), 6.43 (d, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.54 (s, 1H)

Ejemplo 21c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.77 (s, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.04 (s, 3H), 3.19 (m, 2H), 3.73 (s, 8H), 6.15 (t, 1H), 6.79 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.90 (s, 1H)

Ejemplo 21d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.40 (m, 2H), 1.77 (s, 6H), 2.03 (m, 2H), 2.17 (s, 3H), 2.45 (m, 2H), 2.67 (m, 2H), 3.04 (s, 3H), 3.47 (m, 1H), 3.73 (s, 8H), 6.18 (d, 1H), 6.79 (s, 1H), 7.48 (d, 2H), 8.24 (d, 2H), 8.57 (s, 1H)

Ejemplo 21e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.77 (s, 6H), 3.04 (s, 3H), 3.27 (m, 2H), 3.29 (s, 3H), 3.40 (t, 2H), 3.73 (s, 8H), 6.26 (t, 1H), 6.79 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.79 (s, 1H)

Ejemplo 21f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.16 (d, 3H), 1.70 (s, 6H), 2.59 (d, 3H), 2.96 (s, 3H), 3.16 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.70 (d, 1H), 3.91 (m, 1H), 4.16 (d, 1H), 4.53 (s, 1H), 5.99 (m, 1H), 6.66 (s, 1H), 7.44 (d, 2H), 8.16 (d, 2H), 8.67 (s, 1H)

Ejemplo 21g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.00 (t, 3H), 1.16 (d, 3H), 1.70 (d, 6H), 2.96 (s, 3H), 3.06 (m, 2H), 3.16 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.70 (d, 1H), 3.91 (m, 1H), 4.16 (d, 1H), 4.52 (s, 1H), 6.09 (t, 1H), 6.67 (s, 1H), 7.43 (d, 2H), 8.16 (d, 2H), 8.59 (s, 1H)

Ejemplo 21h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ0.42 (m, 2H), 0.65 (m, 2H), 1.23 (d, 3H), 1.78 (d, 6H), 2.56 (m, 1H), 3.03 (s, 3H), 3.23 (m, 1H), 3.50 (m, 1H), 3.65 (m, 1H), 3.78 (d,

1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.60 (s, 1H), 6.43 (d, 1H), 6.74 (s, 1H), 7.51 (d, 2H), 8.24 (d, 2H), 8.54 (s, 1H)

Ejemplo 21i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.23 (d, 3H), 1.77 (d, 6H), 2.18 (s, 6H), 2.34 (t, 2H), 3.03 (s, 3H), 3.19 (m, 3H), 3.49 (m, 1H), 3.65 (m, 1H), 3.77 (d, 1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.59 (s, 1H), 6.16 (t, 1H), 6.73 (s, 1H), 7.49 (d, 2H), 8.23 (d, 2H), 8.90 (s, 1H)

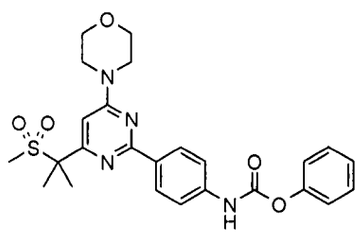
Ejemplo 21j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.24 (s, 3H), 1.41 (m, 2H), 1.78 (d, 6H), 1.81 (m, 2H), 2.02 (t, 2H), 2.16 (s, 3H), 2.64 (m, 2H), 3.03 (s, 3H), 3.22 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.78 (d, 1H), 3.98 (m, 1H), 4.23 (d, 1H), 4.61 (s, 1H), 6.18 (d, 1H), 6.74 (s, 1H), 7.48 (d, 2H), 8.23 (d, 2H), 8.57 (s, 1H)

Ejemplo 21k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.23 (d, 3H), 1.77 (d, 6H), 3.03 (s, 3H), 3.21 (m, 2H), 3.27 (m, 1H), 3.40 (t, 2H), 3.48 (m, 2H), 3.65 (m, 1H), 3.72 (d, 1H), 3.97 (m, 1H), 4.23 (d, 1H), 4.60 (s, 1H), 6.26 (t, 1H), 6.74 (s, 1H), 6.86 (s, 1H), 7.49 (d, 2H), 8.24 (d, 2H), 8.78 (s, 1H)

Prueba (a): Ejemplo (21) 0.05 μM; Ejemplo (21a) 0.73 μM; Ejemplo (21b) 0.36 μM; Ejemplo (21c) 0.48 μM; Ejemplo (21d) 0.27 μM; Ejemplo (21e) 1 μM; Ejemplo (21f) 0.017 μM; Ejemplo (21g) 0.02 μM; Ejemplo (21h) 0.028 μM; Ejemplo (21i) 0.076 μM; Ejemplo (21j) 0.51 μM; Ejemplo (21k) 0.31 μM.

Las preparaciones de fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato y fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il}fenil)carbamato son descritas a continuación.

Fenil (4-{4-[1-metil-1-(metilsulfonil)etil]-6-morfolin-4-ilpirimidin-2-il}fenil)carbamato



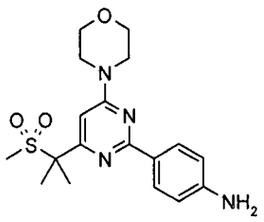
(4-{4-[1-Metil-1-(metilsulfonil)etil]-6-morfolin-4-ilpirimidin-2-il}fenil)amina (1.5 g, 3.98 mmol) fue disuelta en dioxano (15 mL). Bicarbonato de sodio (503 mg, 5.98 mmol) fue añadido, seguido por fenil cloroformato (0.502 mL, 3.98 mmol) y la reacción agitada a

temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre 20 mL DCM y 20 mL agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM, para dar el material deseado como un sólido blanco (700 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.20 (d, 3H), 3.17 (m, 1H), 3.48 (m, 1H), 3.63 (m, 1H), 3.76 (d, 1H), 3.97 (m ,1H), 4.11 (d, 1H), 4.37 (s, 1H), 4.72 (s, 2H), 6.65 (s, 1H), 7.27 (m, 3H), 7.45 (t, 2H), 7.51 (d, 2H), 7.62 (t, 2H), 7.74 (t, 1H), 7.82 (d, 2H), 7.90 (d, 2H), 10.38 (s, 1H)

Espectro LCMS: MH+ 545, tiempo de retención 2.7 min, Método Básico 5 Min

(4–{4–[1–Metil–1–(metilsulfonil)etil]–6–morfolin–4–ilpirimidin–2–il}fenil)amina

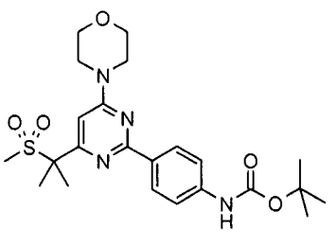


tert–Butil (4–{4–[1–metil–1–(metilsulfonil)etil]–6–morfolin–4–ilpirimidin–2–il}fenil)carbamato (2.6 g, 5.46 mmol) fue disuelto en DCM (20 mL) y ácido trifluoroacético (10 mL) fue añadido. La mezcla de reacción fue agitada a temperatura ambiente durante 2 horas, luego diluida con DCM (20 mL) y lavada con bicarbonato de sodio saturado acuoso (20 mL). La fase orgánica fue recogida, secada sobre sulfato de magnesio, filtrada y concentrada al vacío para dar el material deseado como un sólido color crema (2.1 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.75 (s, 6H), 3.03 (s, 3H), 3.71 (s, 8H), 5.56 (s, 2H), 6.61 (d, 2H), 6.69 (s, 1H), 8.07 (d, 2H)

Espectro LCMS: MH+ 377, tiempo de retención 1.84 min, Método Básico 5 Min

tert–Butil (4–{4–[1–metil–1–(metilsulfonil)etil]–6–morfolin–4–ilpirimidin–2–il}fenil)carbamato

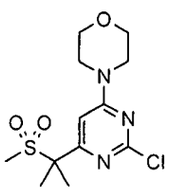


(3*S*)–4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina (1.75 g, 5.47 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 dimetoxietano:agua:etanol (18 mL). *Tert*–Butil [4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]carbamato (2.62 g, 8.2 mmol), solución de carbonato de sodio 2M (8 mL) y catalizador de diclorobis(trifenilfosfina) paladio (192 mg, 0.27 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente, luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El sólido crudo fue cromatografiado en sílice, eluyendo con 0–30% etil acetato en DCM para dar el material deseado como un sólido blanco (2.6 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.50 (s, 9H), 1.77 (s, 6H), 3.04 (s, 3H), 3.73 (s, 8H), 6.80 (s, 1H), 7.57 (d, 2H), 8.26 (d, 2H), 9.54 (s, 1H)

Espectro LCMS: MH+ 477, tiempo de retención 2.66 min, Método Básico 5 Min

4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}morfolina



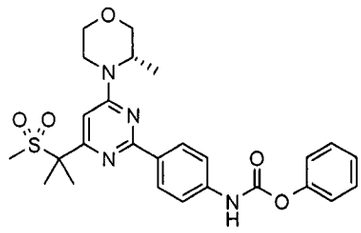
4–{2–Cloro–6–[(metilsulfonil)metil]pirimidin–4–il}morfolina (2.9 g, 9.94 mmol) fue disuelta en DMF (20 mL) y la reacción enfriada hasta –5°C. T–butóxido de sodio (956 mg, 9.94 mmol) fue añadido a la reacción, seguido por yodometano (0.6 mL, 9.94 mmol), manteniendo la temperatura a –5°C. Un segundo equivalentee de t–butóxido de sodio (956 mg, 9.94 mmol) y yodometano (0.6 mL, 9.94 mmol) fueron luego añadidos y la reacción agitada a –5°C durante 1 hora, luego a temperatura ambiente durante 4 horas. DCM (20 mL) fue añadido y la reacción lavada con HCl acuoso 2M (20 mL). La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido crudo fue cromatografiado en sílice,

eluyendo con 0–50% etil acetato en DCM para dar el material deseado como un sólido blanco (1.7 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.68 (s, 6H), 2.99 (s, 3H), 3.67 (s, 8H), 6.91 (s, 1H)

Espectro LCMS: MH+ 320, tiempo de retención 1.67 min, Método Básico 5 Min

Fenil (4–{4–[1–metil–1–(metilsulfonil)etil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato

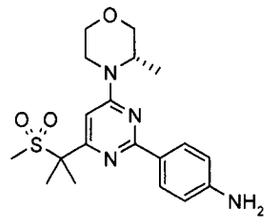


(4–{4–[1–Metil–1–(metilsulfonil)etil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)amina (3.6 g, 8.77 mmol) fue disuelta en dioxano (20 mL). Bicarbonato de sodio (1.1 g, 13.15 mmol) fue añadido, seguido por fenil cloroformato (1.1 mL, 8.77 mmol) y la reacción agitada a temperatura ambiente durante 2 horas. El solvente fue eliminado al vacío, y el aceite resultante particionado entre 20 mL de DCM y 20 mL de agua. La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido color crema obtenido fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM, para dar el material deseado como un sólido blanco (2 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.24 (d, 3H), 1.78 (d, 6H), 3.04 (s, 3H), 3.24 (m, 1H), 3.51 (m, 1H), 3.65 (m, 1H), 3.78 (d, 1H), 3.96 (m, 1H), 4.25 (d, 1H), 4.61 (s, 1H), 6.77 (s, 1H), 7.27 (m, 3H), 7.45 (m, 2H), 7.64 (d, 2H), 8.34 (d, 2H), 10.43 (s, 1H)

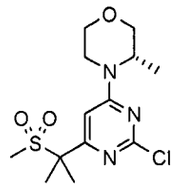
Espectro LCMS: MH+ 511, tiempo de retención 2.7 min, Método Básico 5 Min

(4–{4–[1–Metil–1–(metilsulfonil)etil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)amina



(3*S*)–4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina (2.2 g, 6.59 mmol) fue disuelta en una solución de 18% DMF en una mezcla de 7:3:2 dimetoxietano:agua:etanol (18 mL). [4–(4,4,5,5–Tetrametil–1,3,2–dioxaborolan–2–il)fenil]amina (2.17 g, 9.89 mmol), solución de carbonato de sodio 2M (8 mL) y catalizador de diclorobis(trifenilfosfina) paladio (232 mg, 0.33 mmol) fueron luego añadidos y la reacción refluida a 90°C durante 2 horas bajo una atmósfera de nitrógeno. La reacción se dejó enfriar hasta la temp. ambiente, luego fue particionada entre etil acetato (20 mL) y agua (20 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y concentrados al vacío. El sólido crudo fue cromatografiado en sílice, eluyendo con 0–10% metanol en DCM para dar el material deseado como un aceite marrón (3.6 g).
Espectro LCMS: MH+ 389, tiempo de retención 1.00 min, Método Básico 5 Min

(3*S*)–4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina



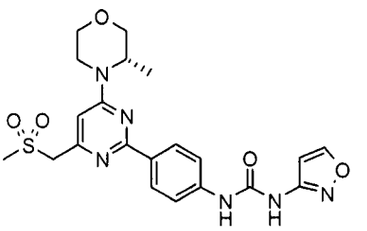
(3*S*)–4–{2–Cloro–6–[(metilsulfonil)metil]pirimidin–4–il}–3–metilmorfolina (2.1 g, 6.87 mmol) fue disuelta en DMF (20 mL) y la reacción enfriada hasta –5°C. T–butóxido de sodio (650 mg, 6.87 mmol) fue añadido a la reacción, seguido por yodometano (0.4 mL, 6.87 mmol), manteniendo la temperatura a –5°C. Un segundo equivalentee de t–butóxido de sodio (650 mg, 6.87 mmol) y yodometano (0.4 mL, 6.87 mmol) fueron luego añadidos y la reacción agitada a –5°C durante 1 hora, luego a temperatura ambiente durante 4 horas. DCM (20 mL) fue añadido y la reacción lavada con ácido clorhídrico acuoso 2M (20 mL). La fase orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada al vacío. El sólido crudo fue cromatografiado en sílice, eluyendo con 0–50% etil acetato en DCM para dar el material deseado (2.2 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.21 (d, 3H), 1.68 (s, 6H), 2.74 (s, 3H), 3.21 (m, 1H), 3.45 (m, 1H), 3.59 (m, 1H), 3.73 (d, 1H), 3.94 (m, 1H), 4.07 (d, 1H), 4.45 (s, 1H), 6.86 (s, 1H)

Espectro LCMS: MH+ 334, tiempo de retención 1.85 min, Método Básico 5 Min

Ejemplo 22:

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea

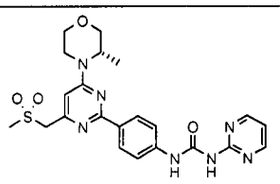
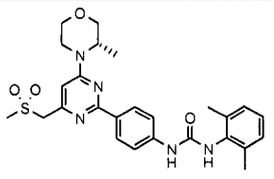
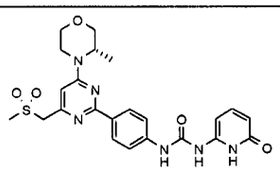
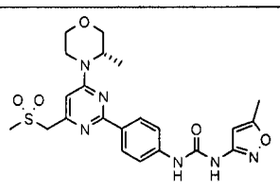
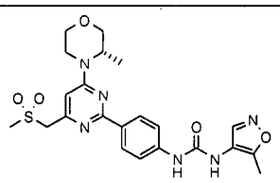
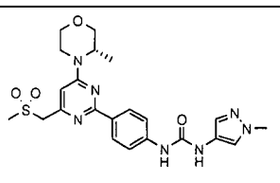


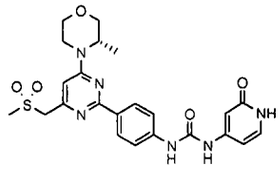
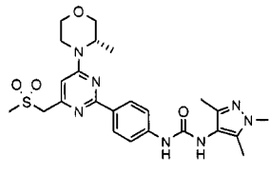
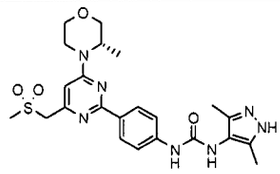
Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato (170 mg, 0.35 mmol) fue disuelto en DMF (1.5 mL). Trietilamina (0.147 mL, 1.06 mmol) fue añadida. 1,2–oxazol–3–amina (198 mg, 2.35 mmol) fue añadida y la reacción agitada a 60°C durante 2 horas. La reacción fue evaporada hasta secarse y purificada por cromatografía en fase inversa para dar el material deseado como un sólido blanco (81 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 – 1.26 (3H, m), 3.21 (3H, s), 3.23 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.01 (1H, m), 4.17 – 4.20 (1H, m), 4.50 (3H, s), 6.81 (1H, s), 6.87 (1H, d), 7.58 (2H, d), 8.29 (2H, d), 8.75 (1H, d), 9.07 (1H, s), 9.62 (1H, s)

Espectro LCMS: MH+ 473, Tiempo de retención 1.63min, Método Ácido Monitor

Los siguientes compuestos fueron preparados de una manera análoga a partir de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
22a		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–pirimidin–2–il–urea	484	1.60
22b		1–(2,6–dimetilfenil)–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	510	1.98
22c		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–(6–oxo–1H–piridin–2–il)urea	499	1.35
22d		3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1–(5–metil–1,2–oxazol–3–il)urea	487	1.72
22e		3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1–(5–metil–1,2–oxazol–4–il)urea	487	1.46
22f		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–	486	1.27

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		2-il]fenil]-3-(1-metilpirazol-4-il)urea		
22g		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(2-oxo-1H-piridin-4-il)urea	499	1.21
22h		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-(1,3,5-trimetilpirazol-4-il)urea	514	1.29
22i		1-(3,5-dimetil-1H-pirazol-4-il)-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	500	1.21

Ejemplo 22a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.22 (3H, s), 3.24 – 3.26 (1H, m), 3.48 – 3.55 (1H, m), 3.65 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.02 (1H, m), 4.20 (1H, d), 4.51 (3H, s), 6.82 (1H, s), 7.16 (1H, t), 7.71 – 7.73 (2H, m), 8.30 – 8.33 (2H, m), 8.70 (2H, d), 10.21 (1H, s), 11.63 (1H, s)

Ejemplo 22b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 – 1.26 (3H, m), 2.23 (6H, s), 3.21 (3H, s), 3.23 (1H, d), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 – 4.20 (1H, m), 4.49 (3H, s), 6.79 (1H, s), 7.08 (3H, d), 7.55 – 7.59 (2H, m), 7.78 (1H, s), 8.23 – 8.27 (2H, m), 9.00 (1H, s)

Ejemplo 22c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.26 (3H, d), 3.22 (3H, s), 3.24 (1H, d), 3.48 – 3.55 (1H, m), 3.64 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.02 (1H, m), 4.19 (1H, d), 4.51 (3H, s), 6.24 (1H, d), 6.81 (1H, s), 7.56 (1H, t), 7.70 (2H, d), 8.28 – 8.30 (2H, m), 9.28 (1H, s)

Ejemplo 22d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.38 (3H, d), 3.21 (3H, s), 3.23 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.68 (1H, m), 3.79 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.50 (3H, s), 6.57 (1H, d), 6.81 (1H, s), 7.56 (2H, d), 8.27 – 8.29 (2H, m), 9.05 (1H, d), 9.46 (1H, s)

Ejemplo 22e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.37 (3H, s), 3.21 (3H, s), 3.22 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, s), 4.49 (3H, s), 6.80 (1H, s), 7.55 – 7.58 (2H, m), 8.18 (1H, s), 8.25 – 8.27 (2H, m), 8.67 (1H, d), 8.99 (1H, s)

Ejemplo 22f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 3.21 (3H, s), 3.22 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.77–3.30 (1H, m) 3.79 (3H, s), 3.97 – 4.01 (1H, m), 4.18 (1H, s), 4.49 (3H, s), 6.79 (1H, s), 7.38 (1H, d), 7.53 – 7.57 (2H, m), 7.76 (1H, s), 8.23 – 8.26 (2H, m), 8.39 (1H, s), 8.84 (1H, s)

Ejemplo 22g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 3.21 (3H, s), 3.23 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.68 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.50 (3H, s), 6.25 – 6.27 (1H, m), 6.46 (1H, d), 6.81 (1H, s), 7.25 (1H, d), 7.55 – 7.57 (2H, m), 8.27 – 8.29 (2H, m), 8.92 (1H, s), 9.05 (1H, s), 11.04 (1H, s)

Ejemplo 22h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.01 (3H, s), 2.10 (3H, s), 3.21 (3H, s), 3.25 (1H, d), 3.47 – 3.54 (1H, m), 3.64 (3H, s), 3.66 – 3.70 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.48 (1H, s), 7.53 – 7.57 (2H, m), 8.22 – 8.24 (2H, m), 8.80 (1H, s)

Ejemplo 22i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.03 (3H, s), 2.09 (3H, s), 3.21 (3H, s), 3.25 (1H, d), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.44 (1H, s), 7.55 (2H, d), 8.23 (2H, d), 8.81 (1H, s), 12.04 (1H, s)

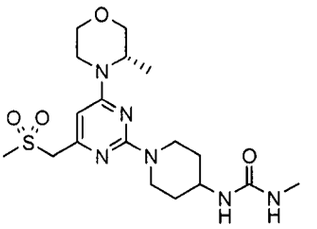
Prueba (a): Ejemplo (22a) 0.06 μM; Ejemplo (22b) 1.6 μM; Ejemplo (22d) 0.0048 μM; Ejemplo (22e) 0.56 μM; Ejemplo (22f) 0.091 μM; Ejemplo (22g) 0.0045 μM; Ejemplo (22h) 1.5 μM; Ejemplo (22i) 4.3 μM.

Prueba (c): Ejemplo (22c) 0.21 μM.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato fue descrita anteriormente.

Ejemplo 23:

3–Metil–1–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]urea

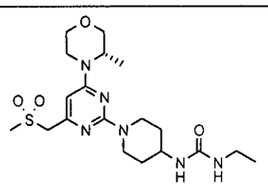


Fenil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]carbamato (220 mg, 0.45 mmol) fue disuelto en DMF (3 mL). Trietilamina (0.188 mL, 1.35mmol) fue añadida, seguido por metilamina 2M en THF (1.2 mL, 2.25 mmol). La mezcla fue agitada a 50°C durante 3 horas. La mezcla de reacción fue evaporada hasta secarse y purificada por cromatografía en fase normal usando a 0–6% metanol en gradiente de DCM para dar un aceite el cual después de la trituración con dietil éter dio el material deseado como un sólido blanco (153 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.17 (3H, d), 1.20 – 1.27 (2H, m), 1.77 (2H, d), 2.54 (3H, d), 2.99 (2H, d), 3.08 (1H, d), 3.12 (3H, s), 3.37 – 3.40 (1H, m), 3.43 (1H, d), 3.57 (1H, d), 3.71 (1H, d), 3.91 (1H, d), 3.94 (1H, d), 4.23 (2H, s), 4.26 (1H, d), 4.42 (2H, d), 5.57 (1H, q), 5.83 (1H, d), 6.14 (1H, s)

Espectro LCMS: MH+ 427, Tiempo de retención 0.85 min, Método Ácido 5 Minutos

El siguiente compuesto fue preparado de una forma análoga a partir de fenil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]carbamato y la amina apropiada.

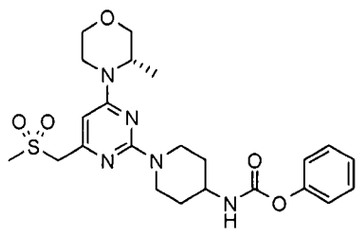
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
23a		1–etil–3–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]urea	441	1.03	Purificado por cromatografía en fase inversa

Ejemplo 23a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.98 (3H, t), 1.13 – 1.18 (3H, m), 1.20 – 1.26 (2H, m), 1.77 (2H, d), 2.97 – 3.03 (4H, m), 3.05 – 3.10 (1H, m), 3.12 (3H, s), 3.38 – 3.45 (1H, m), 3.55 – 3.59 (1H, m), 3.63 (1H, t), 3.71 (1H, d), 3.92 (1H, d), 3.92 (1H, d), 4.23 (2H, s), 4.27 (1H, m), 4.41 (2H, d), 5.64 (1H, t), 5.77 (1H, d), 6.14 (1H, s)

Prueba (a): Ejemplo (23) 5.6 μM; Ejemplo (23a) 3.7 μM.

La preparación de fenil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]carbamato es descrita a continuación.

Fenil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]carbamato



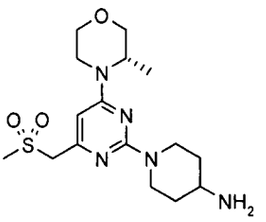
1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piperidin–4–amina (500 mg, 1.35 mmol) fue disuelta en dioxano (10 mL). Bicarbonato de sodio (171 mg, 1.50 mmol) fue añadido. Luego fenil cloroformato (0.171 mL, 1.35 mmol) fue añadido en forma de gotas durante 2 minutos. La lechada fue agitada a RT durante 3 horas. Fenil cloroformato (0.021 mL, 0.27 mmol) y bicarbonato de sodio (21 mg, 0.12 mmol) fueron añadidos. La

agitación a temp. ambiente se continuó durante 1 hora y la mezcla de reacción fue evaporada hasta secarse y particionada entre agua (10 mL) y etil acetato (10 mL). El agua fue extraída con una segunda porción de etil acetato (10 mL). Los productos orgánicos combinados fueron secados sobre sulfato de magnesio y evaporados para dar el material deseado como una espuma (701 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.18 (3H, d), 1.34 – 1.44 (2H, m), 1.86 (2H, d), 2.99 (2H, d), 3.11 (1H, d), 3.13 (3H, s), 3.40 – 3.46 (1H, m), 3.60 (2H, d), 3.72 (2H, d), 3.91 – 3.96 (2H, m), 4.25 (2H, s), 4.28 (1H, m), 4.52 (2H, d), 6.16 (1H, s), 7.10 (2H, d), 7.20 (1H, t), 7.38 (2H, t), 7.76 (1H, d)

Espectro LCMS: MH+ 490, Tiempo de retención 1.58 min, Método Ácido Monitor

1–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piperidin–4–amina

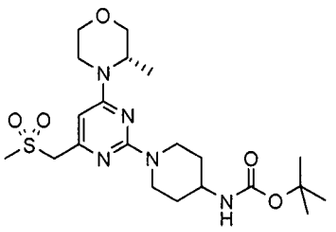


tert–Butil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–4–piperidil]carbamato (1.30 g, 2.77 mmol) fue disuelta en metanol (10 mL). Ácido clorhídrico 4M en dioxano (10 mL) fue añadido. La reacción fue agitada a RT durante 3 horas. Bicarbonato de sodio saturado acuoso fue añadido hasta que el pH7 fue alcanzado y los solventes orgánicos fueron eliminados al vacío. Agua (20 mL) fue añadida y el producto fue extraído en etil acetato (50 mL). La capa acuosa fue extraída con una segunda porción de etil acetato (25 mL). Los productos orgánicos combinados fueron evaporados para dar el material deseado como una espuma amarilla (1.05 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.17 (3H, d), 1.69 – 1.73 (2H, m), 2.75 – 2.80 (1H, m), 2.87 – 2.94 (2H, m), 3.07 (1H, d), 3.11 (1H, m), 3.12 (3H, s), 3.39 – 3.45 (1H, m), 3.55 – 3.62 (1H, m), 3.69 – 3.73 (1H, m), 3.90 – 3.94 (2H, m), 4.22 (2H, s), 4.26 (1H, s), 4.43 (1H, s), 4.46 (1H, d), 6.12 (1H, s)

Espectro LCMS: MH+ 370, Tiempo de retención 0.48 min, Método Ácido Monitor

tert-Butil *N*-[1-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-4-piperidil]carbamato



2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (1.00 g, 3.27 mmol), carbonato de potasio (498 mg, 3.60 mmol) y *tert*-butil N-(4-piperidil)carbamato (721 mg, 3.60 mmol). Acetonitrilo (10 mL) fue añadido y la mezcla fue calentada bajo reflujo durante 4 horas. El acetonitrilo fue evaporado para dejar un sólido blanco el cual fue particionado entre agua (40 mL) y etil acetato (60 mL). Las fases fueron separadas y la capa acuosa fue extraída con una segunda porción de etil acetato (40 mL). Los productos orgánicos combinados fueron evaporados hasta secarse para dar el material deseado como un sólido color crema (1.32 g).

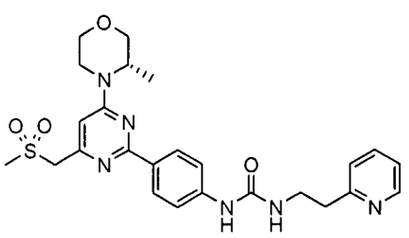
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.16 – 1.18 (3H, m), 1.23 – 1.31 (2H, m), 1.39 (9H, s), 1.74 (2H, d), 2.91 (2H, t), 3.06 – 3.09 (1H, m), 3.11 (3H, s), 3.39 – 3.44 (1H, m), 3.49 (1H, s), 3.55 – 3.59 (1H, m), 3.71 (1H, d), 3.90 (1H, d), 3.94 (1H, d), 4.23 (2H, s), 4.26 (1H, d), 4.50 (2H, d), 6.14 (1H, s), 6.78 (1H, d)

Espectro LCMS: MH+ 470, Tiempo de retención 1.39 min, Método Ácido Monitor

La preparación de 2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina fue descrita anteriormente.

Ejemplo 24:

1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(2-piridin-2-iletil)urea

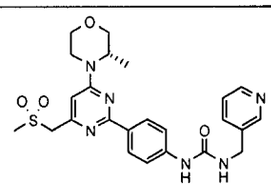
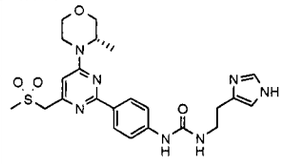
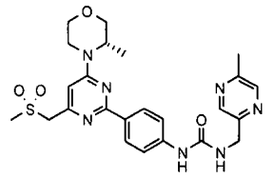


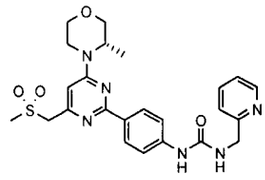
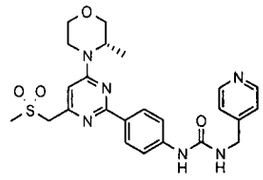
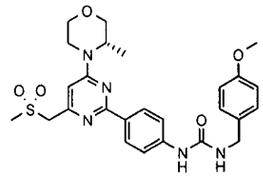
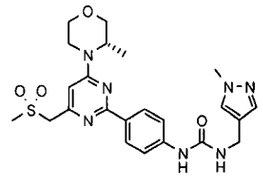
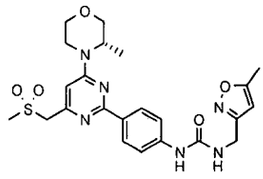
Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]carbamato (242 mg, 0.50 mmol) fue disuelto en DMF (1.5 mL). Trietilamina (0.209 mL, 1.50 mmol) fue añadida. 2-Piridin-2-iletanamina (306 mg, 2.50 mmol) fue añadida. La reacción fue agitada a 40°C durante 2 horas. La mezcla de reacción fue purificada por cromatografía en fase inversa para dar el material deseado como un sólido blanco (239 mg).

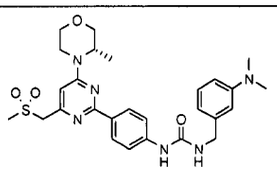
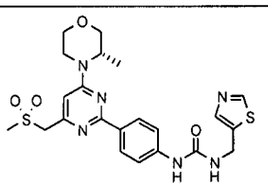
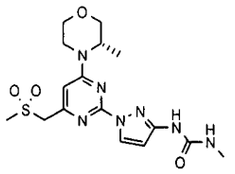
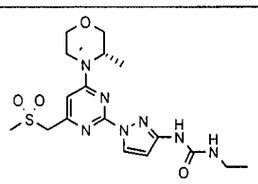
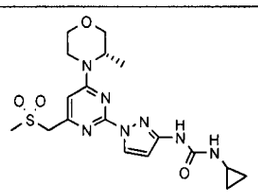
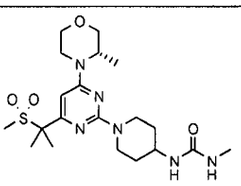
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.94 (2H, t), 3.21 (3H, s), 3.22 – 3.26 (1H, m), 3.48 (1H, d), 3.50 – 3.54 (2H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.26 (1H, t), 6.77 (1H, s), 7.22 – 7.26 (1H, m), 7.30 (1H, d), 7.47 – 7.51 (2H, m), 7.71 – 7.75 (1H, m), 8.19 – 8.22 (2H, m), 8.52 – 8.54 (1H, m), 8.77 (1H, s)

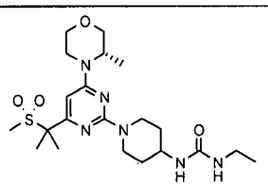
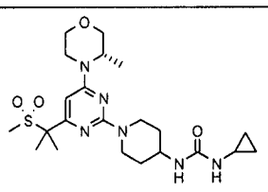
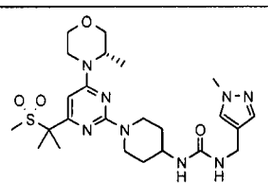
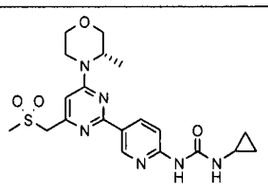
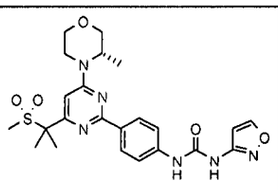
Espectro LCMS: MH+ 511, Tiempo de retención 1.67 min, Método Básico 5 Minutos

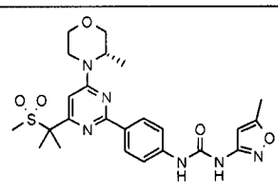
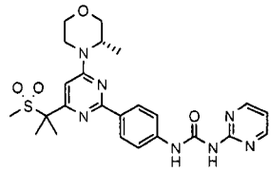
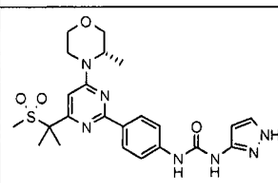
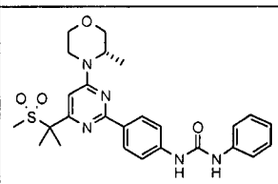
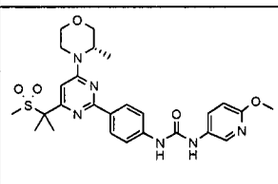
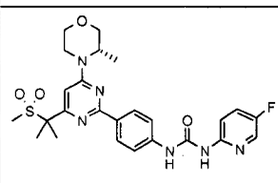
Los siguientes compuestos fueron preparados de una manera análoga a partir del carbamato apropiado y la amina apropiada.

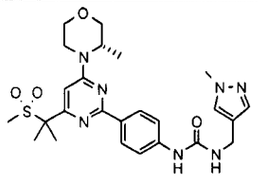
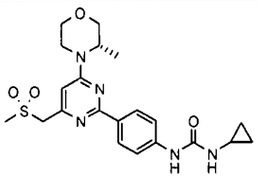
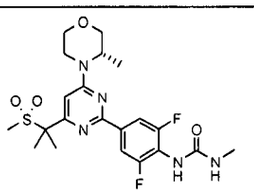
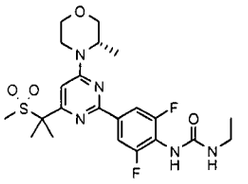
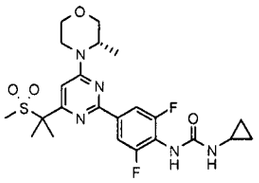
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24a		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(piridin-3-ilmetil)urea	497	1.56
24b		3-[2-(1H-imidazol-4-il)etil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	500	1.42
24c		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-1-[(5-	512	1.52

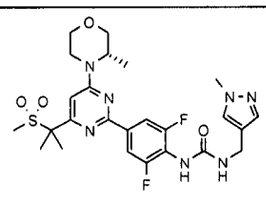
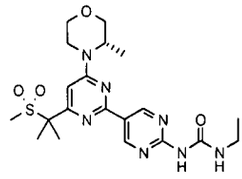
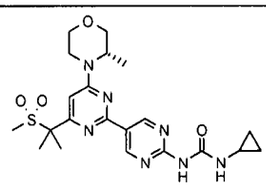
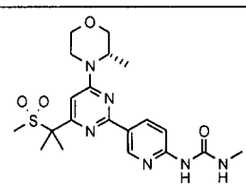
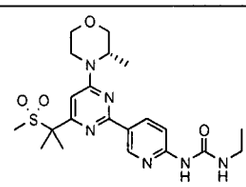
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metilpirazin–2–il)metil]urea		
24d		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–(piridin–2–ilmetil)urea	497	1.62
24e		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–(piridin–4–ilmetil)urea	497	1.55
24f		3–[(4–metoxifenil)metil]–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	526	2.04
24g		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea	500	1.50
24h		3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–1–[(5–metil–1,2–oxazol–3–il)metil]urea	501	1.73

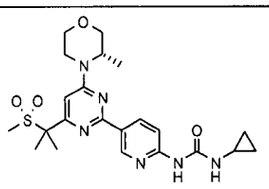
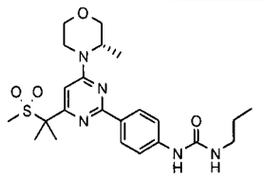
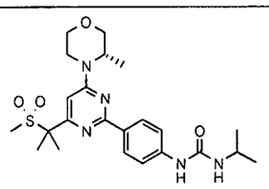
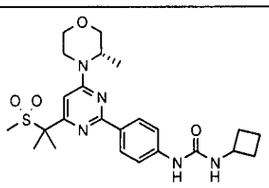
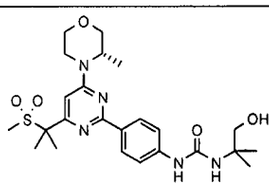
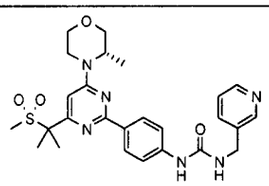
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24i		3–[(3–dimetilaminofenil)metil]–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	539	2.15
24j		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–(1,3–tiazol–5–ilmetil)urea	503	1.58
24k		3–metil–1–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]pirazol–3–il]urea	410	2.18
24l		1–etil–3–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]pirazol–3–il]urea	424	2.29
24m		3–ciclopropil–1–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]pirazol–3–il]urea	436	2.30
24n		3–metil–1–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–4–piperidil]urea	455	1.63

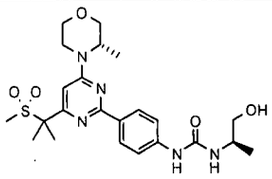
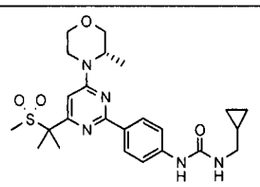
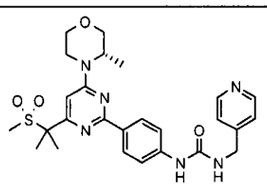
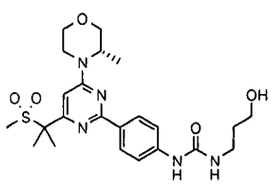
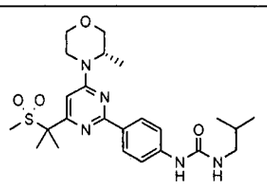
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24o		1-etil-3-[1-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]-4-piperidil]urea	469	1.76
24p		3-ciclopropil-1-[1-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]-4-piperidil]urea	481	1.80
24q		1-[1-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]-4-piperidil]-3-[(1-metilpirazol-4-il)metil]urea	535	1.69
24r		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]piridin-2-il]urea	446	1.56
24s		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	501	1.64

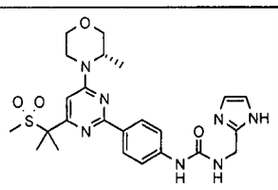
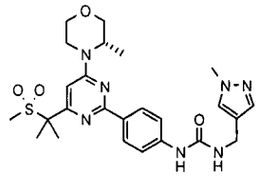
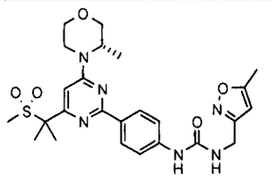
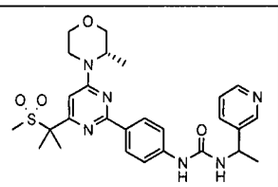
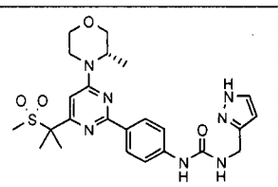
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24t		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-1-(5-metil-1,2-oxazol-3-il)urea	515	2.22
24u		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-pirimidin-2-il-urea	512	2.10
24v		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1H-pirazol-3-il)urea	500	2.05
24w		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-fenil-urea	510	2.40
24x		3-(6-metoxipiridin-3-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	541	2.14
24y		3-(5-fluoropiridin-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-	529	2.39

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea		
24z		1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]pirimidin-2-il]-3-[(1-metilpirazol-4-il)metil]urea	530	1.68
24aa		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	446	1.38
24ab		1-[2,6-difluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-metil-urea	484	2.44
24ac		3-[2,6-difluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-1-etil-urea	498	2.56
24ad		3-ciclopropil-1-[2,6-difluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	510	2.58

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24ae		1-[2,6-difluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea	564	2.46
24af		1-etil-3-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]pirimidin-2-il]urea	464	1.86
24ag		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]pirimidin-2-il]urea	476	1.88
24ah		3-metil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]piridin-2-il]urea	449	1.77
24ai		1-etil-3-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]piridin-2-il]urea	463	1.92

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24aj		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]piridin-2-il]urea	475	1.95
24ak		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-1-propil-urea	476	1.92
24al		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-propan-2-il-urea	476	2.08
24am		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	488	2.15
24an		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	506	1.88
24ao		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-	525	1.83

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		(piridin–3–ilmetil)urea		
24ap		3–[(2R)–1–hidroxipropan–2–il]–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	492	1.71
24aq		3–(ciclopropilmetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	488	2.14
24ar		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]–3–(piridin–4–ilmetil)urea	525	1.81
24as		3–(3–hidroxipropil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	492	1.66
24at		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]–3–(2–metilpropil)urea	490	2.24

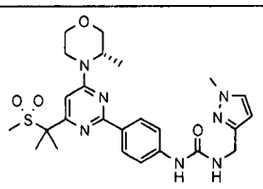
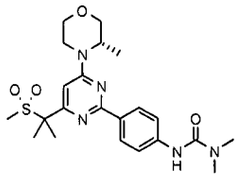
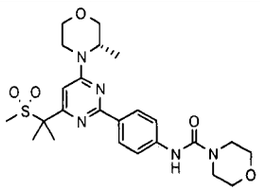
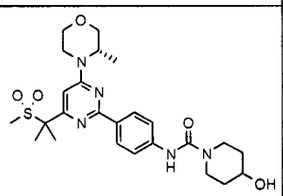
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24au		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	514	1.76
24av		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea	528	1.93
24aw		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-1-[(5-metil-1,2-oxazol-3-il)metil]urea	529	2.01
24ax		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1-piridin-3-iletil)urea	539	1.91
24ay		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1H-pirazol-3-ilmetil)urea	514	1.75

Patente de Invención

Organizacion y
Digitalizacion CSA Ltda

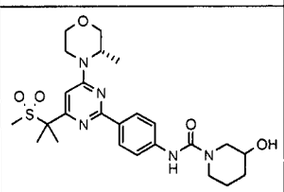
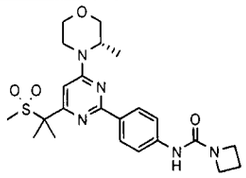
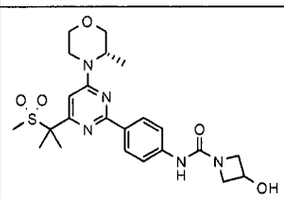
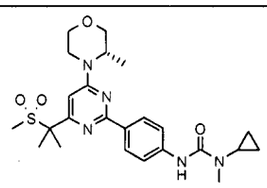
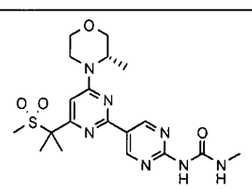
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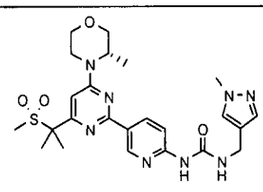
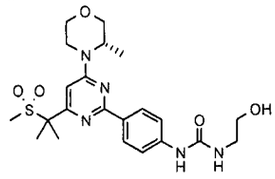
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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24az		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]–3–[(1–metilpirazol–3–il)metil]urea	528	1.84
24ba		1,1–dimetil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	462	1.87
24bb		N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]morfolina–4–carboxamida	504	1.84
24bc		4–hidroxi–N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]piperidina–1–carboxamida	518	1.68

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24bd		3–hidroxi–N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]piperidina–1–carboxamida	518	1.75
24be		N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]azetidina–1–carboxamida	474	1.91
24bf		3–hidroxi–N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]azetidina–1–carboxamida	490	1.62
24bg		1–ciclopropil–1–metil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	488	2.18
24bh		3–metil–1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]pirimidin–2–il]urea	450	1.70

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
24bi		1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piridin–2–il]–3–[(1–metilpirazol–4–il)metil]urea	529	1.75
24bj		3–(2–hidroxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	478	1.61

Ejemplo 24a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.22 – 3.26 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.35 (2H, d), 4.48 (3H, s), 6.77 (1H, t), 6.78 (1H, s), 7.35 – 7.38 (1H, m), 7.52 (2H, d), 7.71 – 7.74 (1H, m), 8.22 (2H, d), 8.46 – 8.47 (1H, m), 8.55 (1H, d), 8.88 (1H, s)

Ejemplo 24b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.67 (2H, t), 3.21 (3H, s), 3.24 (1H, d), 3.34 – 3.39 (2H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.23 (1H, t), 6.77 (1H, s), 6.83 (1H, s), 7.49 – 7.51 (2H, m), 7.55 (1H, d), 8.21 (2H, s), 8.79 (1H, s), 11.81 (1H, s)

Ejemplo 24c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.48 (3H, s), 3.21 (3H, s), 3.22 – 3.26 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.45 (2H, d), 4.49 (3H, s), 6.78 (1H, s), 6.85 (1H, t), 7.50 – 7.53 (2H, m), 8.21 – 8.23 (2H, m), 8.49 – 8.51 (2H, m), 9.01 (1H, s)

Ejemplo 24d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.25 (1H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.44 (2H, d), 4.49 (3H, s), 6.78 (1H, s), 6.84 (1H, t), 7.27 – 7.30 (1H, m), 7.37 (1H, d), 7.51 – 7.55 (2H, m), 7.76 – 7.80 (1H, m), 8.22 (2H, d), 8.53 – 8.55 (1H, m), 9.04 (1H, s)

Ejemplo 24e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.23 – 3.26 (1H, m), 3.50 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 (1H, d), 4.00 – 4.19

(1H, m), 4.36 (2H, d), 4.48 (2H, s), 4.49 (1H, s), 6.78 (1H, s), 6.81 (1H, t), 7.30 – 7.31 (2H, m), 7.51 – 7.55 (2H, m), 8.21 – 8.24 (2H, m), 8.51 – 8.52 (2H, m), 8.96 (1H, s)

Ejemplo 24f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.21 (3H, s), 3.24 (1H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.74 (3H, s), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.25 (2H, d), 4.48 – 4.48 (2H, m), 6.59 (1H, t), 6.78 (1H, s), 6.89 – 6.92 (2H, m), 7.23 – 7.26 (2H, m), 7.50 – 7.52 (2H, m), 8.20 – 8.23 (2H, m), 8.76 (1H, s)

Ejemplo 24g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.24 (1H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 – 4.01 (1H, m), 4.13 (2H, d), 4.19 (1H, s), 4.48 (2H, s), 4.49 (1H, s), 6.42 (1H, t), 6.77 (1H, s), 7.35 (1H, s), 7.49 – 7.51 (2H, m), 7.59 (1H, s), 8.20 – 8.22 (2H, m), 8.69 (1H, s)

Ejemplo 24h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.38 (3H, s), 3.25 (1H, d), 3.48 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.32 (2H, d), 4.48 (2H, s), 4.49 (1H, s), 6.16 (1H, d), 6.71 (1H, t), 6.78 (1H, s), 7.50 – 7.53 (2H, m), 8.21 – 8.24 (2H, m), 8.91 (1H, s)

Ejemplo 24i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.88 (6H, s), 3.21 (3H, s), 3.25 (1H, d), 3.50 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.25 (2H, d), 4.48 (1H, d), 4.49 (2H, s), 6.59 (2H, t), 6.63 (1H, d), 6.68 (1H, d), 6.78 (1H, s), 7.14 (1H, t), 7.51 (2H, d), 8.22 (2H, d), 8.77 (1H, s)

Ejemplo 24j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.21 (3H, d), 3.23 – 3.26 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, s), 4.49 (1H, d), 4.49 (2H, s), 4.54 (2H, d), 6.78 (1H, s), 6.80 (1H, t), 7.50 – 7.54 (2H, m), 7.79 (1H, d), 8.21 – 8.24 (2H, m), 8.87 (1H, s), 8.97 (1H, d)

Ejemplo 24k: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.69 (3H, d), 3.19 (1H, d), 3.25 (3H, s), 3.48 (1H, d), 3.63 (1H, d), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.12 (1H, s), 4.44 (1H, m), 4.48 (2H, s), 6.49 (1H, d), 6.72 (1H, s), 6.78 (1H, s), 8.44 (1H, d), 9.30 (1H, s)

Ejemplo 24l: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.08 (3H, t), 1.25 (3H, d), 3.12 – 3.19 (2H, m), 3.23 (3H, s), 3.24 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.12 (1H, s), 4.45 (1H, m), 4.48 (2H, s), 6.46 (1H, d), 6.78 (1H, s), 6.89 (1H, s), 8.44 (1H, d), 9.22 (1H, s)

Ejemplo 24m: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.39 – 0.43 (2H, m), 0.64 – 0.69 (2H, m), 1.25 (3H, d), 2.56 – 2.60 (1H, m), 3.22 (3H, s), 3.25 (1H, m), 3.45 – 3.52 (1H, m), 3.62 –

3.66 (1H, m), 3.77 (1H, d), 3.95 – 3.99 (1H, m), 4.12 (1H, s), 4.45 (1H, s), 4.48 (2H, s), 6.47 (1H, d), 6.78 (1H, s), 7.09 (1H, s), 8.44 (1H, d), 9.16 (1H, s)

Ejemplo 24n: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.16 (3H, d), 1.18 – 1.24 (2H, m), 1.64 (6H, s), 1.77 (2H, d), 2.54 (3H, d), 2.98 (3H, s), 3.02 (2H, t), 3.08 – 3.12 (1H, m), 3.39 – 3.45 (1H, m), 3.55 – 3.60 (1H, m), 3.62 – 3.66 (1H, m), 3.69 – 3.74 (1H, m), 3.90 – 3.93 (1H, m), 3.98 (1H, d), 4.36 (1H, d), 4.42 (2H, d), 5.57 (1H, q), 5.82 (1H, s), 6.14 (1H, s)

Ejemplo 24o: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.98 (3H, t), 1.15 (3H, t), 1.20 – 1.27 (2H, m), 1.64 (6H, s), 1.77 (2H, d), 2.98 (4H, s), 3.00 – 3.02 (2H, m), 3.05 (1H, d), 3.08 – 3.12 (1H, m), 3.39 – 3.45 (1H, m), 3.55 – 3.60 (1H, m), 3.64 (1H, d), 3.71 (1H, d), 3.90 – 3.93 (1H, m), 3.99 (1H, d), 4.36 (1H, d), 4.42 (2H, d), 5.64 (1H, t), 5.76 (1H, d), 6.14 (1H, s)

Ejemplo 24p: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.29 – 0.33 (2H, m), 0.53 – 0.57 (2H, m), 1.16 (3H, d), 1.31 (2H, m), 1.64 (6H, s), 1.76 (2H, d), 2.09 (3H, s), 2.37 – 2.43 (1H, m), 2.75 (1H, s), 2.98 (3H, s), 2.96 – 3.01 (1H, m), 3.05 – 3.12 (1H, m), 3.39 – 3.45 (1H, m), 3.55 – 3.59 (1H, m), 3.66 (1H, t), 3.71 (1H, d), 3.90 – 3.93 (1H, m), 3.99 (1H, d), 4.36 (1H, d), 4.44 (2H, d), 5.72 (1H, d), 5.97 (1H, d), 6.14 (1H, s)

Ejemplo 24q: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.16 (3H, d), 1.18 – 1.27 (2H, m), 1.64 (6H, s), 1.78 (2H, d), 2.98 (3H, s), 3.00 (1H, s), 3.03 (1H, d), 3.08 – 3.12 (1H, m), 3.39 – 3.45 (1H, m), 3.58 (1H, d), 3.65 (1H, t), 3.71 (1H, t), 3.78 (3H, s), 3.89 – 3.93 (1H, m), 4.00 (3H, d), 4.35 (1H, s), 4.41 (2H, d), 5.82 (1H, d), 5.89 (1H, t), 6.14 (1H, s), 7.28 (1H, s), 7.51 (1H, s)

Ejemplo 24r: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.47 – 0.50 (2H, m), 0.66 – 0.71 (2H, m), 1.25 (3H, d), 2.61 – 2.67 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.19 (1H, d), 4.49 (3H, d), 6.83 (1H, s), 7.54 (1H, d), 8.10 (1H, s), 8.48 – 8.51 (1H, m), 9.09 (1H, d), 9.32 (1H, s)

Ejemplo 24s: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.78 (6H, s), 3.04 (3H, s), 3.19 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.25 (1H, d), 4.61 (1H, s), 6.77 (1H, s), 6.87 (1H, d), 7.58 (2H, d), 8.31 (2H, d), 8.75 (1H, d), 9.07 (1H, s), 9.61 (1H, s)

Ejemplo 24t: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.78 (6H, d), 2.38 (3H, d), 3.04 (3H, s), 3.19 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, d), 6.57 (1H, d), 6.77 (1H, s), 7.55 – 7.58 (2H, m), 8.31 (2H, d), 9.05 (1H, s), 9.46 (1H, s)

Ejemplo 24u: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 – 3.25 (1H, m), 3.47 – 3.53 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.83 (3H, s), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.80 (1H, d), 7.57 (2H, d), 7.83 – 7.86 (1H, m), 8.21 (1H, d), 8.29 (2H, d), 8.62 (1H, s), 8.97 (1H, s)

Ejemplo 24v: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.79 (6H, d), 3.04 (3H, s), 3.19 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.25 (1H, d), 4.63 (1H, s), 5.42 (1H, s), 5.90 (1H, d), 6.78 (1H, s), 7.84 (2H, d), 8.06 (1H, d), 8.34 (2H, d), 9.84 (1H, s) .

Ejemplo 24w: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.20 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.99 (1H, t), 7.30 (2H, d), 7.47 (2H, d), 7.57 (2H, d), 8.30 (2H, d), 8.71 (1H, s), 8.91 (1H, s)

Ejemplo 24x: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.20 – 3.25 (1H, m), 3.27 (3H, s),
3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.24 (1H, d), 4.61 (1H, s), 6.76 (1H, s), 6.99 (1H, t), 7.30 (2H, d), 7.47 (2H, d), 7.57 (2H, d), 8.30 (2H, d), 8.71 (1H, s), 8.91 (1H, s)

Ejemplo 24y: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 – 3.26 (1H, m), 3.48 – 3.54 (1H, m), 3.64 – 3.68 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.25 (1H, d), 4.62 (1H, s), 6.77 (1H, s), 7.61 (2H, d), 7.71 – 7.76 (1H, m), 7.78 – 7.82 (1H, m), 8.29 (1H, d), 8.32 (2H, d), 9.38 (1H, s), 9.87 (1H, s)

Ejemplo 24z: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.77 (6H, s), 3.00 (3H, s), 3.02 – 3.23 (1H, m), 3.46 – 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.80 (3H, s), 3.95 – 3.98 (1H, m), 4.28 (1H, m), 4.29 (2H, d), 4.63 (1H, s), 6.83 (1H, s), 7.39 (1H, s), 7.63 (1H, s), 9.25 (1H, t), 9.36 (2H, s), 10.09 (1H, s)

Ejemplo 24aa: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.41 – 0.45 (2H, m), 0.63 – 0.68 (2H, m), 1.25 (3H, d), 2.53 – 2.59 (1H, m), 3.21 (3H, s), 3.25 (1H, d), 3.47 – 3.54 (1H, m), 3.64 – 3.68 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.44 (1H, d), 6.78 (1H, s), 7.52 (2H, d), 8.22 (2H, d), 8.55 (1H, s)

Ejemplo 24ab: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.79 (6H, d), 2.66 (3H, d), 3.02 (3H, s), 3.20 – 3.27 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97

– 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.27 (1H, q), 6.86 (1H, s), 7.95 – 8.01 (2H, m), 8.14 (1H, s)

Ejemplo 24ac: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.25 (3H, d), 1.79 (6H, d), 3.01 (3H, s), 3.09 – 3.15 (2H, m), 3.20 – 3.27 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.36 (1H, t), 6.85 (1H, s), 7.95 – 8.01 (2H, m), 8.05 (1H, s)

Ejemplo 24ad: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.43 – 0.47 (2H, m), 0.63 – 0.67 (2H, m), 1.25 (3H, d), 1.79 (6H, d), 2.53 – 2.58 (1H, m), 3.02 (3H, s), 3.20 – 3.27 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.66 (1H, d), 6.86 (1H, s), 7.97 (2H, d), 8.00 (1H, s)

Ejemplo 24ae: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.79 (6H, d), 3.02 (3H, s), 3.20 – 3.27 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.81 (3H, s), 3.97 – 4.01 (1H, m), 4.12 (2H, d), 4.27 (1H, d), 4.63 (1H, s), 6.63 (1H, t), 6.86 (1H, s), 7.35 (1H, d), 7.58 (1H, s), 7.97 – 8.01 (2H, m), 8.09 (1H, s)

Ejemplo 24af: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.15 (3H, t), 1.25 (3H, d), 1.78 (6H, d), 3.02 (3H, s), 3.20 – 3.24 (1H, m), 3.27–3.29 (2H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.28 (1H, d), 4.64 (1H, s), 6.84 (1H, s), 9.06 (1H, t), 9.39 (2H, s), 10.01 (1H, s)

Ejemplo 24ag: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.54 – 0.57 (2H, m), 0.70 – 0.74 (2H, m), 1.25 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.68 – 2.73 (1H, m), 3.02 (3H, s), 3.19 – 3.27 (1H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.28 (1H, d), 4.63 (1H, s), 6.84 (1H, s), 9.13 (1H, d), 9.38 (2H, s), 10.07 (1H, s)

Ejemplo 24ah: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.76 (3H, d), 3.03 (3H, s), 3.20 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.25 (1H, d), 4.62 (1H, s), 6.80 (1H, s), 7.42 – 7.45 (1H, m), 8.15 (1H, d), 8.52 – 8.55 (1H, m), 9.14 (1H, d), 9.48 (1H, s)

Ejemplo 24ai: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.12 (3H, t), 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 3.02 (3H, s), 3.19 – 3.23 (2H, m), 3.24 – 3.26 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.25 (1H, d), 4.61 (1H, s), 6.80 (1H, s), 7.46 – 7.49 (1H, m), 8.17 (1H, t), 8.52 – 8.55 (1H, m), 9.14 (1H, d), 9.40 (1H, s)

Ejemplo 24aj: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.47 – 0.51 (2H, m), 0.67 – 0.71 (2H, m), 1.24 (3H, d), 1.78 (3H, s), 1.78 (3H, s), 2.61 – 2.67 (1H, m), 3.02 (3H, s), 3.19 – 3.26 (1H,

m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.26 (1H, d), 4.62 (1H, s), 6.80 (1H, s), 7.53 (1H, d), 8.16 (1H, s), 8.53 – 8.56 (1H, m), 9.13 (1H, d), 9.33 (1H, s)

Ejemplo 24ak: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.90 (3H, t), 1.24 (3H, d), 1.42 – 1.49 (2H, m), 1.78 (6H, d), 3.04 (3H, s), 3.18 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.61 (1H, d), 6.21 (1H, t), 6.74 (1H, s), 7.49 – 7.52 (2H, m), 8.23 – 8.25 (2H, m), 8.66 (1H, s)

Ejemplo 24al: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.12 (6H, d), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.04 (3H, s), 3.21 – 3.24 (1H, m), 3.48 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.76 – 3.81 (2H, m), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, d), 6.07 (1H, d), 6.74 (1H, s), 7.47 – 7.51 (2H, m), 8.23 (2H, d), 8.55 (1H, s)

Ejemplo 24am: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.59 – 1.66 (2H, m), 1.78 (6H, d), 1.84 – 1.89 (2H, m), 2.19 – 2.25 (2H, m), 3.04 (3H, s), 3.21 – 3.25 (1H, m), 3.48 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.15 (1H, q), 4.23 (1H, d), 4.60 (1H, d), 6.47 (1H, d), 6.74 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.58 (1H, s)

Ejemplo 24an: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.25 – 1.25 (5H, m), 1.78 (6H, s), 3.04 (3H, s), 3.19 – 3.24 (1H, m), 3.40 (2H, d), 3.50 (1H, d), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.24 (1H, d), 4.59 (1H, s), 4.96 (1H, t), 6.01 (1H, s), 6.74 (1H, s), 7.46 (2H, d), 8.23 (2H, d), 8.74 (1H, s)

Ejemplo 24ao: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.78 (6H, d), 3.04 (3H, s), 3.19 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.36 (2H, d), 4.60 (1H, d), 6.75 (1H, s), 6.78 (1H, t), 7.36 – 7.39 (1H, m), 7.53 (2H, d), 7.72 – 7.75 (1H, m), 8.25 (2H, d), 8.46 – 8.48 (1H, m), 8.55 (1H, d), 8.88 (1H, s)

Ejemplo 24ap: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.04 (3H, s), 3.19 – 3.25 (1H, m), 3.34 – 3.42 (2H, m), 3.47 – 3.54 (1H, m), 3.65 (1H, d), 3.70 – 3.74 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 4.79 (1H, t), 6.10 (1H, d), 6.74 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.73 (1H, s)

Ejemplo 24aq: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.18 – 0.22 (2H, m), 0.42 – 0.47 (2H, m), 0.94 – 0.98 (1H, m), 1.24 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 3.00 (2H, t), 3.04 (3H, s), 3.18 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 6.27 (1H, t), 6.74 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.70 (1H, s)

Ejemplo 24ar: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.20 – 3.24 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.24 (1H, d), 4.36 (2H, d), 4.60 (1H, s), 6.74 (1H, s), 6.83 (1H, t), 7.30 – 7.31 (2H, m), 7.51 – 7.55 (2H, m), 8.23 – 8.26 (2H, m), 8.51 – 8.52 (2H, m), 9.01 (1H, s)

Ejemplo 24as: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.56 – 1.62 (2H, m), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.14 – 3.19 (2H, m), 3.20 – 3.24 (1H, m), 3.44 – 3.47 (2H, m), 3.49 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.22 (1H, s), 4.52 (1H, t), 4.59 (1H, s), 6.22 (1H, t), 6.74 (1H, s), 7.48 – 7.51 (2H, m), 8.23 (2H, d), 8.75 (1H, s)

Ejemplo 24at: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.88 (6H, d), 1.22 (3H, t), 1.66 – 1.73 (1H, m), 1.74 – 1.76 (3H, m), 1.77 (3H, s), 2.94 (2H, t), 3.04 (3H, s), 3.20 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.22 (1H, s), 4.60 (1H, s), 6.26 (1H, t), 6.74 (1H, s), 7.48 – 7.51 (2H, m), 8.23 (2H, d), 8.68 (1H, s)

Ejemplo 24au: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.24 (1H, d), 4.32 (2H, d), 4.60 (1H, s), 6.64 (1H, t), 6.74 (1H, s), 6.83 (1H, s), 7.04 (1H, s), 7.50 – 7.53 (2H, m), 8.22 – 8.26 (2H, m), 8.96 (1H, s), 11.87 (1H, s)

Ejemplo 24av: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.96 – 4.00 (1H, m), 4.12 (2H, d), 4.23 (1H, s), 4.60 (1H, s), 6.44 (1H, t), 6.74 (1H, s), 7.35 (1H, s), 7.50 (2H, d), 7.60 (1H, s), 8.24 (2H, d), 8.74 (1H, s)

Ejemplo 24aw: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 2.38 (3H, d), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.24 (1H, d), 4.32 (2H, d), 4.60 (1H, s), 6.16 (1H, d), 6.71 (1H, s), 6.74 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.96 (1H, s)

Ejemplo 24ax: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.44 (3H, d), 1.76 (3H, s), 1.76 (3H, s), 3.03 (3H, s), 3.19 – 3.24 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.77 (1H, d), 3.95 – 3.99 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 4.88 (1H, t), 6.74 (1H, s), 6.81 (1H, d), 7.36 – 7.39 (1H, m), 7.48 (2H, d), 7.75 – 7.78 (1H, m), 8.23 (2H, d), 8.45 – 8.47 (1H, m), 8.59 (1H, d), 8.71 (1H, s)

Ejemplo 24ay: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96

– 4.00 (1H, m), 4.22–4.33 (1H, m), 4.28 (2H, d), 4.60 (1H, s), 6.18 (1H, s), 6.52 (1H, s), 6.74 (1H, s), 7.51 (2H, d), 7.67 (1H, s), 8.25 (2H, d), 8.84 (1H, s), 12.64 (1H, s)

Ejemplo 24az: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 – 1.76 (5H, m), 1.77 (3H, s), 3.20 (1H, d), 3.47 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.76 – 3.80 (4H, m), 3.96 – 4.00 (1H, m), 4.23 (2H, d), 4.25 (1H, s), 4.60 (1H, s), 6.14 (1H, d), 6.52 (1H, t), 6.74 (1H, s), 7.51 (2H, d), 7.61 (1H, d), 8.24 (2H, d), 8.84 (1H, s)

Ejemplo 24ba: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 2.95 (6H, s), 3.04 (3H, s), 3.20 – 3.24 (1H, m), 3.49 (1H, d), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, s), 4.60 (1H, s), 6.75 (1H, s), 7.59 (2H, d), 8.23 (2H, d), 8.52 (1H, s)

Ejemplo 24bb: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.45 (4H, t), 3.49 – 3.52 (1H, m), 3.61 – 3.63 (4H, m), 3.65 (1H, s), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.25 (1H, d), 4.60 (1H, s), 6.75 (1H, s), 7.59 (2H, d), 8.25 (2H, d), 8.77 (1H, s)

Ejemplo 24bc: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.29 – 1.38 (2H, m), 1.75–1.77 (2H, m), 1.77 (3H, s), 1.77 (3H, s), 3.04 (4H, s), 3.07 – 3.11 (2H, m), 3.16 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.67 – 3.70 (1H, m), 3.77 (1H, d), 3.85 (2H, q), 3.96 – 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 4.74 (1H, d), 6.74 (1H, s), 7.58 (2H, d), 8.23 (2H, d), 8.72 (1H, s)

Ejemplo 24bd: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.33 – 1.41 (2H, m), 1.69 – 1.73 (1H, m), 1.77 (3H, s), 1.77 (3H, s), 1.85 – 1.88 (1H, m), 2.74 – 2.79 (1H, m), 2.91 – 2.97 (1H, m), 3.04 (3H, s), 3.17 – 3.24 (1H, m), 3.45 – 3.53 (2H, m), 3.62 – 3.66 (1H, m), 3.76 (1H, s), 3.79 (1H, t), 3.93 – 4.00 (2H, m), 4.24 (1H, d), 4.60 (1H, s), 4.88 (1H, d), 6.74 (1H, s), 7.57 – 7.59 (2H, m), 8.21 – 8.24 (2H, m), 8.69 (1H, s)

Ejemplo 24be: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, t), 1.76 (3H, s), 1.77 (3H, s), 2.15 – 2.23 (2H, m), 3.04 (3H, s), 3.18 – 3.24 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.98 (5H, t), 4.22 (1H, s), 4.60 (1H, s), 6.74 (1H, s), 7.62 (2H, d), 8.22 – 8.25 (2H, m), 8.59 (1H, s)

Ejemplo 24bf: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (3H, s), 1.77 (3H, s), 3.04 (3H, s), 3.16 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.62 – 3.66 (1H, m), 3.71 – 3.75 (2H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.14 – 4.18 (2H, m), 4.24 (1H, d), 4.41 – 4.46 (1H, m), 4.60 (1H, s), 5.66 (1H, d), 6.74 (1H, s), 7.62 (2H, d), 8.22 – 8.25 (2H, m), 8.64 (1H, s)

Ejemplo 24bg: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.68 – 0.72 (2H, m), 0.90 (2H, d), 1.23 (3H, d), 1.77 (3H, s), 1.78 (3H, s), 2.70 – 2.74 (1H, m), 2.87 (3H, s), 3.04 (3H, d), 3.17 – 3.24 (1H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.25 (1H, d), 4.59 (1H, s), 6.75 (1H, s), 7.63 – 7.66 (2H, m), 8.24 (2H, d), 8.43 (1H, s)

Ejemplo 24bh: ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.23 (3H, d), 1.77 (3H, s), 1.77 (3H, s), 2.80 (3H, d), 3.02 (3H, s), 3.18 – 3.26 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.77 (1H, d), 3.95 – 3.99 (1H, m), 4.27 (1H, d), 4.63 (1H, s), 6.84 (1H, s), 8.98 (1H, d), 9.37 (2H, s), 10.11 (1H, s)

Ejemplo 24bi: ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.24 (3H, d), 1.78 (6H, d), 3.02 (3H, s), 3.18 – 3.26 (1H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.80 (3H, s), 3.96 – 4.00 (1H, m), 4.24 (2H, d), 4.27 (1H, m), 4.61 (1H, s), 6.79 (1H, s), 7.38 (1H, s), 7.49 – 7.52 (1H, m), 7.62 (1H, s), 8.36 (1H, s), 8.53 – 8.56 (1H, m), 9.12 (1H, d), 9.45 (1H, s).

Ejemplo 24bj: ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.23 (3H, d), 1.77 (6H, d), 3.03 (3H, s), 3.17 (2H, q), 3.23 (1H, d), 3.46 (2H, q), 3.49 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.60 (1H, d), 4.73 (1H, t), 6.25 (1H, t), 6.74 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.81 (1H, s)

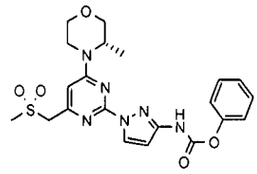
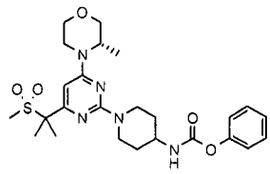
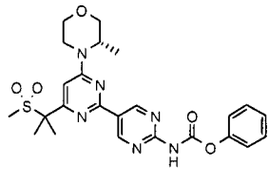
Prueba (a): Ejemplo (24) 0.34 μM; Ejemplo (24a) 0.082 μM; Ejemplo (24b) 0.038 μM; Ejemplo (24c) 0.56 μM; Ejemplo (24d) 4.4 μM; Ejemplo (24e) 0.81 μM; Ejemplo (24f) 4.5 μM; Ejemplo (24g) 0.31 μM; Ejemplo (24h) 4.4 μM; Ejemplo (24i) 0.33 μM; Ejemplo (24j) 0.22 μM; Ejemplo (24k) 0.18 μM; Ejemplo (24l) 0.84 μM; Ejemplo (24m) 0.65 μM; Ejemplo (24n) 3.2 μM; Ejemplo (24o) 3.4 μM; Ejemplo (24p) 0.89 μM; Ejemplo (24q) 5.8 μM; Ejemplo (24r) 0.34 μM; Ejemplo (24s) 0.0047 μM; Ejemplo (24t) 0.012 μM; Ejemplo (24u) 0.12 μM; Ejemplo (24v) 0.055 μM; Ejemplo (24w) 0.034 μM; Ejemplo (24x) 0.1 μM; Ejemplo (24y) 2.2 μM; Ejemplo (24z) 0.37 μM; Ejemplo (24aa) 0.11 μM; Ejemplo (24ab) 0.042 μM; Ejemplo (24ac) 0.048 μM; Ejemplo (24ad) 0.51 μM; Ejemplo (24ae) 0.24 μM; Ejemplo (24bh) 0.012 μM; Ejemplo (24bi) 0.43 μM; Ejemplo (24bj) 0.051 μM.

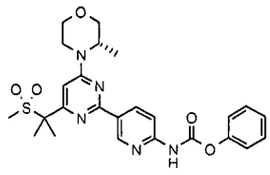
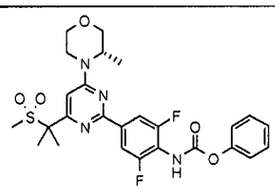
Prueba (c): Ejemplo (24af) 1.4 μM; Ejemplo (24ag) 0.32 μM; Ejemplo (24ah) 0.51 μM; Ejemplo (24ai) 0.26 μM; Ejemplo (24aj) 0.45 μM; Ejemplo (24ak) 0.21 μM; Ejemplo (24al) 0.038 μM; Ejemplo (24am) 0.21 μM; Ejemplo (24an) 1.8 μM; Ejemplo (24ao) 0.24 μM; Ejemplo (24ap) 0.077 μM; Ejemplo (24aq) 2 μM; Ejemplo (24ar) 0.049 μM; Ejemplo (24as) 0.22 μM; Ejemplo (24at) 0.089 μM; Ejemplo (24au) 2.4 μM; Ejemplo (24av) 4.9 μM; Ejemplo (24aw) 3.4 μM; Ejemplo (24ax) 0.64 μM; Ejemplo (24ay) 7.9 μM; Ejemplo (24az)

5.6 μM; Ejemplo (24ba) 5.1 μM; Ejemplo (24bb) 7.8 μM; Ejemplo (24bc) 0.69 μM; Ejemplo (24bd) 3.2 μM; Ejemplo (24be) 4.9 μM; Ejemplo (24bf) 6.7 μM; Ejemplo (24bg) 2.4 μM.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato y fenil (4–{4–[1–metil–1–(metilsulfonil)etil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato es descrita anteriormente.

Los siguientes carbamatos fueron preparados a partir de la anilina o amina apropiada de una forma análoga al fenil *N*–[1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil) pirimidin–2–il]–4–piperidil]carbamato, descrito anteriormente.

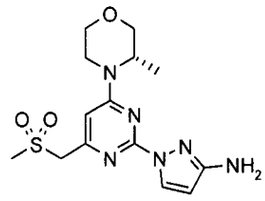
Estructura	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**	**Notas**
	fenil N–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]pirazol–3–il]carbamato	495	2.09	Purificado por cromatografía usando 0–55% etil acetato en isohexano
	fenil N–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–4–piperidil]carbamato	518	2.34	
	fenil N–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]pirimidin–2–	513	2.21	Purificado por cromatografía usando 0–3% metanol en DCM

Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)	Notas
	il]carbamato			
	fenil N-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-metilsulfonilpropan-2-il)pirimidin-2-il]piridin-2-il]carbamato	512	2.60	Purificado por cromatografía usando 0-3% metanol en DCM
	(S)-fenil 2,6-difluoro-4-(4-(3-metilmorfolino)-6-(2-(metilsulfonil)propan-2-il)pirimidin-2-il)fenilcarbamato	547	2.67	

(S)-Fenil 2,6-difluoro-4-(4-(3-metilmorfolino)-6-(2-(metilsulfonil)propan-2-il)pirimidin-2-il)fenilcarbamato: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 1.25 (3H, d), 1.79 (6H, d), 3.00 (3H, s), 3.20-3.27 (1H, m), 3.47 – 3.55 (1H, m), 3.58 (15H, s), 3.65 (1H, d), 3.75 (1H, d), 3.97 – 4.01 (1H, m), 4.28 (1H, d), 4.63 (1H, s), 6.88 (1H, s), 7.21 (2H, d), 7.27 (1H, t), 7.44 (2H, t), 8.08 (2H, d), 9.96 (1H, s)

La preparación de 1-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-amina es descrita a continuación.

1-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-amina

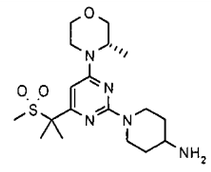


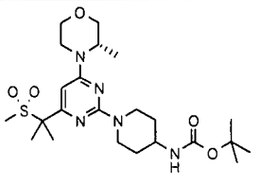
2–Cloro–4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1.00 g), 1H–pirazol–3–amina (300 mg) y carbonato de potasio (498 mg) fueron disueltos en butironitrilo (20 mL). La mezcla fue calentada a reflujo durante 24 horas. La reacción fue diluida con etil acetato (20 mL) y lavada con agua (20 mL). El agua fue extraída con etil acetato (20 mL). Los extractos orgánicos combinados fueron secados sobre sulfato de magnesio y evaporados. El producto crudo fue purificado por cromatografía en sílice, eluyendo con 0–5% metanol en DCM para dar el material deseado (635 mg).

Espectro NMR: 1H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 3.20 (3H, s), 3.24 (1H, m), 3.43 – 3.50 (1H, m), 3.60 – 3.64 (1H, m), 3.75 (1H, d), 3.94 – 3.98 (1H, m), 4.06 – 4.12 (1H, m), 4.43 (1H, s), 4.43 (2H, s), 5.25 (2H, s), 5.75 (1H, s), 5.80 (1H, d), 6.66 (1H, s), 8.26 (1H, d)

Espectro LCMS: MH+ 490, Tiempo de retención 1.58 min, Método Ácido Monitor

1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piperidin–4–amina fue preparada a partir de (3*S*)–4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina y *tert*–butil *N*–(4–piperidil)carbamato en un procedimiento de dos pasos análogo a 1–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piperidin–4–amina.

Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
	1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piperidin–4–amina	398	0.94

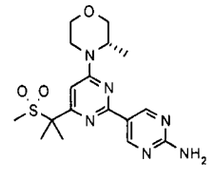
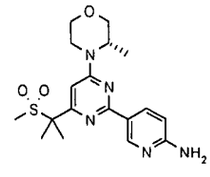
	*tert*–butil N–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–4–piperidil]carbamato	498	2.43

1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piperidin–4–amina: ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.27 (3H, d), 1.75 (6H, s), 1.83 – 1.87 (2H, m), 2.88 (1H, d), 2.91 (5H, s), 2.94 (1H, d), 3.17 – 3.25 (1H, m), 3.50 – 3.57 (1H, m), 3.68 (1H, d), 3.70 (2H, s), 3.75 – 3.77 (1H, m), 3.92 (1H, s), 3.95 – 3.99 (2H, m), 4.30 (1H, d), 4.61 (2H, d), 6.06 (1H, s)

***tert*–Butil N–[1–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–4–piperidil]carbamato:** ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.25 (5H, d), 1.27 (2H, d), 1.30 – 1.35 (2H, m), 1.45 (9H, s), 1.54 (6H, s), 1.98 (2H, d), 2.04 (4H, s), 2.90 (3H, s), 2.95 – 3.01 (2H, m), 3.17 – 3.24 (1H, m), 3.50 – 3.57 (1H, m), 3.66 – 3.70 (2H, m), 3.76 (1H, d), 3.95 – 3.99 (2H, m), 4.29 (1H, d), 4.56 (2H, d), 6.07 (1H, s)

La preparación de (3*S*)–4–{2–cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina fue descrita anteriormente.

5–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]pirimidin–2–amina y 5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piridin–2–amina fueron preparadas a partir de (3*S*)–4–{2–cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina de una forma análoga a (4–{4–[1–Metil–1–(metilsulfonil)etil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)amina, descrita anteriormente.

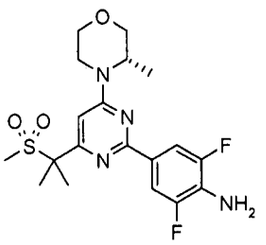
Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
	5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]pirimidin–2–amina	393	1.57
	5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piridin–2–amina	392	1.16

5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]pirimidin–2–amina: ^{1}H NMR (400.13 MHz, DMSO–d6) δ 1.23 (3H, d), 1.75 – 1.76 (6H, m), 3.00 (3H, s), 3.16 – 3.23 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 6.74 (1H, s), 7.11 (2H, s), 9.09 (2H, s)

5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]piridin–2–amina: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.86 (6H, s), 2.93 (3H, s), 3.31 – 3.35 (1H, m), 3.56 – 3.62 (1H, m), 3.72 – 3.75 (1H, m), 3.82 (1H, d), 4.02 – 4.05 (1H, m), 4.12 (1H, d), 4.48 – 4.50 (1H, m), 4.83 (2H, s), 6.52 – 6.55 (1H, m), 6.59 (1H, s), 8.35 – 8.38 (1H, m), 9.08 – 9.09 (1H, m)

La preparación de 2,6–difluoro–4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]anilina es descrita a continuación.

2,6–Difluoro–4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]anilina



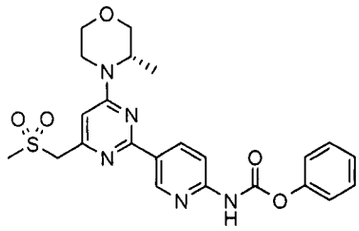
4–Bromo–2,6–difluoro–anilina (400 mg, 1.92 mmol), acetato de potasio (566 mg, 5.77 mmol) y 4,4,5,5–tetrametil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1,3,2–dioxaborolano (587 mg, 2.31 mmol) fueron disueltos en 1,4 dioxano (5 mL). La solución fue desgasificada durante 10 minutos, luego 1,1'–bis(difenilfosfino)ferrocenodicloropaladio fue añadido (95 mg, 0.12 mmol) y la reacción fue agitada a 90°C durante 3 horas. (3*S*)–4–{2–Cloro–6–[1–metil–1–(metilsulfonil)etil]pirimidin–4–il}–3–metilmorfolina (450 mg, 1.35 mmol), etanol (1 mL), carbonato de sodio 2M (1 mL) y 1,1'–bis(difenilfosfino)ferrocenodicloropaladio (95 mg, 0.12 mmol) fueron añadidos y el calentamiento se continuó durante 18 horas. La reacción se dejó enfriar hasta RT, luego agua (50 mL) fue añadida, seguido por etil acetato (50 mL). El sólido no disuelto fue eliminado por filtración. Las fases fueron separadas y la fase acuosa fue extraída con una segunda porción de etil acetato (30 mL). Los productos orgánicos combinados fueron secados sobre sulfato de magnesio, filtrados y evaporados hasta secarse. El producto crudo fue disuelto en DCM (25 mL), filtrado para eliminar el material insoluble y el filtrado purificado por cromatografía en sílice, eluyendo con 0–35% etil acetato en isohexano, para dar el material deseado como un sólido blanco hueso (402 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.76 (6H, d), 3.00 (3H, s), 3.17 – 3.24 (1H, m), 3.45 – 3.51 (1H, m), 3.62 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 5.70 (2H, d), 6.73 (1H, s), 7.83 – 7.85 (2H, m)

Espectro LCMS: MH+ 427, Tiempo de retención 2.35 min, Método Ácido Monitor

La preparación de fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piridin–2–il]carbamato es descrita a continuación.

Fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]piridin–2–il]carbamato



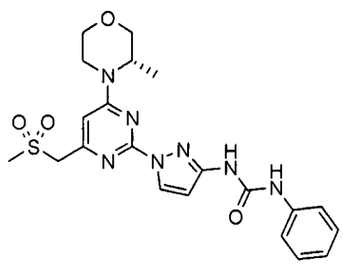
5-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]piridin-2-amina (770 mg, 2.12 mmol) fue disuelta en dioxano (10 mL) y bicarbonato de sodio (267 mg, 3.18 mmol) fue añadido para dar una lechada amarilla fina. Fenil cloroformato (0.267 mL, 2.12 mmol) fue añadido en forma de gotas durante 10 minutos, controlando la exoterma usando un baño de agua y la mezcla fue agitada a RT durante 16 horas. Bicarbonato de sodio (267 mg, 3.18 mmol) y fenil cloroformato (0.267 mL, 2.12 mmol) adicionales fueron añadidos y la mezcla fue agitada a RT durante 2 horas. Nuevamente fenil cloroformato (0.267 mL, 2.12 mmol) fue añadido y la mezcla fue agitada a RT durante 1 hora, luego calentada hasta 35°C durante 16 horas. La reacción fue evaporada hasta secarse y el residuo fue particionado entre agua (15 mL) y etil acetato (20 mL). El sólido blanco fue filtrado y lavado con agua (5 mL), DCM (5 mL) y metanol (5 mL). El sólido fue secado al vacío a 40°C durante 5 horas para dar el producto como un sólido blanco (117 mg).

Espectro LCMS: MH+ 484, tiempo de retención 2.32 min, Método Ácido Monitor

La preparación de 5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]piridin-2-amina fue descrita anteriormente.

Ejemplo 25:

1-[1-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-il]-3-fenil-urea

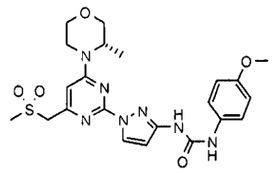
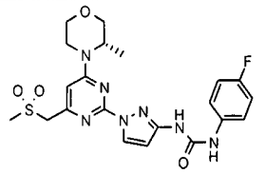


1-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-amina (90 mg, 0.26 mmol) fue disuelta en dioxano (4 mL). Fenil isocianato (0.024 mL, 0.22 mmol) fue añadido a la solución resultante. La mezcla fue calentada a 80°C durante 2 horas. El sólido fue filtrado y lavado con dietil éter (5 mL) para dar el material deseado como un sólido blanco (66 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.23 (3H, s), 3.40 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.98 (1H, d), 4.14 (1H, s), 4.47 (1H, m), 4.51 (2H, d), 6.60 (1H, d), 6.81 (1H, s), 7.01 (1H, t), 7.29 – 7.33 (2H, m), 7.47 (2H, d), 8.51 (1H, d), 9.18 (1H, s), 9.50 (1H, s)

Espectro LCMS: MH+ 472, Tiempo de retención 1.86 min, Método Ácido 5 Min

Los siguientes compuestos fueron preparados de una manera análoga a partir de 1-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-amina y el isocianato apropiado.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
25a		3-(4-metoxifenil)-1-[1-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-il]urea	502	1.98
25b		3-(4-fluorofenil)-1-[1-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]pirazol-3-il]urea	512	2.06

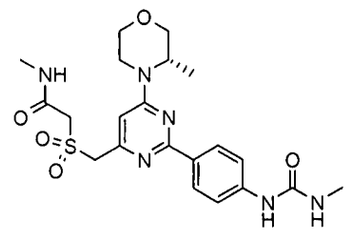
Ejemplo 25a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.47 – 3.53 (1H, m), 3.56 (1H, d), 3.63 – 3.67 (1H, m), 3.73 (3H, s), 3.78 (1H, d), 3.96 – 4.00 (1H, m), 4.14 (1H, s), 4.47 (1H, m), 4.50 (2H, s), 6.57 (1H, d), 6.81 (1H, s), 6.87 – 6.91 (2H, m), 7.35 – 7.39 (2H, m), 8.50 (1H, d), 9.04 (1H, s), 9.42 (1H, s)

Ejemplo 25b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.26 (3H, d), 3.26 (1H, m), 3.46 – 3.53 (1H, m), 3.58 (3H, s), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.96 – 4.00 (1H, m), 4.14 (1H, s), 4.46 (1H, m), 4.50 (2H, s), 6.59 (1H, d), 6.81 (1H, s), 7.13 – 7.18 (2H, m), 7.45 – 7.50 (2H, m), 8.51 (1H, d), 9.17 (1H, s), 9.51 (1H, s)

Prueba (a): Ejemplo (25) 1.9 μM; Ejemplo (25a) 4.4 μM; Ejemplo (25b) 4.4 μM.

Ejemplo 26:

***N*–Metil–2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]acetamida**

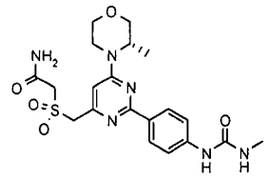
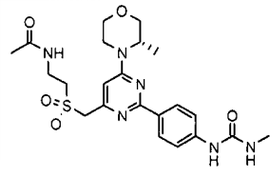


N–Metil–2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida (0.35 mmol) fue disuelta en 1,4–Dioxano (5 mL) y agua (1 mL). m–CPBA (75%) (121 mg) seguido inmediatamente por permanganato de sodio (140 mg) fueron añadidos a la solución y la reacción agitada a RT durante 1 h. m–CPBA (75%) adicional (121 mg) seguido inmediatamente por permanganato de sodio (140 mg) fueron añadidos a la solución y esta agitada a RT durante 1 h. Nuevamente m–CPBA (75%) adicional (121 mg) seguido inmediatamente por permanganato de sodio (140 mg) fueron añadidos y la reacción agitada a RT durante 1 h. La reacción fue cargada en una columna SCX–3 (10 g), la cual fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por HPLC prep. (básica) para dar el material deseado (30 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 – 1.25 (3H, m), 2.66 – 2.70 (3H, m), 2.68 (1H, d), 3.21 – 3.26 (1H, m), 3.46 – 3.53 (3H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.29 (2H, s), 4.47 (1H, s), 4.67 (2H, s), 6.07 (1H, q), 6.76 (1H, s), 7.48 – 7.52 (2H, m), 8.17 – 8.20 (2H, m), 8.31 (1H, t), 8.74 (1H, s)

Espectro de masa: $M+H^+$ 477.

Los siguientes compuestos fueron preparados de una forma análoga a partir de los sulfuros apropiados.

Ejemplo	Estructura	NOMBRE	LCMS MH+
26a		2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]acetamida	463
26b		N–[2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]etil]acetamida	491

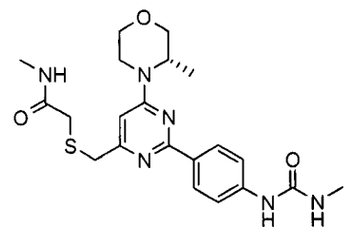
Ejemplo 26a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.66 (3H, d), 3.18 – 3.26 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.27 (2H, s), 4.48 (1H, s), 4.66 (2H, s), 6.07 (1H, q), 6.76 (1H, s), 7.48 – 7.52 (3H, m), 7.79 (1H, s), 8.17 – 8.21 (2H, m), 8.74 (1H, s)

Ejemplo 26b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.83 (3H, s), 2.66 (2H, s), 2.68 (2H, q), 3.21 – 3.26 (1H, m), 3.47 – 3.53 (2H, m), 3.52 (1H, s), 3.57 (2H, q), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.51 (2H, s), 6.06 (1H, q), 6.77 (1H, s), 7.48 – 7.52 (2H, m), 8.14 – 8.21 (3H, m), 8.74 (1H, s)

Prueba (a): Ejemplo (26) 0.029 μM; Ejemplo (26a) 0.037 μM; Ejemplo (26b) 0.041 μM.

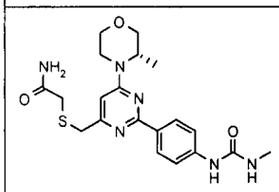
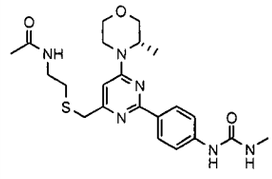
La preparación de *N*–metil–2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida es descrita a continuación.

N–Metil–2–[[2–[4–(metilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfanil]acetamida



N-Metil-2-sulfanil-acetamida (0.61 mmol) fue disuelta en acetonitrilo (4 mL). DBU (0.050 mL) fue luego añadido a la solución y esta agitada a RT durante 5 min. Una solución de 3-metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (151 mg) en acetonitrilo (2 mL) y DBU (0.054 mL) fueron añadidos y la reacción agitada a RT durante 2 h antes de ser concentrada al vacío y usada inmediatamente en el paso subsiguiente.

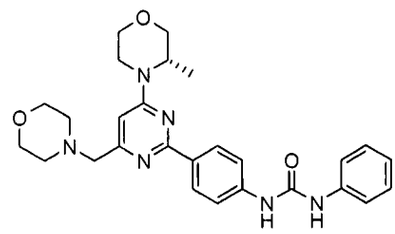
Los siguientes sulfuros fueron hechos de una forma análoga.

Estructura	NOMBRE
	2-[[2-[4-(metilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]acetamida
	N-[2-[[2-[4-(metilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]etil]acetamida

La preparación de 3-metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea fue descrita anteriormente.

Ejemplo 27:

1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(morfolin-4-ilmetil)pirimidin-2-il]fenil]-3-fenil-urea



1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea (90 mg) fue disuelta en DCM (5 mL) y trietilamina (0.045 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro (0.026 mL) fue añadido y la reacción agitada durante 1 h a RT. Morfolina (0.2 mL) fue añadida y la reacción se dejó a RT durante 72 horas antes de ser concentrada al vacío y purificada por HPLC prep. (básica) para dar el compuesto deseado (64 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21 (3H, d), 3.17 (4H, t), 3.46 – 3.52 (4H, m), 3.63 (4H, d), 3.65 (1H, s), 3.76 (1H, d), 3.95 – 3.98 (1H, m), 4.14 (1H, d), 4.49 (1H, s), 6.64 (1H, s), 6.97 (1H, t), 7.29 (2H, d), 7.45 (2H, d), 7.53 (2H, d), 8.25 (2H, d), 8.68 (1H, s), 8.87 (1H, s).

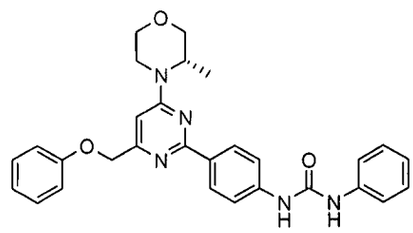
Espectro de masa: $M+H^+$ 489.

Prueba (a): 0.19 μM.

La preparación de 1–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 28:

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(fenoximetil)pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue disuelta en DCM (5 mL), fenol (41 mg) añadido y la reacción se dejó agitar a

RT durante 1 h. DBU (0.2 mL) fue añadido y la mezcla se dejó agitar durante 18 horas antes de ser concentrada al vacío y purificada por HPLC prep. (básica) para dar el material deseado (26 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.19 – 1.21 (3H, m), 3.18 (1H, s), 3.47 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.16 (1H, s), 4.51 (1H, s), 5.08 (2H, s), 6.72 (1H, s), 6.96 – 7.01 (2H, m), 7.07 – 7.10 (2H, m), 7.28 – 7.35 (4H, m), 7.48 (2H, d), 7.57 (2H, d), 8.28 (2H, d), 8.75 (1H, s), 8.95 (1H, s)

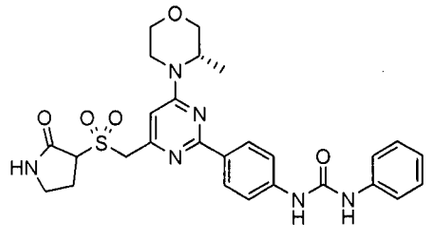
Espectro de masa: $M+H^+$ 496.

Prueba (a): 4.7 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 29:

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[(2–oxopirrolidin–3–il)sulfonilmetil]pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[(2–oxopirrolidin–3–il)sulfanilmetil]pirimidin–2–il]fenil]–3–fenil–urea (0.26 mmol) fue disuelta en 1,4–Dioxano (5 mL) y agua (1 mL). m–CPBA (75%) (113 mg) seguido inmediatamente por permanganato de sodio (125 mg) fue añadido a la solución y se dejó agitar a RT durante 1 h. La reacción fue cargada en una columna SCX–2 (10 g), la cual fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por HPLC prep. (básica) para dar el material deseado (18 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.32 – 2.34 (1H, m), 2.47 (1H, d), 3.24 (2H, t), 3.34 (2H, d), 3.51 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.49 (1H, s), 4.58 – 4.63 (2H, m), 5.01 (1H, d), 6.79 (1H, s), 6.97 – 7.01 (1H, m), 7.28 –

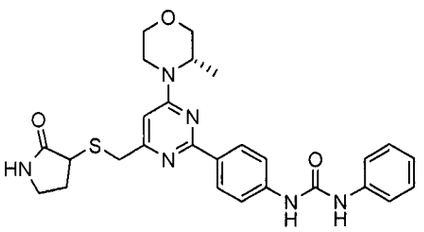
7.32 (1H, m), 7.30 (1H, s), 7.46 – 7.48 (2H, m), 7.56 – 7.58 (2H, m), 8.24 – 8.27 (2H, m), 8.38 (1H, s), 8.72 (1H, s), 8.92 (1H, s)

Espectro de masa: $M+H^+$ 551.

Prueba (a): 0.56 μM.

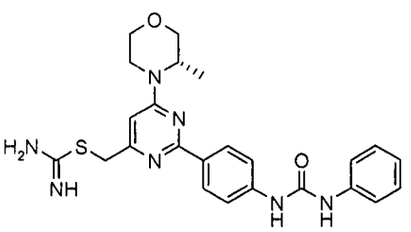
La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[(2–oxopirrolidin–3–il)sulfanilmetil]pirimidin–2–il]fenil]–3–fenil–urea es descrita a continuación.

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[(2–oxopirrolidin–3–il)sulfanilmetil]pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–(Carbamimidoilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea (125 mg) fue disuelta en DMF (3 mL). La solución fue luego tratada con 3–bromo–pirrolidin–2–ona (48 mg) seguido por hidróxido de sodio (42 mg) en agua (1 mL), calentada hasta 40°C y se dejó agitar durante 24 h. La reacción fue diluida en un poco de metanol y cargada en una columna SCX–2 (20 g), la cual fue lavada con metanol y el producto deseado eluido con amoniaco 7N en metanol para dar el material deseado el cual fue usado sin caracterización adicional.

1–[4–[4–(Carbamimidoilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea



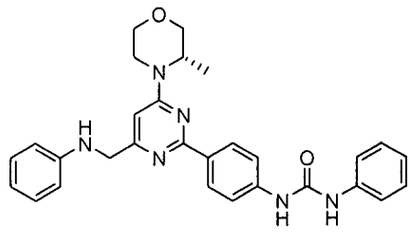
1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea (865 mg) fue disuelta en etanol (30 mL) y tiourea (146 mg) añadida. La reacción

fue luego calentada hasta 70°C durante 30 min, luego se dejó enfriar y fue concentrada al vacío para dar el material deseado el cual fue usado sin caracterización adicional.

La preparación de 1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-fenil-urea fue descrita anteriormente.

Ejemplo 30:

1-[4-[4-(Anilinometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-fenil-urea

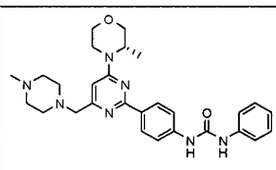


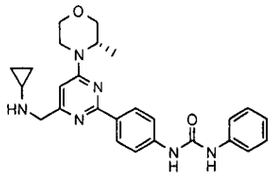
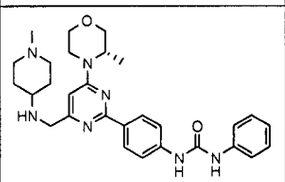
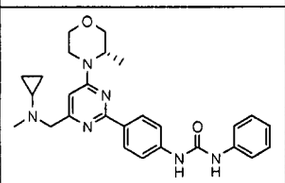
1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-fenil-urea (105 mg, 0.21 mmol) disuelta en una solución de DCM (5 mL) fue añadida a anilina (0.097 mL, 1.06 mmol) y agitada a RT durante 18 h. La mezcla fue sometida a vacío hasta secarse y purificada por HPLC prep. (básica) para dar el material deseado (41 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.15 (3H, d), 3.12 – 3.18 (1H, m), 3.43 – 3.50 (1H, m), 3.59 – 3.63 (1H, m), 3.74 (1H, d), 3.93 – 3.97 (1H, m), 4.10 (1H, d), 4.24 (2H, d), 4.39 (1H, s), 6.20 (1H, t), 6.55 (1H, d), 6.60 (1H, s), 6.63 (1H, d), 6.65 (1H, s), 6.97 – 7.01 (1H, m), 7.06 – 7.10 (2H, m), 7.28 – 7.32 (1H, m), 7.30 (1H, s), 7.46 – 7.49 (2H, m), 7.55 – 7.57 (2H, m), 8.29 – 8.31 (2H, m), 8.69 (1H, s), 8.88 (1H, s).

Espectro de masa: M+H$^+$ 495.

Los siguientes compuestos fueron preparados de una forma análoga.

Ejemplo	Estructura	NOMBRE	LCMS MH+
30a		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[(4-metilpiperazin-1-il)metil]pirimidin-2-il]fenil]-3-fenil-urea	502

30b		1–[4–[4–[(ciclopropilamino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea	459
30c		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[[(1–metil–4–piperidil)amino]metil]pirimidin–2–il]fenil]–3–fenil–urea	516
30d		1–[4–[4–[(ciclopropil–metil–amino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea	473

Ejemplo 30a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 2.22 (3H, s), 2.44 (2H, d), 2.53 (2H, d), 2.56 (2H, s), 2.60 – 2.61 (1H, m), 2.67 – 2.69 (1H, m), 3.15 – 3.23 (1H, m), 3.46 – 3.54 (3H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.15 (1H, d), 4.47 – 4.49 (1H, m), 6.63 (1H, s), 6.97 – 7.01 (1H, m), 7.28 – 7.32 (1H, m), 7.30 (1H, s), 7.46 – 7.48 (2H, m), 7.53 – 7.56 (2H, m), 8.25 – 8.27 (2H, m), 8.69 (1H, s), 8.88 (1H, s)

Ejemplo 30b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.30 – 0.31 (2H, m), 0.37 – 0.40 (2H, m), 1.23 (3H, d), 2.14 – 2.19 (1H, m), 3.15 – 3.23 (1H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.72 (2H, s), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.17 (1H, d), 4.51 (1H, d), 6.67 (1H, s), 6.99 – 7.01 (1H, m), 7.28 – 7.32 (2H, m), 7.46 – 7.48 (2H, m), 7.53 – 7.56 (2H, m), 8.28 (2H, d), 8.69 (1H, s), 8.87 (1H, s)

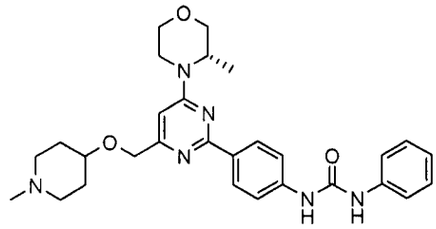
Ejemplo 30d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40– 0.41 (2H, t), 0.45 – 0.49 (2H, m), 1.21 (3H, d), 1.90 – 1.95 (1H, m), 2.34 (3H, s), 3.14 – 3.21 (1H, m), 3.46 – 3.53 (1H, m), 3.63 (3H, t), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.13 (1H, d), 4.49 (1H, s), 6.54 (1H, s), 6.97 – 7.01 (1H, m), 7.28 – 7.32 (1H, m), 7.30 (1H, s), 7.46 – 7.48 (2H, m), 7.54 – 7.56 (2H, m), 8.26 – 8.28 (2H, m), 8.69 (1H, s), 8.87 (1H, s)

Prueba (a): Ejemplo (30) 0.9 μM; Ejemplo (30a) 0.12 μM; Ejemplo (30b) 0.18 μM; Ejemplo (30c) 1.1 μM; Ejemplo (30d) 0.28 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 31:

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[(1–metil–4–piperidil)oximetil]pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea (105 mg) disuelta en una solución de DCM (5 mL) y trietilamina (0.045 mL) fueron añadidas a 4–hidroxi–1–metilpiperidina (5 equivalentes). DBU (0.158 mL) fue añadido y agitado a RT durante 18 h. La mezcla fue sometida a vacío hasta secarse y purificada por HPLC prep. (básica) para dar el material deseado (64 mg) como un sólido blanco.

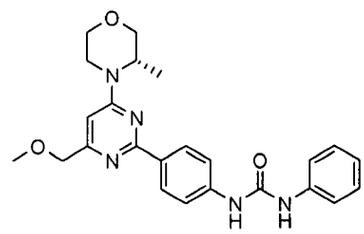
Espectro de masa: $M+H^+$ 517.

Prueba (a): 0.35 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 32:

1–[4–[4–(Metoximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–fenil–urea



1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea (90 mg) fue disuelta en una solución de DCM (5 mL) y trietilamina (0.045 mL).

Metóxido de sodio (33% en metanol) (0.073 mL) fue añadido a la reacción y la mezcla agitada a RT durante 18 h antes de ser apagada con agua y particionada. La fase orgánica fue secada sobre sulfato de magnesio y evaporada para dar una goma la cual fue purificada por HPLC prep. (básica) para dar el compuesto deseado (32 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 3.34 (1H, d), 3.43 (3H, s), 3.49 (1H, t), 3.63 – 3.66 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.41 (2H, s), 4.51 (1H, d), 6.59 (1H, s), 6.99 (1H, t), 7.30 (2H, t), 7.46 – 7.48 (2H, m), 7.55 (2H, d), 8.26 (2H, d), 8.69 (1H, s), 8.88 (1H, s)

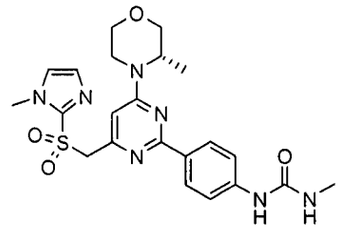
Espectro de masa: M+H$^+$ 434.

Prueba (a): 0.0062 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–fenil–urea fue descrita anteriormente.

Ejemplo 33:

3–Metil–1–[4–[4–[(1–metilimidazol–2–il)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



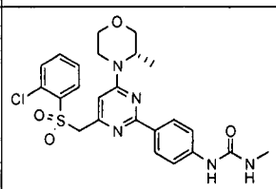
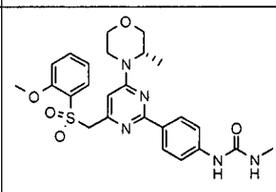
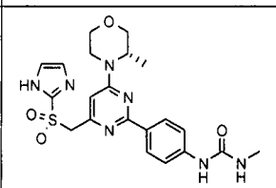
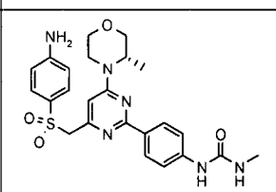
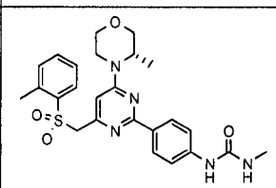
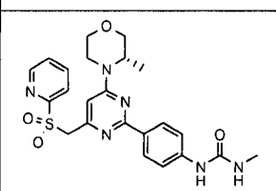
3–Metil–1–[4–[4–[(1–metilimidazol–2–il)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea (0.23 mmol) fue disuelta en 1,4–Dioxano (4 mL) y agua (1 mL). m–CPBA (75%) (80 mg), seguido inmediatamente por permanganato de sodio (92 mg), fue añadido a la solución. La reacción se dejó agitar a RT durante 18 h, luego fue cargada en una columna SCX–2 (10 g), la cual fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. La reacción fue sometida a vacío hasta secarse y purificada por HPLC prep. (básica) para dar el material deseado (37 mg) como un sólido blanco.

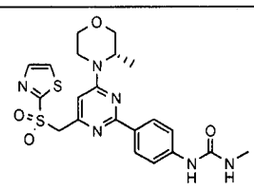
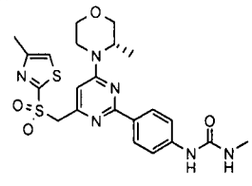
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.17 – 1.22 (3H, m), 2.66 (3H, d), 2.68 (1H, t), 3.14 – 3.22 (1H, m), 3.45 – 3.49 (1H, m), 3.62 (3H, s), 3.77 (1H, d), 3.96 – 3.99 (1H,

m), 4.09 – 4.12 (1H, m), 4.41 (1H, s), 4.75 (2H, s), 6.07 (1H, q), 6.61 (1H, s), 7.20 (1H, d), 7.43 – 7.47 (2H, m), 7.43 – 7.49 (1H, m), 7.95 – 7.97 (2H, m), 8.72 (1H, s)

Espectro de masa: $M+H^+$ 486.

Los siguientes compuestos fueron preparados de una forma análoga a partir de los sulfuros apropiados.

Ejemplo	Estructura	NOMBRE	LCMS MH+
33a		1–[4–[4–[(2–clorofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	516
33b		1–[4–[4–[(2–metoxifenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	512
33c		1–[4–[4–(1H–imidazol–2–ilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	472
33d		1–[4–[4–[(4–aminofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	497
33e		3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(2–metilfenil)sulfonilmetil]pirimidin–2–il]fenil]urea	496
33f		3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	483

Ejemplo	Estructura	NOMBRE	LCMS MH+
33g		3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(1,3–tiazol–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	489
33h		3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidin–2–il]fenil]urea	503

Ejemplo 33a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, q), 2.65 – 2.68 (3H, m), 2.68 (1H, d), 3.17 (1H, d), 3.44 – 3.51 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.09 (1H, t), 4.88 (2H, s), 6.05 (1H, q), 6.71 (1H, s), 7.33 – 7.35 (2H, m), 7.44 – 7.48 (1H, m), 7.65 – 7.69 (1H, m), 7.67 (1H, s), 7.71 – 7.77 (2H, m), 7.83 – 7.85 (1H, m), 8.68 (1H, s).

Ejemplo 33b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.18 (3H, d), 2.66 – 2.69 (3H, m), 3.12 – 3.21 (1H, m), 3.43 – 3.50 (1H, m), 3.59 – 3.63 (1H, m), 3.75 (1H, d), 3.94 – 3.98 (1H, m), 4.05 (4H, m), 4.37 (1H, s), 4.70 – 4.77 (2H, m), 6.04 (1H, q), 6.61 (1H, s), 7.01 – 7.05 (1H, m), 7.34 – 7.36 (2H, m), 7.39 (1H, d), 7.54 – 7.57 (1H, m), 7.67 – 7.74 (3H, m), 8.67 (1H, s).

Ejemplo 33c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 (3H, d), 2.66 (3H, d), 3.12 – 3.20 (1H, m), 3.43 – 3.50 (1H, m), 3.60 – 3.63 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.08 (1H, d), 4.36 (1H, s), 4.71 (2H, s), 6.06 (1H, q), 6.47 (1H, s), 7.34 (2H, s), 7.42 – 7.44 (2H, m), 7.95 – 7.97 (2H, m), 8.70 (1H, s), 13.52 (1H, s)

Ejemplo 33d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.19 (3H, d), 2.66 – 2.69 (3H, m), 3.12 – 3.21 (1H, m), 3.44 – 3.48 (1H, m), 3.60 – 3.64 (1H, m), 3.75 (1H, d), 3.94 – 3.98 (1H, m), 4.05 (1H, t), 4.33 (1H, s), 4.44 (2H, s), 6.06 (1H, t), 6.12 (2H, d), 6.41 (1H, s), 6.58 – 6.62 (2H, m), 7.34 – 7.38 (2H, m), 7.42 – 7.46 (2H, m), 7.99 – 8.01 (2H, m), 8.70 (1H, s)

Ejemplo 33e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.19 (3H, d), 2.67 (6H, m), 3.14 – 3.18 (1H, m), 3.44 – 3.50 (1H, m), 3.60 – 3.64 (1H, m), 3.76 (1H, d), 3.94 – 3.98 (1H, m), 4.06 (1H, q), 4.37 (1H, s), 4.66 (2H, s), 6.05 (1H, d), 6.60 (1H, s), 7.34 (1H, d), 7.36 – 7.38 (2H, m), 7.47 (1H, d), 7.56 – 7.60 (1H, m), 7.66 – 7.68 (1H, m), 7.77 – 7.80 (2H, m), 8.69 (1H, s)

Ejemplo 33f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 (3H, d), 2.65 – 2.68 (3H, m), 3.16 – 3.21 (1H, m), 3.44 – 3.51 (1H, m), 3.60 – 3.64 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.11 (1H, d), 4.38 (1H, s), 4.80 – 4.88 (2H, m), 6.04 (1H, q), 6.68 (1H, s), 7.34 – 7.36 (2H, m), 7.64 – 7.67 (2H, m), 7.78 – 7.81 (1H, m), 7.88 – 7.90 (1H, m), 8.07 – 8.12 (1H, m), 8.69 (1H, s), 8.92 – 8.94 (1H, m)

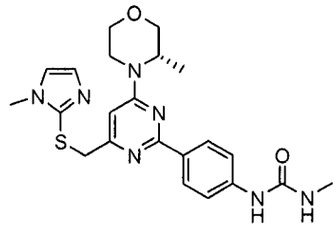
Ejemplo 33g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21 (3H, d), 2.67 (3H, q), 3.16 – 3.21 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.40 (2H, s), 4.91 (2H, d), 6.06 (1H, d), 6.70 (1H, s), 7.40 – 7.42 (2H, m), 7.84 (2H, d), 8.27 – 8.29 (2H, m), 8.71 (1H, s).

Ejemplo 33h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21 – 1.27 (3H, m), 2.52 – 2.61 (3H, m), 2.66 – 2.69 (3H, m), 3.15 – 3.22 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.13 (1H, d), 4.40 (1H, s), 4.87 (2H, d), 6.05 (1H, q), 6.70 (1H, s), 7.41 – 7.43 (2H, m), 7.82 (1H, S)

Prueba (a): Ejemplo (33) 0.84 μM; Ejemplo (33a) 0.06 μM; Ejemplo (33b) 0.066 μM; Ejemplo (33c) 0.0014 μM; Ejemplo (33d) 0.00031 μM; Ejemplo (33e) 0.088 μM; Ejemplo (33f) 0.27 μM; Ejemplo (33g) 0.021 μM; Ejemplo (33h) 0.048 μM.

La preparación de 3–metil–1–[4–[4–[(1–metilimidazol–2–il)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea es descrita a continuación.

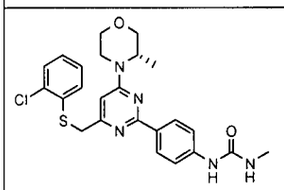
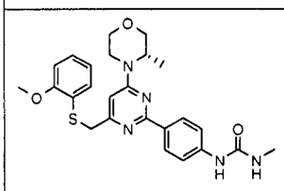
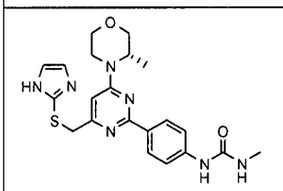
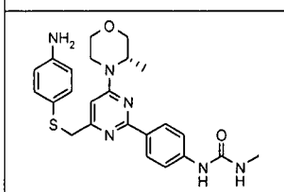
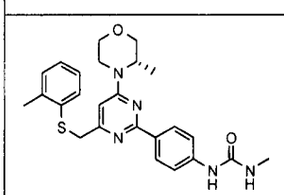
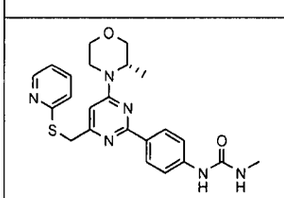
3–Metil–1–[4–[4–[(1–metilimidazol–2–il)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea

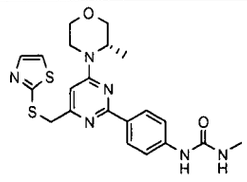
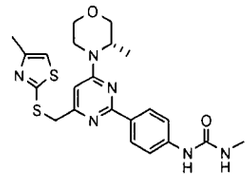


1–Metilimidazol–2–tiol (0.23 mmol) fue disuelto en acetonitrilo (2 mL), DBU (0.035 mL) fue añadido y la reacción se dejó agitar a RT durante 5 min. Una solución de 3–metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea (100 mg) en acetonitrilo (2 mL) y DBU (0.034 mL) fueron añadidos y la mezcla se dejó agitar a RT 18 h,

antes de ser concentrada al vacío para dar el material deseado. El material fue usado sin purificación adicional.

Los siguientes sulfuros fueron preparados de una forma análoga.

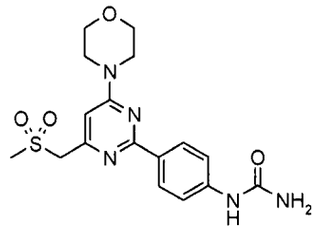
Estructura	NOMBRE
	1–[4–[4–[(2–clorofenil)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea
	1–[4–[4–[(2–metoxifenil)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea
	1–[4–[4–(1H–imidazol–2–ilsulfanilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea
	1–[4–[4–[(4–aminofenil)sulfanilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea
	3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(2–metilfenil)sulfanilmetil]pirimidin–2–il]fenil]urea
	3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfanilmetil)pirimidin–2–il]fenil]urea

Estructura	NOMBRE
	3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(1,3–tiazol–2–ilsulfanilmetil)pirimidin–2–il]fenil]urea
	3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfanilmetil]pirimidin–2–il]fenil]urea

La preparación de 3–metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea fue descrita anteriormente.

Ejemplo 34:

[4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea

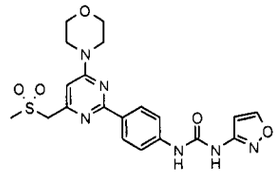
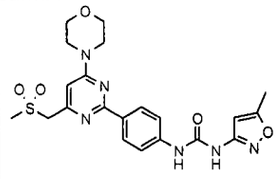
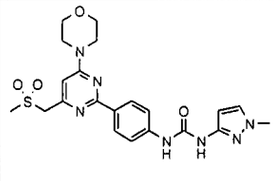


Fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato (110 mg) fue disuelto en DMF (2 mL) y trietilamina (0.098 mL) añadida. 2–Aminopirimidina (108 mg) fue añadida y la reacción agitada a 40°C durante 2 horas. La mezcla cruda fue purificada por HPLC prep. (básica), sin embargo, solamente [4–[4–(Metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea fue aislada de la mezcla (8 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 3.21 (3H, s), 3.71 – 3.72 (8H, m), 4.48 (2H, s), 5.91 (2H, s), 6.81 (1H, s), 7.49 – 7.51 (2H, m), 8.20 – 8.23 (2H, m), 8.76 (1H, s)

Espectro de masa: M+H$^+$ 392.

Los siguientes compuestos fueron preparados en un procedimiento análogo.

Ejemplo	Estructura	NOMBRE	LCMS MH+
34a		1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea	458
34b		1–(5–metil–1,2–oxazol–3–il)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	472
34c		1–(1–metilpirazol–3–il)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	471

Ejemplo 34a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 3.21 (3H, s), 3.73 (8H, s), 4.50 (2H, s), 6.85 – 6.87 (2H, m), 7.56 – 7.59 (2H, m), 8.28 – 8.31 (2H, m), 8.75 (1H, d), 9.07 (1H, s), 9.62 (1H, s)

Ejemplo 34b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 3.15 – 3.25 (3H, s), 3.21 – 3.26 (3H, S), 3.73 (8H, s), 4.49 (2H, s), 6.56 (1H, s), 6.85 (1H, s), 7.55 – 7.57 (2H, m), 8.28 – 8.30 (2H, m), 9.05 (1H, s), 9.47 (1H, s)

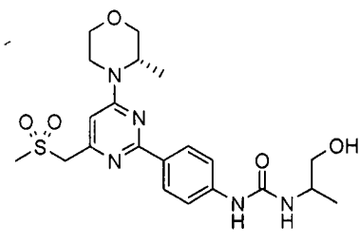
Ejemplo 34c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 3.21 (3H, s), 3.72 (3H, s), 3.74 (8H, s), 4.49 (2H, s), 6.25 (1H, d), 6.84 (1H, s), 7.54 – 7.56 (2H, m), 7.57 (1H, d), 8.26 – 8.28 (2H, m), 8.93 (1H, s), 9.18 (1H, s).

Prueba (a): Ejemplo (34) 0.21 μM; Ejemplo (34a) 0.042 μM; Ejemplo (34b) 0.12 μM; Ejemplo (34c) 0.72 μM.

La preparación de fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato fue descrita anteriormente.

Ejemplo 35:

3–(1–Hidroxipropan–2–il)–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea

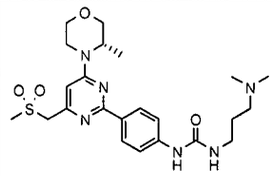
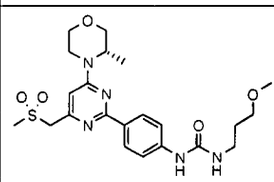
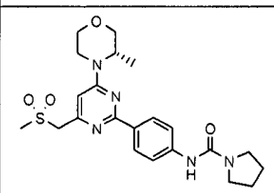


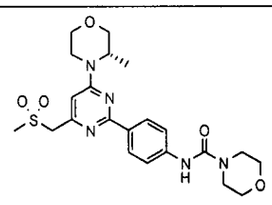
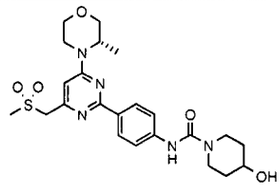
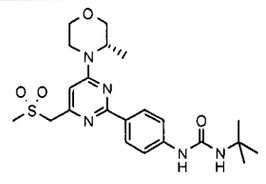
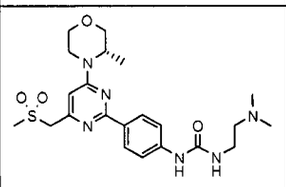
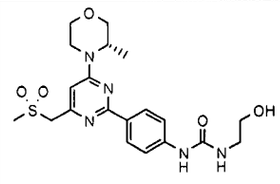
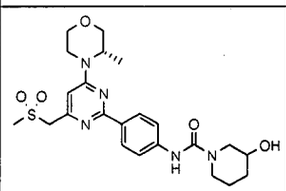
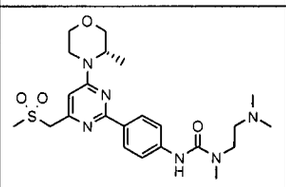
Una solución de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato (110 mg, 0.23 mmol) y trietilamina (0.079 mL, 0.68 mmol) en DMF (2 mL) fue añadida a 2–aminopropan–1–ol (1.14 mmol). La reacción fue agitada a 40°C durante 2 horas y luego purificada por HPLC prep. (básica) para dar el material deseado como un sólido (22 mg).

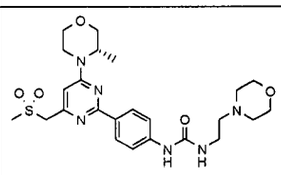
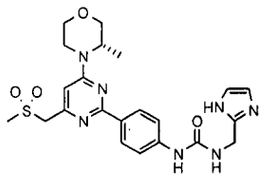
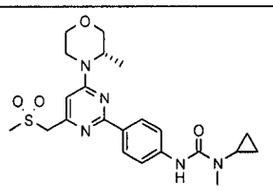
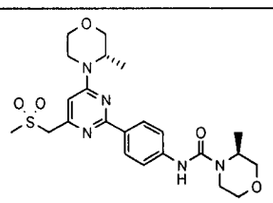
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.24 (3H, d), 3.21 (3H, s), 3.37 – 3.43 (2H, m), 3.47 – 3.53 (2H, m), 3.63 – 3.67 (1H, m), 3.72 (1H, d), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.15 – 4.19 (1H, m), 4.48 (3H, s), 4.78 (1H, t), 6.09 – 6.11 (1H, m), 6.77 (1H, s), 7.47 – 7.49 (2H, m), 8.20 – 8.22 (2H, m), 8.71 (1H, s)

Espectro de masa: M+H$^+$ 463.

Los siguientes compuestos fueron preparados de una forma análoga

Ejemplo	Estructura	NOMBRE	LCMS MH+
35a		3–(3–dimetilaminopropil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	491
35b		3–(3–metoxipropil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	478
35c		N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]pirrolidina–1–carboxamida	460

Ejemplo	Estructura	NOMBRE	LCMS MH+
35d		N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]morfolina–4–carboxamida	476
35e		4–hidroxi–N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]piperidina–1–carboxamida	490
35f		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]–3–tert–butil–urea	462
35g		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	477
35h		3–(2–hidroxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	450
35i		3–hidroxi–N–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]piperidina–1–carboxamida	490
35j		1–(2–dimetilaminoetil)–1–metil–3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]urea	491

Ejemplo	Estructura	NOMBRE	LCMS MH+
35k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-(2-morfolin-4-iletil)urea	486
35l		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	460
35m		1-ciclopropil-1-metil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]urea	460
35n		(3S)-3-metil-N-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]morfolina-4-carboxamida	490

Ejemplo 35a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 – 1.62 (2H, m), 2.10 – 2.14 (6H, s), 2.23 (2H, d), 2.32 – 2.34 (1H, m), 2.44 – 2.47 (1H, m), 3.07 – 3.15 (2H, m), 3.21 (3H, s), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.32 (1H, t), 6.77 (1H, s), 7.48 – 7.52 (2H, m), 8.19 – 8.21 (2H, m), 8.79 (1H, s)

Ejemplo 35b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.68 (2H, t), 3.15 (2H, d), 3.21 (3H, s), 3.25 (4H, s), 3.38 (2H, t), 3.50 (1H, d), 3.67 (1H, d), 3.76 – 3.79 (1H, m), 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.21 (1H, s), 6.77 (1H, s), 7.48 – 7.51 (2H, m), 8.19 – 8.22 (2H, m), 8.70 (1H, s)

Ejemplo 35c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.85 – 1.88 (4H, m), 3.21 (3H, s), 3.40 (5H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.48 (3H, s), 6.78 (1H, s), 7.63 – 7.66 (2H, m), 8.19 – 8.22 (2H, m), 8.31 (1H, s)

Ejemplo 35d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ1.25 (3H, d), 3.21 (3H, s), 3.33 – 3.34 (1H, m), 3.46 (5H, t), 3.61 – 3.63 (4H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.19 (1H, d), 4.49 (3H, s), 6.79 (1H, s), 7.57 – 7.61 (2H, m), 8.21 – 8.23 (2H, m), 8.74 (1H, s)

Ejemplo 35e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.19 – 1.30 (4H, m), 1.31 – 1.39 (1H, m), 1.67 (2H, d), 1.71 – 1.72 (1H, m), 1.74 – 1.78 (2H, m), 3.09 – 3.12 (1H, m), 3.22 (3H, d), 3.48 (1H, d), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.84 (1H, d), 3.83 – 3.88 (1H, m), 3.97 – 4.01 (1H, m), 4.19 (1H, d), 4.48 – 4.51 (3H, m), 4.69 (1H, s), 6.76 (1H, t), 7.57 – 7.59 (2H, m), 8.19 – 8.22 (2H, m), 8.69 (1H, s)

Ejemplo 35f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.31 (9, s), 3.20 (3H, s), 3.22 (1H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.06 (1H, s), 6.77 (1H, s), 7.43 – 7.47 (2H, m), 8.19 – 8.21 (2H, m), 8.48 (1H, s)

Ejemplo 35g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.18 (6H, s), 2.34 (2 h t), 3.17 – 3.25 (5H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.16 (1H, t), 6.77 (1H, s), 7.47 – 7.51 (2H, m), 8.19 – 8.22 (2H, m), 8.89 (1H, s)

Ejemplo 35h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H d), 3.21 (5H, t), 3.46 (3H, t), 3.52 (1H, d), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.15 – 4.19 (1H, m), 4.48 (3H, s), 4.73 (1H, s), 6.26 (1H, t), 6.77 (1H, s), 7.48 – 7.50 (2H, m), 8.21 (2H, d), 8.82 (1H, s)

Ejemplo 35i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.38 (2H, d), 1.70 (1H, d), 1.89 (1H, s), 2.74 – 2.78 (1H, m), 2.96 (1H, s), 3.20 (3H, s), 3.47 – 3.50 (1H, m), 3.51 (1H, s), 3.66 – 3.67 (1H, m), 3.77 – 3.80 (2H, m), 3.98 (2H, d), 4.17 (1H, d), 4.48 (3H, s), 4.83 (1H, d), 6.78 (1H, s), 7.57 – 7.59 (2H, m), 8.19 – 8.21 (2H, m), 8.66 (1H, s)

Ejemplo 35j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 2.26 (6H, s), 2.67 – 2.69 (2H, m), 2.95 (3H, s), 3.21 (3H, s), 3.40 (3H, t), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.18 (1H, d), 4.49 (3H, s), 6.78 (1H, s), 7.50 – 7.53 (2H, m), 8.20 – 8.23 (2H, m), 9.51 (1H, s)

Ejemplo 35k: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 2.39 (2H, d), 2.41 (4H, d), 3.21 (3H, s), 3.24 (2H, t), 3.47 – 3.53 (1H, m), 3.58 – 3.63 (5H, m), 3.67 (1H, d), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.17 (1H, d), 4.48 (3H, s), 6.17 (1H, t), 6.77 (1H, s), 7.49 – 7.51 (2H, m), 8.21 (2H, d), 8.88 (1H, s)

Ejemplo 35l: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.25 (3H, d), 3.19 – 3.23 (3H, m), 3.26 (1H, s), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.16 – 4.19 (1H, m), 4.32 (2H, d), 4.48 (3H, s), 6.63 (1H, t), 6.78 (1H, s), 6.93 (2H, s), 7.51 – 7.53 (2H, m), 8.22 (2H, d), 8.93 (1H, s), 11.84 (1H, s)

Ejemplo 35m: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.69 – 0.73 (2H, m), 0.88 – 0.93 (2H, m), 1.25 (3H, d), 2.70 – 2.76 (1H, m), 2.88 (3H, s), 3.21 (3H, s), 3.22 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.19 (1H, d), 4.49 (3H, s), 6.79 (1H, s), 7.62 – 7.65 (2H, m), 8.21 – 8.23 (2H, m), 8.39 (1H, s)

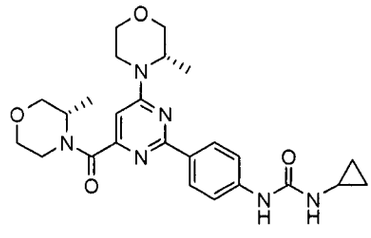
Ejemplo 35n: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21 (3H, d), 1.25 (3H, d), 3.15 – 3.23 (1H, m), 3.20 (3H, s), 3.36 – 3.42 (2H, m), 3.50 (1H, d), 3.53 – 3.57 (1H, m), 3.64 – 3.68 (2H, m), 3.75 (1H, s), 3.78 (2H, d), 3.85 – 3.88 (1H, m), 3.97 – 4.01 (1H, m), 4.20 (2H, d), 4.49 (3H, s), 6.79 (1H, s), 7.58 – 7.61 (2H, m), 8.21 – 8.23 (2H, m), 8.65 (1H, s).

Prueba (a): Ejemplo (35) 0.064 μM; Ejemplo (35a) 6.4 μM; Ejemplo (35b) 0.42 μM; Ejemplo (35c) 3.4 μM; Ejemplo (35d) 3.2 μM; Ejemplo (35e) 2.5 μM; Ejemplo (35f) 0.82 μM; Ejemplo (35g) 0.66 μM; Ejemplo (35h) 0.024 μM; Ejemplo (35i) 0.77 μM; Ejemplo (35j) 3.6 μM; Ejemplo (35k) 1.2 μM; Ejemplo (35l) 0.47 μM; Ejemplo (35m) 2 μM; Ejemplo (35n)1.1 μM.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato fue descrita anteriormente.

Ejemplo 36:

3–Ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolina–4–carbonil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



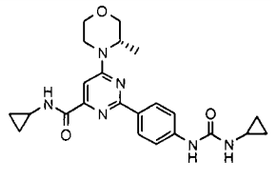
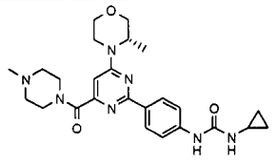
Ácido 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico (95 mg) fue disuelto en DMF (3 mL) y (3*S*)–3–metilmorfolina añadida. DIPEA (0.125 mL) y HATU (137 mg) fueron añadidos y las reacciones agitadas a RT durante 3 h

antes de ser concentradas al vacío y particionadas entre DCM (25 mL) y agua (25 mL). La capa orgánica fue secada sobre sulfato de magnesio, filtrada y evaporada hasta secarse para dar el material deseado como un sólido (88 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (6H, m), 2.52 – 2.61 (1H, m), 3.23–3.29 (2H, m) 3.41 – 3.42 (1H, m), 3.46 – 3.47 (1H, m), 3.50 – 3.55 (2H, m), 3.60 (2H, d), 3.70 – 3.81 (2H, m), 3.97 (2H, d), 4.17 (1H, s), 4.53 (1H, s), 6.43 (1H, s), 6.74 (1H, d), 7.51 (2H, d), 8.20 (2H, t), 8.54 (1H, s)

Espectro de masa: $M+H^+$ 480.

Las siguientes muestras fueron preparadas de una forma análoga

Ejemplo	Estructura	NOMBRE	LCMS MH+
36a		N–ciclopropil–2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxamida	436
36b		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(4–metilpiperazina–1–carbonil)pirimidin–2–il]fenil]urea	479

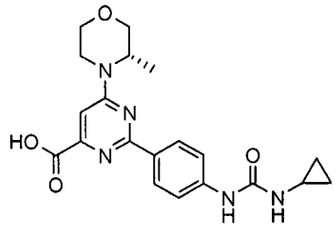
Ejemplo 36a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.39 – 0.44 (2H, m), 0.56 – 0.61 (2H, m), 0.65 – 0.68 (2H, m), 0.74 – 0.76 (2H, m), 1.24 (3H, d), 2.52 – 2.59 (1H, m), 2.53 – 2.61 (1H, m), 3.25 (1H, s), 3.50 (1H, d), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.25 (1H, s), 4.53 (1H, s), 6.42 – 6.43 (1H, m), 7.12 (1H, d), 7.51 (2H, d), 8.38 – 8.41 (2H, m), 8.56 (1H, s), 8.69 (1H, d).

Ejemplo 36b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (3H, d), 2.25 – 2.26 (3H, m), 2.40 – 2.48 (2H, m), 2.43 – 2.48 (2H, m), 2.52 – 2.61 (1H, m), 3.18 – 3.25 (1H, m), 3.46 – 3.52 (3H, m), 3.62 – 3.66 (3H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.22 (1H, d), 4.55 (1H, s), 6.44 (1H, d), 6.73 (1H, s), 7.50 – 7.52 (2H, m), 8.18 – 8.20 (2H, m), 8.54 (1H, s).

Prueba (a): Ejemplo (36) 0.062 μM; Ejemplo (36a) 2.9 μM; Ejemplo (36b) 0.18 μM.

La preparación de ácido 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico es descrita a continuación.

Ácido 2–[4–(Ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico

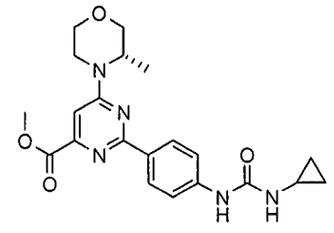


Metil 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato (350 mg) fue disuelto en agua (15 mL) con hidróxido de sodio (67 mg) y la reacción se dejó agitar a RT durante 1 h. Unos 2 equivalentes adicionales de hidróxido de sodio fueron añadidos junto con THF (3 mL). La reacción fue agitada durante 1 h más y luego el THF fue eliminado a presión reducida y la solución acuosa particionada con etil acetato (15 mL). La capa acuosa fue acidificada con ácido clorhídrico concentrado y el precipitado fue filtrado y secado en un horno de vacío a 50°C durante 18 h para dar el material deseado (350 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.60 – 0.64 (2H, m), 1.22 (3H, d), 2.52 – 2.58 (1H, m), 3.17 – 3.21 (1H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.75 (1H, d), 3.95 – 3.99 (1H, m), 4.14 – 4.17 (1H, m), 4.48 (1H, d), 6.92 (1H, s), 7.28 (1H, s), 7.56 (2H, d), 8.22 (2H, d), 9.41 (1H, s)

Espectro de masa: M+H$^+$ 398.

Metil 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato

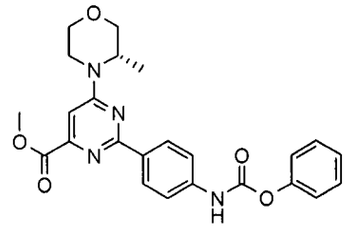


Metil 6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidina-4-carboxilato (547 mg) fue disuelto en DMF (8 mL) y trietilamina (0.59 mL) seguido por la adición de ciclopropilamina (0.491 mL). La reacción fue agitada a 40°C durante 2 horas luego la mezcla fue sometida a vacío hasta secarse y particionada entre DCM (50 mL) y agua (50 mL). La capa orgánica fue secada sobre sulfato de magnesio y sometida a vacío hasta secarse, luego cromatografiada en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (351 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 – 0.44 (2H, m), 0.63 – 0.68 (2H, m), 1.25 (3H, d), 2.52 – 2.58 (1H, m), 2.67 – 2.69 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.76 (1H, d), 3.91 (3H, s), 3.96 – 4.00 (1H, m), 4.23 – 4.27 (1H, m), 4.58 (1H, s), 6.43 (1H, d), 7.14 (1H, s), 7.51 – 7.53 (2H, m), 8.22 – 8.25 (2H, m), 8.56 (1H, s)

Espectro de masa: M+H$^+$ 412.

Metil 6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidina-4-carboxilato

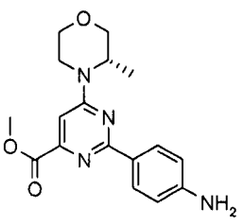


Metil 2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato (400 mg) fue disuelto en dioxano (10 mL) y bicarbonato de sodio (154 mg) y fenilcloroformato (0.154 mL) añadidos en forma de gotas. La mezcla fue agitada a RT durante 16 horas, luego el dioxano eliminado a presión reducida y el residuo particionado entre agua (50 mL) y etil acetato (50 mL). La capa orgánica fue secada sobre sulfato de magnesio, filtrada y evaporada para dar el material deseado como una espuma marrón (624 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (3H, d), 3.11 (1H, s), 3.47 – 3.54 (1H, m), 3.58 (1H, s), 3.63 – 3.67 (1H, m), 3.73 (1H, d), 3.91 (3H, s), 3.96 – 4.00 (1H, m), 4.27 (1H, s), 6.73 – 6.78 (1H, m), 7.14 – 7.20 (1H, m), 7.24 – 7.30 (2H, m), 7.43 – 7.48 (2H, m), 7.64 – 7.66 (2H, m), 8.32 – 8.34 (2H, m), 10.46 (1H, s)

Espectro de masa: M+H$^+$ 449.

Metil 2–(4–aminofenil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato

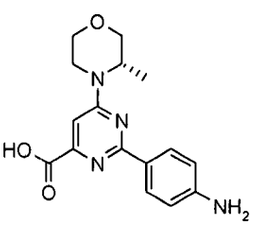


Ácido 2–(4–aminofenil)–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxílico (1.15 g) fue disuelto en metanol (15 mL), ácido sulfúrico (0.01 mL) fue añadido y la reacción fue calentada a 80°C durante 24 h. Una pequeña cantidad de tamiz molecular activado 4A fue añadida a la reacción y agitada durante 2 h. La reacción fue filtrada, sometida a vacío hasta secarse, luego suspendida en etil acetato (250 mL) y lavada una vez con una solución saturada de bicarbonato de sodio (250 mL). La capa orgánica fue filtrada, secada sobre sulfato de magnesio y sometida a vacío hasta secarse para dar el material deseado como un sólido marrón (405 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 3.08 (1H, s), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.75 (1H, d), 3.89 (3H, s), 3.97 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 5.59 (2H, d), 6.59 – 6.63 (2H, m), 7.04 (1H, s), 8.06 – 8.08 (2H, m)

Espectro de masa: M+H$^+$ 329.

Ácido 2–(4–aminofenil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico



Metil 2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxilato (1.00 g) fue disuelto en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (10 mL). Ácido (4–aminofenil)borónico pinacol éster (1.21 g) y carbonato de sodio 2M (5 mL) fueron luego añadidos y la solución desgasificada durante 5 min. Catalizador de diclorobis(trifenilfosfina) paladio (130 mg) fue añadido y la reacción refluida a 90°C durante 18 h bajo una atmósfera de nitrógeno. La reacción se dejó enfriar, fue concentrada al vacío, y el residuo particionado entre etil acetato (100 mL) y agua (100 mL). La fase acuosa fue filtrada y el volumen

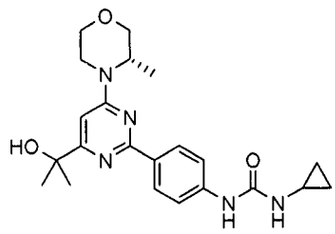
reducido al vacío. La solución resultante fue acidificada con ácido clorhídrico concentrado y sometida a vacío hasta secarse para dar el material deseado.

Espectro de masa: $M+H^+$ 315.

La preparación de metil 2–cloro–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxilato fue descrita anteriormente.

Ejemplo 37:

3–Ciclopropil–1–[4–[4–(2–hidroxipropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



2–[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol (70 mg) fue disuelto en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (4 mL) y ácido 4–(3–ciclopropilureido)fenilborónico (98 mg) y carbonato de sodio 2M (1 mL) fueron añadidos. Catalizador de diclorobis(trifenilfosfina) paladio (10 mg) fue añadido y la solución calentada en un reactor de microondas a 100°C durante 0.5 h. La mezcla fue acidificada con ácido clorhídrico concentrado y cargada directamente en una columna SCX–2 (10 g), la columna lavada con metanol, luego el producto eluido con amoniaco 7N en metanol, para dar el material deseado (55 mg) como un sólido blanco.

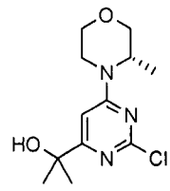
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.41 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.23 (3H, d), 1.45 (6H, s), 2.54 (1H, t), 3.19 – 3.23 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 (1H, d), 4.14 – 4.17 (1H, m), 4.50 (1H, s), 5.17 (1H, s), 6.41 (1H, d), 6.80 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.50 (1H, s)

Espectro de masa: $M+H^+$ 412.

Prueba (a): 0.051 μM.

La preparación de 2–[2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol es descrita a continuación.

2-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]propan-2-ol



Metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato (300 mg) fue disuelto en THF seco y enfriado hasta -78°C. Bromuro de metilmagnesio (3.0 M en dietil éter, 0.74 mL) fue añadido en forma de gotas durante 2 min luego la reacción se dejó agitar a -78°C durante 20 min antes de que se dejara calentar hasta RT. La reacción fue agitada durante unos 20 min adicionales y luego apagada con agua (2 mL). La reacción fue reducida hasta secarse y particionada entre etil acetato (50 mL) y agua (50 mL) y la capa orgánica secada sobre sulfato de magnesio y sometida a vacío hasta secarse hasta dar el material deseado como un sólido blanco (291 mg).

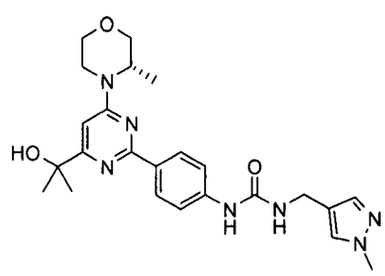
Espectro NMR: (400.13 MHz, DMSO-d_6) δ 1.16 – 1.23 (3H, m), 1.36 (6H, s), 3.15 – 3.23 (1H, m), 3.40 – 3.47 (1H, m), 3.56 – 3.60 (1H, m), 3.71 (1H, d), 3.91 – 3.94 (2H, m), 4.34 (1H, s), 5.28 (1H, s), 6.87 (1H, s).

Espectro de masa: $M+H^+$ 272.

La preparación de metil 2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxilato fue descrita anteriormente.

Ejemplo 38:

1-[4-[4-(2-Hidroxipropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea

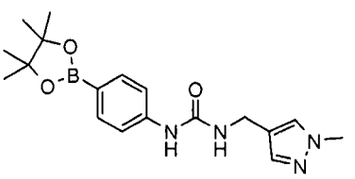


2–[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol (70 mg) fue disuelto en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (4 mL). 3–[(1–Metilpirazol–4–il)metil]–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea (115 mg) y carbonato de sodio 2M (1 mL) fueron añadidos. Catalizador de diclorobis(trifenilfosfina) paladio (10 mg) fue añadido y la solución calentada en un reactor de microondas a 100°C durante 0.5 h. La mezcla fue acidificada con ácido clorhídrico concentrado y cargada directamente en una columna SCX–2 (10 g), la columna lavada con metanol, luego el producto fue eluido con amoniaco 7N en metanol, para dar el material deseado (55 mg) como un sólido blanco.
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, d), 1.45 (6H, s), 3.16 – 3.23 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.78 – 3.80 (1H, m), 3.75 – 3.81 (3H, s), 3.96 – 3.99 (1H, m), 4.13 (3H, d), 4.49 – 4.52 (1H, m), 5.17 (1H, s), 6.39 (1H, t), 6.80 (1H, s), 7.35 (1H, s), 7.47 – 7.49 (2H, m), 7.59 (1H, s), 8.22 – 8.24 (2H, m), 8.65 (1H, s)
Espectro de masa: $M+H^+$ 466.
Prueba (a): 1.3 μM.

La preparación de 2–[2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol fue descrita anteriormente.

La preparación de 3–[(1–metilpirazol–4–il)metil]–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea es descrita a continuación.

3–[(1–Metilpirazol–4–il)metil]–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea



Ácido (4–aminofenil)borónico pinacol éster (200 mg) fue disuelto en THF seco (5 mL) y bicarbonato de sodio (116 mg) añadido seguido por la adición en forma de gotas de fenilcloroformato (0.115 mL). La mezcla fue agitada a RT durante 1 hora. (1–Metilpirazol–4–il)metanamina (102 mg) fue añadida y la reacción se dejó agitar a RT durante 2 h antes de ser calentada hasta 40°C durante 16 h. La mezcla fue concentrada al vacío y el residuo particionado entre DCM (25 mL) y agua (25 mL). Los productos orgánicos fueron secados

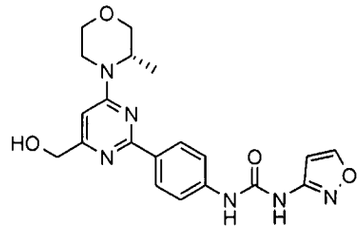
sobre sulfato de magnesio, filtrados y sometidos a vacío hasta secarse. El material fue cromatografiado en sílice, eluyendo con etil acetato, para dar el material deseado (232 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.28 (12 H, s), 3.79 (3H, s), 4.11 (2H, d), 6.39 (1H, t), 7.34 (1H, s), 7.39 – 7.41 (2H, m), 7.52 – 7.54 (2H, m), 7.59 (1H, s), 8.56 (1H, s)

Espectro de masa: M+H$^+$ 357.

Ejemplo 39:

1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea



[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (500 mg) fue disuelto en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (10 mL). 3–(1,2–Oxazol–3–il)–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea (811 mg) y solución acuosa 2M de carbonato de sodio (4 mL) fueron luego añadidas a la solución y la mezcla resultante desgasificada durante 5 min. Catalizador de diclorobis(trifenilfosfina) paladio (73 mg) fue añadido y la solución refluida a 90°C durante 7 h bajo una atmósfera de nitrógeno. La reacción se dejó enfriar, luego fue neutralizada con ácido clorhídrico concentrado y cargada directamente en una columna SCX–2 (50 g), la columna fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por cromatografía en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (318 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.20 – 3.24 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.16 – 4.19 (1H, m), 4.47 (2H, d), 4.50 (1H, s), 5.40 (1H, t), 6.69 (1H, s), 6.87 (1H, d), 7.53 – 7.56 (2H, m), 8.27 – 8.29 (2H, m), 8.75 – 8.75 (1H, m), 9.03 (1H, d), 9.60 (1H, s)

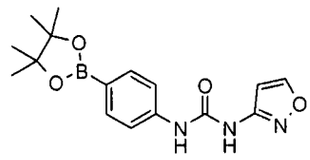
Espectro de masa: M+H$^+$ 411.

Prueba (a): 0.075 μM.

La preparación de [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol ha sido descrita anteriormente.

La preparación de 3-(1,2-oxazol-3-il)-1-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]urea es descrita a continuación.

3-(1,2-Oxazol-3-il)-1-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]urea



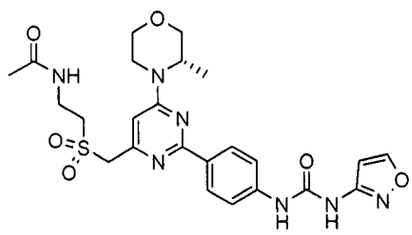
Ácido (4-aminofenil)borónico pinacol éster (1 g) fue disuelto en THF seco (30 mL), bicarbonato de sodio (576 mg) fue añadido seguido por la adición en forma de gotas de fenilcloroformato (0.575 mL). La mezcla fue agitada a RT durante 1 hora, luego 3-aminoisoxazol (0.506 mL) fue añadido y la reacción se dejó agitar a 40°C durante 16 h. Más 3-aminoisoxazol (0.506 mL) y bicarbonato de sodio (576 mg) fueron añadidos y la reacción calentada hasta 75°C durante 8 h. antes de que la mezcla fuera concentrada al vacío y particionada entre DCM (50 mL) y agua (50 mL). La capa orgánica fue secada sobre sulfato de magnesio, filtrada y sometida a vacío hasta secarse. El residuo fue cromatografiado en sílice, eluyendo con etil acetato, para dar el compuesto deseado (1.05 g) como un sólido blanco.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.29 (12 h, s), 5.89 (1H, d), 6.86 (1H, d), 7.47 – 7.49 (2H, m), 7.61 – 7.63 (2H, m), 8.32 (1H, t), 8.75 (1H, d)

Espectro de masa: M+H$^+$ 330.

Ejemplo 40:

***N*-[2-[[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(1,2-oxazol-3-ilcarbamoilamino)fenil]pirimidin-4-il]metilsulfonil]etil]acetamida**

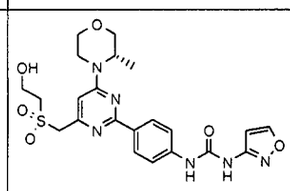


1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea (89 mg, 0.18 mmol) fue parcialmente disuelta en acetonitrilo (4 mL) y *N*–(2–sulfaniletil)acetamida (0.034 mL, 0.32 mmol) añadida. DBU (0.055 mL, 0.36 mmol) fue añadido y la reacción agitada a RT durante 6 h antes de ser sometida a vacío hasta secarse. El material fue disuelto en 1,4–Dioxano (2 mL) y una solución de m–CPBA (75%) (158 mg) en 1,4 Dioxano (2 mL) añadida, seguido inmediatamente por una solución de permanganato de sodio (175 mg) en agua (1 mL). La reacción se dejó agitar a RT durante 1 h, luego cargada en una columna SCX–2 (10 g), la columna fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por HPLC prep. (básica) para dar el material deseado como un sólido (13 mg).

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.26 (3H, d), 1.84 (3H, s), 3.24 (1H, d), 3.52 (2H, t), 3.54 (1H, s), 3.58 (2H, t), 3.65 – 3.68 (1H, m), 3.79 (1H, d), 3.98 – 4.02 (1H, m), 4.20 (1H, s), 4.54 (3H, m), 6.82 (1H, s), 6.88 (1H, d), 7.56 – 7.59 (2H, m), 8.16 – 8.17 (1H, m), 8.28 – 8.31 (2H, m), 8.76 – 8.77 (1H, m), 9.09 (1H, d), 9.62 (1H, s)

Espectro de masa: M+H$^+$ 544.

Los siguientes compuestos fueron preparados de una forma análoga a partir de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea y el tiol apropiado.

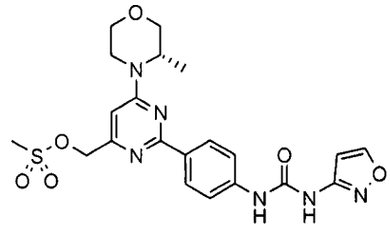
Ejemplo	Estructura	NOMBRE	LCMS MH+
40a		1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea	503

Ejemplo 40a: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.26 (3H, d), 3.24 (1H, d), 3.53 (3H, t), 3.65 – 3.68 (1H, m), 3.79 (1H, d), 3.93 (2H, q), 3.98 – 4.02 (1H, m), 4.20 (1H, s), 4.51 (3H, d), 5.20 (1H, t), 6.80 (1H, s), 6.88 – 6.88 (1H, m), 7.58 (2H, d), 8.29 – 8.31 (2H, m), 8.76 (1H, s), 9.09 (1H, d), 9.64 (1H, s).

Prueba (c): Ejemplo (40) 0.1 μM; Ejemplo (40a) 0.055 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea es descrita a continuación.

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea

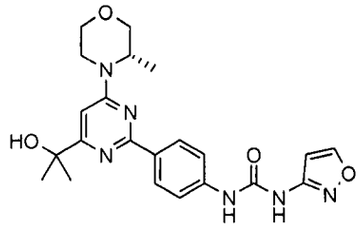


1–[4–[4–(Hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea (300 mg) fue parcialmente disuelta en DCM (10 mL) y trietilamina (0.153 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.086 mL) y la reacción fue agitada durante 45 min a RT. La reacción fue luego lavada con agua (2 mL) y secada sobre sulfato de magnesio. La solución fue sometida a vacío hasta secarse para dar el material deseado como un sólido amarillo.

Espectro de masa: $M+H^+$ 489.

Ejemplo 41:

1–[4–[4–(2–Hidroxipropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1,2–oxazol–3–il)urea



2–[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol (160 mg, 0.59 mmol) fue añadido a 3–(1,2–oxazol–3–il)–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea (242 mg) y catalizador de diclorobis(trifenilfosfina) paladio (21 mg) en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (6 mL). La reacción fue calentada hasta 100°C durante 30 minutos en el reactor de microondas y enfriada hasta RT. La mezcla de reacción fue acidificada con ácido clorhídrico 2M y el material crudo cargado en una columna SCX (10 g), el material deseado fue eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado (52 mg) como un sólido blanco.

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.47 (6H, s), 3.18 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.16 – 4.19 (1H, m), 4.51 – 4.53 (1H, m), 5.20 (1H, s), 6.84 (1H, s), 6.88 (1H, d), 7.55 – 7.57 (2H, m), 8.30 – 8.32 (2H, m), 8.76 (1H, d), 9.06 (1H, s), 9.61 (1H, s)

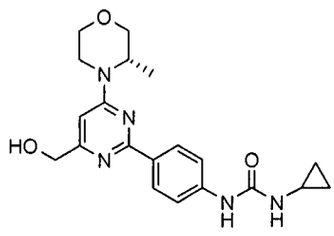
Espectro de masa: $M+H^+$ 439.4

Prueba (c): 0.047 μM.

La preparación de 2–[2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]propan–2–ol y 3–(1,2–oxazol–3–il)–1–[4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenil]urea fue descrita anteriormente.

Ejemplo 42:

3–Ciclopropil–1–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (3.30 g) fue disuelto en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (50 mL). Ácido 4–(3–ciclopropilureido)fenil borónico (4.92 g) y carbonato de sodio 2M (5 mL) fueron luego añadidos y la solución

desgasificada durante 5 min. Catalizador de diclorobis(trifenilfosfina) paladio (476 mg) fue luego añadido a la solución y esta refluida a 90°C durante 7h bajo una atmósfera de nitrógeno. La reacción se dejó enfriar, fue evaporada, y el residuo particionado entre DCM (200 mL) y agua (200 mL). La capa orgánica fue secada sobre sulfato de magnesio, evaporada, y purificada por cromatografía en sílice, eluyendo con 5% metanol en DCM, para dar el material deseado (4.33 g) como un sólido amarillo.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.23 (3H, d), 2.54 – 2.58 (1H, m), 3.17 – 3.22 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.15 – 4.18 (1H, m), 4.45 (2H, d), 4.49 (1H, d), 5.38 (1H, t), 6.41 (1H, d), 6.66 (1H, s), 7.46 – 7.50 (2H, m), 8.18 – 8.22 (2H, m), 8.49 (1H, s),

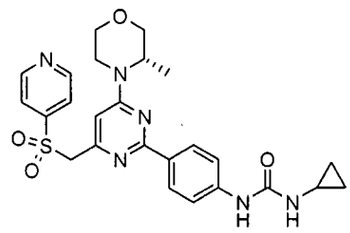
Espectro de masa: $M+H^+$ 384.

Prueba (a): 0.19 μM.

La preparación de [2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol ha sido descrita anteriormente.

Ejemplo 43:

3–Ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]urea



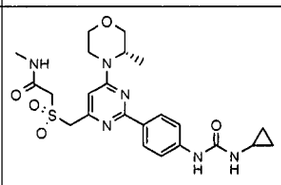
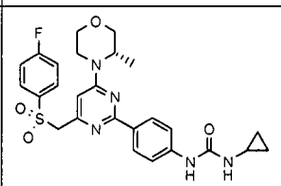
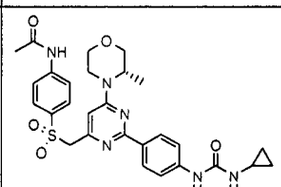
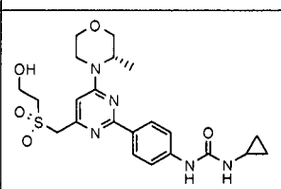
3–Ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea (100 mg, 0.24 mmol) fue parcialmente disuelta en acetonitrilo (4 mL) y piridina–4–tiol (0.38 mmol) añadido. La reacción fue agitada durante 1 h a RT, luego DBU (0.065 mL, 0.43 mmol) fue añadido y la reacción agitada a RT durante 18 h. La reacción fue evaporada hasta secarse y disuelta en 1,4–Dioxano (2 mL). Una solución de m–CPBA (75%) (94 mg) en 1,4 Dioxano (2 mL), seguido inmediatamente por una solución de permanganato de sodio (104 mg) en agua (1 mL), fue añadida a la reacción y se dejó agitar a RT durante 1 h. Una solución adicional de m–CPBA (75%) (94 mg) en 1,4 Dioxano (1 mL), seguido

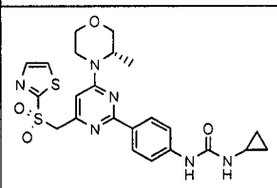
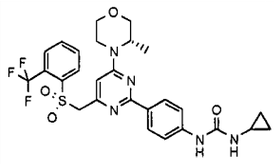
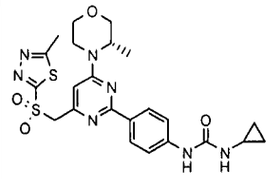
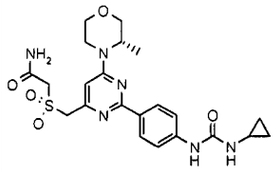
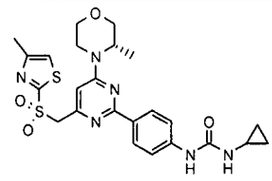
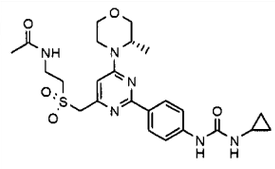
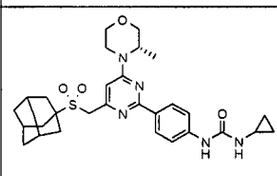
inmediatamente por una solución de permanganato de sodio (104 mg) en agua (0.5 mL), fue añadida y la reacción agitada a RT durante 1 h. La mezcla de reacción fue cargada en una columna SCX–2 (10 g), la columna fue lavada con metanol y el producto eluido con amoniaco 7N en metanol. El material fue adicionalmente purificado por HPLC prep. (básica) para dar el material deseado como un sólido (10 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.21 (3H, d), 2.58 – 2.61 (1H, m), 3.15 – 3.25 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.10 – 4.14 (1H, m), 4.38 (1H, s), 4.86 (2H, t), 6.41 – 6.42 (1H, m), 6.71 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.81 – 7.82 (2H, m), 8.50 (1H, s), 8.90 – 8.91 (2H, m)

Espectro de masa: $M+H^+$ 509.

Los siguientes compuestos fueron preparados de una forma análoga usando el tiol apropiado.

Ejemplo	Estructura	NOMBRE	LCMS MH+
43a		2–[[2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]–N–metil–acetamida	503
43b		3–ciclopropil–1–[4–[4–[(4–fluorofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	526
43c		N–[4–[[2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]fenil]acetamida	565
43d		3–ciclopropil–1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	476

Ejemplo	Estructura	NOMBRE	LCMS MH+
43e		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(1,3–tiazol–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea	515
43f		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[[2–(trifluorometil)fenil]sulfonilmetil]pirimidin–2–il]fenil]urea	576
43g		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(5–metil–1,3,4–tiadiazol–2–il)sulfonilmetil]pirimidin–2–il]fenil]urea	530
43h		2–[[2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]acetamida	489
43i		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidin–2–il]fenil]urea	529
43j		N–[2–[[2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]etil]acetamida	517
43k		1–[4–[4–(1–adamantilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–ciclopropil–urea	598

Ejemplo 43a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.23 – 1.25 (3H, m), 2.57 – 2.60 (1H, m), 2.67 – 2.70 (3H, m), 3.19 – 3.25 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.15 – 4.19 (1H, m), 4.29 (2H, s), 4.48 (1H, s), 4.67 (2H, s), 6.43 – 6.44 (1H, m), 6.77 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.31 (1H, t), 8.54 (1H, s)

Ejemplo 43b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.20 (3H, d), 2.52 – 2.60 (1H, m), 3.15 – 3.20 (1H, m), 3.45 – 3.51 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.10 – 4.13 (1H, m), 4.38 (1H, s), 4.71 (2H, s), 6.40 (1H, d), 6.65 (1H, s), 7.38 – 7.41 (2H, m), 7.43 – 7.48 (2H, m), 7.79 (2H, d), 7.85 – 7.89 (2H, m), 8.51 (1H, s)

Ejemplo 43c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.19 (3H, d), 2.13 (3H, s), 2.53 – 2.61 (1H, m), 3.15 – 3.20 (1H, m), 3.43 – 3.50 (1H, m), 3.60 – 3.63 (1H, m), 3.75 (1H, d), 3.94 – 3.98 (1H, m), 4.09 (1H, s), 4.34 (1H, s), 4.60 (2H, s), 6.41 – 6.42 (1H, m), 6.55 (1H, s), 7.39 (2H, d), 7.70 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.48 (1H, s), 10.37 (1H, s)

Ejemplo 43d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (3H, d), 2.59 – 2.61 (1H, m), 3.15 – 3.20 (1H, m), 3.51 (3H, t), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.92 (2H, q), 3.97 – 4.01 (1H, m), 4.16 – 4.19 (1H, m), 4.50 (3H, s), 5.18 (1H, t), 6.44 (1H, d), 6.76 (1H, s), 7.50 – 7.52 (2H, m), 8.21 – 8.23 (2H, m), 8.54 (1H, s)

Ejemplo 43e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.20 (3H, d), 2.52 – 2.61 (1H, m), 3.15 – 3.20 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.12 (1H, d), 4.40 (2H, s), 4.90 – 4.91 (1H, m), 6.42 (1H, d), 6.71 (1H, s), 7.40 – 7.43 (2H, m), 7.84 (2H, d), 8.27 – 8.29 (2H, m), 8.50 (1H, s)

Ejemplo 43f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.20 – 1.22 (3H, m), 2.53 (1H, m), 3.17 (1H, d), 3.49 (1H, d), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.95 – 3.99 (1H, m), 4.12 (1H, d), 4.40 (1H, s), 4.74 – 4.75 (2H, m), 6.42 – 6.42 (1H, m), 6.70 (1H, s), 7.37 (2H, d), 7.72 (2H, d), 7.80 (1H, d), 7.90 (2H, t), 8.08 (1H, d), 8.48 (1H, s)

Ejemplo 43g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.42 (2H, d), 0.63 – 0.67 (2H, m), 1.23 (3H, d), 2.53 (1H, d), 2.80 (3H, s), 3.20 (1H, d), 3.48 (1H, d), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 4.12 (1H, d), 4.40 (2H, s), 5.04 (2H, t), 6.44 (1H, s), 6.80 (1H, s), 7.43 (2H, d), 7.79 (2H, d), 8.53 (1H, s)

Ejemplo 43i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.21 (3H, d), 2.60 – 2.61 (1H, m), 3.20 (1H, d), 3.34 – 3.39 (3H, s), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.12 (1H, d), 4.41 (1H, s), 4.86 – 4.87 (2H, m), 6.41 – 6.42 (1H, m), 6.71 (1H, s), 7.41 – 7.44 (2H, m), 7.82 (1H, d), 7.87 (2H, d), 8.51 (1H, s)

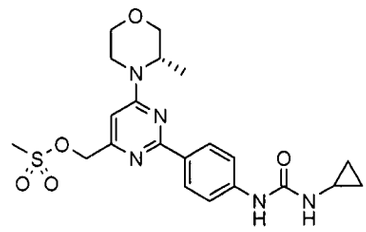
Ejemplo 43j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (3H, t), 1.83 (3H, s), 2.52 – 2.60 (1H, m), 3.19 – 3.25 (1H, m), 3.47 – 3.50 (2H, m), 3.52 (2H, d), 3.56 (2H, d), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.12 (1H, d), 4.50 (2H, d), 6.43 (1H, d), 6.78 (1H, s), 7.50 (2H, d), 8.19 – 8.22 (2H, m), 8.54 (1H, s), 9.00 (1H, s)

Ejemplo 43k: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (3H, d), 1.67 (6H, d), 2.03 (6H, s), 2.12 (3H, s), 2.53 – 2.60 (1H, m), 3.20 – 3.24 (1H, m), 3.47 – 3.51 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.12 (1H, d), 4.39 – 4.45 (3H, m), 6.43 (1H, d), 6.73 (1H, s), 7.49 – 7.51 (2H, m), 8.22 (2H, d), 8.53 (1H, s)

Prueba (a): Ejemplo (43) 0.076 μM; Ejemplo (43a) 0.087 μM; Ejemplo (43b) 0.15 μM; Ejemplo (43c) 0.013 μM; Ejemplo (43d) 0.011 μM; Ejemplo (43e) 0.13 μM; Ejemplo (43f) 0.11 μM; Ejemplo (43h) 0.0071 μM; Ejemplo (43i) 0.058 μM; Ejemplo (43j) 1.8 μM.
Prueba (c): Ejemplo (43g) 1.9 μM; Ejemplo (43k) 2.9 μM

La preparación de 3–ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea es descrita a continuación.

3–Ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea



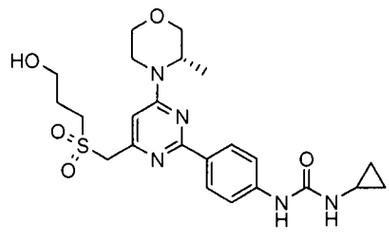
3–Ciclopropil–1–[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea (1.83 g) fue parcialmente disuelta en DCM (50 mL) y trietilamina (1 mL) y la solución fue enfriada hasta 0°C. Metano sulfonil cloruro fue añadido (0.56 mL) y la reacción

fue agitada durante 45 min a RT. La reacción fue luego lavada con agua (10 mL) y los productos orgánicos secados sobre sulfato de magnesio. La solución fue sometida a vacío hasta secarse para dar el material deseado como un sólido amarillo.

Espectro de masa: $M+H^+$ 462.

Ejemplo 44:

3–Ciclopropil–1–[4–[4–(3–hidroxipropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



Monohidrato de permanganato de sodio (38 mg, 0.24 mmol) fue añadido a m–CPBA (33.2 mg, 0.19 mmol) y 3–ciclopropil–1–[4–[4–(3–hidroxipropilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea (44 mg, 0.10 mmol) en Dioxano (2 mL) y agua (1 mL) a 20°C. La solución resultante fue agitada a 20 °C durante 45 minutos y la mezcla cargada en una columna SCX–3 (5 g), el producto deseado fue eluido de la columna usando 7M amoniaco en metanol. El material fue adicionalmente purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado (19 mg) como un sólido blanco.

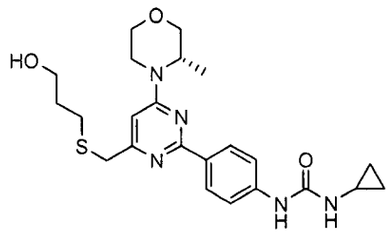
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.24 (3H, d), 1.92 – 1.99 (2H, m), 2.53 – 2.60 (1H, m), 3.18 – 3.26 (1H, m), 3.39 (2H, q), 3.47 – 3.50 (1H, m), 3.55 (2H, q), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.16 – 4.19 (1H, m), 4.46 (3H, s), 4.72 (1H, t), 6.43 (1H, d), 6.78 (1H, s), 7.49 – 7.51 (2H, m), 8.20 – 8.23 (2H, m), 8.53 (1H, s)

Espectro de masa: $M+H^+$ 490

Prueba (a): 1.8 μM.

La preparación de 3–ciclopropil–1–[4–[4–(3–hidroxipropilsulfanilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea es descrita a continuación.

3-Ciclopropil-1-[4-[4-(3-hidroxipropilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



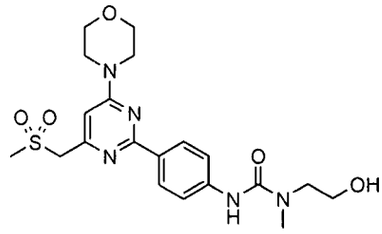
3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (100 mg) fue parcialmente disuelta en acetonitrilo (4 mL) y añadida a 3-sulfanilpropan-1-ol (0.38 mmol). La reacción fue agitada durante 1 h a RT. DBU (0.065 uL) fue añadido a la reacción y la mezcla se dejó agitar a RT durante 18 h. La mezcla fue concentrada al vacío y purificada por HPLC prep. (básica) para dar el material deseado (44 mg) como un sólido blanco.

Espectro de masa: $M+H^+$ 458.

La preparación de 3-ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea fue descrita anteriormente.

Ejemplo 45:

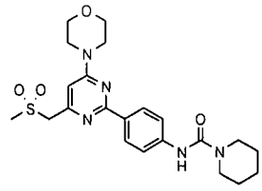
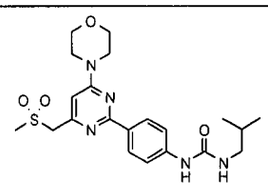
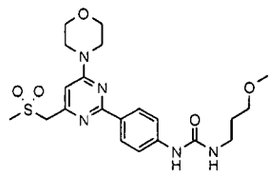
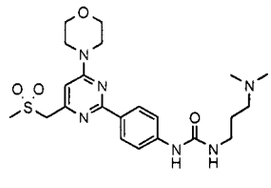
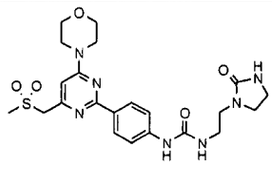
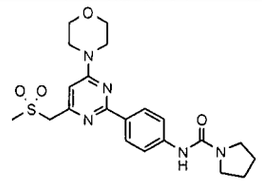
1-(2-Hidroxietil)-1-metil-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea

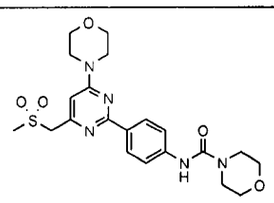
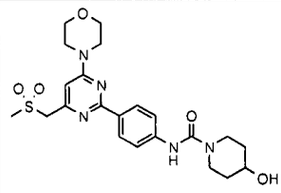
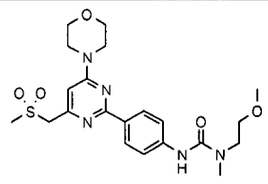
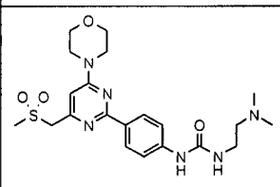
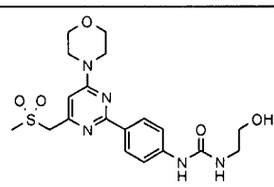
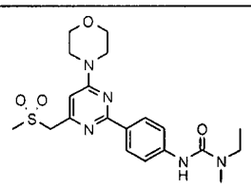


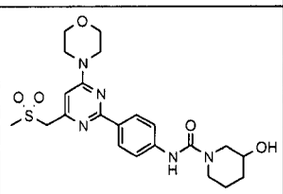
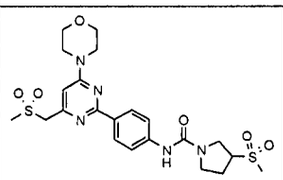
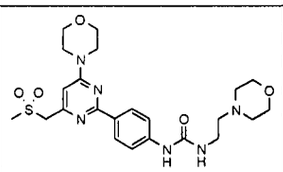
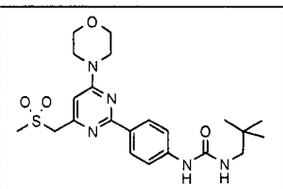
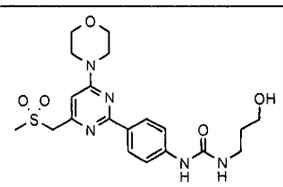
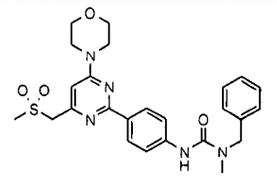
Una solución de fenil *N*-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]carbamato (94 mg, 2 mmol) y trietilamina (0.09 mL, 9.2 mmol) en NMP (1 mL) fue añadida a 2-metilaminoetanol (10 mmol). La mezcla fue calentada a 70°C durante 2 horas y la reacción purificada por HPLC prep., para dar el compuesto deseado.

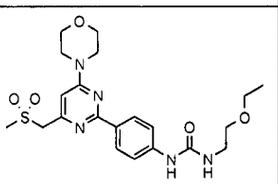
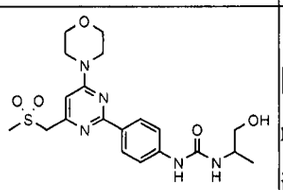
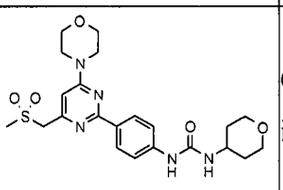
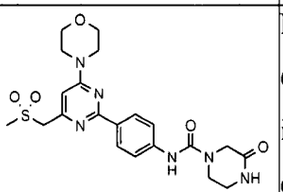
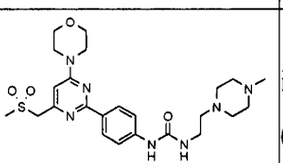
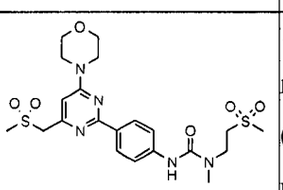
Espectro LCMS: MH+ 450, Tiempo de retención 2.07 min.

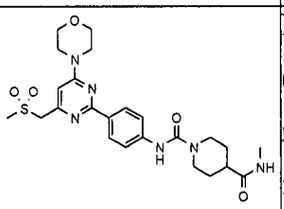
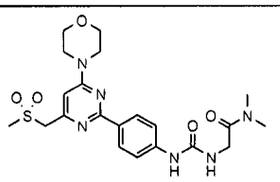
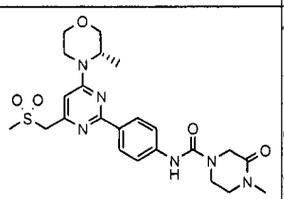
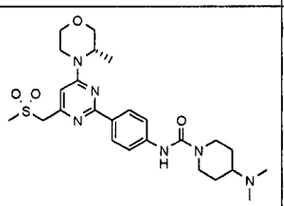
Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
45a		N-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]piperidina-1-carboxamida	460	2.74
45b		1-(2-metilpropil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	448	2.76
45c		1-(3-metoxipropil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	464	2.46
45d		1-(4-dimetilaminobutil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	491	2.8
45e		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-[2-(2-oxoimidazolidin-1-il)etil]urea	504	2.27
45f		N-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]pirrolidina-1-carboxamida	446	2.56

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
45g		N–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]morfolina–4–carboxamida	462	2.4
45h		4–hidroxi–N–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]piperidina–1–carboxamida	476	2.28
45i		1–(1–metoxipropan–2–il)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	464	2.51
45j		1–(2–dimetilaminoetil)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	463	2.52
45k		3–(2–hidroxietil)–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	436	2.21
45l		1–etil–1–metil–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	434	2.54

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
45m		3–hidroxi–N–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]piperidina–1–carboxamida	476	2.35
45n		3–metilsulfonil–N–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]pirrolidina–1–carboxamida	524	2.34
45o		1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]–3–(2–morfolin–4–iletil)urea	505	2.14
45p		1–(2,2–dimetilpropil)–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	462	2.68
45q		3–(3–hidroxipropil)–1–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	450	2.05
45r		1–bencil–1–metil–3–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]urea	496	2.74

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
45s		1-(2-etoxietil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	464	2.29
45t		1-(1-hidroxipropan-2-il)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	450	2.09
45u		1-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-(oxan-4-il)urea	476	2.21
45v		N-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]-3-oxo-piperazina-1-carboxamida	475	2.00
45w		1-[2-(4-metilpiperazin-1-il)etil]-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	518	2.11
45x		1-metil-1-(2-metilsulfoniletil)-3-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]urea	512	2.14

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
45y		N'-metil-N-[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]piperidina-1,4-dicarboxamida	516	2.07
45z		N,N-dimetil-2-[[4-[4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidin-2-il]fenil]carbamoilamino]acetamida	477	2.11
45aa		4-metil-N-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]-3-oxo-piperazina-1-carboxamida	489	1.23
45ab		4-dimetilamino-N-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]piperidina-1-carboxamida	518	1.6

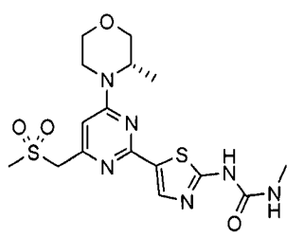
Prueba (a): Ejemplo (45) 0.66 μM; Ejemplo (45a) 0.63 μM; Ejemplo (45b) 0.12 μM; Ejemplo (45c) 0.082 μM; Ejemplo (45d) 0.56 μM; Ejemplo (45e) 0.56 μM; Ejemplo (45f) 1.6 μM; Ejemplo (45g) 0.041 μM; Ejemplo (45h) 0.14 μM; Ejemplo (45i) 3 μM; Ejemplo (45j) 0.72 μM; Ejemplo (45k) 0.049 μM; Ejemplo (45l) 1.1 μM; Ejemplo (45m) 0.17 μM; Ejemplo (45n) 0.63 μM; Ejemplo (45o) 0.9 μM; Ejemplo (45p) 0.92 μM; Ejemplo (45q) 0.032 μM; Ejemplo (45r) 0.41 μM; Ejemplo (45s) 0.3 μM; Ejemplo (45t) 0.082 μM; Ejemplo (45u) 0.42

μM; Ejemplo (45v) 1.2 μM; Ejemplo (45w) 0.74 μM; Ejemplo (45x) 1.1 μM; Ejemplo (45y) 1.2 μM; Ejemplo (45z) 1 μM; Ejemplo (45aa) 0.83 μM; Ejemplo (45ab) 0.39 μM.

La preparación de fenil *N*–[4–[4–(metilsulfonilmetil)–6–morfolin–4–il–pirimidin–2–il]fenil]carbamato y fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]fenil]carbamato fue descrita anteriormente.

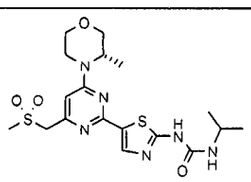
Ejemplo 46:

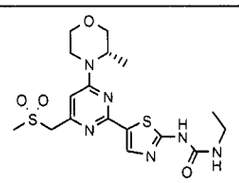
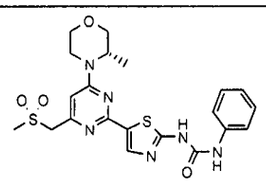
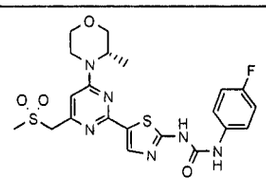
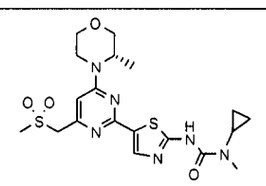
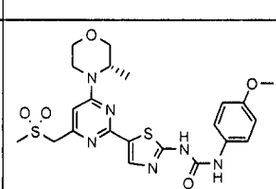
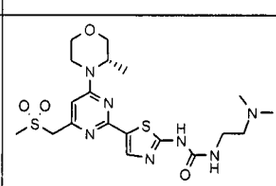
3–Metil–1–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]urea

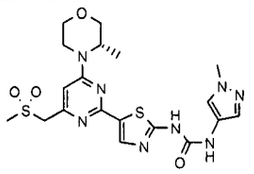
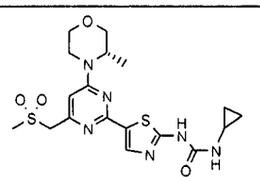


Una mezcla de fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]carbamato (100 mg, 0.2 mmol), metilamina (1 mmol), y trietilamina (0.085 mL, 0.6 mmol) en NMP (2 mL), fue calentada a 70°C durante 2 horas. El material fue purificado por HPLC prep. para dar el material deseado como un sólido blanco (27 mg).
Espectro LCMS: MH+ 427, Tiempo de retención 1.44 min

Los siguientes compuestos fueron preparados de una forma análoga.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
46a		1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]–3–propan–2–il–urea	455	1.84

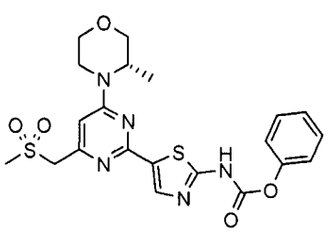
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
46b		1–etil–3–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]urea	441	1.48
46c		1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]–3–fenil–urea	489	1.86
46d		3–(4–fluorofenil)–1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]urea	507	1.88
46e		1–ciclopropil–1–metil–3–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]urea	467	1.69
46f		3–(4–metoxifenil)–1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–2–il]–1,3–tiazol–2–il]urea	519	1.82
46g		3–(2–dimetilaminoetil)–1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidin–	484	1.39

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		2-il]-1,3-tiazol-2-il]urea		
46h		1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]-3-(1-metilpirazol-4-il)urea	493	1.25
46i		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]urea	453	1.59

Prueba (a): Ejemplo (46) 0.14 μM; Ejemplo (46a) 0.35 μM; Ejemplo (46b) 0.0061 μM; Ejemplo (46c) 0.45 μM; Ejemplo (46d) 0.85 μM; Ejemplo (46e) 0.71 μM; Ejemplo (46f) 1.2 μM; Ejemplo (46g) 0.73 μM; Ejemplo (46h) 0.063 μM; Ejemplo (46i) 0.097 μM.

La preparación de fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]carbamato es descrita a continuación.

Fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]carbamato

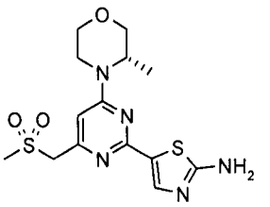


Una solución de 5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-amina (1 g, 2.71 mmol), hidrógeno carbonato de sodio (342 mg), y fenil

cloroformato (0.511 mL) en dioxano fue agitada a RT durante 2 horas y luego concentrada al vacío. El residuo fue particionado entre DCM y agua y la capa orgánica secada sobre sulfato de sodio y evaporada para dar una espuma. La espuma fue triturada con una mezcla de hexano y dietil éter para dar el material deseado como un sólido blanco (1.1 g).

Espectro LCMS: MH+490, tiempo de retención 2.17, Método Ácido Monitor.

5-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-amina

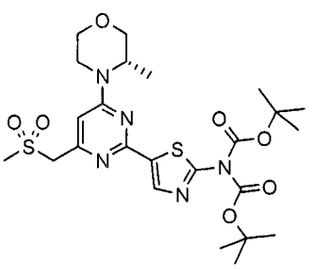


Una solución de *tert*-butil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]-*N*-[(2-metilpropan-2-il)oxicarbonil]carbamato (1.7 g, 2.9 mmol) y TFA (8 mL) en DCM (15 mL) fue agitada a RT durante 16 horas. El solvente fue eliminado a presión reducida y el residuo se hizo básico con solución de amoniaco acuosa. El producto fue extraído con etil acetato, los productos orgánicos secados sobre sulfato de sodio, filtrados y evaporados para dar el material deseado como un sólido blanco (1 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.16 – 1.22 (3H, m), 3.13 – 3.18 (1H, m), 3.19 (3H, s), 3.43 – 3.50 (1H, m), 3.60 – 3.63 (1H, m), 3.75 (1H, d), 3.94 – 3.97 (1H, dd), 4.04 (1H, d), 4.37 (1H, s), 4.40 (2H, s), 5.75 (1H, s), 6.64 (1H, s), 7.40 (2H, s), 7.73 (1H, s)

Espectro LCMS: MH+ 370, tiempo de retención 1.38 min Método Básico Monitor.

tert-Butil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]-1,3-tiazol-2-il]-*N*-[(2-metilpropan-2-il)oxicarbonil]carbamato

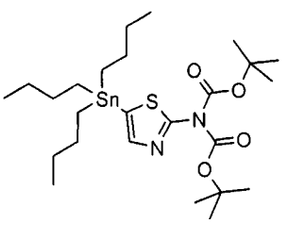


Una mezcla de *tert*–butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(5–tributilestanil–1,3–tiazol–2–il)carbamato (3 g, 5.1 mmol), 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfonilmetil)pirimidina (1 g, 3.2 mmol) y paladio tetrakis (trifenilfosfina) (50 mg), en tolueno (10 mL) fue calentada a 105°C durante 2 horas bajo nitrógeno. La mezcla fue cromatografiada en sílice para dar el material deseado (1.7 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.53 (9H, s), 3.18 (3H, s), 3.55 (1H, t), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, d), 4.10 (1H, s), 3.90 (1H, s), 3.98 (2H, s), 6.80 (1H, s), 8.18 (1H, s)

Espectro LCMS: MH+ 570, tiempo de retención 2.89 min Método Básico Monitor.

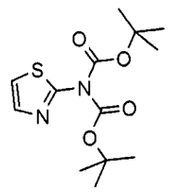
tert–Butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(5–tributilestanil–1,3–tiazol–2–il)carbamato



n–Butil litio (1.6 M en hexanos, 30 mL, 0.48 mol), fue añadido a diisopropilamina (6.7 mL, 0.48 mol) en THF (480 mL) a 0°C. La mezcla fue agitada a 0°C durante 30 min y luego enfriada hasta –78°C. *tert*–Butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(1,3–tiazol–2–il)carbamato (12 g, 0.05 mol) fue añadido y la solución agitada durante 30 minutos. Tributilestaño cloruro (16.3 mL) fue añadido y la solución agitada durante 30 minutos antes de que se dejara calentar hasta RT. La reacción fue apagada con una solución saturada acuosa de cloruro de amonio (20 mL) y el producto extraído con etil acetato. Los productos orgánicos fueron secados sobre sulfato de sodio, concentrados al vacío y cromatografiados en sílice, eluyendo con 5–15% etil acetato en hexano, para dar el material deseado como un sólido claro (9 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.49 (18H, s), 7.50 (1H, d), 7.55 (1H, d)

tert–Butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(1,3–tiazol–2–il)carbamato



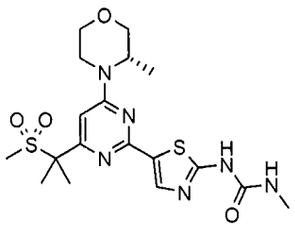
Una solución de 2–aminotiazol (5 g, 0.05 mol), (2–metilpropan–2–il)oxicarbonil *tert*–butil carbonato (27.8 g, 0.15 mol) y DMAP (100 mg) en THF (100 mL) fue agitada a reflujo toda la noche. La mezcla se dejó enfriar y fue concentrada al vacío. El residuo fue cromatografiado en sílice, eluyendo con 8% etil acetato en hexano, para dar el material deseado como un sólido blanco (12 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.49 (18H, s), 7.50 (1H, d), 7.55 (1H, d)

Espectro LCMS MH– 299, tiempo de retención 2.6 min Método Básico Monitor

Ejemplo 47:

3–Metil–1–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]urea

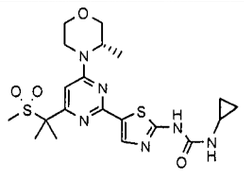
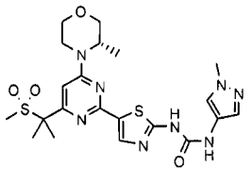
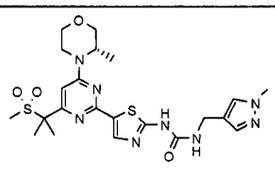
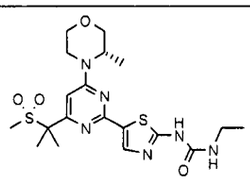


Una solución de fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]carbamato (200 mg, 0.39 mmol), metil amina (1.5 mmol) y trietilamina (0.163 mL, 1.16 mmol) en NMP (3 mL) fue calentada a 70°C durante 2 horas. La mezcla fue cromatografiada en sílice, eluyendo con 0–5% metanol en etil acetato para dar el material deseado.

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.70 (6H, s), 3.19 (3H, s), 3.20 (1H, dd), 3.45 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.52 (1H, s), 6.40 (1H, s), 6.65 (1H, s), 8.09 (1H, s), 10.70 (1H, s)

Espectro LCMS: MH+ 455, tiempo de retención 1.78 min.

Los siguientes compuestos fueron preparados de una forma análoga.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
47a		3–ciclopropil–1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]urea	481	1.94
47b		1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]–3–(1–metilpirazol–4–il)urea	521	1.62
47c		1–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]–3–[(1–metilpirazol–4–il)metil]urea	535	1.81
47d		1–etil–3–[5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]urea	469	1.95

Ejemplo 47a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.45 (2H, q), 0.68 (2H, q), 1.20 (3H, d), 1.70 (6H, s), 3.05 (3H, s), 3.20 (1H, dd), 3.48 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, dd), 4.18 (1H, d), 4.55 (1H, s), 6.68 (1H, s), 6.75 (1H, s), 8.05 (1H, s), 11.0 (1H, s).

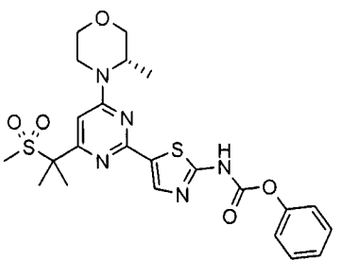
Ejemplo 47b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.70 (6H, s), 3.03 (3H, s), 3.20 (1H, dd), 3.48 (1H, dd), 3.65 (1H, d), 3.70–3.80 (4H, m), 3.99 (1H, dd), 4.15 (1H, d), 4.53 (1H, s), 6.70 (1H, s), 7.42 (1H, s), 7.82 (1H, s), 8.10 (1H, s), 8.72 (1H, s), 10.75 (1H, s)

Ejemplo 47c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.70 (6H, s), 2.68 (3H, s), 3.05 (3H, s), 3.18 (1H, dd), 3.48 (1H, dd), 3.62 (1H, d), 3.75 (1H, d), 3.98 (1H, d), 4.05 (1H, q), 4.18 (2H, s), 4.51 (1H, s), 6.68 (1H, s), 6.78 (1H, s), 7.35 (1H, s), 7.62 (1H, s), 8.09 (1H, s), 10.60 (1H, s).

Prueba (a): Ejemplo (47) 0.26 μM; Ejemplo (47a) 1.2 μM; Ejemplo (47b) 0.41 μM; Ejemplo (47c) 1.4 μM; Ejemplo (47d) 0.97 μM.

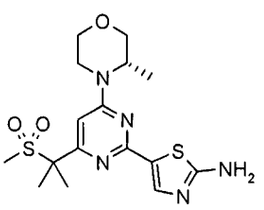
La preparación de fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]carbamato es descrita a continuación.

Fenil *N*–[5–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–il]carbamato



Una mezcla de 5–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–amina (1.05 g, 2.6 mmol), fenil cloroformato (618 mg, 3.9 mmol) e hidrógeno carbonato de sodio (311 mg, 3.9 mmol) en dioxano (10 mL) fue agitada a RT durante 2 horas, luego diluida con etil acetato y lavada con agua (150 mL) y salmuera (100 mL). Los productos orgánicos fueron secados sobre sulfato de magnesio y concentrados al vacío. El residuo fue recristalizado a partir de dietil éter y hexano para dar el producto deseado como un sólido beige (1 g).

5–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidin–2–il]–1,3–tiazol–2–amina



Una mezcla de 2–cloro–4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidina (1.2 g, 3.6 mmol), *tert*–butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(5–tributilestanil–1,3–tiazol–2–il)carbamato (3.1 g, 5.2 mmol), y paladio tetrakis (trifenilfosfina) (200 mg) en tolueno (30 mL) fue calentada a 110°C bajo una atmósfera de nitrógeno toda la noche. La mezcla fue diluida con etil acetato y lavada con agua. Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y evaporados. El residuo fue disuelto en DCM (50 mL) y ácido trifluroacético (15 mL) añadido. Después de que se dejó agitar durante 2 horas la mezcla fue evaporada y se añadió agua. La mezcla se hizo básica con solución de amoniaco acuosa y extraída con etil acetato. Los productos orgánicos fueron secados sobre sulfato de magnesio, filtrados y evaporados hasta un sólido. El residuo fue triturado con una mezcla de dietil éter y hexano para dar el material deseado (1.05 g).

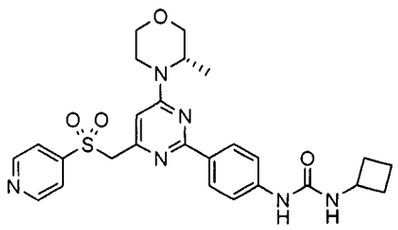
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.18 (3H, d), 1.65 (6H, s), 3.0 (3H, s), 3.15 (3H, dd), 3.45 (1H, dd), 3.60 (1H, dd), 3.71 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.50 (1H, S), 6.60 (1H, s), 7.35 (2H, s), 7.75 (1H, s).

Espectro LCMS: MH+ 398 tiempo de retención 1.76 min método básico monitor

La preparación de 2–cloro–4–[(3S)–3–metilmorfolin–4–il]–6–(2–metilsulfonilpropan–2–il)pirimidina y *tert*–butil *N*–[(2–metilpropan–2–il)oxicarbonil]–*N*–(5–tributilestanil–1,3–tiazol–2–il)carbamato fue descrita anteriormente.

Ejemplo 48:

3–Ciclobutil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]urea



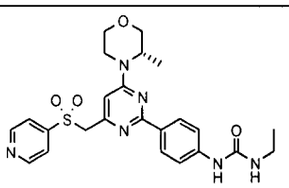
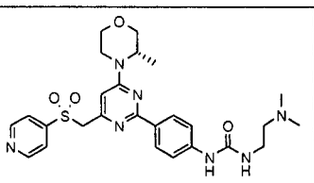
Ciclobutilamina (0.074 mL, 0.87 mmol) fue añadida a una solución de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]carbamato (0.095 g, 0.17 mmol) y trietilamina (0.073 mL, 0.52 mmol) en DMF (3 mL), luego calentada hasta 50°C bajo nitrógeno. La solución resultante fue agitada a 50 °C durante 2 horas. El solvente

fue eliminado al vacío y el producto crudo purificado por HPLC prep. para dar el material deseado como un sólido blanco (0.089 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20–1.22(3H, d), 1.59–1.66(2H, m), 1.82–1.92(2H, m), 2.18–2.25(2H, m), 3.15–3.22(1H, td), 3.45–3.52(1H, td), 3.62–3.65(1H, td), 3.75–3.78(1H, d), 3.96–3.99(1H, dd), 4.09–4.17(2H, m), 4.39(1H, bs), 4.87(2H, s), 6.52–6.54(1H, d), 6.71(1H, s), 7.33–7.35(2H, d), 7.64–7.67(2H, d), 7.80–7.82(2H, q), 8.61(1H, s), 8.90–8.91(2H, q).

Espectro LCMS: MH+ 523 tiempo de retención 1.96 min.

Los siguientes compuestos fueron preparados de una forma análoga a partir de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
48a		3–etil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]urea	497	1.74
48b		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]urea	540	1.83

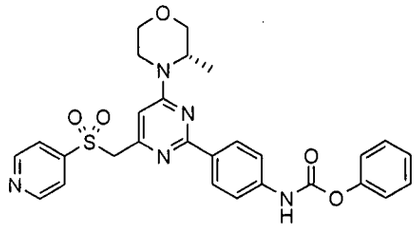
Ejemplo 48a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.05–1.09(3H, t), 1.20–1.22(3H, d), 3.09–3.16(2H, m), 3.16–3.22(1H, td), 3.45–3.52(1H, td), 3.62–3.65(1H, dd), 3.75–3.78(1H, d), 3.96–3.99(1H, dd), 4.10–4.14(1H, d), 4.39(1H, bs), 4.88(2H, s), 6.14–6.17(1H, t), 6.71(1H, s), 7.35–7.37(2H, d), 7.65–7.67(2H, d), 7.81–7.82(2H, d), 8.64(1H, s), 8.90–8.91(2H, d).

Ejemplo 48b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20–1.21(3H, d), 2.41(2H, bs), 2.74(3H, s), 2.90(3H, s), 3.15–3.23(1H, td), 3.2–3.4(2H, m), 3.45–3.51(1H, td), 3.61–3.65(1H, dd), 3.75–3.78(1H, d), 3.96–3.99(1H, dd), 4.10–4.13(1H, d), 4.39(1H, bs), 4.87(2H, s), 6.25(1H, t), 6.72(1H, s), 7.35–7.37(2H, d), 7.65–7.67(2H, d), 7.81–7.82(2H, q), 7.96(1H, s), 8.89–8.91(2H, d).

Prueba (c): Ejemplo (48) 0.038 μM; Ejemplo (48a) 0.25 μM.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]carbamato

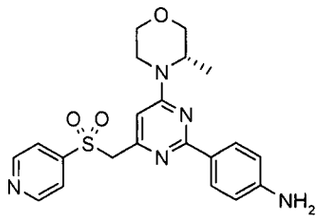


Fenil cloroformato (0.029 mL, 0.23 mmol) fue añadido a una solución de 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]anilina (0.097 g, 0.23 mmol) y bicarbonato de sodio (0.029 g, 0.34 mmol) en dioxano a RT. La lechada resultante fue agitada a RT durante 2 horas. Fenil cloroformato adicional (2 x 0.005 mL) fue añadido para terminar la reacción. Agua fue luego añadida a la reacción y el sólido filtrado, y secado en un horno de vacío para dar el material deseado como un sólido blanco hueso (0.098 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21–1.23(3H, d), 3.16–3.24(1H, td), 3.46–3.52(1H, td), 3.62–3.66(1H, dd), 3.76–3.79(1H, d), 3.96–4.00(1H, dd), 4.13–4.16(1H, bd), 4.41(1H, bs), 4.90(2H, s), 6.76(s, 1H), 7.23–7.31(3H, m), 7.43–7.51(4H, m), 7.74–7.77(2H, m), 7.81–7.83(2H, dd), 8.90–8.92(2H, dd), 10.39(1H, s).

Espectro LCMS: MH+ 546 tiempo de retención 2.35 min.

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]anilina

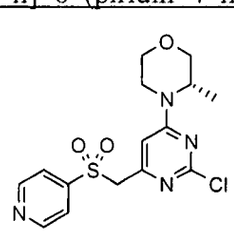


trans-Diclorobis(trifenilfosfina)paladio (II) (0.039 g, 0.06 mmol) fue añadido a una mezcla de 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina (0.411 g, 1.11 mmol), 4-(4,4,5,5-Tetrametil-1,3,2-dioxaborolan-2-il)anilina (0.366 g, 1.67 mmol) y carbonato de sodio (0.233 mL, 5.56 mmol) en 18% DMF en una mezcla de 7:3:2 DME:agua:etanol (100mL) a RT bajo nitrógeno. La solución resultante fue agitada a 90 °C durante 5 horas. La reacción fue enfriada y diluida con etil acetato y agua. La mezcla de reacción fue extraída con etil acetato y los productos orgánicos combinados secados ($MgSO_4$), filtrados y evaporados. El producto crudo fue cromatografiado en sílice, eluyendo con 0 – 5% metanol en DCM, para dar el material deseado como un sólido blanco (0.453 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19-1.20(3H, d), 3.12-3.19(1H, td), 3.44-3.50(1H, td), 3.61-3.64(1H, dd), 3.74-3.77(1H, d), 3.95-3.98(1H, dd), 4.07-4.11(1H, d), 4.37(1H, bs), 4.83(2H, s), 5.50-5.52(2H, d), 6.45-6.47(2H, d), 6.60(1H, s), 7.48-7.50(2H, d), 7.80-7.81(2H, q), 8.89-8.90(2H, q).

Espectro LCMS: MH+ 426 tiempo de retención 1.80 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina



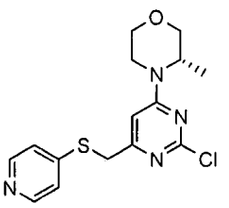
Una solución de peróxido de hidrógeno (1.799 mL, 58.19 mmol) fue añadida en forma de gotas a una solución agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfanilmetil)pirimidina (0.980 g, 2.91 mmol), tungstato dihidrato de sodio (0.005 mL, 0.06 mmol) y ácido sulfúrico 2N (0.075 mL) en dioxano (200 mL) a 55°C, durante un período de 5 minutos al aire. La solución resultante fue agitada a 55 °C durante 3 horas. Agua (200 mL) fue añadida y la reacción fue enfriada, los sólidos filtrados, lavados con agua y secados en el horno de vacío a 50°C toda la noche para dar el material deseado como un sólido blanco

(0.580 g). Material adicional fue obtenido extrayendo la capa acuosa con DCM. Los extractos fueron secados ($MgSO_4$), filtrados, evaporados y cromatografiados en sílice, eluyendo con 0 – 3% metanol en DCM, para dar una porción adicional del material deseado (0.144 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.17–1.19(3H, d), 3.14–3.22(1H, td), 3.40–3.47(1H, td), 3.56–3.60(1H, dd), 3.71–3.74(1H, d), 3.90(1H, bs), 3.91–3.95(1H, dd), 4.20(1H, bs), 4.79(2H, s), 6.79(1H, s), 7.77–7.79(2H, q), 8.92–8.93(2H, q).

Espectro LCMS: MH+ 369 tiempo de retención 1.39 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfanilmetil)pirimidina

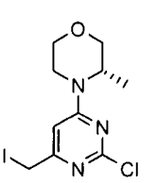


4–Mercaptopiridina (0.752 g, 6.77 mmol) fue añadida a 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.596 g, 4.51 mmol) en acetonitrilo (100 mL) a RT al aire. DBU (0.3 mL, 2.01 mmol) fue luego añadido y la solución resultante fue agitada a RT durante 2 minutos. El solvente fue eliminado y DCM fue añadido. La mezcla de reacción fue lavada secuencialmente con agua, la capa orgánica secada ($MgSO_4$), filtrada y evaporada. El producto crudo fue cromatografiado en sílice, eluyendo con 0 – 2% metanol en DCM. Las fracciones impuras fueron cromatografiadas adicionalmente en sílice, eluyendo con 0 – 4.5% metanol en DCM y combinadas con las fracciones puras iniciales para dar el material deseado como una goma amarilla (0.980 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.14–1.16(3H, d), 3.11–3.18(1H, td), 3.37–3.44(1H, td), 3.53–3.57(1H, dd), 3.64–3.67(1H, d), 3.86–3.90(2H, dd), 4.01(2H, s), 4.14(1H, bs), 6.43(1H, s), 7.04–7.06(2H, d), 8.29–8.30(2H, d).

Espectro LCMS: MH+ 337 tiempo de retención 1.62 min.

2–Cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina

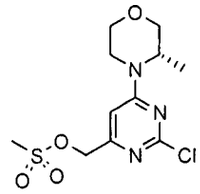


Yoduro de sodio (1.006 ml, 24.61 mmol) fue añadido a 2–cloro–4–[(3S)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidina (1.584 g, 4.92 mmol) en DCM a RT. La solución resultante fue refluida a 40°C durante 18 horas. La mezcla de reacción fue diluida con DCM y lavada con agua. La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto deseado (1.596 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.27–1.28(3H, d), 3.20–3.27(1H, td), 3.46–3.53(1H, td), 3.62–3.65(1H, dd), 3.72–3.75(1H, d), 3.93–3.97(2H, dd), 4.17(2H, s), 4.26(1H, bs), 6.41(1H, s).

Espectro LCMS: MH+ 354 tiempo de retención 1.85 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidina



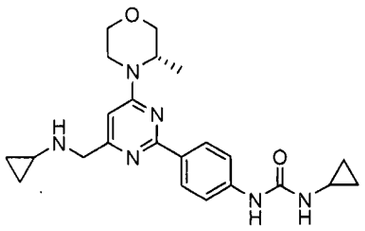
Metanosulfonil cloruro (0.488 mL, 6.31 mmol) fue añadido en forma de gotas a [2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol (1.025 g, 4.21 mmol), y trietilamina (0.880 mL, 6.31 mmol) en DCM a 0°C durante un período de 2 minutos. La solución resultante se dejó calentar gradualmente hasta RT durante un período de 2 horas. La mezcla de reacción fue diluida con DCM (50 mL), y lavada con agua. La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado (1.584 g) el cual fue usado sin purificación adicional.

Espectro LCMS: MH+ 322 tiempo de retención 1.60 min.

La preparación de [2–cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metanol fue descrita anteriormente.

Ejemplo 49:

3–Ciclopropil–1–[4–[4–[(ciclopropilamino)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea

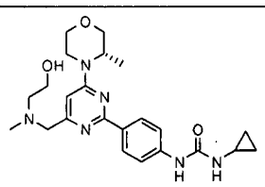
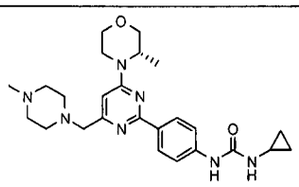


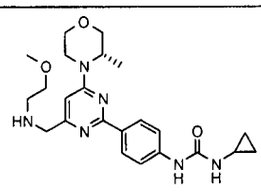
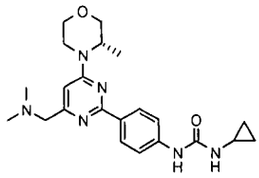
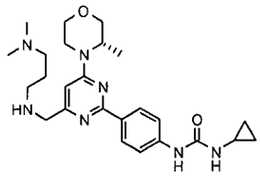
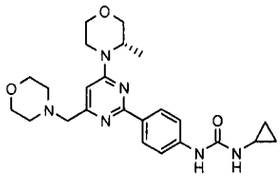
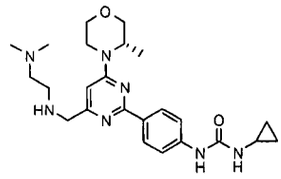
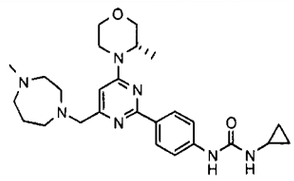
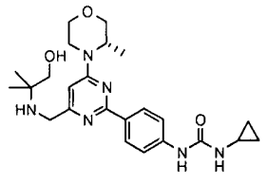
3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (107 mg, 0.23 mmol) fue disuelta en DCM (5 mL) y añadida a ciclopropilamina (1.16 mmol). Trietilamina (0.162 mL, 1.16 mmol) fue añadida a la solución y agitada a RT durante 18 horas. La reacción fue evaporada hasta secarse y purificada por HPLC prep. (básica) para dar el material deseado como un sólido blanco (27 mg).

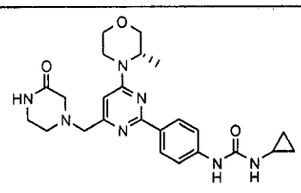
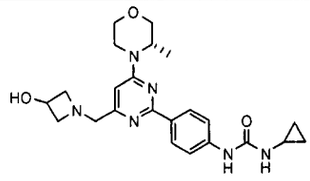
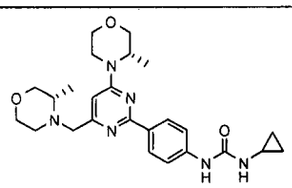
Espectro NMR: 1H NMR (400.13 MHz, DMSO-d_6) δ 0.29 – 0.31 (2H, m), 0.34 – 0.44 (4H, m), 0.62 – 0.67 (2H, m), 1.21 – 1.27 (3H, m), 2.13 – 2.17 (1H, m), 2.53 – 2.58 (1H, m), 3.14 – 3.21 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.71 (2H, d), 3.75 (1H, s), 3.95 – 3.99 (1H, m), 4.14 – 4.17 (1H, m), 4.49 – 4.51 (1H, m), 6.46 (1H, d), 6.65 (1H, s), 7.47 – 7.50 (2H, m), 8.21 – 8.23 (2H, m), 8.55 (1H, s).

Espectro de masa: $M+H^+$ 423.

Los siguientes compuestos fueron hechos de una forma análoga a partir de 3-ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+
49a		3-ciclopropil-1-[4-[4-[(2-hidroxietil-metil-amino)metil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	441
49b		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[(4-metilpiperazin-1-il)metil]pirimidin-2-il]fenil]urea	466

Ejemplo	Estructura	NOMBRE	LCMS MH+
49c		3–ciclopropil–1–[4–[4–[(2–metoxietilamino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	441
49d		3–ciclopropil–1–[4–[4–(dimetilaminometil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	411
49e		3–ciclopropil–1–[4–[4–[(3–dimetilaminopropilamino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	468
49f		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(morfolin–4–ilmetil)pirimidin–2–il]fenil]urea	453
49g		3–ciclopropil–1–[4–[4–[(2–dimetilaminoetilamino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	454
49h		3–ciclopropil–1–[4–[4–[(4–metil–1,4–diazepan–1–il)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	480
49i		3–ciclopropil–1–[4–[4–[[(1–hidroxi–2–metil–propan–2–il)amino]metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	455

Ejemplo	Estructura	NOMBRE	LCMS MH+
49j		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(3–oxopiperazin–1–il)metil]pirimidin–2–il]fenil]urea	456
49k		3–ciclopropil–1–[4–[4–[(3–hidroxiazetidin–1–il)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	439
49l		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[[(3S)–3–metilmorfolin–4–il]metil]pirimidin–2–il]fenil]urea	467

Ejemplo 49a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 – 1.27 (3H, m), 2.30 (3H, s), 2.53 – 2.58 (1H, m), 3.14 – 3.21 (1H, m), 3.46 – 3.58 (7H, m), 3.62 – 3.66 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.15 – 4.18 (1H, m), 4.45 (1H, t), 4.48 (1H, s), 6.42 (1H, d), 6.73 (1H, s), 7.47 – 7.49 (2H, m), 8.19 – 8.21 (2H, m), 8.50 (1H, s).

Ejemplo 49b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 (3H, d), 2.17 (3H, s), 2.30 – 2.37 (8H, m), 2.53 – 2.58 (1H, m), 3.14 – 3.21 (1H, m), 3.47 – 3.50 (3H, m), 3.63 – 3.66 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.12 – 4.15 (1H, m), 4.45 – 4.47 (1H, m), 6.43 (1H, d), 6.61 (1H, s), 7.46 – 7.50 (2H, m), 8.19 – 8.21 (2H, m), 8.51 (1H, s).

Ejemplo 49c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 – 1.26 (3H, m), 3.14 – 3.22 (1H, m), 3.26 (3H, s), 3.39 – 3.49 (5H, m), 3.62 – 3.66 (2H, m), 3.67 (2H, s), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.16 (1H, d), 4.48 (1H, s), 6.54 (1H, s), 6.66 (1H, s), 7.50 (2H, d), 8.19 (2H, q), 8.62 (1H, s).

Ejemplo 49d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 – 1.22 (3H, m), 2.25 (6H, s), 2.52 – 2.57 (1H, m), 3.17 (1H, d), 3.42 (2H, s), 3.46 – 3.50

(1H, m), 3.62 – 3.66 (1H, m), 3.75 (1H, d), 3.95 – 3.98 (1H, m), 4.14 – 4.18 (1H, m), 4.46 – 4.48 (1H, m), 6.44 (1H, d), 6.61 (1H, s), 7.47 – 7.50 (2H, m), 8.19 – 8.22 (2H, m), 8.53 (1H, s).

Ejemplo 49e: ningún espectro

Ejemplo 49f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 (3H, d), 2.52 – 2.57 (1H, m), 3.14 – 3.21 (1H, m), 3.49 (2H, s), 3.50 (2H, t), 3.63 (7H, m), 3.66 (1H, d), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.13 – 4.16 (1H, m), 4.49 (1H, d), 6.42 (1H, d), 6.64 (1H, s), 7.47 – 7.49 (2H, m), 8.19 – 8.21 (2H, m), 8.51 (1H, s).

Ejemplo 49g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.22 (3H, d), 2.13 (6H, s), 2.32 – 2.35 (2H, m), 2.52 – 2.57 (1H, m), 2.62 (2H, t), 3.14 – 3.22 (1H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.67 (3H, s), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.14 – 4.18 (1H, m), 4.49 (1H, s), 6.42 (1H, d), 6.65 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.50 (1H, s).

Ejemplo 49h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.24 (3H, d), 1.46 (1H, d), 1.73 – 1.77 (2H, m), 2.27 (4H, s), 2.37 (1H, d), 2.43 (1H, s), 2.56 – 2.61 (2H, m), 2.73 – 2.76 (3H, m), 3.14 – 3.21 (1H, m), 3.47 – 3.53 (1H, m), 3.59 – 3.68 (3H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.14 – 4.17 (1H, m), 4.45 (1H, s), 6.43 (1H, d), 6.65 (1H, s), 7.47 – 7.49 (2H, m), 8.19 – 8.21 (2H, m), 8.51 (1H, s)

Ejemplo 49i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.01 (6H, s), 1.21 – 1.27 (3H, m), 1.36 (1H, t), 2.07 (1H, t), 2.52 – 2.57 (1H, m), 3.15 – 3.21 (1H, m), 3.23 (2H, d), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (3H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.12 – 4.16 (1H, m), 4.50 – 4.52 (1H, m), 6.49 (1H, s), 6.69 (1H, s), 7.47 – 7.50 (2H, m), 8.16 – 8.22 (2H, m), 8.56 (1H, s),

Ejemplo 49j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.21 – 1.27 (3H, m), 2.53 – 2.58 (1H, m), 2.68 (2H, q), 3.09 (2H, s), 3.18 (1H, t), 3.20 (2H, t), 3.46 – 3.53 (1H, m), 3.57 (2H, s), 3.62 – 3.66 (1H, m), 3.75 (1H, d), 3.95 – 3.99 (1H, m), 4.15 – 4.18 (1H, m), 4.48 – 4.51 (1H, m), 6.44 (1H, d), 6.63 (1H, s), 7.48 – 7.50 (2H, m), 7.74 (1H, s), 8.19 – 8.22 (2H, m), 8.53 (1H, s),

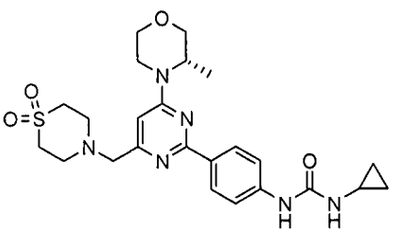
Prueba (a): Ejemplo (49) 0.033 μM; Ejemplo (49a) 0.15 μM; Ejemplo (49b) 0.014 μM; Ejemplo (49c) 0.04 μM; Ejemplo (49e) 0.032 μM; Ejemplo (49f) 0.2 μM; Ejemplo (49g0 0.087 μM; Ejemplo (49h) 0.18 μM; Ejemplo (49i) 0.016 μM; Ejemplo (49k) 0.014 μM; Ejemplo (49l) 1.6 μM.

Prueba (c): Ejemplo (49d) 0.62 μM; Ejemplo (49j) 0.13 μM.

La preparación de 3–ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea fue descrita anteriormente.

Ejemplo 50:

3–Ciclopropil–1–[4–[4–[(1,1–dioxo–1,4–tiazinan–4–il)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



3–Ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea (107 mg, 0.23 mmol) fue disuelta en DCM (5 mL) y añadida a tiomorfolina (1.16 mmol). Trietilamina (0.162 mL, 1.16 mmol) fue añadida a la solución y agitada a RT durante 18 horas. La reacción fue evaporada hasta secarse y disuelta en una mezcla de 1,4–dioxano (4 mL) y agua (1 mL). Ácido meta–cloroperbenzoico (100 mg, 0.58 mmol) y permanganato de sodio (110 mg, 0.69 mmol) fueron añadidos en porciones simples a la solución y esta agitada a RT durante 1 hora. La solución cruda fue cargada en una columna SCX–2, eliminada con amoniaco 7N en metanol y evaporada hasta secarse. El sólido fue purificado por HPLC prep. (básica) para dar el material deseado como un sólido blanco (11 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.22 (3H, d), 2.53 – 2.58 (1H, m), 3.00 (1H, s), 3.02 (3H, t), 3.15 – 3.22 (5H, m), 3.50 (1H, d), 3.63 – 3.67 (1H, m), 3.70 (2H, s), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.18 (1H, s), 4.53 (1H, s), 6.42 (1H, d), 6.70 (1H, s), 7.47 – 7.50 (2H, m), 8.19 – 8.21 (2H, m), 8.50 (1H, s).

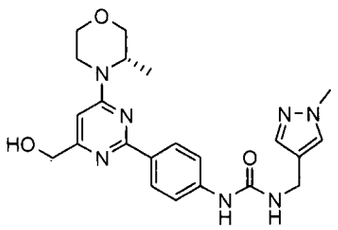
Espectro de masa: M+H$^+$ 501.

Prueba (a): 0.0016 μM.

La preparación de 3–ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea fue descrita anteriormente.

Ejemplo 51:

1-[4-[4-(Hidroximetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea



[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (1.00 g, 4.10 mmol) fue añadido a 3-[(1-metilpirazol-4-il)metil]-1-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]urea (2.193 g, 6.16 mmol) y carbonato de sodio (8.21 mL, 16.41 mmol) en 18% DMF en DME:EtOH:Agua 7:2:3 (18 mL) y la solución fue desgasificada durante 5 minutos. Diclorobis(trifenilfosfina)paladio(II) (0.144 g, 0.21 mmol) fue añadido a la mezcla. La solución resultante fue agitada a 85°C durante 18 horas. La reacción se dejó enfriar y fue neutralizada con ácido clorhídrico concentrado. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX -2 (50g), luego fue adicionalmente purificado por cromatografía flash en sílice, gradiente de elución 0 a 7% metanol en DCM, para dar el material deseado como un sólido blanco (963 mg).

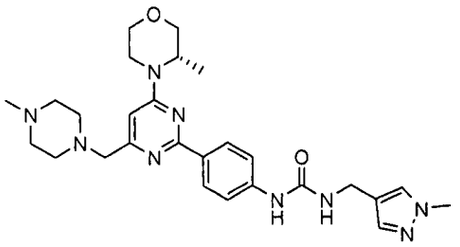
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 3.19 – 3.23 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.78 (1H, d), 3.79 (3H, s), 3.96 – 3.99 (1H, m), 4.13 (3H, d), 4.45 – 4.50 (3H, m), 5.38 (1H, t), 6.39 (1H, t), 6.66 (1H, s), 7.35 (1H, s), 7.45 – 7.49 (2H, m), 7.59 (1H, s), 8.19 – 8.21 (2H, m), 8.64 (1H, s), m/z

Espectro LCMS: MH+ 438, tiempo de retención 1.37 minutos.

Las preparaciones de [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (1.00 g, 4.10 mmol) y 3-[(1-metilpirazol-4-il)metil]-1-[4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil]urea fueron descritas anteriormente.

Ejemplo 52:

1-[4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[(4-metilpiperazin-1-il)metil]pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea

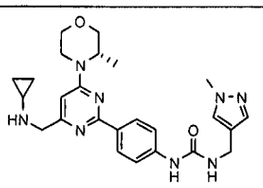


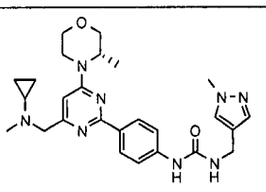
1-Metilpiperazina (0.067 mL, 0.60 mmol) fue añadida a una solución de trietilamina (0.084 mL, 0.60 mmol) y 1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea (155 mg, 0.30 mmol) en DCM (5 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 18 horas. La mezcla de reacción fue evaporada. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (65 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.17 (3H, s), 2.35 (8H, s), 3.14 – 3.21 (1H, m), 3.47 – 3.50 (3H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, s), 3.79 (3H, s), 3.95 – 3.99 (1H, m), 4.13 (3H, d), 4.46 (1H, d), 6.42 (1H, t), 6.61 (1H, s), 7.35 (1H, s), 7.47 (2H, d), 7.59 (1H, s), 8.20 (2H, d), 8.66 (1H, s).

Espectro LCMS: MH+ 520, tiempo de retención 1.49 minutos.

Los siguientes compuestos fueron preparados de una forma análoga a partir de 1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
52a		1-[4-[4-[(ciclopropilamino)metil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea	477	1.66

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
52b		1–[4–[4–[(ciclopropil–metil–amino)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea	491	1.89

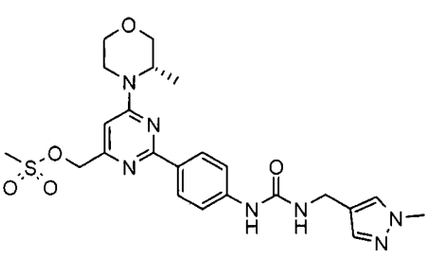
Ejemplo 52a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.28 – 0.33 (2H, m), 0.37 – 0.39 (1H, m), 1.21 – 1.26 (3H, m), 1.36 (1H, t), 2.13 – 2.17 (1H, m), 2.82 (1H, s), 3.14 – 3.21 (1H, m), 3.43 – 3.51 (1H, m), 3.62 – 3.65 (1H, m), 3.71 (2H, d), 3.77 – 3.79 (4H, m), 3.95 – 3.99 (1H, m), 4.12 – 4.17 (3H, m), 4.50 (1H, d), 6.55 (1H, s), 6.64 (1H, s), 7.35 (1H, s), 7.48 (2H, d), 7.59 (1H, s), 8.17 – 8.23 (2H, m), 8.79 (1H, s).

Ejemplo 52b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 (2H, t), 0.44 – 0.49 (2H, m), 1.20 (3H, d), 1.89 – 1.94 (1H, m), 2.33 (3H, s), 3.16 – 3.20 (2H, m), 3.45 – 3.52 (1H, m), 3.65 (3H, d), 3.79 (3H, s), 3.94 – 3.98 (1H, m), 4.13 (3H, d), 4.46 (1H, s), 6.40 (1H, t), 6.52 (1H, s), 7.35 (1H, s), 7.46 – 7.49 (2H, m), 7.59 (1H, s), 8.21 (2H, d), 8.64 (1H, s).

Prueba (a): Ejemplo (52) 1.4 μM; Ejemplo (52a) 0.33 μM; Ejemplo (52b) 0.57 μM.

La preparación de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea es descrita a continuación

1–[4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea



Metanosulfonil cloruro (0.246 mL, 3.15 mmol) fue añadido en forma de gotas durante un período de 10 minutos a una solución de trietilamina (0.440 mL, 3.15 mmol) y 1–[4–[4–

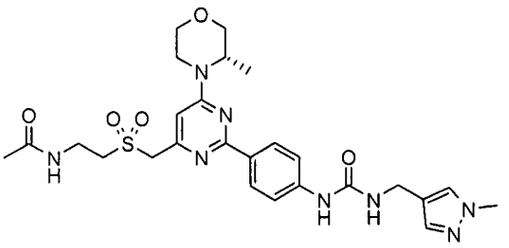
(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea (920 mg, 2.10 mmol) en DCM (30 mL) a 0°C bajo nitrógeno. La solución resultante fue agitada a 20°C durante 45 minutos. La mezcla de reacción fue lavada con agua (10 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado el cual fue usado sin purificación adicional.

Espectro LCMS: MH+ 516, tiempo de retención 1.72 min.

La preparación de –[4–[4–(hidroximetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea fue descrita anteriormente.

Ejemplo 53:

***N*–[2–[[6–[(3*S*)–3–metilmorfolin–4–il]–2–[4–[(1–metilpirazol–4–il)metilcarbamoilamino]fenil]pirimidin–4–il]metilsulfonil]etil]acetamida**



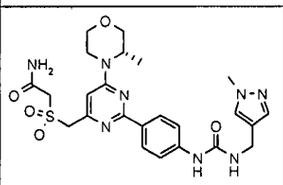
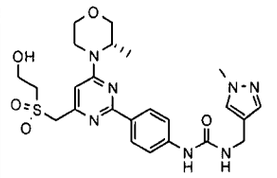
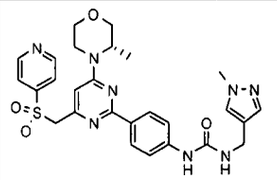
Ácido meta–cloroperbenzoico (156 mg, 0.90 mmol) disuelto en Dioxano (2 mL), y monohidrato de permanganato de sodio (192 mg, 1.20 mmol) disuelto en agua (1 mL) fueron añadidos en forma de gotas a *N*–[2–[[6–[(3*S*)–3–metilmorfolin–4–il]–2–[4–[(1–metilpirazol–4–il)metilcarbamoilamino]fenil]pirimidin–4–il]metilsulfanil]etil]acetamida (162 mg, 0.30 mmol) en dioxano (6 mL) y agua (2 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 1 hora. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol y las fracciones puras fueron evaporadas hasta secarse. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (61 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.83 (3H, s), 3.18 (1H, m), 3.50 – 3.58 (6H, m), 3.66 – 3.67 (1H, m), 3.76 (1H, s), 3.80 (3H, s), 3.97 (1H, s), 4.13

(2H, d), 4.51 (3H, m), 6.40 (1H, d), 6.78 (1H, s), 7.35 (1H, s), 7.48 – 7.51 (2H, m), 7.59 (1H, s), 8.15 (1H, s), 8.21 (2H, d), 8.69 (1H, s).

Espectro LCMS: MH+ 571, tiempo de retención 1.42 min.

Los siguientes compuestos fueron preparados de una forma análoga a partir de los sulfuros apropiados.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
53a		2–[[6–[(3S)–3–metilmorfolin–4–il]–2–[4–[(1–metilpirazol–4–il)metilcarbamoilamino]fenil]pirimidin–4–il]metilsulfonil]acetamida	543	1.40
53b		1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea	530	1.43
52c		1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea	563	1.63

Ejemplo 53a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.19 – 3.25 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 – 4.00 (1H, m), 4.13 (3H, d), 4.27 (2H, s), 4.48 (1H, s), 4.67 (2H, s), 6.42 (1H, t), 6.76 (1H, s), 7.35 (1H, s), 7.48 – 7.52 (3H, m), 7.59 (1H, s), 7.79 (1H, s), 8.20 (2H, d), 8.69 (1H, s).

Ejemplo 53b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24 (3H, d), 3.22 (1H, d), 3.51 (3H, t), 3.63 – 3.67 (1H, m), 3.80 (4H, s), 3.92 (2H, q), 3.97 – 4.01 (1H, m), 4.13 (3H, d), 4.50 (3H,

s), 5.18 (1H, t), 6.42 (1H, t), 6.76 (1H, s), 7.35 (1H, s), 7.49 – 7.51 (2H, m), 7.59 (1H, s), 8.22 (2H, d), 8.68 (1H, s).

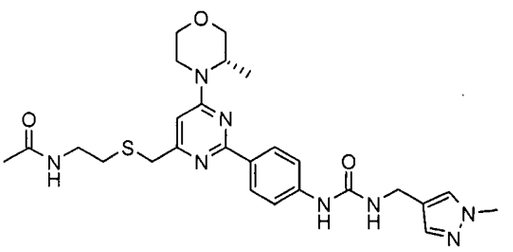
Ejemplo 53c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.20 – 1.26 (3H, m), 3.15 – 3.22 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.78 (1H, s), 3.80 (3H, s), 3.95 – 3.99 (1H, m), 4.12 (3H, d), 4.39 (1H, s), 4.87 (2H, s), 6.39 (1H, t), 6.71 (1H, s), 7.34 – 7.39 (3H, m), 7.59 (1H, s), 7.66 (2H, d), 7.81 – 7.82 (2H, m), 8.64 (1H, s), 8.90 – 8.91 (2H, m).

Prueba (a): Ejemplo (53) 0.64 μM; Ejemplo (53a) 0.6 μM; Ejemplo (53c) 0.03 μM.

Prueba (c): Ejemplo (53b) 3 μM.

La preparación de *N*–[2–[[6–[(3*S*)–3–metilmorfolin–4–il]–2–[4–[(1–metilpirazol–4–il)metilcarbamoilamino]fenil]pirimidin–4–il]metilsulfanil]etil]acetamida es descrita a continuación.

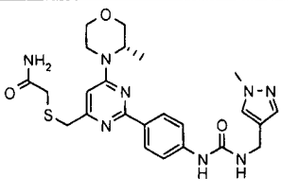
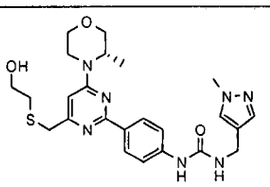
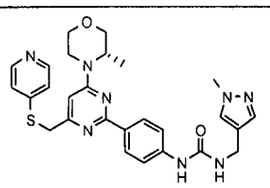
N–[2–[[6–[(3*S*)–3–Metilmorfolin–4–il]–2–[4–[(1–metilpirazol–4–il)metilcarbamoilamino]fenil]pirimidin–4–il]metilsulfanil]etil]acetamida



N–Acetilcisteamina (0.056 mL, 0.53 mmol) fue añadida a DBU (0.091 mL, 0.60 mmol) y 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea (155 mg, 0.30 mmol) en acetonitrilo (4 mL) bajo nitrógeno. La solución resultante fue agitada a RT durante 5 horas. La mezcla de reacción fue evaporada para dar el material deseado el cual fue usado sin purificación adicional.

Espectro LCMS: MH+ 539, tiempo de retención 1.66 min.

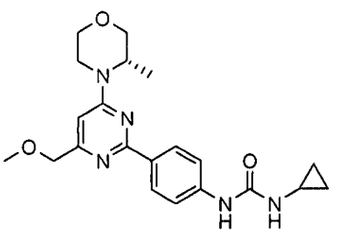
Los siguientes sulfuros fueron preparados de una forma análoga a partir de 1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]–3–[(1–metilpirazol–4–il)metil]urea y el tiol apropiado.

Estructura	NOMBRE
	2-[[6-[(3S)-3-metilmorfolin-4-il]-2-[4-[(1-metilpirazol-4-il)metilcarbamoilamino]fenil]pirimidin-4-il]metilsulfanil]acetamida
	1-[4-[4-(2-hidroxietilsulfanilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea
	1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfanilmetil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea

La preparación de 1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea fue descrita anteriormente.

Ejemplo 54:

3-Ciclopropil-1-[4-[4-(metoximetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfoniloximetil)pirimidin-2-il]fenil]urea (75 mg, 0.16 mmol) y carbonato de potasio (90 mg, 0.65 mmol) fueron suspendidos en metanol (3 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 100°C durante 10 minutos en el reactor de microondas y enfriada hasta RT. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol. El producto crudo fue adicionalmente purificado por HPLC preparativa usando mezclas polares

decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (15 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.22 (3H, d), 2.54 – 2.58 (1H, m), 3.18 – 3.23 (1H, m), 3.40 (3H, s), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.75 (1H, d), 3.95 – 3.98 (1H, m), 4.16 – 4.19 (1H, m), 4.39 (2H, s), 4.50 (1H, s), 6.42 (1H, d), 6.57 (1H, s), 7.47 – 7.50 (2H, m), 8.19 – 8.21 (2H, m), 8.51 (1H, s).

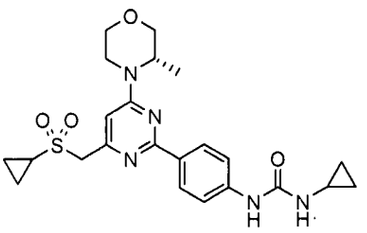
Espectro LCMS: MH+ 398, tiempo de retención 1.86 min.

Prueba (c): 0.11 μM

La preparación de 3–ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(metilsulfoniloximetil)pirimidin–2–il]fenil]urea fue descrita anteriormente.

Ejemplo 55:

3–Ciclopropil–1–[4–[4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea



Ácido [4–(3–ciclopropilureido)fenil]borónico pinacol éster (80 mg, 0.26 mmol), carbonato de sodio (1.055 mL, 2.11 mmol), diclorobis(trifenilfosfina)paladio(II) (14.8 mg, 0.02 mmol) y 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (70 mg, 0.21 mmol) fueron suspendidos en 18% DMF en una mezcla de DME:Etanol:Agua 7:2:3 (4 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 100°C durante 10 minutos en el reactor de microondas y enfriada hasta RT. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol. El producto crudo fue adicionalmente purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como una goma incolora (33.0 mg).

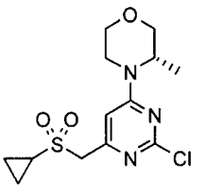
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.41 – 0.43 (2H, m), 0.64 – 0.66 (2H, m), 0.98 – 1.01 (2H, m), 1.04 – 1.08 (2H, m), 1.24 (3H, d), 2.56 (1H, s), 2.86 (1H, d), 3.18 (1H, d), 3.50 (1H, d), 3.67 (1H, d), 3.76 – 3.79 (1H, m), 4.50 (2H, s), 6.43 (1H, d), 6.77 (1H, s), 7.49 – 7.51 (2H, m), 7.55 – 7.57 (1H, m), 7.60 – 7.65 (2H, m), 8.21 – 8.23 (2H, m), 8.53 (1H, s).

Espectro LCMS: MH+ 472, tiempo de retención 1.80 min.

Prueba (a): 0.062 μM.

La preparación de 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina es descrita a continuación.

2–Cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



Sal sódica del ácido ciclopropanosulfínico (381 mg, 2.97 mmol) fue añadida en una porción a 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (700 mg, 1.98 mmol) en acetonitrilo (20 mL) a RT. La suspensión resultante fue agitada a 90 °C durante 3 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en DCM (50 mL), y lavada con agua (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 40% etil acetato en DCM, para dar el material deseado como un sólido blanco (458 mg).

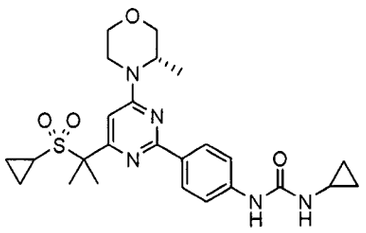
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.95 – 0.98 (2H, m), 1.02 – 1.06 (2H, m), 1.18 – 1.23 (3H, m), 2.77 – 2.83 (1H, m), 3.19 – 3.25 (1H, m), 3.42 – 3.49 (1H, m), 3.58 – 3.62 (1H, m), 3.73 (1H, d), 3.92 – 3.96 (2H, m), 4.30 (1H, s), 4.48 (2H, s), 6.92 (1H, s).

Espectro LCMS: MH+ 332, tiempo de retención 1.68 min.

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

Ejemplo 56:

3-Ciclopropil-1-[4-[4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Ácido [4-(3-ciclopropilureido)fenil]borónico pinacol éster (199 mg, 0.66 mmol), 2-cloro-4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (190 mg, 0.53 mmol), carbonato de sodio (1.320 mL, 2.64 mmol) y diclorobis(trifenilfosfina)paladio(II) (37.1 mg, 0.05 mmol) fueron suspendidos en 18% DMF en una solución de DME:Agua:EtOH 7:3:2 (4 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 100°C durante 20 minutos en el reactor de microondas y enfriada hasta RT. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol y las fracciones puras fueron evaporadas hasta secarse. El producto crudo fue adicionalmente purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (85 mg).

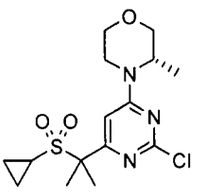
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 0.78 – 0.83 (1H, m), 0.81 (1H, d), 0.95 (2H, d), 1.23 (3H, d), 1.81 (6H, d), 2.56 (1H, q), 2.73 – 2.77 (1H, m), 3.20 – 3.24 (1H, m), 3.48 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.20 – 4.23 (1H, m), 4.57 – 4.59 (1H, m), 6.42 (1H, d), 6.77 (1H, s), 7.49 – 7.51 (2H, m), 8.23 – 8.25 (2H, m), 8.52 (1H, s).

Espectro LCMS: MH+ 500, tiempo de retención 2.04 min.

Prueba (a): 2.4 μM.

La preparación de 2-cloro-4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidina es descrita a continuación.

2-Cloro-4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



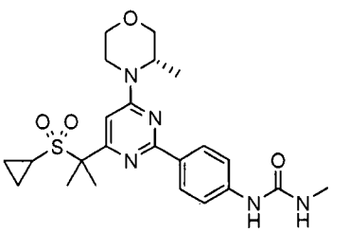
Yodometano (0.033 mL, 0.53 mmol) fue añadido a *tert*–butóxido de sodio (50.7 mg, 0.53 mmol) y 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (175 mg, 0.53 mmol) en DMF (2 mL) a –10°C. La suspensión densa resultante fue agitada a RT durante 15 minutos para facilitar la agitación. Yodometano (0.033 mL, 0.53 mmol) y *tert*–butóxido de sodio (50.7 mg, 0.53 mmol) fueron nuevamente añadidos a la reacción y la suspensión resultante agitada a RT durante15 minutos. La mezcla de reacción fue diluida con DCM (20 mL) y lavada con agua (20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado (153 mg).

Espectro LCMS: MH+ 360, tiempo de retención 2.13 min.

La preparación de 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

Ejemplo 57:

1–[4–[4–(2–Ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea



Metilamina (0.699 mL, 1.40 mmol) fue añadida a fenil *N*–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (150 mg, 0.28 mmol) y trietilamina (0.117 mL, 0.84 mmol) en DMF (2 mL). La solución resultante fue agitada a 40°C durante 2 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo

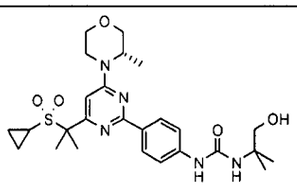
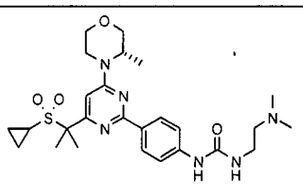
1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (74.0 mg).

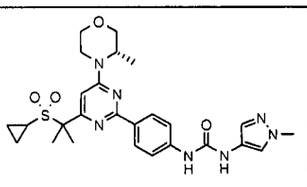
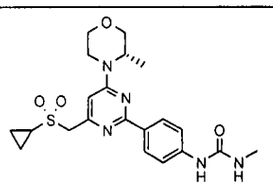
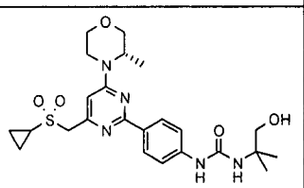
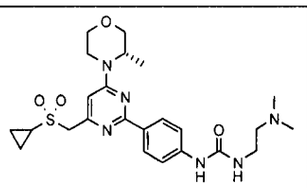
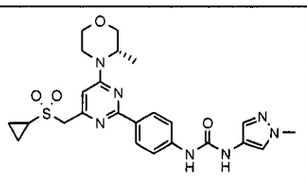
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.77 – 0.85 (2H, m), 0.91 – 0.98 (2H, m), 1.22 – 1.23 (3H, m), 1.81 (6H, d), 2.67 (3H, t), 2.72 – 2.78 (1H, m), 3.20 – 3.24 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.20 – 4.23 (1H, m), 4.57 – 4.59 (1H, m), 6.06 (1H, q), 6.77 (1H, s), 7.48 – 7.52 (2H, m), 8.22 – 8.25 (2H, m), 8.72 (1H, s).

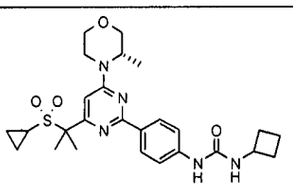
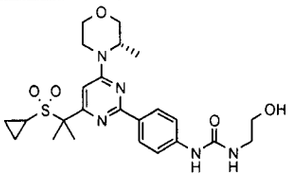
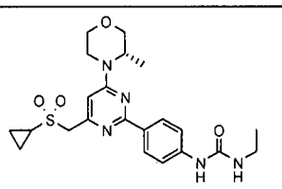
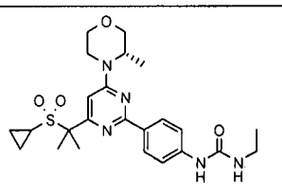
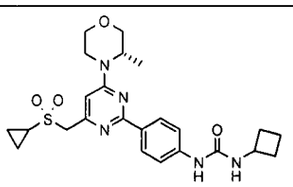
Espectro LCMS: MH+ 474, tiempo de retención 1.92 min.

Prueba (c): Ejemplo (57) 0.25 μM; Ejemplo (57a) 0.064 μM; Ejemplo (57b) 0.089 μM; Ejemplo (57c) 0.36 μM; Ejemplo (57d) 0.84 μM; Ejemplo (57e) 0.38 μM; Ejemplo (57f) 0.72 μM; Ejemplo (57g) 0.095 μM; Ejemplo (57h) 0.066 μM; Ejemplo (57i) 0.27 μM; Ejemplo (57j) 0.07 μM; Ejemplo (57k) 0.34 μM; Ejemplo (57l) 0.088μM.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
57a		1–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1–hidroxi–2–metil–propan–2–il)urea	532	2.03
57b		1–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	531	2.00

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
57c		1–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1–metilpirazol–4–il)urea	540	1.93
57d		1–[4–[4–(ciclopropilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	446	1.56
57e		1–[4–[4–(ciclopropilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1–hidroxi–2–metil–propan–2–il)urea	504	1.70
57f		1–[4–[4–(ciclopropilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	503	1.66
57g		1–[4–[4–(ciclopropilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(1–metilpirazol–4–il)urea	512	1.63

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
57h		3-ciclobutil-1-[4-[4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	514	2.28
57i		1-[4-[4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	504	1.72
57j		1-[4-[4-(ciclopropilsulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etil-urea	460	1.71
57k		1-[4-[4-(2-ciclopropilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etil-urea	488	2.04
57l		3-ciclobutil-1-[4-[4-(ciclopropilsulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	486	1.96

Ejemplo 57a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.79 – 0.83 (2H, m), 0.94 – 0.97 (2H, m), 1.22 (3H, d), 1.24 (6H, s), 1.81 (6H, d), 2.74 – 2.78 (1H, m), 3.21 (1H, t), 3.39 (2H, d), 3.50 (1H, d), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.20 – 4.23 (1H, m), 4.56 – 4.59 (1H, m), 4.95 (1H, t), 6.00 (1H, s), 6.76 (1H, s), 7.44 – 7.46 (2H, m), 8.22 (2H, d), 8.72 (1H, s).

Ejemplo 57b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.79 – 0.84 (2H, m), 0.95 (2H, d), 1.23 (3H, d), 1.81 (6H, d), 2.18 (6H, s), 2.34 (2H, t), 2.73 – 2.77 (1H, m), 3.17 – 3.23 (3H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.19 – 4.23 (1H, m), 4.58 (1H, d), 6.15 (1H, t), 6.77 (1H, s), 7.47 – 7.50 (2H, m), 8.22 – 8.24 (2H, m), 8.88 (1H, s).

Ejemplo 57c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.81 – 0.83 (2H, m), 0.96 (2H, d), 1.22 – 1.24 (3H, m), 1.82 (6H, d), 2.73 – 2.77 (1H, m), 3.21 – 3.25 (1H, m), 3.47 – 3.51 (1H, m), 3.64 – 3.68 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.97 – 4.00 (1H, m), 4.22 (1H, d), 4.57 – 4.60 (1H, m), 6.78 (1H, s), 7.38 (1H, d), 7.53 – 7.56 (2H, m), 7.76 (1H, s), 8.27 (2H, d), 8.38 (1H, s), 8.82 (1H, s)

Ejemplo 57d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.97 – 1.01 (2H, m), 1.03 – 1.09 (2H, m), 1.23 – 1.25 (3H, m), 2.67 (3H, t), 2.83 – 2.90 (1H, m), 3.18 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.20 (1H, d), 4.50 (3H, m), 6.06 (1H, q), 6.77 (1H, s), 7.48 – 7.51 (2H, m), 8.20 – 8.23 (2H, m), 8.72 (1H, s).

Ejemplo 57e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.98 – 1.01 (2H, m), 1.05 – 1.09 (2H, m), 1.23 (3H, d), 1.25 (6H, s), 2.85 – 2.89 (1H, m), 3.18 (1H, d), 3.39 (2H, d), 3.47 – 3.51 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.15 – 4.18 (1H, m), 4.47 (1H, s), 4.50 (2H, s), 4.95 (1H, t), 6.00 (1H, s), 6.77 (1H, s), 7.43 – 7.47 (2H, m), 8.21 (2H, d), 8.72 (1H, s).

Ejemplo 57f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.99 – 1.01 (2H, m), 1.05 – 1.08 (2H, m), 1.24 (3H, d), 2.18 (6H, s), 2.34 (2H, t), 2.86 (1H, d), 3.17 (1H, d), 3.20 (2H, m), 3.51 (1H, s), 3.66 – 3.67 (1H, m), 3.76 – 3.79 (1H, m), 4.02 (1H, d), 4.20 (1H, d), 4.50 (3H, m), 6.15 (1H, s), 6.77 (1H, s), 7.47 – 7.49 (2H, m), 8.20 – 8.23 (2H, m), 8.88 (1H, s).

Ejemplo 57g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.99 – 1.02 (2H, m), 1.04 – 1.10 (2H, m), 1.25 (3H, d), 2.85 – 2.89 (1H, m), 3.18 (2H, m), 3.48 – 3.51 (1H, m), 3.64 – 3.68 (1H, m), 3.77 (1H, s), 3.79 (3H, s), 3.97 – 4.01 (1H, m), 4.48 (1H, s), 4.51 (2H, s), 6.78 (1H, d), 7.38 – 7.39 (1H, m), 7.53 – 7.55 (2H, m), 7.76 (1H, s), 8.24 – 8.27 (2H, m), 8.38 (1H, s), 8.82 (1H, s).

Ejemplo 57h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.77 – 0.84 (2H, m), 0.91 – 0.96 (2H, m), 1.22 – 1.23 (3H, m), 1.59 – 1.64 (2H, m), 1.80 (6H, s), 1.81 – 1.85 (2H, m), 2.17 – 2.25 (2H, m), 2.73 – 2.77 (1H, m), 3.16 – 3.24 (1H, m), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77

(1H, d), 3.96 – 4.00 (1H, m), 4.11 (1H, m), 4.19 (1H, m), 4.56 – 4.59 (1H, m), 6.46 (1H, d), 6.77 (1H, s), 7.46 – 7.49 (2H, m), 8.24 (2H, d), 8.55 (1H, s).

Ejemplo 57i: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.77 – 0.83 (2H, m), 0.94 (2H, t), 1.23 (3H, d), 1.81 (6H, d), 2.73 – 2.77 (1H, m), 3.18 (2H, d), 3.20 – 3.24 (1H, m), 3.46 (2H, q), 3.48 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.21 (1H, d), 4.58 (1H, d), 4.72 (1H, t), 6.25 (1H, t), 6.75 (1H, d), 7.47 – 7.50 (2H, m), 8.23 – 8.25 (2H, m), 8.79 (1H, s).

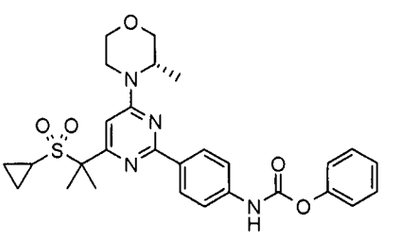
Ejemplo 57j: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.97 – 1.01 (2H, m), 1.03 – 1.10 (2H, m), 1.04 – 1.09 (3H, m), 1.23 – 1.25 (3H, m), 2.85 – 2.89 (1H, m), 3.09 – 3.16 (2H, m), 3.21 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.15 (1H, d), 4.50 (3H, m), 6.16 (1H, t), 6.77 (1H, s), 7.47 – 7.50 (2H, m), 8.20 – 8.23 (2H, m), 8.65 (1H, s).

Ejemplo 57k: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.78 – 0.83 (2H, m), 0.95 (2H, d), 1.07 (3H, t), 1.23 (3H, d), 1.81 (6H, d), 2.75 (1H, d), 3.15 (2H, d), 3.18 (1H, s), 3.50 (1H, d), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.19 – 4.23 (1H, m), 4.58 (1H, d), 6.16 (1H, t), 6.74 – 6.77 (1H, m), 7.48 – 7.50 (2H, m), 8.23 (2H, d), 8.65 (1H, s).

Ejemplo 57l: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.97 – 1.03 (2H, m), 1.03 – 1.09 (2H, m), 1.23 – 1.25 (3H, m), 1.57 – 1.66 (2H, m), 1.83 – 1.88 (2H, m), 2.17 – 2.24 (2H, m), 2.83 – 2.88 (1H, m), 3.21 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.14 (2H, m), 4.50 (3H, m), 6.45 (1H, d), 6.77 (1H, s), 7.45 – 7.49 (2H, m), 8.20 – 8.23 (2H, m), 8.55 (1H, s).

La preparación de fenil *N*–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

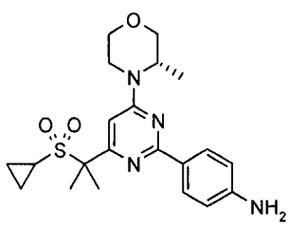


Fenil cloroformato (0.215 mL, 1.71 mmol) fue añadido en forma de gotas a 4–[4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (712 mg, 1.71 mmol) y bicarbonato de sodio (215 mg, 2.56 mmol) en dioxano (15 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en etil acetato (100 mL) y lavada con agua (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el material deseado (983 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.77 – 0.84 (2H, m), 0.95 (2H, t), 1.23 (3H, s), 1.82 (6H, d), 2.74 – 2.78 (1H, m), 3.18 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.64 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.80 (1H, s), 7.22 – 7.30 (3H, m), 7.40 – 7.48 (2H, m), 7.55 – 7.64 (2H, m), 8.35 (2H, d), 10.42 (1H, s).

Espectro LCMS: MH+ 537, tiempo de retención 2.87 min.

4–[4–(2–Ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Diclorobis(trifenilfosfina)paladio(II) (96 mg, 0.14 mmol) fue añadido a ácido (4–aminofenil)borónico pinacol éster (747 mg, 3.41 mmol), 2–cloro–4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (982 mg, 2.73 mmol) y carbonato de sodio (6.82 mL, 13.64 mmol) en 18% DMF en DME:agua:etanol 7:3:2 (20 mL). La solución resultante fue agitada a 80°C durante 16 horas. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol. El producto crudo fue adicionalmente purificado por cromatografía flash en sílice, gradiente de elución 0 a 2.5% metanol en DCM, para dar el material deseado como un sólido cristalino amarillo (712 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.79 – 0.83 (2H, m), 0.94 – 0.96 (2H, s), 1.21 (3H, d), 1.79 (6H, d), 2.74 (1H, m), 3.17 (1H, d), 3.49 (1H, d), 3.62 – 3.66 (1H, m),

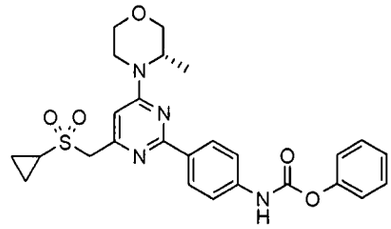
3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.16 – 4.19 (1H, m), 4.54 (1H, d), 5.51 – 5.53 (2H, m), 6.59 (2H, t), 6.67 (1H, s), 8.07 (2H, d).

Espectro LCMS: MH+ 417, tiempo de retención 2.22 min.

La preparación de 2–cloro–4–(2–ciclopropilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

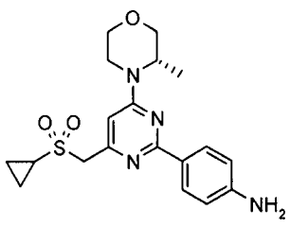


Fenil cloroformato (0.315 mL, 2.50 mmol) fue añadido en forma de gotas a 4–[4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (972 mg, 2.50 mmol) y bicarbonato de sodio (315 mg, 3.75 mmol) en dioxano (20 mL). La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en etil acetato (100 mL) y lavada con agua (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado (1.35 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.98 – 1.03 (2H, m), 1.06 – 1.10 (2H, m), 1.26 (3H, d), 2.86 – 2.93 (1H, m), 3.48 – 3.52 (1H, m), 3.58 (1H, s), 3.64 – 3.68 (1H, m), 3.77 – 3.80 (1H, m), 3.98 – 4.06 (1H, m), 4.17 (1H, d), 4.50 (1H, s), 4.56 (2H, s), 6.86 (1H, s), 7.24 – 7.29 (3H, m), 7.43 – 7.47 (2H, m), 7.65 (2H, d), 8.31 (2H, d), 10.47 (1H, s).

Espectro LCMS: MH+ 509, tiempo de retención 2.29 min.

4–[4–(Ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Diclorobis(trifenilfosfina)paladio(II) (96 mg, 0.14 mmol) fue añadido a ácido (4–aminofenil)borónico pinacol éster (747 mg, 3.41 mmol), 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (905 mg, 2.73 mmol) y carbonato de sodio (6.82 mL, 13.64 mmol) en 18% DMF en DME:agua:etanol 7:3:2 (20 mL). La solución resultante fue agitada a 80°C durante 6 horas. La reacción cruda fue purificada por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando 7M amoniaco en metanol. El producto crudo fue adicionalmente purificado por cromatografía flash en sílice, gradiente de elución 0 a 2.5% metanol en DCM, para dar el material deseado como un sólido amarillo (972 mg).

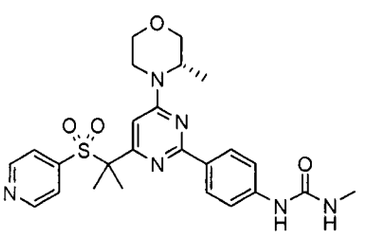
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.97 – 1.02 (2H, m), 1.03 – 1.10 (2H, m), 1.23 (3H, d), 2.81 – 2.87 (1H, m), 3.15 – 3.22 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.12 – 4.15 (1H, m), 4.45 (3H, s), 5.53 (2H, d), 6.58 – 6.61 (2H, m), 6.66 (1H, s), 8.03 – 8.07 (2H, m).

Espectro LCMS: MH+ 389, tiempo de retención 1.82.

La preparación de 2–cloro–4–(ciclopropilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

Ejemplo 58:

3–Metil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea

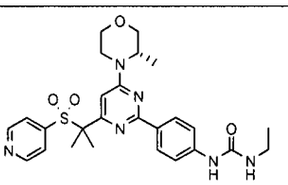
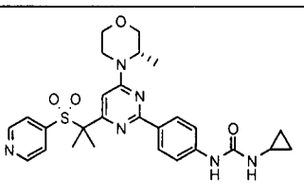
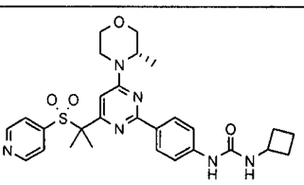


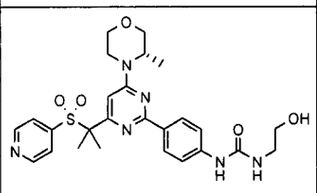
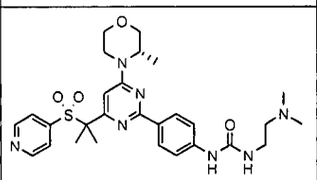
Metilamina (solución 2M en THF) (0.55mL, 1.10 mmol) fue añadida a fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato (125 mg, 0.22 mmol) y trietilamina (0.092 mL, 0.66 mmol) en DMF (4 mL). La solución resultante fue agitada a 50°C toda la noche. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido blanco (91 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22–1.23 (3H, d), 1.82–1.83 (6H, d), 2.66–2.67 (3H, d), 3.15–3.23 (1H, td), 3.47–3.53 (1H, td), 3.63–3.53 (1H, dd), 3.76–3.79 (1H, d), 3.96–4.00 (1H, dd), 4.18–4.21 (1H, d), 4.57 (1H, bs), 6.03–6.07 (1H, q), 6.71 (1H, s), 7.35–7.37 (2H, d), 7.47–7.48 (2H, q), 7.65–7.68 (2H, d), 8.70 (1H, s), 8.74–8.75 (2H, q).

Espectro LCMS: MH+ 511, tiempo de retención 2.03 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
58a		3–etil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	525	2.17
58b		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	537	2.19
58c		3–ciclobutil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	551	2.39

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
58d		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-piridin-4-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	541	1.90
58e		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-piridin-4-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	568	2.36

Ejemplo 58a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.05–1.09 (3H, t), 1.22–1.23 (3H, d), 1.82–1.83 (6H, d), 3.09–3.22 (3H, m), 3.47–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.96–3.99 (1H, dd), 4.18–4.22 (1H, d), 4.57 (1H, bs), 6.13–6.15 (1H, t), 6.71 (1H, s), 7.34–7.36 (2H, d), 7.47–7.48 (2H, q), 7.65–7.68 (2H, d), 8.62 (1H, s), 8.74–8.75 (2H, q).

Ejemplo 58b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40–0.44 (2H, m), 0.63–0.68 (2H, m), 1.22–1.23 (3H, d), 1.82–1.83 (6H, d), 2.54–2.59 (1H, m), 3.15–3.23 (1H, td), 3.47–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.96–4.00 (1H, dd), 4.18–4.21 (1H, d), 4.57 (1H, bs), 6.41–6.42 (1H, d), 6.72 (1H, s), 7.35–7.38 (2H, d), 7.47–7.48 (2H, q), 7.66–7.68 (2H, d), 8.50 (1H, s), 8.74–8.75 (2H, q).

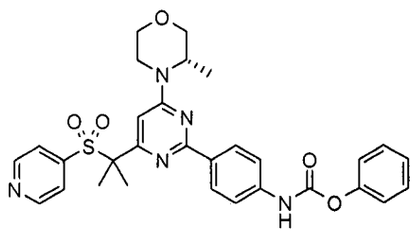
Ejemplo 58c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22–1.23 (3H,d), 1.58–1.66 (2H, m), 1.82–1.83 (6H, d), 1.83–1.89 (2H, m), 2.18–2.25 (2H, m), 3.15–3.22 (1H, td), 3.47–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.96–4.00 (1H, dd), 4.11–4.21 (2H, m), 4.57 (1H,bs), 6.43–6.45 (1H, d), 6.72 (1H, s), 7.32–7.34 (2H, d), 7.46–7.48 (2H, q), 7.65–7.68 (2H, d), 8.83 (1H, s), 8.74–8.75 (2H, q).

Ejemplo 58d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22–1.23 (3H, d), 1.82–1.83 (6H, d), 3.16–3.23 (3H, m), 3.44–3.48 (2H, q), 3.48–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.96–4.00 (1H, dd), 4.18–4.22 (1H, d), 4.56 (1H, bs), 4.71–4.74 (1H, t), 6.22–6.25 (1H, t), 6.72 (1H, s), 7.33–7.36 (2H, d), 7.47–7.48 (2H, q), 7.66–7.68 (2H, d), 8.74–8.75 (2H, q), 8.77 (1H, s).

Ejemplo 58e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22–123 (3H, d), 1.82–1.83 (6H, d), 2.19 (6H, s), 2.32–2.36 (2H, t), 3.15–3.22 (3H, m), 3.47–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.96–4.00 (1H, dd), 4.18–4.21 (1H, d), 4.56 (1H, bs), 6.13–6.15 (1H, t), 6.72 (1H, s), 7.33–7.35 (2H, d), 7.47–7.48 (2H, q), 7.66–7.68 (2H, d), 8.74–8.75 (2H, q), 8.85 (1H, s).

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato

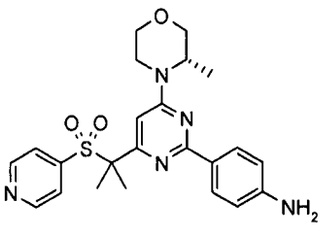


Fenil cloroformato (0.177 mL, 1.41 mmol) fue añadido a 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]anilina (0.640 g, 1.41 mmol) y bicarbonato de sodio (0.178 g, 2.12 mmol) en dioxano (175 mL) a RT al aire. La lechada resultante fue agitada a RT durante 2 horas. Dos porciones más de fenil cloroformato (2 x 0.005 mL) fueron añadidas y la reacción se dejó agitar a RT. Agua fue luego añadida a la reacción y los sólidos fueron filtrados y secados en un horno de vacío a 55°C toda la noche para dar el material deseado como un sólido color canela (0.758 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23–1.24 (3H, d), 1.83–1.84 (6H, d), 3.17–3.24 (1H, td), 3.48–3.53 (1H, td), 3.64–3.67 (1H, dd), 3.76–3.79 (1H, d), 3.97–4.00 (1H, dd), 4.21–4.24 (1H, d), 4.59 (1H, bs), 6.76 (1H, s), 7.24–7.31 (3H, m), 7.43–7.50 (6H, m), 7.75–7.78 (2H, d), 8.74–8.76 (2H, d), 10.39 (1H, s).

Espectro LCMS: MH+572, tiempo de retención 2.82 min.

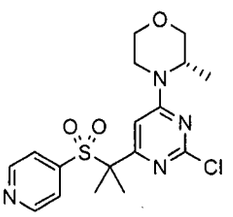
4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(2–piridin–4–ilsulfonilpropan–2–il)pirimidin–2–il]anilina



trans-Diclorobis (trifenilfosfina)paladio (II) (0.050 g, 0.07 mmol) fue añadido a 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(2-piridin-4-ilsulfonilpropan-2-il)pirimidina (0.560 g, 1.41 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0.464 g, 2.12 mmol) y carbonato de sodio (3.53 mL, 7.05 mmol) en 18% DMF en una mezcla de DME:agua:etanol (7:3:2) (30 mL) a RT bajo nitrógeno. La solución resultante fue agitada a 80°C durante 5 horas. La reacción se dejó enfriar y fue particionada entre etil acetato y agua. La capa acuosa fue extraída con etil acetato dos veces y los productos orgánicos combinados secados ($MgSO_4$), filtrados y evaporados para proporcionar el material deseado (0.640 g) el cual fue usado sin purificación adicional.

Espectro LCMS: MH+454, tiempo de retención 2.18 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-4-ilsulfonilpropan-2-il)pirimidina



Yodometano (0.164 mL, 2.63 mmol) fue añadido a 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina (0.970 g, 2.63 mmol) y *tert*-butóxido de sodio (0.253 g, 2.63 mmol) en DMF (15 mL) a 0°C al aire. *tert*-Butóxido de sodio adicional (0.253 g, 2.63 mmol) y yodometano (0.164 mL, 2.63 mmol) fueron añadidos y la solución resultante agitada a 0 °C durante 1 hora. La solución se dejó calentar lentamente hasta RT. Agua y etil acetato fueron añadidos y la solución fue separada. La capa acuosa fue extraída con etil acetato dos veces y los productos orgánicos combinados secados ($MgSO_4$), filtrados y evaporados en sílice. El producto crudo fue cromatografiado en sílice, eluyendo con 0 – 60% etil acetato en DCM, para dar el material deseado como un aceite amarillo el cual se solidificó en reposo (0.56 g).

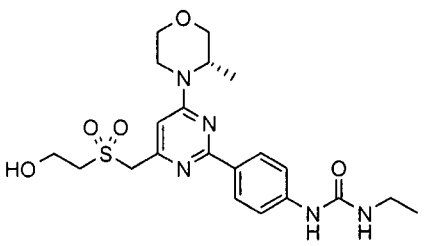
Espectro NMR: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.27–1.29 (3H, d), 1.71–1.72 (6H, d), 3.22–3.29 (1H, td), 3.48–3.54 (1H, td), 3.64–3.67 (1H, dd), 3.73–3.76 (1H, d), 3.95–3.98 (2H, dd), 4.29 (1H, bs), 6.63 (1H, s), 7.39–7.41 (2H, dd), 8.78–8.79 (2H, dd).

Espectro LCMS: MH+ 397, tiempo de retención 1.73 min.

La preparación de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–4–ilsulfonilmetil)pirimidina fue descrita anteriormente.

Ejemplo 59:

3–Etil–1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea

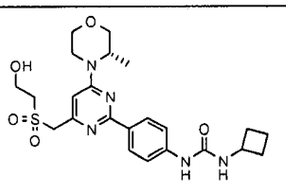
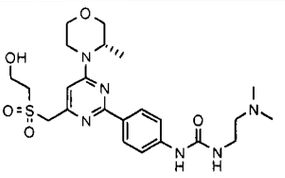


Fenil *N*–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (0.073 g, 0.14 mmol), etilamina (0.70 mmol) y trietilamina (0.42 mmol) fueron combinados y calentados a 50°C bajo una atmósfera de aire toda la noche. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes para dar el material deseado como un sólido blanco (0.047 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.06–1.09 (3H, t), 1.24–1.25 (3H, d), 3.10–3.17 (2H, m), 3.19–3.26 (1H, td), 3.47–3.53 (3H, m), 3.64–3.67 (1H, dd), 3.77–3.80 (1H, d), 3.90–3.94 (2H, q), 3.97–4.01 (1H, dd), 4.15–4.19 (1H, d), 4.48 (1H, bs), 4.50 (2H, s), 5.17–5.20 (1H, t), 6.15–6.18 (1H, t), 6.76 (1H, s), 7.49–7.51 (2H, d), 8.20–8.23 (2H, d), 8.66 (1H, s).

Espectro LCMS: MH+ 464, tiempo de retención 1.62 min.

Los siguientes compuestos fueron preparados de una forma análoga a partir de fenil *N*–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
59a		3–ciclobutil–1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	490	1.84
59b		3–(2–dimetilaminoetil)–1–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	507	1.61

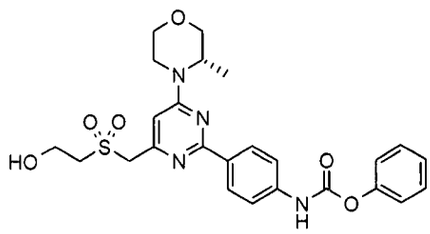
Ejemplo 59a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.24–1.25 (3H, d), 1.57–1.69 (2H, m), 1.82–1.92 (2H, m), 2.18–2.25 (2H, m), 3.18–3.27 (1H, td), 3.47–3.53 (3H, m), 3.64–3.67 (1H, dd), 3.77–3.79 (1H, d), 3.90–3.94 (2H, q), 3.97–4.01 (1H, dd), 4.10–4.18 (2H, m), 4.47 (1H, bs), 4.50 (2H, s), 5.17–5.20 (1H, t), 6.46–6.48 (1H, d), 6.76 (1H, s), 7.47–7.49 (2H, d), 8.20–8.22 (2H, d), 8.56 (1H, s).

Ejemplo 59b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.35–1.37 (3H, d), 3.37 (6H, s), 2.56–2.59 (2H, t), 3.31–3.38 (5H, m), 3.49 (2H, s), 3.56–3.63 (1H, td), 3.72–3.76 (1H, dd), 3.82–3.85 (1H, d), 4.03–4.07 (1H, dd), 4.14–4.17 (2H, t), 4.17–4.20 (1H, d), 4.42–4.43 (2H, d), 4.48 (1H, bs), 5.61 (1H, bs), 6.45 (1H, s), 7.46–7.48 (2H, d), 8.19–8.21 (2H, d).

Prueba (c): Ejemplo (59a) 0.037 μM; Ejemplo (57b) 0.043 μM.

La preparación de fenil *N*–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(2–hidroxietilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

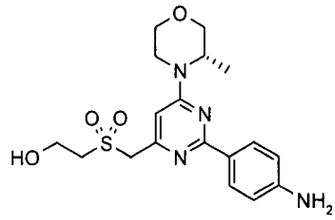


Fenil cloroformato (0.046 mL, 0.36 mmol) fue añadido a 2-[[2-(4-aminofenil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etanol (0.143 g, 0.36 mmol) y bicarbonato de sodio (0.046 g, 0.55 mmol) en dioxano (20 mL) a RT al aire. La lechada resultante fue agitada a RT durante 2 horas. Agua fue añadida y la mezcla extraída con DCM tres veces. Los productos orgánicos combinados fueron secados ($MgSO_4$), filtrados y concentrados al vacío para dar el material deseado como un sólido amarillo (0.228 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 3.20-3.26 (1H, td), 3.51-3.54 (3H, m), 3.58 (1H, s), 3.64-3.68 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.95 (2H, m), 3.97-4.01 (1H, dd), 4.18-4.21 (1H, d), 4.48 (1H, bs), 4.52 (2H, s), 5.18-5.20 (1H, t), 6.80 (1H, s), 7.25-7.30 (3H, m), 7.43-7.47 (2H, t), 7.63-7.65 (3H, d), 8.31-8.33 (2H, d), 10.44 (1H, s).

Espectro LCMS: MH+ 513, tiempo de retención 2.28 min.

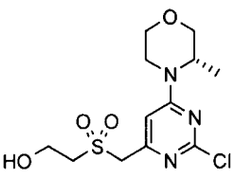
2-[[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etanol



trans-Diclorobis(trifenilfosfina)paladio (II) (0.013 g, 0.02 mmol) fue añadido a 2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etanol (0.122 g, 0.36 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0.119 g, 0.54 mmol) y carbonato de sodio (0.908 mL, 1.82 mmol) en 18% DMF en una mezcla de DME:agua:etanol (7:3:2) (10 mL) a RT bajo nitrógeno. La solución resultante fue agitada a 80°C durante 2 horas. La reacción fue enfriada y particionada entre etil acetato y agua. La mezcla de reacción fue extraída con etil acetato dos veces y los productos orgánicos combinados secados ($MgSO_4$), filtrados y concentrados al vacío para dar el producto deseado (0.143 g).

Espectro LCMS: MH+ 393, tiempo de retención 1.30 min.

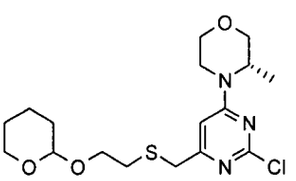
2–[[2–Cloro–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–4–il]metilsulfonil]etanol



Una solución acuosa 30% de peróxido de hidrógeno (0.225 mL, 7.29 mmol) fue añadida a una solución agitada de 2–cloro–4–[(3S)–3–metilmorfolin–4–il]–6–[2–(oxan–2–iloxi)etilsulfanilmetil]pirimidina (0.141 g, 0.36 mmol), tungstato dihidrato de sodio (2.4 mg, 0.0073 mmol) en agua (0.2 mL) y ácido sulfúrico 2N (0.011 mL) en 1,4–dioxano (1.4 mL) y metanol (1.4 mL) y calentada hasta 55°C al aire. La solución resultante fue agitada a 55°C durante 4 horas, luego agua (50 mL) fue añadida y la reacción enfriada. Una solución acuosa 10% de metabisulfito de sodio fue añadida y luego la solución entera fue extraída con DCM. Los productos orgánicos fueron secados ($MgSO_4$), filtrados y concentrados al vacío para dar el material deseado como un aceite opaco (0.198 g).

Espectro LCMS: MH+ 336, tiempo de retención 1.18 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–(oxan–2–iloxi)etilsulfanilmetil]pirimidina



DIPEA (0.211 g, 1.63 mmol) fue añadida en forma de gotas a 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (0.231 g, 0.65 mmol) y 2–(tetrahidro–2H–piran–2–iloxi)etanotiol (0.133 g, 0.82 mmol) en acetonitrilo a RT al aire. La solución resultante fue agitada a RT durante 1 hora. El solvente fue eliminado y la mezcla de reacción diluida con DCM y lavada con agua. La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, eluyendo con 0 – 2% metanol en DCM, para dar el material deseado como un aceite incoloro (0.141 g).

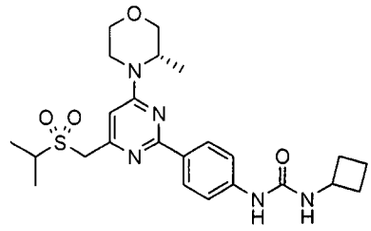
Espectro NMR: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.24–1.26 (3H, d), 1.40–1.55 (4H, m), 1.60–1.67 (1H, m), 1.69–1.77 (1H, m), 2.68–2.71 (2H, t), 3.17–3.24 (1H, td), 3.41–3.47 (2H, m), 3.50–3.58 (1H, m), 3.59 (2H, s), 3.62–3.63 (1H, d), 3.69–3.72 (1H, d), 3.76–3.86 (2H, m), 3.91–3.95 (1H, dd), 3.97 (1H, bs), 4.25 (1H, bs)< 4.52–4.54 (1H, t), 6.44 (1H, s).

Espectro LCMS: m/z (ES+) (M+H)+=386; HPLC tR=2.11 min. MH+ 386, tiempo de retención 2.11 min.

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

Ejemplo 60:

3–Ciclobutil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(propan–2–ilsulfonilmetil)pirimidin–2–il]fenil]urea



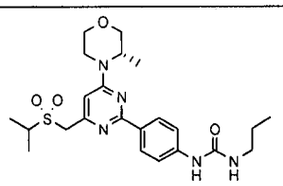
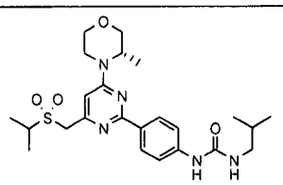
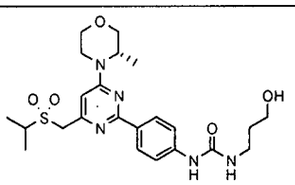
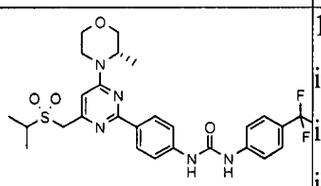
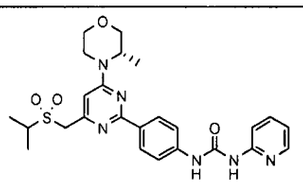
Ciclobutilamina (70 mg, 0.98 mmol) fue añadida a fenil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato (100 mg, 0.20 mmol) y trietilamina (0.082 mL, 0.59 mmol) en DMF (2 mL). La solución resultante fue agitada a 50°C durante 2 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (57 mg).

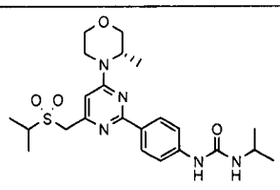
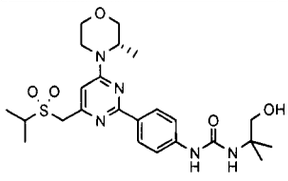
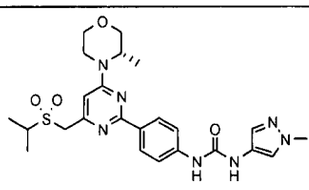
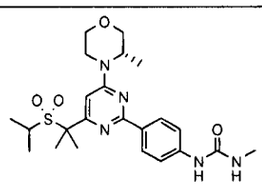
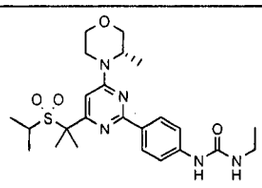
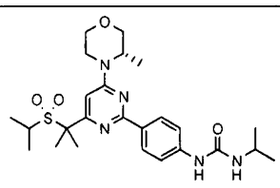
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.57 – 1.68 (2H, m), 1.81 – 1.91 (2H, m), 2.18 – 2.25 (2H, m), 3.18 – 3.25 (1H, m), 3.25 – 3.27 (1H, m), 3.47 – 3.54 (2H, m), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.11 – 4.17 (2H, m), 4.46 (2H, s), 6.47 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.55 (1H, s)

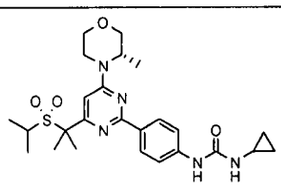
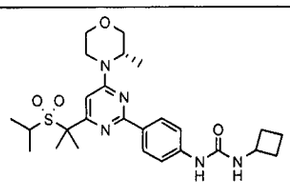
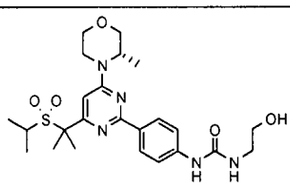
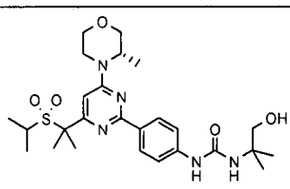
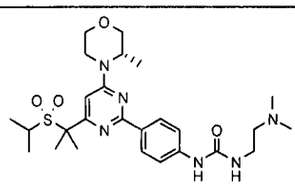
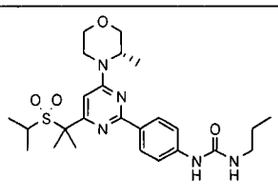
Espectro LCMS: MH+ 488, tiempo de retención 1.99 min.

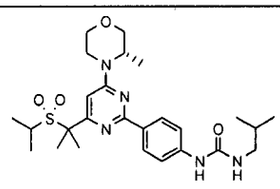
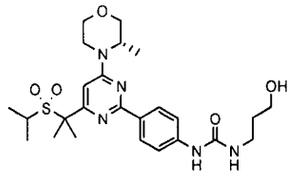
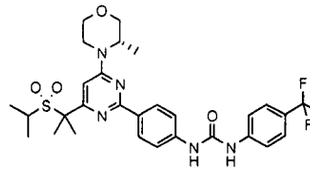
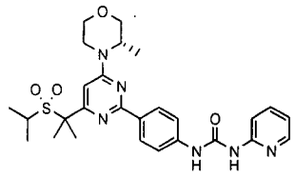
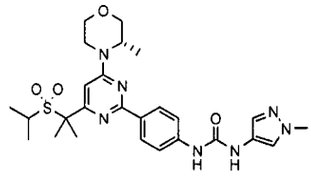
Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato o

fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
60a		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-1-propil-urea	476	1.91
60b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	490	2.10
60c		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	492	1.45
60d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	578	2.70
60e		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-3-piridin-2-il-urea	511	2.16

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
60f		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-3-propan-2-il-urea	476	2.00
60g		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea	506	1.81
60h		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	514	1.71
60i		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	476	1.96
60j		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	490	2.14
60k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-propan-2-il-urea	504	2.29

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
60l		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	502	2.12
60m		3–ciclobutil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	516	2.34
60n		3–(2–hidroxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	506	1.78
60o		3–(1–hidroxi–2–metil–propan–2–il)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	534	2.07
60p		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	533	2.07
60q		3–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]–1–propil–urea	504	2.26

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
60r		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	518	2.43
60s		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	520	1.82
60t		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	606	2.95
60u		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-piridin-2-il-urea	539	2.54
60v		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	542	1.97

Ejemplo 60a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.25 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.43 – 1.49 (2H, m), 3.04 – 3.07 (1H, m), 3.21 – 3.26 (1H, m), 3.47 – 3.52 (2H, m), 3.64 – 3.67 (1H, m), 3.67 – 3.87 (3H, m), 3.98 – 4.00 (1H, m), 4.20 (1H, d), 4.47 (2H, s), 6.23 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Ejemplo 60b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.25 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.71 (1H, quinteto), 2.95 (2H, t), 3.20 – 3.27 (1H, m), 3.47 – 3.54 (3H, m), 3.65

(1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.19 (1H, d), 4.47 (2H, s), 6.27 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Ejemplo 60c: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.35 – 1.37 (6H, m), 1.60 (2H, quinteto), 3.17 (2H, q), 3.21 – 3.25 (1H, m), 3.45 – 3.54 (4H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.00 (1H, m), 4.17 (1H, d), 4.46 – 4.49 (3H, m), 6.21 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.70 (1H, s)

Ejemplo 60d: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.36 (3H, d), 1.38 (3H, d), 3.20 – 3.27 (2H, m), 3.48 – 3.55 (2H, m), 3.66 (1H, dd), 3.79 (1H, d), 4.00 (1H, dd), 4.19 (1H, d), 4.48 (2H, s), 6.80 (1H, s), 7.59 (2H, d), 7.64 – 7.70 (4H, m), 8.27 (2H, d), 9.04 (1H, s), 9.15 (1H, s)

Ejemplo 60e: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.37 (3H, d), 1.38 (3H, d), 3.20 – 3.24 (1H, m), 3.27 (1H, s), 3.48 – 3.56 (2H, m), 3.66 (1H, dd), 3.79 (1H, d), 4.00 (1H, dd), 4.19 (1H, d), 4.49 (2H, s), 6.81 (1H, s), 7.02 – 7.05 (1H, m), 7.55 (1H, d), 7.65 (2H, d), 7.75 – 7.79 (1H, m), 8.27 – 8.31 (3H, m), 9.47 (1H, s), 10.63 (1H, s)

Ejemplo 60f: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.11 (6H, d), 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 3.19 – 3.25 (2H, m), 3.47 – 3.54 (2H, m), 3.65 (1H, dd), 3.73 – 3.82 (2H, m), 3.99 (1H, dd), 4.17 (1H, d), 4.46 (2H, s), 6.07 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.52 (1H, s)

Ejemplo 60g: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.24 (6H, s), 1.35 (3H, d), 1.37 (3H, d), 3.18 (1H, d), 3.22 – 3.27 (1H, m), 3.39 (1H, d), 3.47 – 3.55 (2H, m), 3.64 – 3.66 (1H, m), 3.78 (1H, d), 3.98 – 4.00 (1H, m), 4.17 (1H, d), 4.46 (2H, s), 4.95 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.46 (2H, d), 8.17 (2H, d), 8.73 (1H, s)

Ejemplo 60h: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.36 (3H, d), 1.38 (3H, d), 3.18 – 3.25 (2H, m), 3.48 – 3.54 (2H, m), 3.66 (1H, dd), 3.78 (1H, d), 3.79 (3H, s), 3.99 (1H, dd), 4.18 (1H, d), 4.47 (2H, s), 6.78 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.22 (2H, d), 8.40 (1H, s), 8.83 (1H, s)

Ejemplo 60i: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 2.66 (3H, d), 3.16 – 3.24 (1H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.06 – 6.08 (1H, m), 6.78 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.74 (1H, s)

Ejemplo 60j: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 3.10 – 3.15 (2H, m), 3.16 – 3.24 (1H, m), 3.50 (1H, dt), 3.65 (1H,

dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.66 (1H, s)

Ejemplo 60k: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.08 – 1.13 (12H, m), 1.22 (3H, d), 1.79 (6H, d), 3.18 – 3.24 (2H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 – 3.82 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.06 (1H, d), 6.78 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.53 (1H, s)

Ejemplo 60l: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.33 – 0.37 (2H, m), 0.56 – 0.60 (2H, m), 1.02 (3H, d), 1.05 (3H, d), 1.15 (3H, d), 1.73 (6H, d), 2.47 – 2.52 (1H, m), 3.14 (1H, dt), 3.43 (1H, dt), 3.58 (1H, dd), 3.63 – 3.72 (2H, m), 3.89 – 3.92 (1H, m), 4.16 (1H, d), 4.50 (1H, s), 6.36 (1H, d), 6.72 (1H, s), 7.44 (2H, d), 8.16 (2H, d), 8.46 (1H, s)

Ejemplo 60m: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.57 – 1.66 (2H, m), 1.79 (6H, d), 1.83 – 1.90 (2H, m), 2.18 – 2.25 (2H, m), 3.20 (1H, dt), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.12 – 4.18 (1H, m), 4.22 (1H, d), 4.55 (1H, s), 6.46 (1H, d), 6.78 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.56 (1H, s)

Ejemplo 60n: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 3.16 – 3.24 (2H, m), 3.44 – 3.53 (3H, m), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.24 (2H, s), 8.80 (1H, s)

Ejemplo 60o: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.13 (3H, d), 1.22 (3H, d), 1.24 (6H, s), 1.79 (6H, d), 3.17 – 3.24 (1H, m), 3.39 (2H, d), 3.50 (1H, dt), 3.65 (1H, dd), 3.71 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.78 (1H, s), 7.46 (2H, d), 8.22 (2H, d), 8.73 (1H, s)

Ejemplo 60p: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.79 (6H, d), 2.18 (6H, s), 2.32 – 2.35 (2H, m), 3.17 – 3.22 (3H, m), 3.50 (1H, dt), 3.66 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.89 (1H, s)

Ejemplo 60q: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.89 (3H, t), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.41 – 1.50 (2H, m), 1.79 (6H, d), 3.04 – 3.09 (2H, m), 3.18 – 3.24 (2H, m), 3.50 (1H, dt), 3.65 (1H, dd), 3.70 – 3.78 (1H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.21 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.65 (1H, s)

Ejemplo 60r: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.89 (6H, d), 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.67 – 1.74 (1H, m), 1.79 (6H, d), 2.95 (2H, t), 3.22 (1H, dd), 3.50 (1H, dt), 3.65

(1H, dd), 3.70 – 3.79 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.25 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.64 (1H, s)

Ejemplo 60s: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.22 (3H, d), 1.60 (2H, quinteto), 1.79 (6H, d), 3.15 – 3.24 (3H, m), 3.45 – 3.53 (3H, m), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.22 (1H, d), 4.47 (1H, t), 4.55 (1H, s), 6.21 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.71 (1H, s)

Ejemplo 60t: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.10 (3H, d), 1.13 (3H, d), 1.23 (3H, d), 1.81 (6H, d), 3.22 – 3.25 (1H, m), 3.66 (1H, dd), 3.71 – 3.79 (1H, m), 3.97 – 4.00 (2H, m), 4.04 – 4.08 (1H, m), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.59 (2H, d), 7.64 – 7.70 (4H, m), 8.31 (2H, d), 9.04 (1H, s), 9.14 (1H, s)

Ejemplo 60u: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.10 (3H, d), 1.14 (3H, d), 1.24 (3H, d), 1.81 (6H, d), 3.18 – 3.27 (1H, m), 3.51 (1H, dt), 3.66 (1H, ddd), 3.73 – 3.80 (2H, m), 3.99 (1H, dd), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.02 – 7.05 (1H, m), 7.57 (1H, t), 7.65 (2H, d), 7.74 – 7.79 (1H, m), 8.29 – 8.33 (3H, m), 9.45 (1H, s), 10.59 (1H, s)

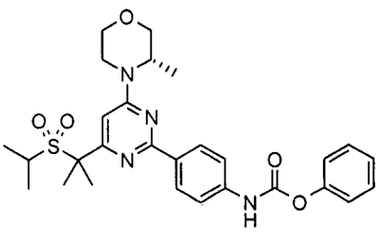
Ejemplo 60v: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.09 (3H, d), 1.13 (3H, d), 1.23 (3H, d), 1.80 (6H, d), 3.18 – 3.24 (2H, m), 3.51 (1H, dt), 3.64 – 3.68 (1H, m), 3.71 – 3.78 (1H, m), 3.79 (3H, s), 3.98 (1H, dd), 4.23 (1H, d), 4.56 (1H, s), 6.80 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.27 (2H, d), 8.39 (1H, s), 8.84 (1H, s)

Prueba (c): Ejemplo (60) 1.0 μM; Ejemplo (60a) 3.3 μM; Ejemplo (60b) 1.8 μM; Ejemplo (60b) 1.8 μM; Ejemplo (60c) 0.77 μM; Ejemplo (60d) 0.59 μM; Ejemplo (60e) 1.3 μM; Ejemplo (60f) 0.87 μM; Ejemplo (60g) 0.22 μM; Ejemplo (60h) 1.9 μM; Ejemplo (60i) 0.12 μM; Ejemplo (60j) 0.19 μM; Ejemplo (60k) 0.18 μM; Ejemplo (60l) 0.064 μM; Ejemplo (60m) 0.059 μM; Ejemplo (60n) 0.15 μM; Ejemplo (60o) 0.086 μM; Ejemplo (60p) 0.14 μM; Ejemplo (60q) 0.16 μM; Ejemplo (60r) 0.21 μM; Ejemplo (60s) 0.3 μM; Ejemplo (60t) 1.4 μM; Ejemplo (60u) 0.16 μM; Ejemplo (60v) 0.27μM.

La preparación de fenil (4–{4–[(isopropilsulfonil)metil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il}fenil)carbamato fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–propan–2–ilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]carbamato

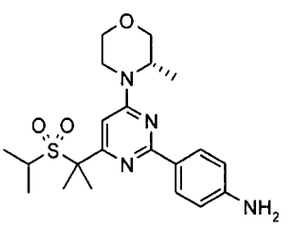


Fenil cloroformato (0.42 mL, 3.34 mmol) fue añadido en forma de gotas a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]anilina (1.4 g, 3.34 mmol) y carbonato de sodio (0.421g, 5.02 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en DCM (50 mL) y lavada con agua (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el producto crudo el cual fue triturado con dietil éter para dar el producto deseado (1.57 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.23 (3H, d), 1.80 (6H, d), 3.17 – 3.25 (1H, m), 3.47 – 3.54 (1H, m), 3.66 (1H, dd), 3.72 – 3.79 (2H, m), 3.97 – 4.00 (1H, m), 4.24 (1H, d), 4.57 (1H, s), 6.82 (1H, s), 7.25 (3H, d), 7.45 (2H, t), 7.64 (2H, d), 8.34 (2H, d), 10.43 (1H, s)

Espectro LCMS: MH+ 539, tiempo de retención 2.76 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidin-2-il]anilina



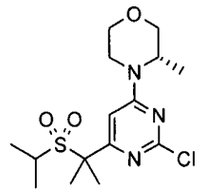
Diclorobis(trifenilfosfina)paladio(II) (116 mg, 0.17 mmol) fue añadido a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidina (1.2 g, 3.32 mmol), y carbonato de sodio (5 mL, 10.00 mmol) en 18% DMF en una mezcla de DME:agua:etanol (7:3:2) (20 mL). La solución resultante fue agitada a 90°C durante 4 horas.

La mezcla de reacción fue diluida con etil acetato (20 mL), y lavada con agua (2 x 20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 5 a 60% etil acetato en isohexano, para dar el material deseado como un sólido color crema (1.40 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (3H, d), 1.12 (3H, d), 1.21 (3H, d), 1.77 (6H, d), 3.13 – 3.21 (1H, m), 3.46 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.69 – 3.77 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.53 (1H, d), 5.55 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.06 (2H, d)

Espectro LCMS: MH+ 419, tiempo de retención 2.11 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-propan-2-ilsulfonilpropan-2-il)pirimidina



Yodometano (0.23 mL, 3.75 mmol) fue añadido a tert-butóxido de sodio (360 mg, 3.75 mmol) y (3*S*)-4-{2-Cloro-6-[(isopropilsulfonil)metil]pirimidin-4-il}-3-metilmorfolina (2.5 g, 7.49 mmol) en DMF (2 mL) a -10°C. La suspensión densa resultante fue agitada a RT durante 15 minutos para facilitar la agitación. Yodometano (0.23 mL, 3.75 mmol) y *tert*-butóxido de sodio (360 mg, 3.75 mmol) fueron nuevamente añadidos a la reacción y la suspensión resultante agitada a RT durante 15 minutos. La mezcla de reacción fue diluida con DCM (20 mL) y lavada con agua (20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 50% etil acetato en DCM, para dar el material deseado como un sólido beige (1.20 g).

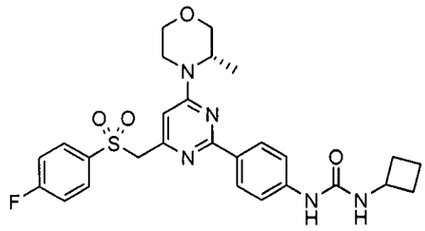
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.14 (3H, d), 1.20 (3H, d), 1.70 (6H, s), 3.16 – 3.24 (1H, m), 3.41 – 3.48 (1H, m), 3.59 (1H, dd), 3.67 (1H, q), 3.72 (1H, d), 3.94 (1H, dd), 4.06 (1H, d), 4.42 (1H, s), 6.91 (1H, s)

Espectro LCMS: MH+ 362, tiempo de retención 2.08 min.

La preparación de (3*S*)-4-{2-Cloro-6-[(isopropilsulfonil)metil]pirimidin-4-il}-3-metilmorfolina fue descrita anteriormente.

Ejemplo 61:

3-Ciclobutil-1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

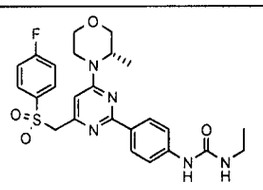
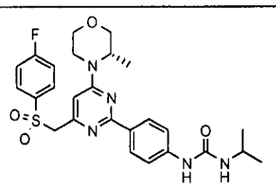
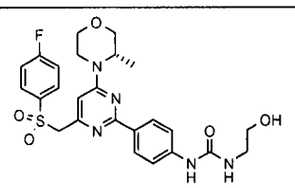
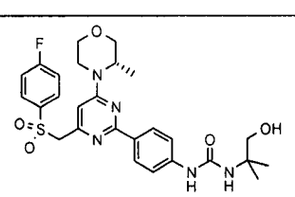
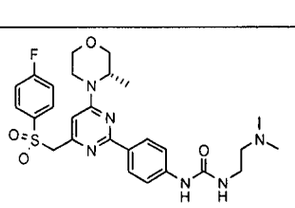


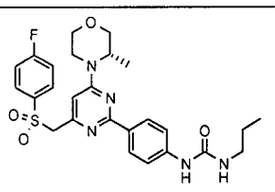
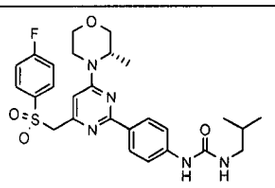
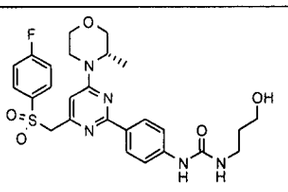
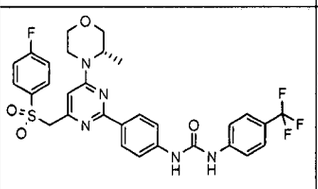
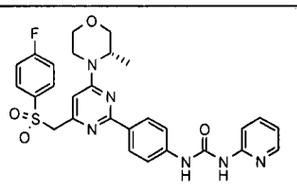
Ciclobutilamina (0.96 mmol) fue añadida a fenil *N*-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (120 mg, 0.21 mmol) y trietilamina (0.090 mL, 0.59 mmol) en DMF (2 mL). La solución resultante fue agitada a 50°C durante 3 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y MeCN como eluentes, para dar el material deseado como un sólido blanco (117 mg).

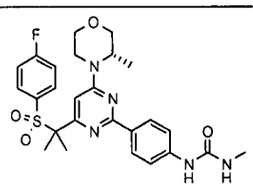
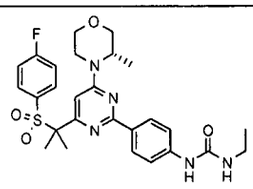
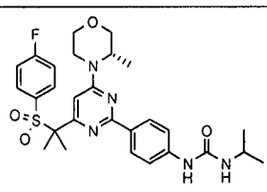
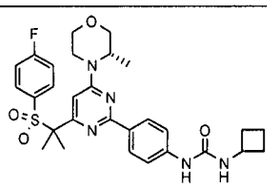
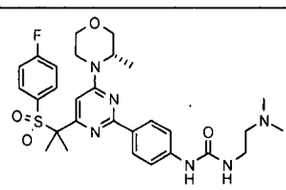
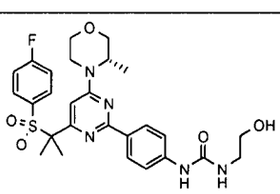
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.57 – 1.66 (2H, m), 1.81 – 1.91 (2H, m), 2.18 – 2.24 (2H, m), 3.17 (1H, dt), 3.47 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.08 – 4.19 (2H, m), 4.38 (1H, s), 4.71 (2H, s), 6.42 (1H, d), 6.64 (1H, s), 7.36 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 – 7.89 (2H, m), 8.53 (1H, s)

Espectro LCMS: MH+ 540, tiempo de retención 2.25 min.

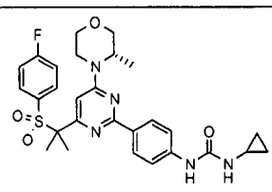
Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
61a		1-etil-3-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	514	2.02
61b		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea	528	2.17
61c		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	530	1.72
61d		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea	558	1.99
61e		3-(2-dimetilaminoetil)-1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	557	1.98

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
61f		3-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea	528	2.18
61g		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	542	2.34
61h		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	544	1.76
61i		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	630	2.82
61j		1-[4-[4-[(4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea	563	2.40

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
61k		1–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	528	2.19
61l		1–etil–3–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	542	2.34
61m		1–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–propan–2–il–urea	556	2.49
61n		3–ciclobutil–1–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	568	2.57
61o		3–(2–dimetilaminoetil)–1–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	585	1.91
61p		1–[4–[4–[2–(4–fluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–hidroxietil)urea	558	2.01

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
61q		3-ciclopropil-1-[4-[4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	554	2.35

Ejemplo 61a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 3.09 – 3.21 (3H, m), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H, s), 4.71 (2H, s), 6.13 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 – 7.88 (2H, m), 8.64 (1H, s)

Ejemplo 61b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.20 (3H, d), 3.18 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.73 – 3.81 (2H, m), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.71 (2H, s), 6.03 (1H, d), 6.64 (1H, s), 7.36 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 – 7.89 (2H, m), 8.51 (1H, s)

Ejemplo 61c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 3.13 – 3.21 (3H, m), 3.44 – 3.50 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H, s), 4.71 – 4.74 (3H, m), 6.22 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 – 7.89 (2H, m), 8.78 (1H, s)

Ejemplo 61d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.24 (6H, s), 3.14 – 3.20 (2H, m), 3.39 (1H, d), 3.48 (1H, t), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.11 (1H, d), 4.37 (1H, s), 4.72 (2H, s), 4.95 (1H, s), 5.98 (1H, s), 6.64 (1H, s), 7.34 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.86 – 7.89 (2H, m), 8.72 (1H, s)

Ejemplo 61e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.18 (6H, s), 2.34 (2H, t), 3.14 – 3.21 (3H, m), 3.48 (1H, dt), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.04 – 4.12 (1H, m), 4.37 (1H, s), 4.71 (2H, s), 6.13 (1H, t), 6.64 (1H, s), 7.37 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 – 7.89 (2H, m), 8.86 (1H, s)

Ejemplo 61f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.20 (3H, d), 1.46 (2H, sexteto), 3.06 (2H, q), 3.17 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.37 (1H, s), 4.71 (2H, s), 6.17 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.86 – 7.89 (2H, m), 8.62 (1H, s)

Ejemplo 61g: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.89 (6H, d), 1.20 (3H, d), 1.67 – 1.72 (1H, m), 2.94 (2H, t), 3.17 (1H, t), 3.48 (1H, t), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.72 (2H, s), 6.21 (1H, t), 6.65 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.79 (2H, d), 7.85 – 7.89 (2H, m), 8.62 (1H, s)

Ejemplo 61h: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.60 (2H, quinteto), 3.14 – 3.21 (3H, m), 3.45 – 3.51 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.38 (1H, s), 4.47 (1H, t), 4.71 (2H, s), 6.17 (1H, t), 6.64 (1H, s), 7.38 (2H, d), 7.46 (2H, t), 7.78 (2H, d), 7.85 – 7.89 (2H, m), 8.68 (1H, s)

Ejemplo 61i: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 9.10 (1H, s), 9.02 (1H, s), 7.86 – 7.89 (4H, m), 7.64 – 7.70 (4H, m), 7.45 – 7.49 (4H, m), 6.68 (1H, s), 4.73 (2H, s), 4.39 (1H, s), 4.13 (1H, d), 3.98 (1H, d), 3.77 (1H, d), 3.64 (1H, dd), 3.49 (1H, td), 3.19 (1H, td), 1.21 (3H, d)

Ejemplo 61j: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 3.19 (1H, dt), 3.50 (1H, dt), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.12 (1H, d), 4.39 (1H, s), 4.74 (2H, s), 6.68 (1H, s), 7.02 – 7.05 (1H, m), 7.45 – 7.59 (5H, m), 7.75 – 7.79 (1H, m), 7.86 – 7.90 (4H, m), 8.30 (1H, d), 9.42 (1H, s), 10.52 (1H, s)

Ejemplo 61k: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.27 (3H, d), 1.84 (6H, d), 2.71 (3H, d), 3.19 – 3.26 (1H, m), 3.52 – 3.57 (1H, m), 3.70 (1H, dd), 3.82 (1H, d), 4.02 (1H, dd), 4.22 (1H, d), 4.59 (1H, s), 6.09 – 6.10 (1H, m), 6.73 (1H, s), 7.36 (2H, t), 7.44 (2H, d), 7.60 – 7.63 (2H, m), 7.83 (2H, d), 8.76 (1H, s)

Ejemplo 61l: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.22 (3H, d), 1.79 (6H, d), 3.09 – 3.20 (3H, m), 3.50 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.17 (1H, d), 4.55 (1H, s), 6.13 (1H, t), 6.68 (1H, s), 7.31 (2H, t), 7.38 (2H, d), 7.54 – 7.58 (2H, m), 7.78 (2H, d), 8.62 (1H, s)

Ejemplo 61m: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.11 (6H, d), 1.22 (3H, d), 1.79 (6H, d), 3.11 – 3.20 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.75 – 3.80 (2H, m), 3.98 (1H, d), 4.17 (1H, d), 4.54 (1H, s), 6.03 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.36 (2H, d), 7.54 – 7.58 (2H, m), 7.78 (2H, d), 8.50 (1H, s)

Ejemplo 61n: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 1.57 – 1.66 (2H, m), 1.78 (6H, d), 1.82 – 1.91 (2H, m), 2.14 – 2.25 (2H, m), 3.17 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.09 – 4.18 (2H, m), 4.54 (1H, s), 6.43 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.36 (2H, d), 7.54 – 7.58 (2H, m), 7.78 (2H, d), 8.53 (1H, s)

Ejemplo 61o: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.79 (6H, d), 2.18 (6H, s), 2.34 (2H, t), 3.13 – 3.21 (3H, m), 3.50 (1H, t), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.17 (1H, d), 4.55 (1H, s), 6.14 (1H, t), 6.67 (1H, s), 7.31 (2H, t), 7.37 (2H, d), 7.54 – 7.58 (2H, m), 7.78 (2H, d), 8.85 (1H, s)

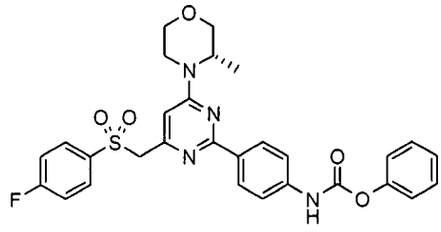
Ejemplo 61p: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.79 (6H, d), 3.14 – 3.21 (3H, m), 3.44 – 3.53 (3H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.68 (1H, s), 7.31 (2H, t), 7.37 (2H, d), 7.54 – 7.58 (2H, m), 7.78 (2H, d), 8.77 (1H, s)

Ejemplo 61q: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.62 – 0.67 (2H, m), 1.22 (3H, d), 1.79 (6H, d), 2.54 – 2.58 (1H, m), 3.17 (1H, dt), 3.49 (1H, dt), 3.65 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 6.40 (1H, d), 6.68 (1H, s), 7.31 (2H, t), 7.39 (2H, d), 7.54 – 7.58 (2H, m), 7.79 (2H, d), 8.50 (1H, s)

Prueba (c): Ejemplo (61) 0.33 μM; Ejemplo (61a) 0.75 μM; Ejemplo (61b) 0.038 μM; Ejemplo (61c) 0.41 μM; Ejemplo (61d) 0.18 μM; Ejemplo (61e) 0.12 μM; Ejemplo (61g) 0.45 μM; Ejemplo (61h) 0.79 μM; Ejemplo (61k) 0.12 μM; Ejemplo (61l) 0.099 μM; Ejemplo (61m) 0.03 μM; Ejemplo (61n) 0.038 μM; Ejemplo (61o) 0.045 μM; Ejemplo (61q) 0.077 μM;

La preparación de fenil *N*–[4–[4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato



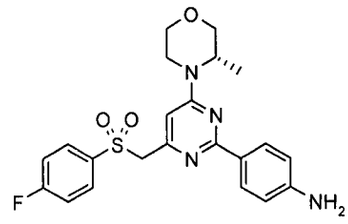
Fenil cloroformato (0.474 mL, 3.77 mmol) fue añadido en forma de gotas a 4–[4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (1.67 g, 3.77 mmol) y bicarbonato de sodio (476 mg, 5.66 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada

hasta secarse y redisuelta en DCM (50 mL) y lavada con agua (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el producto crudo el cual fue triturado con dietil éter para dar el producto deseado (1.90 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 3.15 – 3.22 (1H, m), 3.35 (1H, s), 3.45 – 3.52 (1H, m), 3.63 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.39 (1H, s), 4.73 (2H, s), 6.69 (1H, s), 7.24 – 7.26 (2H, m), 7.43 – 7.48 (4H, m), 7.53 (2H, d), 7.86 – 7.90 (4H, m), 10.39 (1H, s)

Espectro LCMS: MH+ 563, tiempo de retención 2.65 min.

4–[4–[(4–Fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina

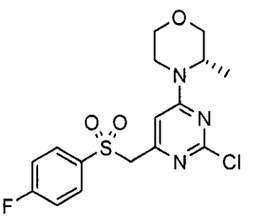


Diclorobis(trifenilfosfina)paladio(II) (136 mg, 0.19 mmol) fue añadido a 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (1.107 g, 5.05 mmol) y 2–cloro–4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.50 g, 3.89 mmol) y carbonato de sodio (5 mL, 10.00 mmol) en 18% DMF en DME:agua:etanol (7:3:2) (20 mL). La solución resultante fue agitada a 90°C durante 4 horas. La mezcla de reacción fue diluida con etil acetato (20 mL), y lavada con agua (2 x 20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 5 a 60% etil acetato en isohexano, para dar el material deseado como un sólido color crema (1.670 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.18 (3H, d), 3.10 – 3.18 (1H, m), 3.44 – 3.50 (1H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.07 (1H, d), 4.35 (1H, s), 4.67 (2H, s), 5.52 (2H, s), 6.49 (2H, d), 6.53 (1H, s), 7.45 (2H, t), 7.62 (2H, d), 7.84 – 7.88 (2H, m)

Espectro LCMS: MH+ 443, tiempo de retención 1.96 min.

2–Cloro–4–[(4–fluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina

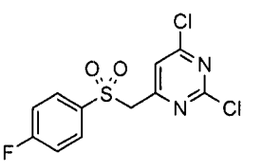


Trietilamina (1.117 ml, 8.01 mmol) fue añadida a 2,4–dicloro–6–[(4–fluorofenil)sulfonilmetil]pirimidina (2.34 g, 7.29 mmol) en DCM (36.4 mL) a 0°C seguido por (3*S*)–3–metilmorfolina (0.737 g, 7.29 mmol) en DCM (20 mL) durante 15 minutos. La reacción fue luego agitada a RT durante 16 horas. La mezcla de reacción fue lavada con agua (50 mL), la capa orgánica secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 50% etil acetato en DCM, para dar el material deseado como un sólido beige (1.530 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.17 (3H, d), 3.13 – 3.20 (1H, m), 3.27 – 3.28 (1H, m), 3.39 – 3.46 (1H, m), 3.57 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.17 (1H, s), 4.65 (2H, s), 6.71 (1H, s), 7.48 (2H, t), 7.83 – 7.87 (2H, m)

Espectro LCMS: MH+ 386, tiempo de retención 1.94 min.

2,4–Dicloro–6–[(4–fluorofenil)sulfonilmetil]pirimidina

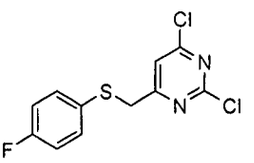


Ácido 3–cloroperoxibenzoico (3.78 g, 21.89 mmol) fue añadido en forma de porciones a 2,4–dicloro–6–[(4–fluorofenil)sulfanilmetil]pirimidina (2.11 g, 7.30 mmol), en DCM (36.5 mL) y la reacción fue agitada a RT durante 2 horas. La mezcla de reacción fue lavada con una solución saturada acuosa de hidrógeno carbonato de sodio (50 mL) y la capa orgánica secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto deseado (2.35 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 4.99 (2H, s), 7.48 – 7.52 (2H, m), 7.76 (1H, s), 7.85 – 7.88 (2H, m)

Espectro LCMS: MH+ 319, tiempo de retención 2.01 min.

2,4–Dicloro–6–[(4–fluorofenil)sulfanilmetil]pirimidina

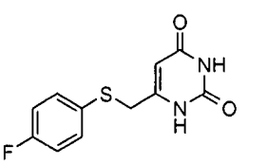


Oxicloruro de fósforo (15.2 g, 99.1 mmol) fue añadido a 6–[(4–fluorofenil)sulfanilmetil]–1*H*–pirimidina–2,4–diona (2.5 g, 9.91 mmol), y la solución resultante fue agitada a reflujo durante 7 horas. La reacción se dejó enfriar y el oxicloruro de fósforo fue eliminado a presión reducida para dar un aceite marrón. Esto fue disuelto en DCM y agua helada (50 mL) añadida seguido por bicarbonato de sodio sólido (hasta que la efervescencia se detiene). La capa acuosa fue extraída con DCM (2 x 50 mL) y los productos orgánicos secados ($MgSO_4$), filtrados y evaporados para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 40% etil acetato en isohexano, para dar el material deseado como una goma amarilla (2.11 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 4.21 (2H, s), 7.09 – 7.14 (2H, m), 7.34 – 7.38 (2H, m), 7.58 (1H, s)

Espectro LCMS: M–H+ 287, tiempo de retención 2.51 min.

6–[(4–Fluorofenil)sulfanilmetil]–1*H*–pirimidina–2,4–diona



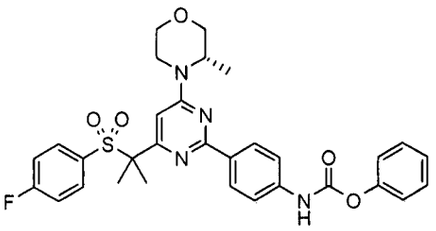
DBU (4.02 mL, 26.91 mmol) fue añadido a 4–fluorobencenotiol (3.45 g, 26.91 mmol), en DMF (90 mL) a RT. La solución resultante fue agitada a 20°C durante 15 minutos. 6–(Clorometil)–1*H*–pirimidina–2,4–diona (2.88 g, 17.94 mmol) fue luego añadida y la reacción agitada durante 4 horas. La mezcla de reacción fue concentrada y diluida con DCM (100 mL), y lavada con agua (100 mL). La capa acuosa fue acidificada con ácido clorhídrico 2M para dar un sólido blanco el cual fue filtrado y lavado con agua, luego secado al vacío para dar el producto deseado (2.5 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 3.80 (2H, s), 5.20 (1H, s), 7.18 – 7.23 (2H, m), 7.45 – 7.49 (2H, m), 10.90 (1H, s), 10.93 (1H, s)

Espectro LCMS: M–H– 251, tiempo de retención 0.80 min.

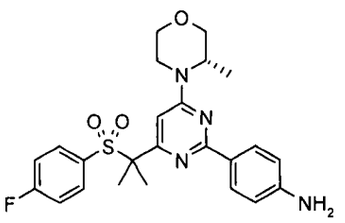
La preparación de fenil *N*-[4-[4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Fenil cloroformato (0.482 mL, 3.83 mmol) fue añadido en forma de gotas a 4-[4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1.8 g, 3.83 mmol) y bicarbonato de sodio (0.482 g, 5.74 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en DCM (50 mL) y lavada con agua (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el producto crudo el cual fue triturado con dietil éter para dar el material deseado como un sólido blanco (2.26 g).
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.80 (6H, d), 3.18 (1H, dt), 3.50 (1H, dt), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.55 (1H, s), 6.72 (1H, s), 7.24 – 7.33 (5H, m), 7.45 (2H, t), 7.52 (2H, d), 7.55 – 7.58 (2H, m), 7.88 (2H, d), 10.39 (1H, s)
Espectro LCMS: MH+ 591, tiempo de retención 3.10 min.

4-[4-[2-(4-Fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



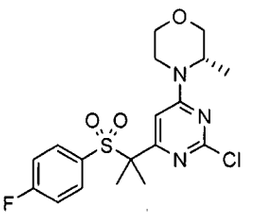
Diclorobis(trifenilfosfina)paladio(II) (170 mg, 0.24 mmol) fue añadido a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1.376 g, 6.28 mmol) y 2-cloro-4-[2-(4-

fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2 g, 4.83 mmol), y carbonato de sodio (5 mL, 10.00 mmol) en 18% DMF en DME:agua:etanol (7:3:2) (20 mL). La solución resultante fue agitada a 90°C durante 4 horas. La mezcla de reacción fue diluida con etil acetato (20 mL), y lavada con agua (2 x 20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 5 a 60% etil acetato en isohexano, para dar el material deseado como un sólido color crema (1.80 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.76 (6H, d), 3.14 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.51 (1H, d), 5.50 (2H, s), 6.49 (2H, d), 6.58 (1H, s), 7.31 (2H, t), 7.54 – 7.57 (2H, m), 7.62 (2H, d)

Espectro LCMS: MH+ 471, tiempo de retención 2.57 min.

2-Cloro-4-[2-(4-fluorofenil)sulfonilpropan-2-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Yodometano (0.32 mL, 5.20 mmol) fue añadido a tert-butóxido de sodio (498 mg, 5.20 mmol) y 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2 g, 5.18 mmol) en DMF (2 mL) a -10°C. La suspensión densa resultante fue agitada a RT durante 15 minutos para facilitar la agitación. Yodometano (0.32 mL, 5.20 mmol) y tert-butóxido de sodio (498 mg, 5.20 mmol) fueron nuevamente añadidos a la reacción y la suspensión resultante agitada a RT durante 15 minutos. La mezcla de reacción fue diluida con DCM (20 mL) y lavada con agua (20 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 50% etil acetato en DCM. Las fracciones puras fueron evaporadas hasta secarse para dar el producto deseado como un sólido blanco (2.00 g).

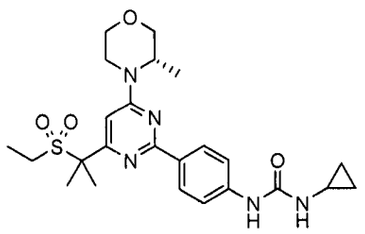
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 (6H, d), 3.17 (1H, dt), 3.43 (1H, dt), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.01 (1H, d), 4.38 (1H, s), 6.75 (1H, s), 7.44 (2H, t), 7.58 – 7.61 (2H, m)

Espectro LCMS: MH+ 414, tiempo de retención 2.35 min.

La preparación de 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

Ejemplo 62:

3-Ciclopropil-1-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

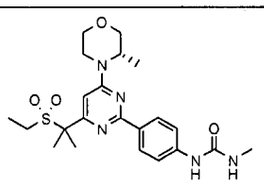
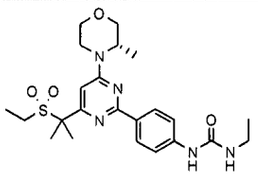
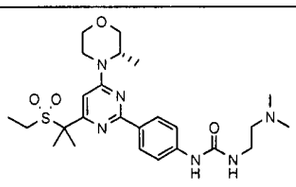
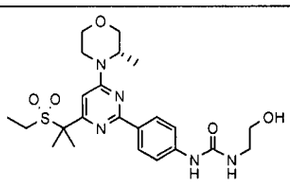
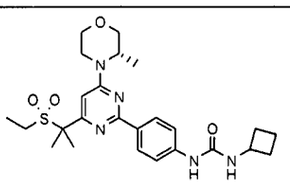
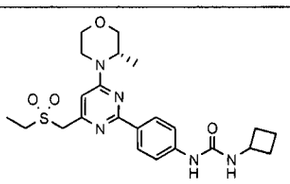
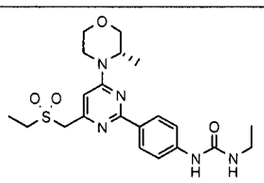


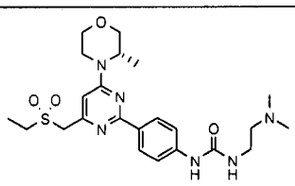
A una solución de fenil *N*-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0.29 mmol) en DMF (2 mL) fue añadido trietilamina (0.120 mL, 0.86 mmol) seguido por ciclopropilamina (0.100 mL, 1.44 mmol) y la reacción calentada a 50°C durante 2 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido blanco (85 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.14 (3H, t), 1.23 (3H, d), 1.79 (6H, s), 2.55 (1H, m), 3.17 – 3.21 (1H, m), 3.23 (2H, d), 3.46 – 3.50 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.43 (1H, d), 6.75 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.54 (1H, s).

Espectro LCMS: MH+ 488, tiempo de retención 2.19 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
62a		1-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea	502	2.42
62b		1-etil-3-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	476	2.16
62c		3-(2-dimetilaminoetil)-1-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	519	2.10
62d		1-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	492	1.83
62e		3-ciclobutil-1-[4-[4-(2-etilsulfonilpropan-2-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	462	2.00
62f		3-ciclobutil-1-[4-[4-(etilsulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	474	2.14
62g		1-etil-3-[4-[4-(etilsulfonilmetil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	448	1.87

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
62h		3–(2–dimetilaminoetil)–1–[4–[4–(etilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	491	1.83

Ejemplo 62a: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.14 (3H, t), 1.23 (3H, d), 1.54 – 1.68 (2H, m), 1.78 (6H, s), 1.83 –1.90 (2H, d), 2.18 – 2.25 (2H, m), 3.17 – 3.21 (1H, m), 3.23 (2H, q), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.15 (1H, q), 4.22 (1H, d), 4.59 (1H, s), 6.46 (1H, d), 6.75 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.56 (1H, s)

Ejemplo 62b: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.14 (3H, t), 1.23 (3H, d), 1.78 (6H, d), 3.09 – 3.16 (2H, m), 3.18 (1H, m), 3.22 (2H, t), 3.46 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.58 (1H, s), 6.16 (1H, t), 6.75 (1H, d), 7.50 (2H, d), 8.22 (2H, d), 8.66 (1H, s)

Ejemplo 62c: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.14 (3H, t), 1.23 (3H, d), 1.78 (6H, d), 3.09 – 3.16 (2H, m), 3.18 (1H, m), 3.22 (2H, t), 3.46 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.58 (1H, s), 6.16 (1H, t), 6.75 (1H, d), 7.50 (2H, d), 8.22 (2H, d), 8.66 (1H, s)

Ejemplo 62d: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.14 (3H, t), 1.22 – 1.24 (3H, m), 1.78 (6H, s), 3.17 (1H, t), 3.20 – 3.22 (2H, s), 3.24 (2H, m), 3.46 (2H, q), 3.48 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.21 – 4.24 (1H, m), 4.57 – 4.60 (1H, m), 4.73 (1H, t), 6.25 (1H, t), 6.75 (1H, s), 7.48 – 7.51 (2H, m), 8.23 (2H, d), 8.80 (1H, s)

Ejemplo 62e: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.14 (3H, t), 1.27 (3H, d), 1.78 (6H, m), 2.68 (3H, d), 3.18 (1H, m), 3.24 (2H, m), 3.46 – 3.53 (1H, m), 3.63 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.23 (1H, d), 4.59 (1H, s), 6.07 (1H, t), 6.75 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.74 (1H, s)

Ejemplo 62f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 – 1.25 (3H, m), 1.35 (3H, t), 1.59 – 1.66 (2H, m), 1.83 – 1.86 (2H, m), 2.19 – 2.23 (2H, m), 3.18 (1H, m), 3.33 (2H, m), 3.47 –

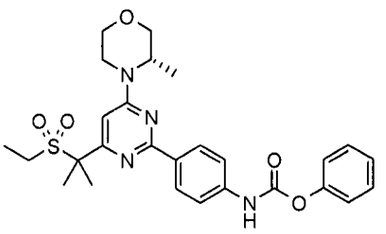
3.50 (1H, m), 3.66 (1H, d), 3.76 – 3.79 (1H, m), 3.96 (1H, d), 4.14 (2H, d), 4.45 (3H, m), 6.47 (1H, d), 6.78 (1H, s), 7.47 – 7.49 (2H, m), 8.18 – 8.20 (2H, m), 8.56 (1H, s)

Ejemplo 62g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.35 (3H, t), 3.09 – 3.16 (2H, m), 3.21 – 3.26 (1H, m), 3.33 (2H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.14 (1H, d), 4.45 (3H, s), 6.17 (1H, t), 6.77 (1H, s), 7.48 – 7.51 (2H, m), 8.18 – 8.20 (2H, m), 8.66 (1H, s)

Ejemplo 62h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 – 1.25 (3H, m), 1.35 (3H, t), 2.18 (6H, s), 2.34 (2H, t), 3.20 (3H, q), 3.33 (2H, d), 3.47 – 3.53 (1H, m), 3.63 – 3.67 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.14 (1H, d), 4.45 (3H, s), 6.16 (1H, t), 6.77 (1H, s), 7.47 – 7.51 (2H, m), 8.18 – 8.20 (2H, m), 8.89 (1H, s)

La preparación de fenil *N*–[4–[4–(2–etilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(2–etilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

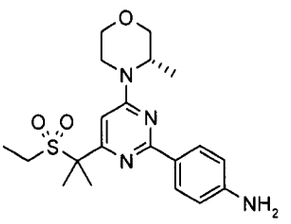


Fenil cloroformato (0.373 mL, 2.97 mmol) fue añadido en forma de gotas a 4–[4–(2–etilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (1.20 g, 2.97 mmol) y bicarbonato de sodio (0.374 g, 4.45 mmol) en dioxano (25 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y particionada entre etil acetato (150 mL) y agua (150 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el material deseado como un sólido blanco (1.40 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.79 (6H, d), 3.24 (3H, q), 3.47 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.96 – 4.00 (1H, m), 4.24 (1H, d), 4.60 (1H, s), 6.74 – 6.79 (2H, m), 7.24 – 7.27 (2H, m), 7.43 – 7.47 (2H, m), 7.61 – 7.64 (2H, m), 8.33 (2H, d), 10.43 (1H, s)

Espectro LCMS: MH+ 525, tiempo de retención 2.84 min.

4–[4–(2–Etilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina

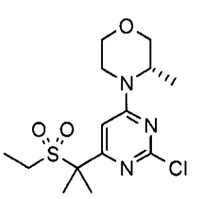


Diclorobis(trifenilfosfina)paladio(II) (0.360 g, 0.51 mmol) fue añadido a una solución desgasificada de 2–cloro–4–(2–etilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.784 g, 5.13 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (1.404 g, 6.41 mmol) y carbonato de sodio (12.82 mL, 25.64 mmol) en una mezcla de 18% DMF en DME:agua:etanol (7:3:2) (25 mL). La solución resultante fue agitada a 85°C durante 2 horas. La mezcla de reacción fue concentrada y particionada entre DCM (150 mL), y agua (100 mL) y los productos orgánicos lavados con salmuera (100 mL), secados ($MgSO_4$), filtrados y evaporados para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 2.5% metanol en DCM, para dar el material deseado como un sólido marrón (1.20 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.13 (3H, t), 1.21 (3H, d), 1.76 (6H, d), 3.14 – 3.18 (1H, m), 3.23 (2H, q), 3.45 – 3.52 (1H, m), 3.62 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.17 – 4.21 (1H, m), 4.54 – 4.56 (1H, m), 5.54 (2H, d), 6.61 (1H, d), 6.62 (2H, t), 8.06 (2H, d)

Espectro LCMS: MH+ 405, tiempo de retención 2.14 min.

2–Cloro–4–(2–etilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



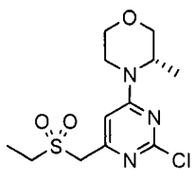
Yodometano (0.321 mL, 5.13 mmol) fue añadido a tert–butóxido de sodio (0.493 g, 5.13 mmol) y 2–cloro–4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.64 g, 5.13 mmol) en DMF (75 mL) a –5°C. La solución fue agitada a –5°C durante 15 minutos.

Yodometano adicional (0.321 mL, 5.13 mmol) y *ter*t–butóxido de sodio (0.493 g, 5.13 mmol) fueron añadidos y la reacción agitada a –5°C durante 15 minutos. La mezcla de reacción fue diluida con DCM (200 mL) y lavada con agua (2 x 100 mL) y salmuera (100 mL). Los productos orgánicos fueron secados ($MgSO_4$), filtrados y evaporados para dar el material deseado como un sólido marrón (1.784 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.16 (3H, t), 1.21 (3H, d), 1.69 (6H, s), 3.15 – 3.19 (2H, m), 3.14 – 3.24 (1H, m), 3.41 – 3.48 (1H, m), 3.57 – 3.61 (1H, m), 3.72 (1H, d), 3.92 – 3.95 (1H, m), 4.05 – 4.44 (2H, m), 6.87 (1H, s)

Espectro LCMS: MH+ 348, tiempo de retención 1.79 min.

2–Cloro–4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



Sal sódica del ácido etano sulfónico (3.94 g, 33.94 mmol) fue añadida en una porción a 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (12.0 g, 33.94 mmol) en acetonitrilo (250 mL) a RT. La suspensión resultante fue agitada a 80°C durante 16 horas. La mezcla de reacción fue evaporada hasta secarse y el residuo particionado entre DCM (250 mL) y agua (200 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 40% etil acetato en DCM, para dar el material deseado como un sólido amarillo (5.94 g).

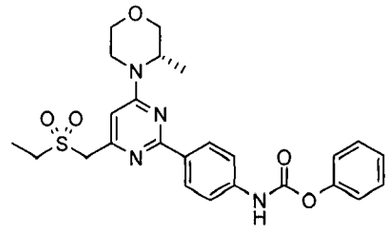
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.23 (3H, m), 1.28 (3H, t), 3.22 (2H, d), 3.32 (1H, s), 3.42 – 3.49 (1H, m), 3.58 – 3.62 (1H, m), 3.73 (1H, d), 3.92 – 3.96 (2H, m), 4.25 – 4.31 (1H, m), 4.43 (2H, s), 6.92 (1H, s)

Espectro LCMS: MH+ 320, tiempo de retención 1.46 min.

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

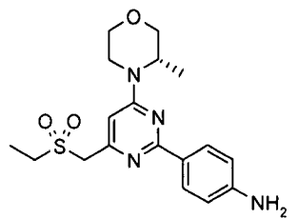


Fenil cloroformato (0.207 mL, 1.65 mmol) fue añadido en forma de gotas a 4–[4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (620 mg, 1.65 mmol) y bicarbonato de sodio (208 mg, 2.47 mmol) en dioxano (15 mL) bajo nitrógeno. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue evaporada hasta secarse y el residuo particionado entre etil acetato (200 mL) y agua (200 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para dar el material deseado como un sólido blanco (885 mg).

Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.21 – 1.29 (3H, m), 1.35 (3H, t), 3.20 – 3.28 (2H, m), 3.47 – 3.54 (2H, m), 3.64 – 3.68 (1H, m), 3.78 (1H, d), 3.97 – 4.01 (1H, m), 4.20 (1H, d), 4.48 (3H, s), 6.83 (1H, s), 7.24 – 7.30 (3H, m), 7.42 – 7.48 (2H, m), 7.64 (2H, d), 8.28 – 8.30 (2H, m), 10.45 (1H, s)

Espectro LCMS: MH+ 497, tiempo de retención 2.57 min.

4–[4–(Etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Diclorobis(trifenilfosfina)paladio(II) (0.162 g, 0.23 mmol) fue añadido a una solución desgasificada de 2–cloro–4–(etilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (0.74 g, 2.31 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.634 g, 2.89

mmol) y carbonato de sodio (5.78 mL, 11.57 mmol) en una mezcla de 18% DMF en DME:agua:etanol (7:3:2) (20 mL). La solución resultante fue agitada a 85°C durante 30 minutos. La mezcla de reacción fue concentrada y diluida con DCM (100 mL), luego lavada con agua (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 2.5% metanol en DCM. El material obtenido fue adicionalmente purificado usando una columna SCX, eluyendo con 7M amoniaco en metanol, para dar el material deseado como un sólido amarillo (0.62 g).

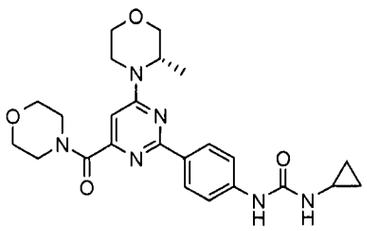
Espectro NMR: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.34 (3H, t), 3.16 – 3.19 (1H, m), 3.32 (2H, m), 3.45 – 3.52 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.96 – 3.99 (1H, m), 4.12 (1H, s), 4.42 (3H, d), 5.56 (2H, s), 6.59 – 6.62 (2H, m), 6.67 (1H, s), 8.01 – 8.04 (2H, m)

Espectro LCMS: MH+ 377, tiempo de retención 1.83 min.

La preparación de 2-cloro-4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

Ejemplo 63:

3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(morfolina-4-carbonil)pirimidin-2-il]fenil]urea

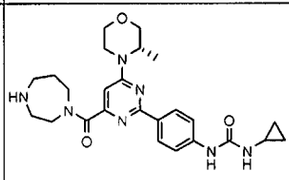
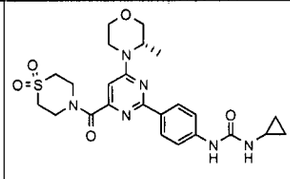
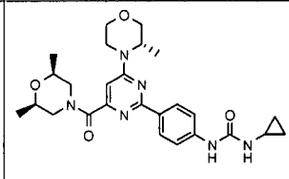
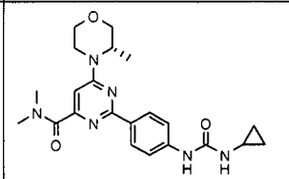


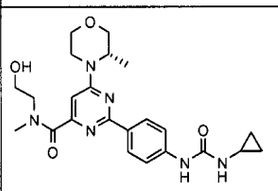
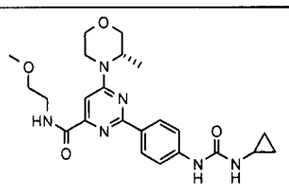
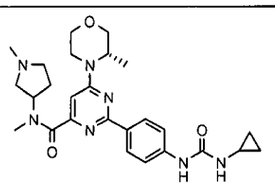
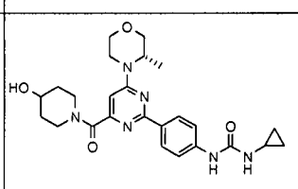
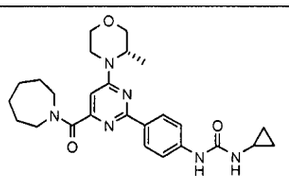
Ácido 2-[4-(Ciclopropilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxílico (100 mg, 0.25 mmol) fue añadido a morfolina (0.066 mL, 0.75 mmol), DIPEA (0.132 mL, 0.75 mmol) y HATU (144 mg, 0.38 mmol) en DMF seco (3 mL) a RT durante un período de 30 minutos bajo nitrógeno. La solución resultante fue agitada a RT durante 3 horas y el producto crudo purificado por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido blanco (98 mg).

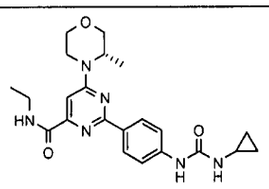
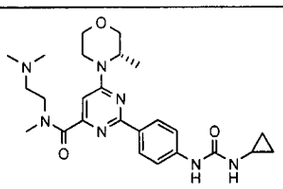
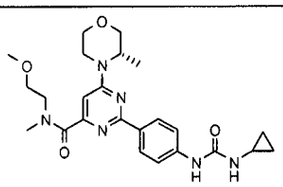
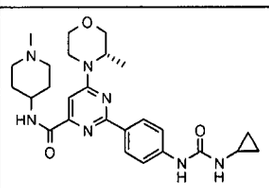
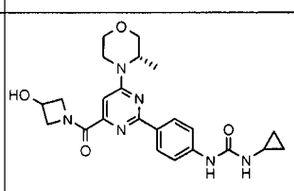
Espectro NMR: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.63–0.68 (2H, m), 1.23–1.25 (3H, d), 2.54–2.59 (1H, m), 3.18–3.27 (1H, m), 3.46–3.49 (3H, m), 3.60–3.69 (7H, m), 3.74–3.77 (1H, d), 3.95–3.99 (1H, dd), 4.21–4.24 (1H, d), 4.56 (1H, s), 6.43–6.44 (1H, d), 6.77 (1H, s), 7.50–7.52 (2H, d), 8.18–8.20 (2H, d), 8.54 (1H, s)

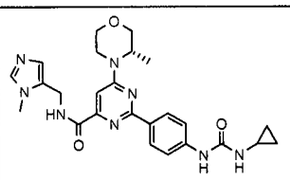
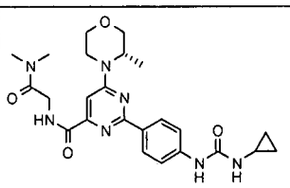
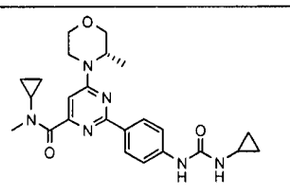
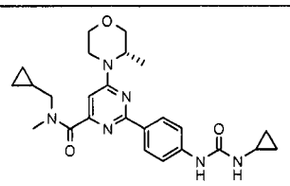
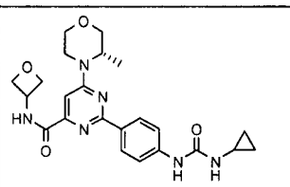
Espectro LCMS: MH+ 467, tiempo de retención 1.69 min

Los siguientes compuestos fueron preparados de una forma análoga a partir de ácido 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico usando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
63a		3–ciclopropil–1–[4–[4–(1,4–diazepán–1–carbonil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	479	1.6
63b		3–ciclopropil–1–[4–[4–(1,1–dioxo1,4–tiazinano–4–carbonil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	514	1.74
63c		3–ciclopropil–1–[4–[4–[(2R,6S)–2,6–dimetilmorfolina–4–carbonil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	494	1.93
63d		2–[4–(ciclopropilcarbamoilamino)fenil]–N,N–dimetil–6–[(3S)–3–	424	1.69

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metilmorfolin-4-il]pirimidina-4-carboxamida		
63e		2-[4-(ciclopropilcarbamoilamino)fenil]-N-(2-hidroxietil)-N-metil-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxamida	455	1.53
63f		2-[4-(ciclopropilcarbamoilamino)fenil]-N-(2-metoxietil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxamida	455	1.92
63g		2-[4-(ciclopropilcarbamoilamino)fenil]-N-metil-6-[(3S)-3-metilmorfolin-4-il]-N-(1-metilpirrolidin-3-il)pirimidina-4-carboxamida	494	1.72
63h		3-ciclopropil-1-[4-[4-(4-hidroxipiperidina-1-carbonil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	481	1.54
63i		1-[4-[4-(azepano-1-carbonil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropil-urea	479	2.15

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
63j		2-[4-(ciclopropilcarbamoilamino)fenil]-N-etil-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxamida	425	2.00
63k		2-[4-(ciclopropilcarbamoilamino)fenil]-N-(2-dimetilaminoetil)-N-metil-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxamida	482	1.68
63l		2-[4-(ciclopropilcarbamoilamino)fenil]-N-(2-metoxietil)-N-metil-6-[(3S)-3-metilmorfolin-4-il]pirimidina-4-carboxamida	469	1.77
63m		2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]-N-(1-metil-4-piperidil)pirimidina-4-carboxamida	494	1.93
63n		3-ciclopropil-1-[4-[4-(3-hidroxiazetidina-1-carbonil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	453	1.62

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
63o		2–[4–(ciclopropilcarbamoilamino)fenil]–N–[(3–metilimidazol–4–il)metil]–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxamida	491	1.79
63p		2–[4–(ciclopropilcarbamoilamino)fenil]–N–(dimetilcarbamoilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxamida	482	1.80
63q		N–ciclopropil–2–[4–(ciclopropilcarbamoilamino)fenil]–N–metil–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxamida	451	1.85
63r		2–[4–(ciclopropilcarbamoilamino)fenil]–N–(ciclopropilmetil)–N–metil–6–[(3S)–3–metilmorfolin–4–il]pirimidina–4–carboxamida	465	2.02
63s		2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3S)–3–metilmorfolin–4–il]–N–(oxetan–3–il)pirimidina–4–	453	1.84

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		carboxamida		

Ejemplo 63a: ^{1}H NMR (400MHz, $CDCl_3$) δ 0.68–0.68 (2H, d), 0.86–0.87 (2H, d), 1.34–1.35 (3H, d), 1.86–1.90 (1H, m), 1.94–2.02 (1H, m), 2.62–2.64 (1H, t), 2.99–3.04 (2H, m), 3.06–3.11 (2H, m), 3.30–3.37 (1H, td), 3.56–3.59 (1H, d), 3.63–3.68 (3H, m), 3.72–3.75 (1H, d), 3.78–3.84 (3H, m), 4.02–4.06 (1H, dd), 4.15–4.18 (1H, d), 4.49 (1H, s), 4.98–4.99 (1H, d), 6.62–6.64 (1H, d), 7.07–7.08 (1H, d), 7.48–7.50 (2H, d), 8.30–8.33 (2H, m)

Ejemplo 63b: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.63–0.67 (2H, m), 1.23–1.24 (3H, d), 1.64–1.70 (2H, m), 1.75–1.80 (2H, m), 2.54–2.58 (1H, m), 3.2–3.21 (1H, d), 3.36–3.44 (2H, dt), 3.46–3.53 (1H, m), 3.57–3.60 (1H, q), 3.62–3.65 (2H, m), 3.74–3.77 (1H, d), 3.95–3.98 (1H, dd), 4.21–4.24 (1H, d), 4.54 (1H, s), 6.43–6.44 (1H, d), 6.70–6.71 (1H, d), 7.49–7.51 (2H, d), 8.18–8.20 (2H, d), 8.45 (1H, s)

Ejemplo 63c: ^{1}H NMR (400MHz, $CDCl_3$) δ 0.68–0.72 (2H, m), 0.86–0.90 (2H, m), 1.13–1.15 (3H, dd), 1.27–1.29 (3H, d), 1.35–1.37 (3H, d), 2.54–2.61 (1H, t), 2.62–2.66 (1H, m), 2.82–2.91 (1H, m), 3.31–3.39 (1H, td), 3.57–3.63 (1H, td), 3.73–3.76 (3H, m), 3.82–3.85 (1H, d), 4.03–4.07 (1H, dd), 4.11–4.18 (2H, m), 4.51 (1H, s), 4.56–4.60 (1H, dd), 4.96 (1H, s), 6.69 (1H, s), 7.069 (1H, s), 7.51–7.53 (2H, d), 8.31–8.33 (2H, d),

Ejemplo 63d: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.42–0.44 (2H, m), 0.63–0.68 (2H, m), 1.23–1.25 (3H, d), 2.54–2.59 (1H, m), 2.99–3.01 (6H, d), 3.46–3.53 (1H, td), 3.62–3.66 (1H, dd), 3.74–3.77 (1H, d), 3.95–3.99 (1H, dd), 4.21–4.24 (1H, d), 4.55 (1H, s), 6.43–6.44 (1H, d), 6.71 (1H, s), 7.49–7.51 (2H, d), 8.19–8.21 (2H, d), 8.54 (1H, s)

Ejemplo 63e: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.44 (2H, m), 0.63–0.67 (2H, m), 1.23–1.25 (3H, d), 2.32–2.34 (1H, m), 2.54–2.61 (1H, m), 3.03 (3H, s), 3.18–3.25 (1H, td), 3.36–3.41 (1H, q), 3.49–3.50 (1H, d), 3.52–3.54 (1H, d), 3.57 (1H, s), 3.63–3.66 (1H, dd), 3.74–3.77 (1H, d), 3.95–3.99 (1H, dd), 4.21–4.23 (1H, d), 4.52 (1H, s), 4.74 (1H, s), 6.45–6.46 (1H, d), 6.70 (1H, s), 7.50–7.52 (2H, d), 8.17–8.20 (2H, m), 8.56 (1H, s)

Ejemplo 63f: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.45 (2H, m), 0.63–0.68 (2H, m), 1.24–1.26 (3H, d), 2.33–2.35 (1H, m), 2.67–2.69 (1H, m), 2.70 (1H, s), 2.74 (2H, s), 2.90 (3H, s), 3.49–3.53 (2H, m), 3.63–3.67 (1H, dd), 3.76–3.78 (1H, d), 3.96–4.00 (1H, dd), 4.35 (1H, s), 4.56–4.58 (1H, d), 6.43–6.44 (1H, d), 7.13 (1H, s), 7.52–7.54 (2H, d), 7.96 (1H, s), 8.38–8.40 (2H, d), 8.57 (1H, s)

Ejemplo 63g: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.44 (2H, m), 0.63–0.68 (2H, m), 1.23–1.25 (3H, d), 2.20 (2H, s), 2.27 (1H, s), 2.33–2.35 (2H, m), 2.67–2.69 (3H, m), 2.74 (1H, s), 2.90–2.91 (2H, d), 2.97 (2H, s), 3.17–3.21 (1H, m), 3.47–3.52 (1H, m), 3.63–3.66 (1H, dd), 3.74–3.77 (1H, d), 3.96–3.98 (1H, dd), 4.22–4.24 (1H, d), 4.32–4.34 (1H, d), 4.56 (1H, s), 6.43–6.45 (1H, m), 6.69–6.70 (1H, d), 7.49–7.53 (2H, dd), 8.19–8.21 (2H, dd), 8.54 (1H, s),

Ejemplo 63h: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.63–0.67 (2H, m), 1.23–1.24 (3H, d), 1.43 (2H, s), 1.74–1.84 (2H, d), 2.53–2.57 (1H, m), 3.14–3.18 (1H, m), 3.21–2.24 (2H, m), 3.46–3.52 (1H, td), 3.56 (1H, m), 3.62–3.66 (1H, dd), 3.74–3.77 (2H, d), 3.95–3.98 (1H, dd), 4.00–4.04 (1H, m), 4.21 (1H, d), 4.55 (1H, s), 4.77–4.78 (1H, d), 6.43–6.44 (1H, d), 6.71 (1H, s), 7.49–7.52 (2H, d), 8.18–8.20 (2H, d), 8.54 (1H, s)

Ejemplo 63i: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.63–0.68 (2H, m), 1.23–1.24 (3H, d), 1.60–1.61 (4H, d), 1.74–1.75 (4H, d), 2.67–2.69 (1H, m), 3.17–3.25 (1H, m), 3.37–3.40 (1H, t) 3.56–3.59 (1H, t), 3.62–3.65 (1H, dd), 3.74–3.77 (1H, d), 3.94–3.99 (1H, dd), 4.22–4.24 (1H, d), 4.54 (1H, s), 6.43–6.44 (1H, d), 6.69 (1H, s), 7.49–7.51 (2H, d), 8.18–2.20 (2H, d), 8.53 (1H, s)

Ejemplo 63j: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.45 (2H, m), 0.63–0.68 (2H, m), 1.15–1.19 (3H, t), 1.24–1.26 (3H, d), 2.56–2.60 (1H, m), 3.25–3.26 (1H, m), 3.33–3.42 (2H, m), 3.47–3.53 (1H, td), 3.64–3.67 (1H, dd), 3.75–3.78 (1H, d), 3.96–4.00 (1H, dd), 4.35–4.27 (1H, d), 4.57 (1H, s), 6.43–6.44 (1H, d), 7.13 (1H, s), 7.52–7.54 (2H, d), 8.40–8.42 (2H, d), 8.57 (1H, s) 8.91–8.93 (1H, t)

Ejemplo 63k: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.44 (2H, m), 0.63–0.68 (2H, m), 1.22–1.25 (3H, m), 2.01 (2H, s), 2.24 (2H, s), 2.55–2.58 (1H, m), 2.99–3.01 (3H, d), 3.27 (3H, s), 3.35–3.39 (3H, m), 3.46–3.49 (1H, dd), 3.52–3.56 (1H, td), 3.62–3.66 (1H, dd), 3.74–3.77 (1H, d), 3.96–3.98 (1H, d), 4.21–4.24 (1H, d), 4.55 (1H, s), 6.43–6.44 (1H, d), 6.68–6.70 (1H, d), 7.50–7.52 (2H, d), 8.20–8.22 (2H, d), 8.54 (1H, s)

Ejemplo 63l: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.44 (2H, m), 0.63–0.68 (2H, m), 1.23–1.25 (3H, d), 2.55–2.58 (1H, m), 3.02 (3H, s), 3.19 (2H, s), 3.24–3.25 (1H, m), 3.46–3.47

(1H, d), 3.49–3.54 (3H, m), 3.59–3.60 (1H, d), 3.61–3.66 (2H, dd), 3.74–3.78 (1H, d), 3.95–3.98 (1H, dd), 4.21–4.22 (1H, d), 4.51 (1H, s), 6.44 (1H, s), 6.69–6.71 (1H, s), 7.50–7.52 (2H, d), 8.18–8.20 (2H, d), 8.55 (1H, s)

Ejemplo 63m: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.45 (2H, m), 0.63–0.68 (2H, m), 1.24–1.25 (3H, d), 1.74–1.78 (4H, m), 1.97–2.04 (3H, m), 2.55–2.61 (1H, m), 2.76–2.79 (2H, d), 3.21–3.26 (1H, m), 3.27 (1H, s), 3.47–3.53 (1H, td), 3.63–3.67 (1H, dd), 3.73–3.78 (2H, d), 3.80–3.84 (1H, m), 3.96–4.00 (1H, dd), 4.24–4.27 (1H, d), 4.58 (1H, s), 6.44–6.45 (1H, d), 7.12 (1H, s), 7.52–7.54 (2H, d), 8.38–8.40 (2H, d), 8.51–8.54 (1H, d), 8.57 (1H, s)

Ejemplo 63n: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.44 (2H,m), 0.63–0.68 (2H, m), 1.23–1.25 (3H, d), 2.56–2.59 (1H, m), 3.19–3.23 (1H, dd), 3.46–3.53 (1H, td), 3.62–3.66 (1H, dd), 3.75–3.78 (1H, d), 3.80–3.84 (1H, m), 3.96–3.99 (1H, dd), 4.23 (1H, s), 4.26–4–31 (1H, qd), 4.42–4.47 (1H, m), 4.53–4.58 (2H, m), 4.88–4.94 (1H, m), 5.72–5.73 (1H, d), 6.44–6.45 (1H, d), 7.04 (1H, s), 7.52–7.54 (2H, d), 8.20–8.23 (2H, d), 8.56 (1H, s)

Ejemplo 63o: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.63–0.68 (2H, m), 1.24–1.26 (3H, d), 2.55–2.59 (1H, m), 3.21–3.25 (1H, m), 3.47–3.53 (1H, td), 3.63–3.64 (1H, d), 3.66 (3H, s), 3.75–3.78 (1H, d), 3.96–4.00 (1H, dd), 4.24–4.28 (1H, d), 4.52–4.54 (2H, d), 4.58 (1H, s), 6.42–6.44 (1H, d), 6.65 (1H, s), 7.15 (1H, s), 7.50–7.51 (1H, t), 7.52–7.53 (2H, d), 8.38–8.40 (2H, d), 8.56 (1H, s)

Ejemplo 63p: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.45 (2H, m), 0.63–0.68 (2H, m), 1.25–1.27 (3H, d), 2.56–2.59 (1H, m), 2.91 (3H, s), 3.03 (3H, s), 3.20–3.24 (1H, m), 2.48–3.54 (1H, td), 3.64–3.68 (1H, dd), 3.76–3.79 (1H, d), 3.97–4.00 (1H, dd), 4.18–4.20 (2H, d), 4.26 (1H, d), 4.59 (1H, s), 6.46–6.47 (1H, d), 7.14 (1H, s), 7.54–7.56 (2H, d), 8.34–8.36 (2H, d), 8.59 (1H, s), 8.99–9.02 (1H, t)

Ejemplo 63q: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.40–0.44 (2H, m), 0.49–0.53 (4H, m), 0.63–0.67 (2H, m), 1.22–1.24 (3H, d), 2.55–2.61 (2H, m), 2.87–2.88 (1H, d), 2.93 (2.95 (1H, m), 3.17–3.25 (1H, td) , 3.27 (1H, s), 3.47–3.54 (1H, td), 3.62–3.67 (1H, dd), 3.75–3.78 (1H, d), 3.94–3.98 (1H, dd), 4.21–4.24 (1H, d), 4.52 (1H, s), 6.42–6.43 (1H, d), 6.73 (1H, s), 7.49–7.51 (2H, d), 8.19–8.22 (2H, d), 8.53 (1H, s)

Ejemplo 63r: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.14–0.18 (1H, m), 0.30–0.34 (1H, m), 0.40–0.43 (2H, m), 0.44–0.48 (1H, dq), 0.51–0.56 (1H, dq), 0.63–0.67 (2H, m), 1.06–1.10 (1H, m), 1.22–1.25 (3H, m), 2.54–2.59 (1H, m), 3.03–3.06 (3H, d), 3.16–3.19 (1H, m), 3.20–3.25 (1H, m), 3.35–3.37 (1H, m), 3.46–3.53 (1H, td), 3.62–3.66 (1H, dd), 3.74–3.77 (1H, d), 3.95–3.98

(1H, dd), 4.22–4.24 (1H, d), 4.55 (1H, s) 6.44–6.45 (1H, d), 6.70–6.71 (1H, d), 7.49–7.59 (2H, dd), 8.18–8.21 (2H, dd), 8.54–8.55 (1H, d)

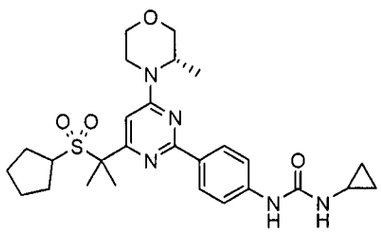
Ejemplo 63s: ^{1}H NMR (400MHz, DMSO–d_6) δ 0.41–0.45 (2H, m), 0.64–0.68 (2H, m), 1.24–1.25 (3H, d), 2.55–2.60 (1H, m), 3.17–3.25 (1H, m), 3.47–3.54 (1H, td), 3.63–3.67 (1H, dd), 3.75–3.78 (1H, d), 3.96–4.00 (1H, dd), 4.25–4.27 (1H, d), 4.57 (1H, s), 4.74–4.80 (4H, m), 5.04–5.13 (1H, m), 6.44–6.45 (1H, d), 7.11 (1H, s), 7.53–7.55 (2H, d), 8.46–8.48 (2H, d), 8.58 (1H, s), 9.38–9.40 (1H, d)

Prueba (c): Ejemplo (63) 0.41 μM; Ejemplo (63a) 0.092 μM; Ejemplo (63b) 0.5 μM; Ejemplo (63c) 0.26 μM.

La preparación de ácido 2–[4–(ciclopropilcarbamoilamino)fenil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina–4–carboxílico fue descrita anteriormente.

Ejemplo 64:

1–[4–[4–(2–Ciclopentilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–ciclopropil–urea

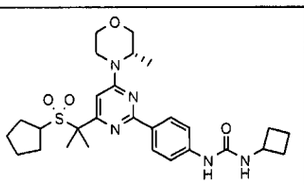
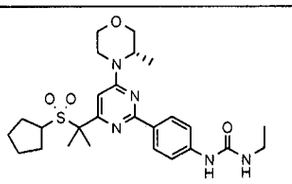
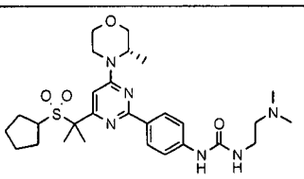
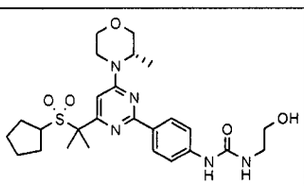
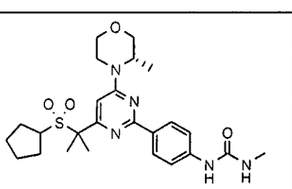


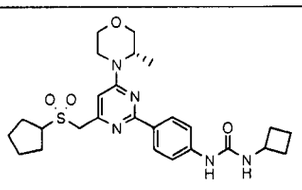
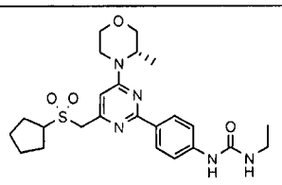
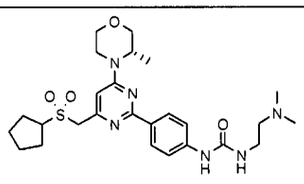
Trietilamina (0.175 mL, 1.25 mmol) fue añadida a una mezcla de fenil *N*–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (200 mg, 0.31 mmol) y ciclopropilamina (1.25 mmol) en NMP (2 mL) y calentada a 75°C durante 6 horas. La mezcla de reacción fue purificada por HPLC preparativa usando mezclas polares decrecientes de agua (conteniendo 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido (136 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.39 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.22 (3H, d), 1.40 – 1.48 (4H, m), 1.52 – 1.59 (4H, m), 1.70 – 1.80 (6H, m), 3.16 – 3.24 (1H, m), 3.46 – 3.54 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.91 – 4.01 (2H, m), 4.23 (1H, d), 4.60 (1H, s), 6.44 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.24 (2H, d), 8.55 (1H, s)

Espectro LCMS: MH+ 528, tiempo de retención 2.43 min

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64a		3–ciclobutil–1–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	542	2.7
64b		1–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea	516	2.42
64c		1–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	559	2.35
64d		1–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–hidroxietil)urea	532	2.04
64e		1–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–	502	2.26

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		urea		
64f		3–ciclobutil–1–[4–[4–(ciclopentilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	514	2.36
64g		1–[4–[4–(ciclopentilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea	488	2.13
64h		1–[4–[4–(ciclopentilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	531	2.08

Ejemplo 64a: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.39 – 1.68 (10H, m), 1.69 – 1.80 (6H, m), 1.86 (2H, q), 2.17 – 2.25 (2H, m), 3.16 – 3.24 (1H, m), 3.46 – 3.55 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.95 (1H, quinteto), 4.14 (1H, q), 4.22 (1H, d), 4.60 (1H, s), 6.46 (1H, d), 6.78 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.57 (1H, s)

Ejemplo 64b: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.22 (3H, d), 1.41 – 1.48 (4H, m), 1.51 – 1.57 (4H, m), 1.70 – 1.79 (6H, m), 3.12 (2H, q), 3.16 – 3.24 (1H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.91 – 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 6.17 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.67 (1H, s)

Ejemplo 64c: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.41 – 1.48 (4H, m), 1.52 – 1.58 (4H, m), 1.69 – 1.79 (6H, m), 2.19 (6H, s), 2.33 (2H, t), 3.16 – 3.24 (3H, m), 3.50 (1H,

td), 3.65 (1H, dd), 3.77 (1H, d), 3.90 – 4.01 (2H, m), 4.22 (1H, d), 4.59 (1H, s), 6.15 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.90 (1H, s)

Ejemplo 64d: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.41 – 1.47 (4H, m), 1.50 – 1.58 (4H, m), 1.70 – 1.79 (6H, m), 3.15 – 3.24 (3H, m), 3.44 – 3.54 (3H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.91 – 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s)

Ejemplo 64e: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.41 – 1.49 (4H, m), 1.51 – 1.58 (4H, m), 1.68 – 1.81 (6H, m), 2.67 (3H, d), 3.16 – 3.24 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.91 – 4.00 (2H, m), 4.22 (1H, d), 4.60 (1H, s), 6.07 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.75 (1H, s)

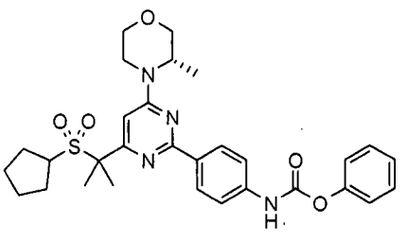
Ejemplo 64f: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.57 – 1.74 (6H, m), 1.82 – 1.90 (2H, m), 1.93 – 2.07 (4H, m), 2.17 – 2.25 (2H, m), 3.16 – 3.27 (1H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.73 – 3.83 (1H, m), 3.99 (1H, dd), 4.10 – 4.20 (2H, m), 4.45 (2H, s), 4.49 (1H, s), 6.47 (1H, d), 6.79 (1H, s), 7.47 (2H, d), 8.19 (2H, d), 8.56 (1H, s)

Ejemplo 64g: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.60 – 1.74 (4H, m), 1.89 – 2.06 (4H, m), 3.09 – 3.16 (2H, m), 3.18 – 3.26 (1H, m), 3.46 – 3.54 (1H, m), 3.65 (1H, dd), 3.75 – 3.83 (2H, m), 3.99 (1H, dd), 4.17 (1H, d), 4.43 (2H, s), 4.49 (1H, s), 6.16 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.66 (1H, s)

Ejemplo 64h: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.24 (3H, d), 1.60 – 1.74 (4H, m), 1.91 – 2.07 (4H, m), 2.19 (6H, s), 2.34 (2H, t), 3.16 – 3.22 (3H, m), 3.50 (2H, td), 3.65 (2H, dd), 3.74 – 3.83 (2H, m), 3.99 (2H, dd), 4.16 (1H, d), 4.44 (2H, s), 4.51 (1H, s), 6.17 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.89 (1H, s)

La preparación de fenil *N*–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(2–ciclopentilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

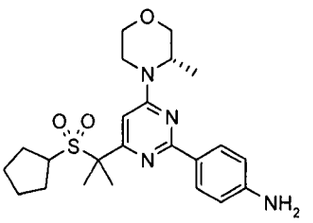


Fenil cloroformato (0.635 mL, 5.06 mmol) fue añadido a 4-[4-(2-ciclopentilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1.5 g, 3.37 mmol) e hidrógeno carbonato de sodio (0.425 g, 5.06 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue diluida con etil acetato (200 mL), y lavada con agua (125 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido blanco (1.30 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.41 – 1.47 (2H, m), 1.50 – 1.57 (2H, m), 1.69 – 1.78 (4H, m), 1.79 (6H, d), 3.21 (1H, td), 3.51 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.92 – 4.01 (2H, m), 4.24 (1H, d), 4.62 (1H, s), 6.82 (1H, s), 7.23 – 7.31 (3H, m), 7.42 – 7.48 (2H, m), 7.64 (2H, d), 8.34 (2H, d), 10.45 (1H, s)

Espectro LCMS: MH+ 565, tiempo de retención 3.0 min

4-[4-(2-Ciclopentilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



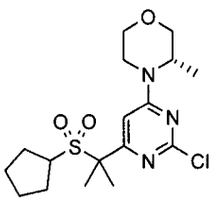
Bis(trifenilfosfina)paladio(II) cloruro (200 mg, 0.28 mmol) fue añadido a 2-cloro-4-(2-ciclopentilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1.66 g, 4.28 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1.406 g, 6.42 mmol) y carbonato de sodio (10 mL, 20.00 mmol) en una mezcla de etanol (5 mL), DMF (10 mL), agua (7 mL) y DME (25 mL) a RT. La mezcla resultante fue desgasificada, luego agitada a 95°C durante 18 horas. La mezcla de reacción se dejó enfriar y fue diluida con etil acetato (200 mL), luego lavada con agua (2 x 150 mL), y salmuera (150 mL). La capa orgánica fue

secada (Na_2SO_4), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 60% etil acetato en isohexano, y el residuo obtenido fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido rosado pálido (1.52 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.41 – 1.50 (2H, m), 1.52 – 1.60 (2H, m), 1.69 – 1.80 (10H, m), 3.17 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.90 – 3.99 (2H, m), 4.18 (1H, d), 4.56 (1H, s), 5.57 (2H, s), 6.61 (2H, d), 6.68 (1H, s), 8.06 (2H, d)

Espectro LCMS: MH+ 445, tiempo de retención 2.42 min

2-Cloro-4-(2-ciclopentilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

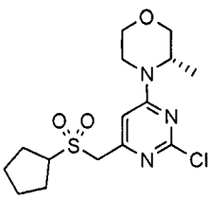


Tert-butóxido de sodio (5.56 mmol) fue añadido a una solución de 2-cloro-4-(ciclopentilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2 g, 5.56 mmol) en DMF (10 mL) a -5°C, seguido por la adición en forma de gotas de yodometano (0.365 mL) a -5°C. Tert-butóxido de sodio (5.56 mmol) y yodometano (0.365 mL) adicional fueron añadidos y la reacción agitada a -5°C toda la noche. La mezcla de reacción fue diluida con etil acetato (250 mL), y lavada con agua (2 x 150 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido color crema (1.66 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (4H, d), 1.46 – 1.61 (6H, m), 1.69 – 1.84 (12H, m), 1.70 (9H, s), 3.20 (3H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.75 (1H, s), 3.85 (2H, q), 3.96 (1H, d), 4.06 (1H, d), 4.46 (1H, s), 6.90 (1H, s)

Espectro LCMS: MH+ 388, tiempo de retención 2.47 min

2-Cloro-4-(ciclopentilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

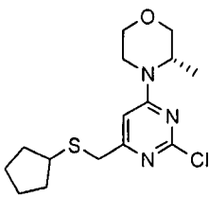


Peróxido de hidrógeno (19.54 mL, 632 mmol) fue añadido a 2-cloro-4-(ciclopentilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (10.36 g, 31.60 mmol), tungstato dihidrato de sodio (0.208 g, 0.63 mmol) (disuelto en una mínima cantidad de agua) y solución de ácido sulfúrico 2M (0.177 mL) en dioxano (100 mL) a 55°C al aire. La solución resultante fue agitada a 55°C durante 2 horas. La mezcla de reacción fue diluida con etil acetato (100 mL), y lavada con agua, luego una solución acuosa 10% de metabisulfito de sodio. La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 5 a 70% etil acetato en isohexano, para dar el material deseado como una goma incolora (9.7 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.64 (4H, m), 1.95 (4H, m), 3.24 (1H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.71 (1H, m), 3.95 (2H, m), 4.35 (1H, s), 4.40 (2H, s), 6.91 (1H, s)

Espectro de masa: MH+360

2-Cloro-4-(ciclopentilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



DIPEA (9.62 mL, 55.57 mmol) fue añadida a ciclopentanotiol (5.93 mL, 55.57 mmol), en DMF (80 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 20 minutos. 2-Cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (13.1g, 37.05 mmol) fue añadida a la reacción y agitada durante 2 horas a RT. La mezcla de reacción fue diluida con etil acetato (500 mL), y lavada con agua (2 x 200 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo

fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 30% etil acetato en isohexano, para dar el material deseado como una goma incolora (11.13 g).

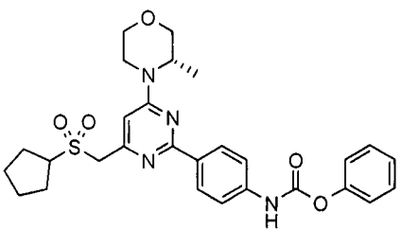
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.43 (2H, m), 1.53 (2H, m), 1.65 (2H, m), 1.94 (2H, m), 3.16 (2H, m), 3.44 (1H, td), 3.71 (1H, d), 3.95 (2H, m), 4.35 (1H, s), 6.79 (1H, s)

Espectro de masa: MH+ 328

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente

La preparación de fenil *N*–[4–[4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación

Fenil *N*–[4–[4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

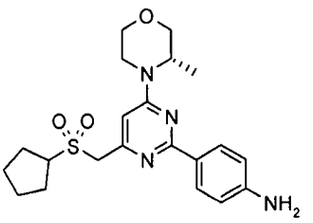


Fenil cloroformato (0.759 mL, 6.05 mmol) fue añadido a 4–[4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (1.68 g, 4.03 mmol) e hidrógeno carbonato de sodio (0.508 g, 6.05 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue diluida con etil acetato (200 mL), y lavada con agua (125 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido blanco (2.10 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.25 (3H, d), 1.57 – 1.76 (4H, m), 1.93 – 2.08 (4H, m), 3.24 (1H, td), 3.47 – 3.54 (1H, m), 3.66 (1H, dd), 3.75 – 3.84 (2H, m), 3.99 (1H, dd), 4.20 (1H, d), 4.47 (2H, s), 4.52 (1H, s), 6.84 (1H, s), 7.24 – 7.31 (3H, m), 7.42 – 7.48 (2H, m), 7.64 (2H, d), 8.29 (2H, d), 10.47 (1H, s)

Espectro LCMS: MH+ 537, tiempo de retención 2.75 min

4–[4–(Ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Bis(trifenilfosfina)paladio(II) cloruro (118 mg, 0.17 mmol) fue añadido a 2–cloro–4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.67 g, 4.64 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (1.525 g, 6.96 mmol) y carbonato de sodio (10 mL, 20.00 mmol) en una mezcla de etanol (6 mL), DMF (10 mL), agua (6 mL) y DME (20 mL) a RT. La mezcla resultante fue desgasificada, luego agitada a 95°C durante 18 horas. La mezcla de reacción fue diluida con etil acetato (400 mL), y lavada con agua (2 x 150 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 60% etil acetato en isohexano, para dar el material deseado como un sólido cristalino color crema (1.680g).

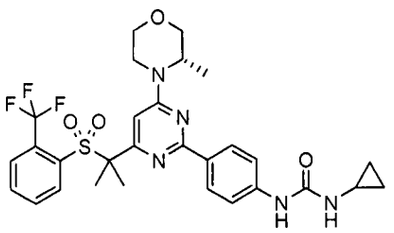
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.58 – 1.73 (4H, m), 1.93 – 2.06 (4H, m), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.74 – 3.82 (2H, m), 3.97 (1H, dd), 4.14 (1H, d), 4.39 (2H, s), 4.47 (1H, s), 5.57 (2H, s), 6.60 (2H, d), 6.67 (1H, s), 8.03 (2H, d)

Espectro LCMS: MH+ 417, tiempo de retención 2.09 min

La preparación de 2–cloro–4–(ciclopentilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

Ejemplo 65:

3–Ciclopropil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidin–2–il]fenil]urea

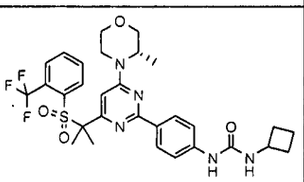


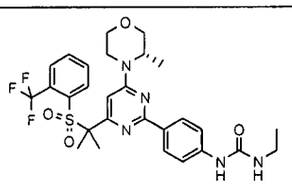
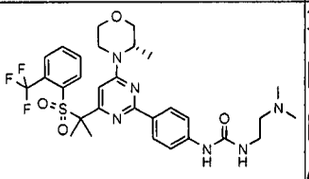
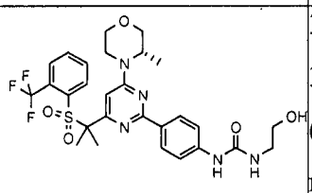
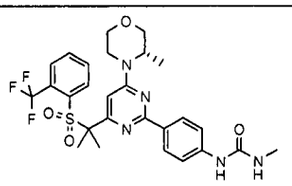
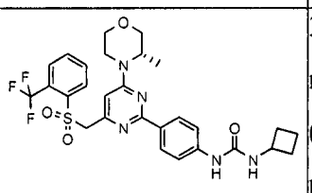
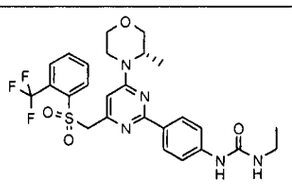
Trietilamina (0.197 mL, 1.40 mmol) fue añadida a una mezcla de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]carbamato (200 mg,0.35 mmol) y ciclopropilamina (1.40 mmol) en NMP (2 mL) y calentada a 75°C durante 6 horas. La mezcla de reacción fue purificada por HPLC preparativa usando mezclas polares decrecientes de agua (con 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido (163 mg).

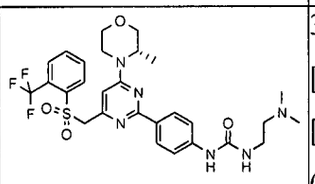
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 – 0.43 (2H, m), 0.63 – 0.66 (2H, m), 1.20 (3H, d), 1.84 (6H, d), 3.11 – 3.19 (1H, m), 3.49 (1H, dd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.62 (1H, s), 6.41 (1H, d), 6.67 (1H, s), 7.32 (2H, d), 7.59 (2H, d), 7.78 (1H, d), 7.82 – 7.91 (2H, m), 7.97 (1H, d), 8.48 (1H, s)

Espectro LCMS: MH+ 604, tiempo de retención 2.59 min

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
65a		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]urea	618	2.83

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
65b		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]urea	592	2.60
65c		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]urea	635	2.53
65d		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]urea	608	2.22
65e		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[2-[2-(trifluorometil)fenil]sulfonilpropan-2-il]pirimidin-2-il]fenil]urea	578	2.42
65f		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]fenil]urea	590	2.56
65g		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]fenil]urea	564	2.39

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
65h		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[[2–(trifluorometil)fenil]sulfonilmetil]pirimidin–2–il]fenil]urea	607	1.32

Ejemplo 65a: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.57 – 1.68 (4H, m), 1.84 (6H, d), 2.18 – 2.25 (2H, m), 3.12 – 3.18 (1H, m), 3.45 – 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.09 – 4.18 (2H, m), 4.60 (1H, s), 6.43 (1H, d), 6.66 (1H, s), 7.29 (2H, d), 7.59 (2H, d), 7.78 (1H, d), 7.82 – 7.91 (2H, m), 7.97 (1H, d), 8.50 (1H, s)

Ejemplo 65b: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.06 (3H, t), 1.20 (3H, d), 1.82 (6H, d), 3.08 – 3.19 (2H, m), 3.49 (1H, dd), 3.64 (1H, dd), 3.77 (1H, d), 3.94 – 3.99 (1H, m), 4.12 (1H, d), 4.62 (1H, s), 6.14 (1H, t), 6.68 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.77 – 7.80 (1H, m), 7.82 – 7.91 (2H, m), 7.97 (1H, d), 8.60 (1H, s)

Ejemplo 65c: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.84 (6H, d), 2.20 (6H, s), 2.34 (2H, t), 3.09 – 3.21 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.61 (1H, s), 6.14 (1H, t), 6.67 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.78 (2H, dd), 7.82 – 7.91 (2H, m), 7.97 (2H, d), 8.83 (1H, s)

Ejemplo 65d: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.19 (3H, d), 1.85 (6H, d), 3.11 – 3.20 (3H, m), 3.43 – 3.53 (3H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.60 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.67 (1H, s), 7.30 (2H, d), 7.59 (2H, d), 7.78 (1H, dd), 7.82 – 7.91 (2H, m), 7.95 – 7.99 (1H, m), 8.74 (1H, s)

Ejemplo 65e: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.20 (3H, d), 1.84 (6H, d), 2.66 (3H, d), 3.15 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.61 (1H, s), 6.02 – 6.07 (1H, m), 6.66 (1H, s), 7.31 (2H, d), 7.59 (2H, d), 7.76 – 7.80 (1H, m), 7.82 – 7.91 (2H, m), 7.95 – 7.99 (1H, m), 8.67 (1H, s)

Ejemplo 65f: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.10 (3H, t), 1.20 (3H, d), 1.58 – 1.67 (2H, m), 1.81 – 1.92 (2H, m), 2.16 – 2.25 (2H, m), 3.12 – 3.22 (1H, m), 3.44 – 3.52 (1H, m), 3.63 (1H, d), 3.97 (1H, d), 4.06 – 4.17 (2H, m), 4.44 (1H, s), 4.77 (2H, s), 6.45 (1H, d), 6.71

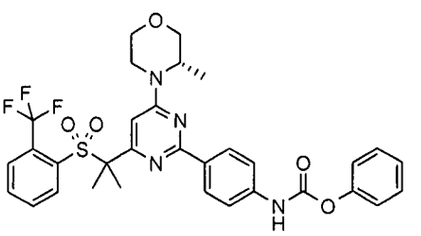
(1H, s), 7.33 (2H, d), 7.71 (2H, d), 7.76 – 7.82 (1H, m), 7.87 – 7.93 (2H, m), 8.09 (1H, d), 8.52 (1H, s)

Ejemplo 65g: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.21 (3H, d), 3.08 – 3.22 (3H, m), 3.48 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.44 (1H, s), 4.78 (2H, s), 6.15 (1H, t), 6.70 (1H, s), 7.35 (2H, d), 7.72 (2H, d), 7.79 (1H, t), 7.87 – 7.93 (2H, m), 8.08 (1H, d), 8.61 (1H, s)

Ejemplo 65h: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 2.19 (6H, s), 2.33 (2H, t), 3.13 – 3.22 (3H, m), 3.44 – 3.53 (1H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.10 (1H, d), 4.44 (1H, s), 4.76 (2H, s), 6.14 (1H, t), 6.70 (1H, s), 7.34 (2H, d), 7.71 (2H, d), 7.79 (1H, t), 7.87 – 7.92 (2H, m), 8.08 (1H, d), 8.84 (1H, s)

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidin–2–il]fenil]carbamato



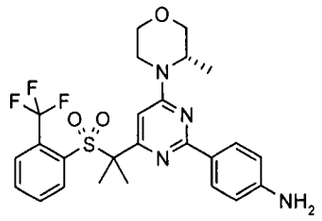
Fenil cloroformato (0.542 mL, 4.32 mmol) fue añadido a 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidin–2–il]anilina (1.5 g, 2.88 mmol) e hidrógeno carbonato de sodio (0.363 g, 4.32 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante fue agitada a RT durante 2 horas luego diluida con etil acetato (200 mL), y lavada con agua (125 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido blanco (1.38 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 1.85 (6H, d), 3.16 (1H, td), 3.45 – 3.54 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.63 (1H, s),

6.71 (1H, s), 7.23 – 7.29 (3H, m), 7.42 – 7.47 (4H, m), 7.69 (2H, d), 7.78 (1H, d), 7.82 – 7.92 (2H, m), 7.98 (1H, d), 10.37 (1H, s)

Espectro LCMS: MH+ 641, tiempo de retención 3.08 min

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidin–2–il]anilina

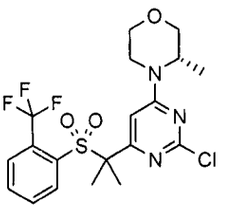


Bis(trifenilfosfina)paladio(II) cloruro (200 mg, 0.28 mmol) fue añadido a 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidina (1.91 g, 4.12 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (1.353 g, 6.18 mmol) y carbonato de sodio (10 mL, 20.00 mmol) en una mezcla de etanol (5 mL), DMF (10 mL), agua (7 mL) y DME (25 mL) a RT. La mezcla resultante fue desgasificada, luego agitada a 95°C durante 18 horas. La mezcla de reacción se dejó enfriar y fue diluida con etil acetato (200 mL), y lavada con agua (2 x 200 mL), y salmuera (100 mL). La capa orgánica fue secada (Na_2SO_4), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 60% etil acetato en isohexano, y el material resultante triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido blanco (1.50 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.18 (3H, d), 1.82 (6H, d), 3.12 (1H, td), 3.47 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.57 (1H, s), 5.47 (2H, s), 6.42 (2H, d), 6.56 (1H, s), 7.44 (2H, d), 7.78 – 7.89 (3H, m), 7.92 – 7.96 (1H, m)

Espectro LCMS: MH+ 521, tiempo de retención 2.56 min

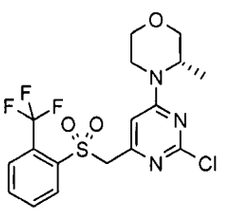
2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[2–(trifluorometil)fenil]sulfonilpropan–2–il]pirimidina



Tert-butóxido de sodio (4.59 mmol) fue añadido a una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidina (2 g, 4.59 mmol) en DMF (10 mL) a -5°C, seguido por la adición en forma de gotas de yodometano (0.030 mL) a -5°C. Tert-butóxido de sodio (4.59 mmol) y yodometano (0.030 mL) adicionales fueron añadidos y la reacción agitada a -5°C durante toda la noche. Los productos orgánicos fueron eliminados al vacío y el residuo particionado entre etil acetato (200 mL) y agua (100 mL). La capa orgánica fue lavada con agua (100 mL), secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido color crema (1.91 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.13 (1H, td), 3.41 (1H, td), 3.57 (1H, dd), 3.71 (1H, d), 3.89 – 3.98 (2H, m), 4.46 (1H, s), 6.72 (1H, s), 7.87 – 8.02 (4H, m)

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidina



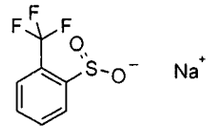
2-(Trifluorometil)bencenosulfinato de sodio (10.24 g, 44 mmol) fue añadido a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (13 g, 36.77 mmol), en acetonitrilo (500 mL) a RT bajo nitrógeno. La mezcla resultante fue agitada a 80°C durante 3 horas. 2-(trifluorometil)bencenosulfinato de sodio adicional (10.2 g, 44 mmol) fue añadido y la reacción calentada a 80°C durante 1 hora. La mezcla de reacción se dejó enfriar y fue concentrada al vacío. El material fue disuelto en etil acetato (500 mL), y lavado con agua (200 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente

de elución 0 a 40% etil acetato en isohexano, para dar el material deseado como un sólido color crema/naranja (9.48 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.17 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.27 (1H, s), 4.68 (2H, s), 6.79 (1H, s), 7.94 (3H, m), 8.08 (1H, d)

Espectro LCMS: MH+ 436; tiempo de retención 2.35 min.

2-(Trifluorometil)bencenosulfinato de sodio



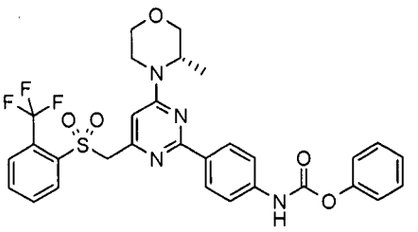
Sulfito de sodio (3.92 mL, 81.88 mmol) fue disuelto en agua y agitado a RT 10 minutos. Bicarbonato de sodio (13.74 g, 163.52 mmol) fue añadido y la mezcla agitada a 50°C durante 1 hora. 2-(Trifluorometil)benceno-1-sulfonil cloruro (12.62 mL, 81.76 mmol) fue añadido en forma de gotas a la mezcla de reacción la cual fue luego agitada a 50°C durante 18 horas. La mezcla de reacción fue evaporada hasta secarse y el residuo suspendido en metanol (250 mL) y agitado a RT durante 20 minutos. El sólido fue eliminado por filtración y el filtrado evaporado para dar el material deseado (20.00 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.40 (1H, d), 7.51 (1H, d), 7.64 (1H, d), 8.05 (1H, d)

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil] sulfonilmetil]pirimidin-2-il]fenil]carbamato

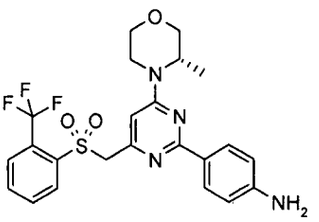


Fenil cloroformato (0.535 mL, 4.26 mmol) fue añadido a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]anilina (1.4 g, 2.84 mmol) e hidrógeno carbonato de sodio (0.358 g, 4.26 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante fue agitada a RT durante 2 horas, luego la mezcla de reacción fue diluida con etil acetato (200 mL), y lavada con agua (125 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con una mezcla de dietil éter e isohexano para dar el material deseado como un sólido blanco (1.70 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 (1H, d), 4.47 (1H, s), 4.79 (2H, s), 6.75 (1H, s), 7.23 – 7.31 (3H, m), 7.42 – 7.51 (4H, m), 7.77 – 7.83 (2H, m), 7.87 – 7.92 (2H, m), 8.09 (1H, d), 10.39 (1H, s)

Espectro LCMS: MH+ 613, tiempo de retención 2.92 min

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidin-2-il]anilina



Bis(trifenilfosfina)paladio(II) cloruro (300 mg, 0.43 mmol) fue añadido a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidina (1.66 g, 3.81 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1.252 g, 5.71 mmol) y carbonato de sodio (10 mL, 20.00 mmol) en una mezcla de etanol (6 mL), DMF (10 mL), agua (6 mL) y DME (20 mL) a RT. La mezcla resultante fue desgasificada, luego agitada a 95°C durante 18 horas. La mezcla de reacción se dejó enfriar, luego fue diluida con etil acetato (400 mL), y lavada con agua (2 x 200 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada

para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 60% etil acetato en isohexano, para dar el material deseado como un sólido cristalino color crema (1.40 g).

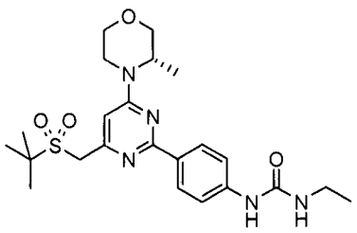
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.19 (3H, d), 3.14 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.04 – 4.11 (1H, m), 4.41 (1H, s), 4.72 (2H, s), 5.51 (2H, s), 6.47 (2H, d), 6.59 (1H, s), 7.56 (2H, d), 7.76 – 7.81 (1H, m), 7.86 – 7.92 (2H, m), 8.07 (1H, d)

Espectro LCMS: MH+ 493, tiempo de retención 2.35 min

La preparación de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[[2–(trifluorometil)fenil] sulfonilmetil]pirimidina fue descrita anteriormente.

Ejemplo 66:

3–Etil–1–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]urea

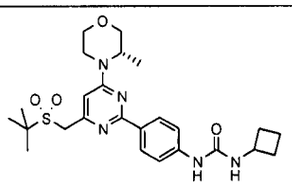
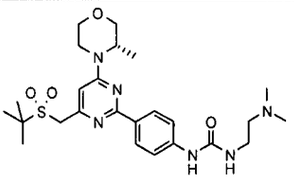
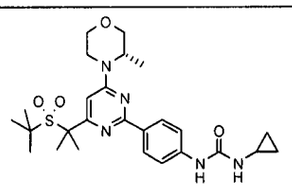
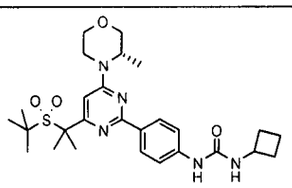
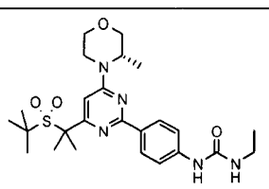


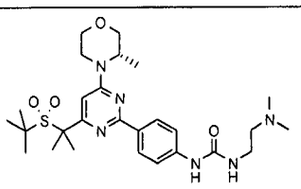
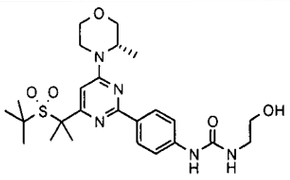
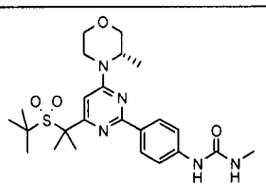
Etilamina hidrocloruro (86.4 mg, 1.03 mmol) fue añadido a fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]carbamato (120 mg, 0.23 mmol) y trietilamina (0.21 mL, 1.49 mmol) en DMF (2 mL). La mezcla de reacción se dejó reposar a RT durante 65 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (con 1% NH_3) y acetonitrilo como eluentes, para dar el material deseado como un sólido incoloro (79.0 mg).

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.25 (3H, d), 1.39 (9H, s), 3.10 – 3.25 (3H, m), 3.45 – 3.54 (1H, m), 3.63 – 3.69 (1H, m), 3.79 (1H, d), 3.95 – 4.03 (1H, m), 4.18 (1H, d), 4.46 (3H, s), 6.18 (1H, t), 6.75 (1H, s), 7.50 (2H, m), 8.21 (2H, d), 8.68 (1H, s)

Espectro LCMS: MH+ 476, tiempo de retención 2.04 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
66a		3–ciclobutil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]urea	502	2.25
66b		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]urea	519	1.97
66c		3–ciclopropil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	516	2.36
66d		3–ciclobutil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	530	2.64
66e		3–etil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]urea	504	2.34

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
66f		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-tert-butilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	547	2.27
66g		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-tert-butilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	520	1.98
66h		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(2-tert-butilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea	490	2.27

Ejemplo 66a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.39 (9H, s), 1.54 – 1.69 (2H, m), 1.79 – 1.92 (2H, m), 2.15 – 2.27 (2H, m), 3.15 – 3.25 (1H, m), 3.51 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.10 – 4.22 (2H, m), 4.46 (3H, s), 6.46 (1H, d), 6.75 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.1 (1H, s)

Ejemplo 66b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 – 1.25 (3H, m), 1.39 (9H, s), 2.19 (6H, s), 2.34 (2H, t), 3.19 – 3.25 (1H, m), 3.45 – 3.56 (1H, m), 3.62 – 3.68 (1H, m), 3.79 (1H, d), 3.95 – 4.02 (1H, m), 4.08 (2H, q), 4.18 (1H, d), 4.46 (3H, s), 6.17 (1H, t), 6.75 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.90 (1H, s)

Ejemplo 66c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.41 – 0.44 (2H, m), 0.63 – 0.68 (2H, m), 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.55 – 2.59 (1H, m), 3.18 (1H, dt), 3.51 (1H, dt), 3.66 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.22 (1H, d), 4.51 (1H, br, s), 6.44 (1H, d), 6.88 (1H, s), 7.52 (2H, d), 8.27 (2H, d), 8.55 (1H, s)

Ejemplo 66d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.58 – 1.68 (2H, m), 1.80 – 1.91 (8H, m), 2.15 – 2.25 (2H, m), 3.12 – 3.23 (1H, m), 3.45 – 3.55 (1H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.94 – 4.02 (1H, m), 4.08 – 4.26 (2H, m), 4.51 (1H, br, s), 6.47 (1H, d), 6.88 (1H, s), 7.49 (2H, d), 8.26 (2H, d), 8.58 (1H, s)

Ejemplo 66e: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 3.10 – 3.24 (3H, m), 3.44 – 3.55 (1H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.94 – 4.01 (1H, m), 4.22 (1H, d), 4.51 (1H, br, s), 6.17 (1H, t), 6.88 (1H, s), 7.51 (2H, d), 8.26 (2H, d), 8.67 (1H, s)

Ejemplo 66f: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.19 (6H, s), 2.35 (2H, t), 3.13 – 3.23 (3H, m), 3.45 – 3.54 (1H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.94 – 4.01 (1H, m), 4.22 (1H, d), 4.52 (1H, br, s), 6.17 (1H, t), 6.88 (1H, s), 7.50 (2H, d), 8.26 (2H, d), 8.91 (1H, s)

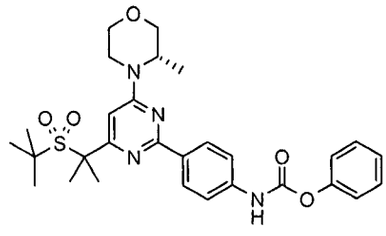
Ejemplo 66g: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 3.12 – 3.22 (3H, m), 3.43 – 3.54 (3H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.95 – 4.01 (1H, m), 4.22 (1H, d), 4.51 (1H, br, s), 4.74 (1H, t), 6.27 (1H, t), 6.88 (1H, s), 7.50 (2H, d), 8.27 (2H, d), 8.82 (1H, s)

Ejemplo 66h: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.15 (9H, s), 1.21 (3H, d), 1.85 (3H, s), 1.88 (3H, s), 2.67 (3H, d), 3.14 – 3.23 (1H, m), 3.46 – 3.55 (1H, m), 3.63 – 3.69 (1H, m), 3.78 (1H, d), 3.96 – 4.02 (1H, m), 4.22 (1H, d), 4.52 (1H, br, s), 6.06 – 6.12 (1H, m), 6.88 (1H, s), 7.52 (2H, d), 8.26 (2H, d), 8.77 (1H, s)

Prueba (c): Ejemplo (66c) 0.15 μM; Ejemplo (66d) 0.16 μM; Ejemplo (66e) 0.26 μM; Ejemplo (66f) 0.04 μM; Ejemplo (66g) 0.3 μM.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]fenil]carbamato



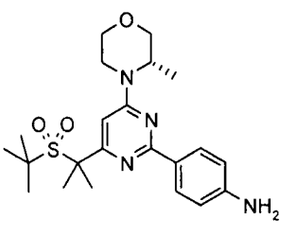
Fenil cloroformato (0.368 mL, 2.93 mmol) fue añadido a 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]anilina (1.153 g, 2.67 mmol) e hidrógeno carbonato de sodio (0.336 g, 4.00 mmol) en dioxano (20 mL) a RT. La lechada resultante fue

agitada a RT durante 2 horas. La mezcla de reacción fue particionada entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$), filtrada y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 20%–70% etil acetato en isohexano, para dar el material deseado como un sólido casi incoloro (1.42 g).

Espectro NMR: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.25 (9H, s), 1.32 (3H, d), 1.95 (3H, s), 1.97 (3H, s), 3.31 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.18 (1H, d), 4.47 (1H, br), 6.88 (1H, s), 7.10 (1H, br, s), 7.20 – 7.27 (3H, m), 7.41 (2H, t), 7.55 (2H, d), 8.43 (2H, d)

Espectro LCMS: MH+ 553, tiempo de retención 3.05 min.

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidin–2–il]anilina

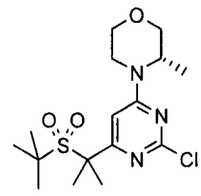


Diclorobis(trifenilfosfina)–paladio(II) (0.103 g, 0.15 mmol) fue añadido a 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidina (1.10 g, 2.93 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.833 g, 3.80 mmol) y carbonato de sodio acuoso 2M (5.27 mL, 10.53 mmol) en DMF (6 mL), DME (5 mL), etanol (5 mL) y agua (12.5 mL) a RT bajo nitrógeno. La reacción fue purgada con nitrógeno durante 15 minutos y la mezcla resultante fue agitada a 80°C durante 16 horas. La mezcla de reacción fue diluida con etil acetato y lavada con agua. La solución orgánica fue secada ($MgSO_4$), filtrada, y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%–100% etil acetato en isohexano, para dar el material deseado como un sólido amarillo (1.19 g).

Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (9H, s), 1.30 (3H, d), 1.93 (3H, s), 1.95 (3H, s), 3.28 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 3.90 (2H, s), 4.03 (1H, dd), 4.16 (1H, d), 4.46 (1H, br), 6.72 (2H, d), 6.79 (1H, s), 8.26 (2H, d)

Espectro LCMS: MH+ 433, tiempo de retención 2.42 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–tert–butilsulfonilpropan–2–il)pirimidina

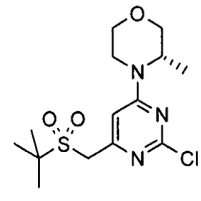


Tert–butóxido de sodio (0.345 g, 3.59 mmol) fue añadido a 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidina (1.250 g, 3.59 mmol) en DMF (30 mL) a 0°C bajo nitrógeno. Yodometano (0.224 mL, 3.59 mmol) fue añadido y la solución resultante fue agitada a 0°C durante 15 minutos. *Tert*–butóxido de sodio adicional (0.345 g, 3.59 mmol) fue añadido seguido por yodometano (0.224 mL, 3.59 mmol) y la solución resultante fue agitada a 0°C durante 1 hora. La reacción fue diluida con DCM (100 mL) y lavada con agua (100 mL) y salmuera (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y el solvente evaporado para dar una goma la cual se cristalizó lentamente. El producto crudo fue cromatografiado en sílice, eluyendo con 0–40% etil acetato en DCM, para dar el material deseado como un sólido incoloro (1.14 g).

Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (9H, s), 1.30 (3H, d), 1.84 (3H, s), 1.86 (3H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.99 – 4.05 (2H, m), 4.30 (1H, br, s), 6.89 (1H, s).

Espectro LCMS: MH+ 376, 378, tiempo de retención 2.52 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidina



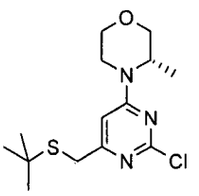
Una solución de peróxido de hidrógeno (9.48 mL, 107.30 mmol) (35% solución acuosa) fue añadida en forma de gotas a una solución agitada de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfanilmetil)pirimidina (9.82 g, 31.1 mmol), tungstato dihidrato de sodio (0.205 g, 0.62 mmol) y ácido sulfúrico (0.6 mL, 1M, 0.6 mmol) en dioxano (80 mL). La mezcla fue calentada a 55°C al aire durante 1 hora. Cuando la reacción se completó, la solución fue diluida con agua y enfriada. Una solución de metabisulfito de sodio (10% p/v) fue añadida

para destruir el peróxido remanente. La solución fue extraída con DCM, secada ($MgSO_4$) y filtrada para dar el material deseado como una goma casi incolora (9.34 g).

Espectro NMR: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.44 (9H, s), 3.29 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.78 (1H, d), 3.97 – 4.13 (2H, m), 4.21 (2H, s), 4.30 (1H, br, s), 6.71 (1H, s).

Espectro LCMS: MH+ 348, 350, tiempo de retención 1.82 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfanilmetil)pirimidina



N–Etildiisopropilamina (8.61 mL, 49.78 mmol) fue añadida a 2–metil–2–propanetiol (4.21 mL, 37.33 mmol), en DMF (55 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 20 minutos. 2–Cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (11.00 g, 31.11 mmol) fue añadida a la mezcla de reacción en una porción. La mezcla fue agitada durante 4 horas a RT. La mezcla de reacción fue colocada en un baño de agua a 60°C durante 1.5 horas, luego particionada entre etil acetato y agua. La capa orgánica fue lavada con agua adicional y luego fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado como una goma amarilla (10.02 g).

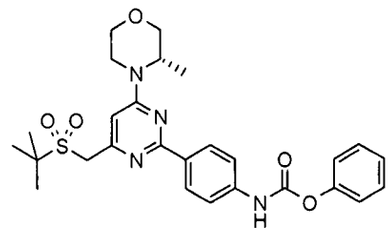
Espectro NMR: 1H NMR (399.9 MHz, CDCl3) δ 1.31 (3H, d), 1.34 (9H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.66 – 3.71 (3H, m), 3.78 (1H, d), 3.97 – 4.07 (2H, m), 4.31 (1H, br, s), 6.56 (1H, s)

Espectro LCMS: MH+ 316, 318, tiempo de retención 2.61 min.

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil)pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(tert-butilsulfonilmetil)pirimidin-2-il]fenil]carbamato

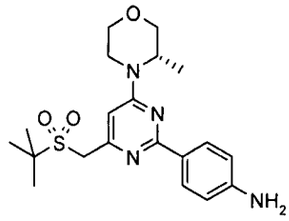


Fenil cloroformato (0.227 mL, 1.81 mmol) fue añadido a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(tert-butilsulfonilmetil)pirimidin-2-il]anilina (665 mg, 1.64 mmol) e hidrógeno carbonato de sodio (207 mg, 2.47 mmol) en dioxano (12 mL). La lechada resultante fue agitada a RT durante 1 hora. La mezcla fue particionada entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%-80% etil acetato en isohexano, para dar el material deseado como una película seca amarilla (860 mg).

Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 (9H, s), 3.32 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.20 (1H, d), 4.34 (2H, s), 4.46 (1H, br), 6.68 (1H, s), 7.10 (1H, s), 7.19 – 7.27 (3H, m), 7.40 (2H, t), 7.53 (2H, d), 8.37 (2H, d)

Espectro LCMS: MH+ 525, tiempo de retención 2.69 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(tert-butilsulfonilmetil)pirimidin-2-il]anilina



Diclorobis(trifenilfosfina)-paladio(II) (63 mg, 0.09 mmol) fue añadido a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(tert-butilsulfonilmetil)pirimidina (626 mg, 1.8 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (513 mg, 2.34 mmol) y carbonato de sodio acuoso 2M (3.24 mL, 6.48 mmol) en DMF (3.75 mL), DME (5 mL), etanol (5 mL) y agua (12.5 mL) a RT bajo nitrógeno. La mezcla de reacción fue purgada con nitrógeno durante 15 minutos y la mezcla resultante fue agitada a 80°C durante 16 horas. La mezcla fue particionada entre etil

acetato y agua. La solución orgánica fue secada ($MgSO_4$), filtrada, y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%–100% etil acetato en isohexano, para dar el material deseado como un sólido amarillo (681 mg).

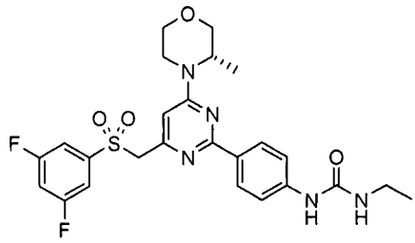
Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.43 (9H, s), 3.30 (1H, m), 3.60 (1H, m), 3.74 (1H, dd), 3.81 (1H, d), 3.89 (2H, s), 4.03 (1H, dd), 4.18 (1H, d), 4.31 (2H, d), 4.44 (1H, br), 6.61 (1H, s), 6.71 (2H, d), 8.21 (2H, d)

Espectro LCMS: MH+ 405, tiempo de retención 1.98 min.

La preparación de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(tert–butilsulfonilmetil) pirimidina fue descrita anteriormente.

Ejemplo 67:

1–[4–[4–[(3,5–Difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea

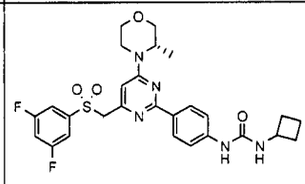
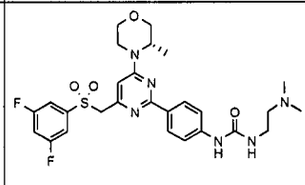
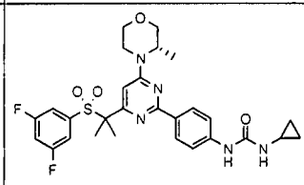
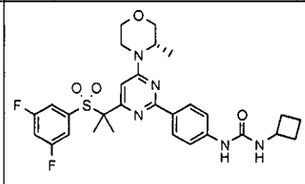
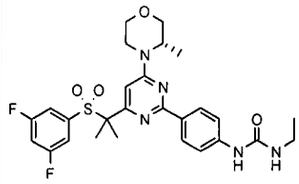


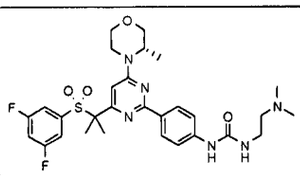
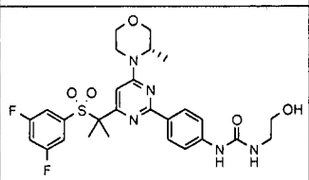
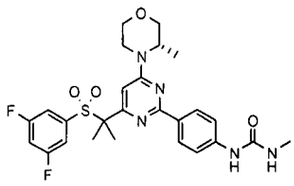
Fenil *N*–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (120 mg, 0.207 mmol) fue añadido a una mezcla de etilamina hidrocloruro (86 mg, 1.03 mmol) y trietilamina (0.2 mL, 1.49 mmol) en DMF (1.5 mL) a RT. La mezcla de reacción se dejó reposar a RT durante 65 horas. El producto crudo fue purificado por HPLC preparativa usando mezclas polares decrecientes de agua (con 1% amoniaco) y acetonitrilo como eluentes, para dar el material deseado como un sólido incoloro (19.0 mg).

Espectro NMR: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.07 (3H, t), 1.22 (3H, d), 3.09 – 3.3 (3H, m), 3.44 – 3.3 (1H, m), 3.61 – 3.67 (1H, m), 3.78 (1H, d), 3.94 – 4.01 (1H, m), 4.09 – 4.18 (1H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.16 (1H, t), 6.71 (1H, s), 7.40 (2H, d), 7.58 – 7.64 (2H, m), 7.72 – 7.83 (3H, m), 8.65 (1H, s).

Espectro LCMS: MH+ 532, tiempo de retención 2.29 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
67a		3–ciclobutil–1–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	558	2.51
67b		1–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	575	2.25
67c		3–ciclopropil–1–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	572	2.60
67d		3–ciclobutil–1–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	586	2.81
67e		3–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1–etil–urea	560	2.59

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
67f		1–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea	603	2.57
67g		1–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–hidroxietil)urea	576	2.23
67h		1–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	546	2.44

Ejemplo 67a: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.56 – 1.70 (2H, m), 1.80 – 1.94 (2H, m), 2.15 – 2.27 (2H, m), 3.14 – 3.24 (1H, m), 3.44 – 3.53 (1H, m), 3.61 – 3.67 (1H, m), 3.77 (1H, d), 3.95 – 4.02 (1H, m), 4.08 – 4.20 (2H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.46 (1H, d), 6.71 (1H, s), 7.38 (2H, d), 7.59 – 7.64 (2H, m), 7.72 – 7.83 (3H, m), 8.55 (1H, s).

Ejemplo 67b: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.22 (3H, d), 2.19 (6H, s), 2.34 (2H, t), 3.14 – 3.23 (3H, m), 3.44 – 3.54 (1H, m), 3.62 – 3.66 (1H, m), 3.77 (1H, d), 3.94 – 4.00 (1H, m), 4.06 – 4.14 (1H, m), 4.41 (1H, br, s), 4.87 (2H, s), 6.16 (1H, t), 6.71 (1H, s), 7.39 (2H, d), 7.58 – 7.64 (2H, m), 7.74 – 7.83 (3H, m), 8.88 (1H, s).

Ejemplo 67c: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.39 – 0.45 (2H, m), 0.62 – 0.69 (2H, m), 1.23 (3H, d), 1.82 (6H, s), 2.54 – 2.60 (1H, m), 3.13 – 3.22 (1H, m), 3.46 – 3.54 (1H, m), 3.62 – 3.68 (1H, m), 3.78 (1H, d), 3.95 – 4.00 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 6.43 (1H, s), 6.71 (1H, s), 7.16 – 7.23 (2H, d), 7.41 (2H, d), 7.60 – 7.67 (1H, m), 7.84 (2H, d), 8.53 (1H, s).

Ejemplo 67d: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.56 – 1.69 (2H, m), 1.78 – 1.92 (8H, m), 2.17 – 2.26 (2H, m), 3.12 – 3.22 (1H, m), 3.46 – 3.53 (1H, m), 3.61 – 3.68 (1H, m), 3.78 (1H, d), 3.95 – 4.02 (1H, m), 4.10 – 4.22 (2H, m), 4.59 (1H, br, s), 6.46 (1H, d), 6.71 (1H, s), 7.15 – 7.23 (2H, m), 7.38 (2H, d), 7.60 – 7.68 (1H, m), 7.84 (2H, d), 8.55 (1H, s).

Ejemplo 67e: ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.08 (3H, t), 1.23 (3H, d), 1.83 (6H, s), 3.09 – 3.22 (3H, m), 3.50 (1H, t), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.19 (1H, d), 4.60 (1H, br, s), 6.16 (1H, s), 6.71 (1H, s), 7.21 (2H, s), 7.41 (2H, d), 7.59 – 7.69 (1H, m), 7.84 (2H, d), 8.65 (1H, s).

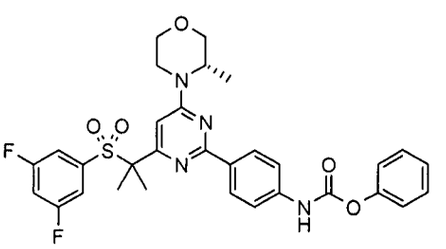
Ejemplo 67f: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.80 – 1.83 (6H, m), 2.18 (6H, s), 2.34 (2H, t), 3.12 – 3.23 (3H, m), 3.44 – 3.54 (1H, m), 3.63 – 3.67 (1H, m), 3.77 (1H, d), 3.94 – 4.01 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 6.15 (1H, t), 6.70 (1H, s), 7.15 – 7.23 (2H, m), 7.39 (2H, d), 7.59 – 7.66 (1H, m), 7.84 (2H, d), 8.86 (1H, s).

Ejemplo 67g: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.80 – 1.83 (6H, m), 3.12 – 3.23 (3H, m), 3.40 – 3.53 (3H, m), 3.62 – 3.67 (1H, m), 3.77 (1H, d), 3.95 – 4.01 (1H, m), 4.18 (1H, d), 4.59 (1H, br, s), 4.73 (1H, t), 6.24 (1H, t), 6.70 (1H, s), 7.16 – 7.23 (2H, m), 7.39 (2H, d), 7.59 – 7.66 (1H, m), 7.84 (2H, d), 8.78 (1H, s).

Ejemplo 67h: ^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.82 (6H, s), 2.66 (3H, d), 3.12 – 3.22 (1H, m), 3.44 – 3.54 (1H, m), 3.60 – 3.68 (1H, m), 3.77 (1H, d), 3.93 – 4.00 (1H, m), 4.18 (1H, d), 4.58 (1H, br, s), 6.03 – 6.09 (1H, m), 6.70 (1H, s), 7.14 – 7.23 (2H, m), 7.40 (2H, d), 7.63 (1H, t), 7.83 (2H, d), 8.71 (1H, s).

La preparación de fenil *N*–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

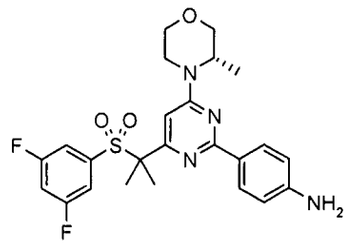


Fenil cloroformato (0.413 mL, 3.29 mmol) fue añadido a 4–[4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (1.46 g, 2.99 mmol) e hidrógeno carbonato de sodio (0.377 g, 4.48 mmol) en dioxano (25 mL). La lechada resultante fue agitada a RT durante 1 hora. La mezcla fue particionada entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$), filtrada, y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%–80% etil acetato en isohexano, para dar una goma incolora. Este material fue triturado con dietil éter para dar el material deseado como un sólido cristalino incoloro (1.808 g).

Espectro NMR: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.36 (3H, d), 1.89 (6H, s), 3.34 (1H, dt), 3.63 (1H, dt), 3.79 (1H, dd), 3.86 (1H, d), 4.08 (1H, dd), 4.14 (1H, d), 4.48 – 4.58 (1H, m), 6.66 (1H, s), 6.88 – 6.95 (1H, m), 7.04 (1H, s), 7.08 – 7.13 (2H, m), 7.19 – 7.28 (3H, m), 7.38 – 7.44 (4H, m), 7.98 (2H, d).

Espectro LCMS: MH+ 609, tiempo de retención 3.26 min.

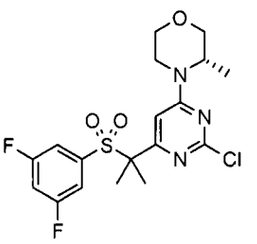
4–[4–[2–(3,5–Difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Una corriente de nitrógeno fue pasada a través de una mezcla de 2–cloro–4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.4 g, 3.24 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.923 g, 4.21 mmol) y carbonato de sodio acuoso 2M (5.83 mL, 11.67 mmol) en DMF (6 mL), DME (5 mL), etanol (5 mL) y agua (12.5 mL) a RT. La mezcla de reacción fue tratada con diclorobis(trifenilfosfina)paladio(II) (0.114 g, 0.16 mmol) y fue agitada a 80°C durante 1 hora. La mezcla de reacción fue diluida con etil acetato y lavada con agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%–60% etil acetato en isohexano, para dar el material deseado como un sólido amarillo pálido (1.496 g).

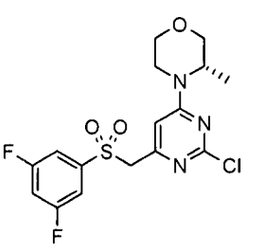
Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.88 (6H, s), 3.32 (1H, dt), 3.63 (1H, dt), 3.77 (1H, dd), 3.82 (1H, s), 3.86 (2H, s), 4.05 (1H, dd), 4.12 (1H, d), 4.46 – 4.54 (1H, m), 6.57 – 6.62 (3H, m), 6.88 – 6.93 (1H, m), 7.08 – 7.12 (2H, m), 7.82 (2H, d).
Espectro LCMS: MH+ 489, tiempo de retención 2.77 min.

2–Cloro–4–[2–(3,5–difluorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



Tert–butóxido de sodio (0.336 g, 3.49 mmol) fue añadido a 2–cloro–4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (1.41 g, 3.49 mmol) en DMF (30 mL) a 0°C bajo nitrógeno. Yodometano (0.217 mL, 3.49 mmol) fue añadido y la solución resultante fue agitada a 0°C durante 15 minutos. *Tert*–butóxido de sodio (0.336 g, 3.49 mmol) fue añadido seguido por yodometano (0.217 mL, 3.49 mmol) y la solución resultante fue agitada a 0°C durante 1 hora. La reacción fue vertida en agua (100 mL). El precipitado resultante fue aislado por filtración y secado al vacío, para dar el producto deseado como un sólido incoloro (1.434 g).
Espectro NMR: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.77 (6H, s), 3.32 (1H, dt), 3.58 (1H, dt), 3.72 (1H, dd), 3.81 (1H, d), 3.97 – 4.05 (2H, m), 4.36 (1H, br, s), 6.69 (1H, s), 7.07 – 7.16 (3H, m).
Espectro LCMS: MH+ 432, 434, tiempo de retención 2.78 min.

2–Cloro–4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina

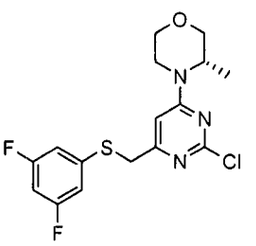


Una solución de tungstato dihidrato de sodio (199 mg, 0.60 mmol) en agua (2 mL) fue añadida a una solución agitada de 2–cloro–4–[(3,5–difluorofenil)sulfanilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (11.23 g, 30.2 mmol) y ácido sulfúrico 2M (0.302 mL, 0.60 mmol) en dioxano (40 mL). Peróxido de hidrógeno (3.22 mL, 104.19 mmol) fue añadido y la mezcla fue agitada a RT toda la noche. Un precipitado fue recogido por filtración y secado al vacío. El filtrado fue particionado entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 5% – 20% etil acetato en DCM, y el producto obtenido combinado con el material precipitado para dar el material deseado como un sólido casi incoloro (11.27 g).

Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 3.31 (1H, dt), 3.56 (1H, dt), 3.71 (1H, dd), 3.80 (1H, d), 3.98 – 4.10 (2H, m), 4.31 (2H, s), 6.55 (1H, s), 7.12 (1H, tt), 7.30 – 7.36 (2H, m).

Espectro LCMS: MH+ 404,406, tiempo de retención 2.32 min.

2–Cloro–4–[(3,5–difluorofenil)sulfanilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



DIPEA (8.07 mL, 46.67 mmol) fue añadida a 3,5–difluorobencenotiol (5.00 g, 34.22 mmol), en DMF (55 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 20 minutos. 2–Cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (11.00 g, 31.11 mmol) fue añadida a la mezcla de reacción en una porción. La mezcla fue agitada durante 4 horas a RT. La mezcla de reacción fue calentada en un baño de agua a 60°C durante 1.5 horas antes de ser particionada entre etil acetato y agua. La solución orgánica fue lavada con agua adicional, secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado como una goma (12.24 g).

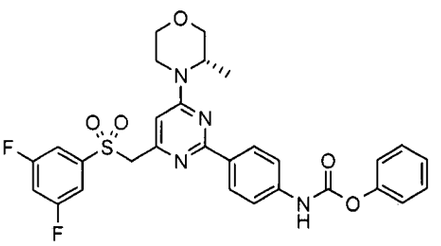
Espectro NMR: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.27 (3H, d), 3.24 (1H, dt), 3.52 (1H, dt), 3.66 (1H, dd), 3.76 (1H, d), 3.96 – 4.04 (4H, m), 4.21 (1H, br, s), 6.41 (1H, s), 6.59 – 6.66 (1H, m), 6.80 – 6.86 (2H, m).

Espectro LCMS: MH+ 372,374, tiempo de retención 2.66 min.

La preparación de 2–cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

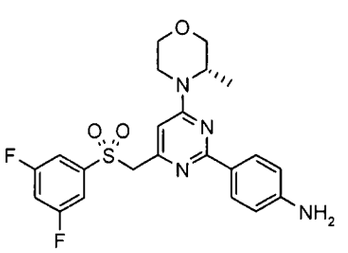


Fenil cloroformato (0.208 mL, 1.66 mmol) fue añadido a 4–[4–[(3,5–difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (693 mg, 1.50 mmol) e hidrógeno carbonato de sodio (190 mg, 2.26 mmol) en dioxano (10 mL). La lechada resultante fue agitada a RT durante 1 hora. La mezcla fue particionada entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%–80% etil acetato en isohexano, para dar el producto deseado como una película seca amarilla (827 mg).

Espectro NMR: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.35 (3H, d), 3.33 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.83 (1H, d), 4.16 (1H, d), 4.38 – 4.48 (3H, m), 6.48 (1H, s), 6.98 – 7.08 (2H, m), 7.19 – 7.28 (4H, m), 7.32 – 7.47 (5H, m), 8.02 (2H, d).

Espectro LCMS: MH+ 581, tiempo de retención 2.91 min.

4–[4–[(3,5–Difluorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Una corriente de nitrógeno fue pasada a través de 2-cloro-4-[(3,5-difluorofenil) sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0.727 g, 1.8 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0.513 g, 2.34 mmol) y carbonato de sodio acuoso 2M (3.24 mL, 6.48 mmol) en DMF (3.75 mL), DME (5 mL), etanol (5 mL) y agua (12.5 mL) durante 15 minutos. La mezcla de reacción fue tratada con diclorobis(trifenilfosfina)paladio(II) (0.063 g, 0.09 mmol) y la mezcla fue agitada a 80°C durante 16 horas. La mezcla fue particionada entre etil acetato y agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 25%-60% etil acetato en isohexano, para dar el producto deseado como un sólido amarillo (0.735 g).

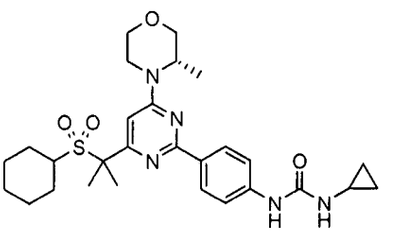
Espectro NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t), 3.31 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.80 – 3.93 (3H, m), 4.01 – 4.08 (1H, dd), 4.15 (1H, d), 4.40 (3H, s), 6.40 (1H, s), 6.62 (2H, d), 7.01 (1H, tt), 7.32 – 7.38 (2H, m), 7.85 (2H, d).

Espectro LCMS: MH+ 461, tiempo de retención 2.46 min.

La preparación de 2-cloro-4-[(3,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

Ejemplo 68:

1-[4-[4-(2-Ciclohexilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropil-urea



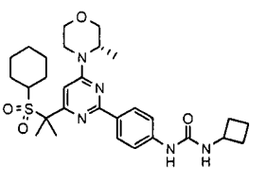
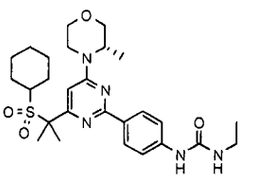
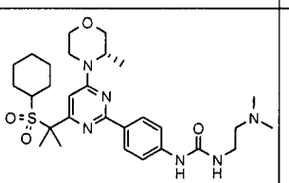
A una solución de ciclopropilamina (53 mg, 0.93 mmol) en DMF (2 mL) fue añadida trietilamina (0.09 mL, 0.64 mmol) seguido por fenil *N*-[4-[4-(2-ciclohexilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (118 mg, 0.20 mmol). La mezcla resultante fue calentada hasta 50°C y agitada durante 2 horas. La mezcla de reacción fue enfriada y diluida con DMF adicional (1 mL) antes de purificar la mezcla de reacción cruda por HPLC preparativa, usando mezclas polares decrecientes de agua (con 1% solución

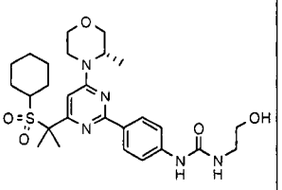
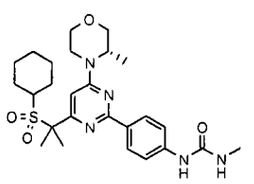
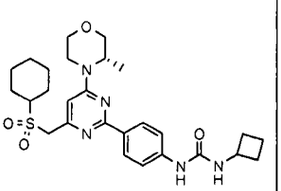
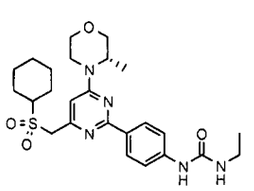
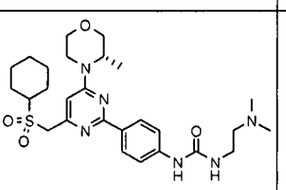
de amoniaco ac.) y acetonitrilo como eluentes, para dar el material deseado como un sólido blanco (75 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.00 – 1.19 (3H, m), 1.22 (3H, d), 1.24 – 1.37 (2H, m), 1.47 – 1.53 (1H, m), 1.64 – 1.82 (10H, m), 2.53 – 2.59 (1H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 – 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 – 4.62 (1H, m), 6.44 (1H, d), 6.75 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.55 (1H, s).

Espectro LCMS: MH+ 542, tiempo de retención 2.37 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–(ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
68a		3–ciclobutil–1–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	556	2.59
68b		3–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1–etil–urea	530	2.35
68c		1–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–	573	2.26

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		il]pirimidin–2–il]fenil]–3–(2–dimetilaminoetil)urea		
68d		1–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–hidroxietil)urea	546	1.99
68e		1–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	516	2.19
68f		3–ciclobutil–1–[4–[4–(ciclohexilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]urea	529	2.57
68g		3–[4–[4–(ciclohexilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–1–etil–urea	503	2.32
68h		1–[4–[4–(ciclohexilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–	545	2.25

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		3-(2-dimetilaminoetil)urea		

Ejemplo 68a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.02 – 1.18 (3H, m), 1.22 (3H, d), 1.25 – 1.35 (2H, m), 1.47 – 1.53 (1H, m), 1.57 – 1.91 (14H, m), 2.18 – 2.25 (2H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.11 – 4.26 (2H, m), 4.55 – 4.61 (1H, m), 6.48 (1H, d), 6.75 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.58 (1H, s).

Ejemplo 68b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 – 1.17 (6H, m), 1.22 (3H, d), 1.25 – 1.36 (2H, m), 1.47 – 1.53 (1H, m), 1.64 – 1.84 (10H, m), 3.10 – 3.16 (2H, m), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 – 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.55 – 4.62 (1H, m), 6.17 (1H, t), 6.75 (1H, s), 7.51 (2H, d), 8.25 (2H, d), 8.68 (1H, s).

Ejemplo 68c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 – 1.19 (3H, m), 1.22 (3H, d), 1.25 – 1.37 (2H, m), 1.48 – 1.53 (1H, m), 1.64 – 1.84 (10H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 – 3.24 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 – 4.62 (1H, m), 6.17 (1H, t), 6.75 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.91 (1H, s).

Ejemplo 68d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 – 1.18 (3H, m), 1.22 (3H, d), 1.25 – 1.37 (2H, m), 1.47 – 1.53 (1H, m), 1.63 – 1.84 (10H, m), 3.16 – 3.24 (3H, m), 3.44 – 3.53 (3H, m), 3.65 (1H, dd), 3.70 – 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 – 4.63 (1H, m), 4.73 (1H, t), 6.26 (1H, t), 6.75 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.82 (1H, s).

Ejemplo 68e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.00 – 1.18 (3H, m), 1.22 (3H, d), 1.25 – 1.36 (2H, m), 1.47 – 1.52 (1H, m), 1.64 – 1.84 (10H, m), 2.66 (3H, d), 3.20 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.71 – 3.78 (2H, m), 3.98 (1H, dd), 4.23 (1H, d), 4.56 – 4.61 (1H, m), 6.08 (1H, q), 6.75 (1H, s), 7.52 (2H, d), 8.25 (2H, d), 8.76 (1H, s).

Ejemplo 68f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 – 1.31 (6H, m), 1.41 – 1.49 (2H, m), 1.57 – 1.69 (3H, m), 1.82 – 1.92 (4H, m), 2.18 – 2.28 (4H, m), 3.22 (1H, td), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.09 – 4.22 (2H, m), 4.40 – 4.51 (3H, m), 6.48 (1H, d), 6.77 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.58 (1H, s).

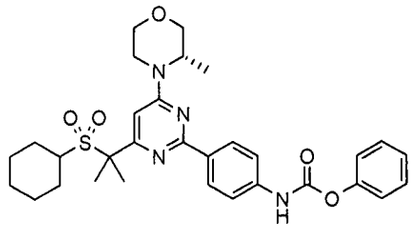
Ejemplo 68g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.15 – 1.33 (6H, m), 1.39 – 1.50 (2H, m), 1.65 – 1.71 (1H, m), 1.86 – 1.92 (2H, m), 2.21 – 2.28 (2H, m), 3.09 – 3.16 (2H, m), 3.22 (1H, td), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.13

– 4.21 (1H, m), 4.40 – 4.51 (3H, m), 6.18 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.68 (1H, s).

Ejemplo 68h: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.16 – 1.33 (6H, m), 1.39 – 1.50 (2H, m), 1.65 – 1.71 (1H, m), 1.86 – 1.92 (2H, m), 2.18 (6H, s), 2.21 – 2.27 (2H, m), 2.34 (2H, t), 3.17 – 3.26 (3H, m), 3.34 (1H, tt), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.14 – 4.21 (1H, m), 4.40 – 4.51 (3H, m), 6.18 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.90 (1H, s).

La preparación de fenil *N*–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

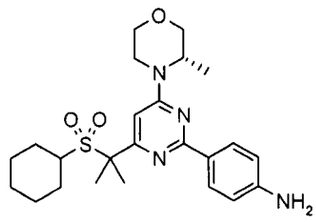


A una solución de 4–[4–(2–ciclohexilsulfonilpropan–2–il)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (1.1 g, 2.40 mmol) en 1,4–dioxano (12 mL) fue añadido bicarbonato de sodio (0.302 g, 3.60 mmol). Fenil cloroformato (0.316 mL, 2.52 mmol) fue luego añadido en forma de gotas y la mezcla resultante fue agitada a RT durante 3 horas. La mezcla resultante fue evaporada hasta secarse y el residuo particionado entre agua (10 mL) y DCM (10 mL). La capa orgánica fue separada y evaporada hasta secarse. El residuo fue triturado con dietil éter para dar el material deseado como un sólido (1.328 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.99 – 1.18 (3H, m), 1.20 – 1.37 (5H, m), 1.46 – 1.52 (1H, m), 1.63 – 1.83 (10H, m), 3.21 (1H, td), 3.51 (1H, td), 3.65 (1H, dd), 3.69 – 3.79 (3H, m), 3.98 (1H, dd), 4.21 – 4.28 (1H, m), 4.56 – 4.64 (1H, m), 7.24 – 7.30 (3H, m), 7.45 (2H, t), 7.65 (2H, d), 8.36 (2H, d), 10.43 (1H, s).

Espectro LCMS: MH+ 579, tiempo de retención 3.11 min.

4-[4-(2-Ciclohexilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

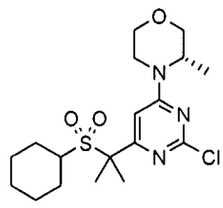


Una mezcla de 2-cloro-4-(2-ciclohexilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1.18 g, 2.94 mmol), solución acuosa 2M de carbonato de sodio (5.5 mL, 11.00 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0.907 g, 4.14 mmol) en una mezcla de DMF (5 mL), agua (12.50 mL), etanol (5.00 mL) y DME (5.00 mL) fue purgada con nitrógeno durante 10 minutos antes de ser tratada con bis(trifenilfosfina)paladio(II) cloruro (0.111 g, 0.16 mmol). La mezcla agitada fue calentada hasta 80°C y agitada bajo nitrógeno durante 2.5 horas. La mezcla de reacción fue enfriada y tratada con etil acetato (50 mL) y agua (50 mL). La capa orgánica fue separada y la acuosa extraída nuevamente con etil acetato (2 x 30 mL). Los productos orgánicos combinados fueron lavados con salmuera, secados ($MgSO_4$) y evaporados para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano, para dar el material deseado (1.130 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.99 – 1.23 (6H, m), 1.25 – 1.36 (2H, m), 1.47 – 1.53 (1H, m), 1.65 – 1.83 (10H, m), 3.18 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.73 – 3.81 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.52 – 4.58 (1H, m), 5.54 – 5.57 (2H, m), 6.62 (2H, d), 6.64 (1H, s), 8.08 (2H, d).

Espectro LCMS: MH+ 459, tiempo de retención 2.56 min.

2-Cloro-4-(2-ciclohexilsulfonilpropan-2-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



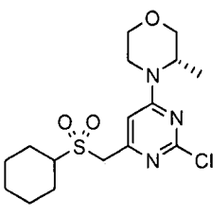
Una solución enfriada (baño de hielo/agua) de 2-cloro-4-(ciclohexilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1.26 g, 3.37 mmol) en DMF (16 mL) fue tratada con *tert*-

butóxido de sodio (0.324 g, 3.37 mmol). La mezcla fue agitada a 0°C durante 5 minutos. Yodometano (0.210 mL, 3.37 mmol) fue luego añadido y la mezcla agitada a 0°C durante unos 10 minutos adicionales. *Tert*–butóxido de sodio adicional (0.324 g, 3.37 mmol) fue luego añadido y la agitación se continuó durante unos 5 minutos adicionales antes de la adición de más yodometano (0.210 mL, 3.37 mmol). La mezcla resultante fue agitada a 0°C durante unos 15 minutos adicionales. El baño de enfriamiento fue luego eliminado y la reacción se dejó calentar, con agitación hasta RT. Agua (75 mL) fue añadida a la mezcla de reacción y el precipitado resultante recogido por filtración por succión, lavado con más agua (40 mL) y secado para proporcionar el material deseado (1.180 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.04 – 1.15 (1H, m), 1.19 – 1.37 (7H, m), 1.54 – 1.60 (1H, m), 1.69 (6H, s), 1.70 – 1.80 (4H, m), 3.17 – 3.25 (1H, m), 3.45 (1H, td), 3.52 – 3.62 (2H, m), 3.72 (1H, d), 3.94 (1H, dd), 4.07 (1H, d), 4.39 – 4.48 (1H, m), 6.89 (1H, s).

Espectro LCMS: MH+ 402, tiempo de retención 2.72 min.

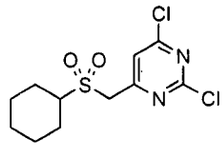
2–Cloro–4–(ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



A una solución enfriada (baño de hielo/agua) de 2,4–dicloro–6–(ciclohexilsulfonilmetil) pirimidina (1.65 g, 5.34 mmol) en DCM (25 mL) fue añadida trietilamina (0.820 mL, 5.88 mmol). La solución resultante fue tratada, en forma de gotas durante 8 minutos, con una solución de (3S)–3–metilmorfolina (609 mg, 6.02 mmol) en DCM (5 mL). La mezcla fue agitada a 6°C durante 30 minutos. El baño de enfriamiento fue luego retirado y la mezcla de reacción se dejó agitar toda la noche. Agua (25 mL) fue luego añadida y la mezcla de reacción agitada durante 5 minutos. La capa orgánica fue luego separada, secada ($MgSO_4$) y evaporada para dar un aceite marrón crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano, para dar el material deseado (1.440 g).

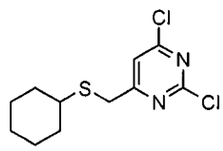
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.15 – 1.45 (8H, m), 1.63 – 1.68 (1H, m), 1.81 – 1.87 (2H, m), 2.11 – 2.17 (2H, m), 3.15 – 3.25 (2H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.73 (1H, d), 3.92 – 4.01 (2H, m), 4.30 (1H, br s), 4.39 (2H, s), 6.90 (1H, s).
Espectro LCMS: MH+ 374, tiempo de retención 2.24 min.

2,4–Dicloro–6–(ciclohexilsulfonilmetil)pirimidina



A una solución agitada de 2,4–dicloro–6–(ciclohexilsulfanilmetil)pirimidina (1.53 g, 5.52 mmol) en DCM (28 mL) fue añadido, en forma de porciones, ácido 3–cloroperoxibenzoico (3.09 g, 13.80 mmol) durante un período de 20 minutos bajo nitrógeno, de manera de controlar la temperatura por debajo de 28°C. La suspensión resultante fue agitada a RT durante 3 horas, luego solución de hidrógeno carbonato de sodio saturada acuosa (40 mL) fue añadida y la mezcla de reacción agitada durante 5 minutos. La capa orgánica fue luego separada, secada ($MgSO_4$) y evaporada hasta secarse. El sólido resultante fue redisuelto en DCM (40 mL) y solución de hidrógeno carbonato de sodio saturada acuosa (40 mL) añadida. La mezcla fue agitada durante 15 minutos antes de separar la capa orgánica, secar (sobre $MgSO_4$) y evaporar para proporcionar el material deseado (1.650 g).
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.12 – 1.46 (5H, m), 1.61 – 1.69 (1H, m), 1.80 – 1.88 (2H, m), 2.10 – 2.17 (2H, m), 3.22 (1H, tt), 4.73 (2H, s), 7.85 (1H, s).
Espectro LCMS: M–H– 307, tiempo de retención 2.26 min.

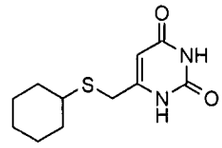
2,4–Dicloro–6–(ciclohexilsulfanilmetil)pirimidina



Una suspensión de 6–(ciclohexilsulfanilmetil)–1H–pirimidina–2,4–diona (3.6 g, 14.98 mmol) en oxicloruro de fósforo (15 mL, 160.93 mmol) fue calentada hasta 100°C, durante un período de 15 minutos. La solución naranja oscura resultante fue agitada a 100°C durante 7 horas. La mezcla de reacción fue luego enfriada antes de evaporarse hasta obtener un aceite marrón

viscoso el cual fue particionado entre DCM (20 mL) y agua helada (20 mL). Hidrógeno carbonato de sodio sólido fue luego añadido cuidadosamente y en forma de porciones, durante 30 minutos de manera de controlar la efervescencia. Alícuotas adicionales de agua (30 mL) y DCM fueron añadidas durante la adición. Una vez que la efervescencia había cesado y el pH había sido ajustado a 8, la mezcla fue transferida a un embudo de separación y la capa orgánica separada. La capa acuosa fue extraída nuevamente con DCM (2 x 50 mL) y las capas orgánicas combinadas lavadas con salmuera (100 mL), secadas ($MgSO_4$) y evaporadas para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 40% etil acetato en isohexano, para dar el material deseado (1.60 g).
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.18 – 1.31 (5H, m), 1.51 – 1.58 (1H, m), 1.63 – 1.71 (2H, m), 1.86 – 1.93 (2H, m), 2.70 – 2.77 (1H, m), 3.85 (2H, s), 7.81 (1H, s).
Espectro LCMS: M–H– 275, tiempo de retención 3.04 min.

6–(Ciclohexilsulfanilmetil)–1*H*–pirimidina–2,4–diona



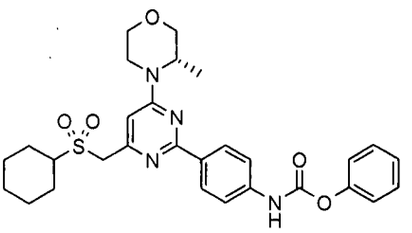
Una solución de ciclohexanotiol (10 mL, 81.74 mmol) en DMF (150 mL) fue tratada con 1,8–diazabiciclo[5.4.0]undec–7–eno (14 mL, 93.80 mmol). La solución resultante fue agitada a RT durante 20 minutos. 6–(clorometil)pirimidina–2,4(1H,3H)–diona (10 g, 62.28 mmol) fue luego añadida, en forma de porciones, durante un período de 30 minutos, bajo nitrógeno, de manera de mantener la temperatura interna por debajo de 35°C. La solución resultante fue agitada a RT toda la noche. La mezcla de reacción fue luego evaporada hasta secarse y el residuo fue particionado entre DCM (100 mL) y agua (150 mL). Al mezclar se formó un precipitado, este fue eliminado por filtración por succión, y secado al vacío, a 55°C durante 2 horas para proporcionar el material deseado (6.45 g). Material deseado adicional (3.62 g) fue obtenido ajustando el filtrado a pH2 por la adición en forma de gotas de ácido clorhídrico 2M y eliminando el precipitado, lavando el precipitado con agua (100 mL) y secándolo en un horno de vacío.

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.16 – 1.34 (5H, m), 1.51 – 1.58 (1H, m), 1.63 – 1.72 (2H, m), 1.87 – 1.96 (2H, m), 2.65 – 2.72 (1H, m), 3.41 (2H, s), 5.49 (1H, s), 10.75 – 10.96 (2H, m).

Espectro LCMS: MH+ 241, tiempo de retención 0.99 min.

La preparación de fenil *N*–[4–[4–(ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–(ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

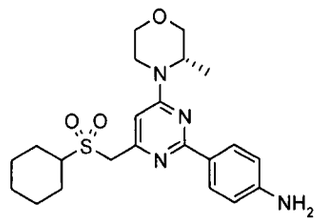


Bicarbonato de sodio (113 mg, 1.35 mmol) fue añadido a una solución de 4–[4–(ciclohexilsulfonilmetil)–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (370 mg, 0.86 mmol) en 1,4–dioxano (5 mL). Fenil cloroformato (0.124 mL, 0.99 mmol) fue añadido en forma de gotas y la mezcla resultante fue agitada a RT durante 5 horas. La mezcla resultante fue evaporada hasta secarse y el residuo particionado entre DCM (5 mL) y agua (5 mL). La capa orgánica fue separada y evaporada hasta secarse. El residuo crudo fue triturado con dietil éter para dar el material deseado (429 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.16 – 1.33 (6H, m), 1.40 – 1.50 (2H, m), 1.64 – 1.70 (1H, m), 1.85 – 1.92 (2H, m), 2.21 – 2.28 (2H, m), 3.19 – 3.36 (2H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.78 (1H, d), 3.99 (1H, dd), 4.16 – 4.23 (1H, m), 4.43 – 4.52 (3H, m), 6.81 (1H, s), 7.24 – 7.30 (3H, m), 7.43 – 7.47 (2H, m), 7.63 (2H, d), 8.30 (2H, d), 10.44 (1H, s).

Espectro LCMS: MH+ 551, tiempo de retención 2.88 min.

4–[4–(Ciclohexilsulfonilmetil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Una mezcla de 2-cloro-4-(ciclohexilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (437 mg, 1.17 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (381 mg, 1.74 mmol) y solución acuosa 2M de carbonato de sodio (0.60 mL, 1.20 mmol) en una mezcla de DMF (2 mL), etanol (2 mL), agua (5 mL) y DME (2 mL) fue purgada con nitrógeno durante 5 minutos antes de la adición de bis(trifenilfosfina)paladio(II) cloruro (41.0 mg, 0.06 mmol). La mezcla de reacción fue calentada hasta 80°C, bajo nitrógeno, y agitada durante 3.5 horas. La mezcla de reacción fue enfriada y particionada entre etil acetato (25 mL) y agua (30 mL). La capa orgánica fue separada y la acuosa reextraída con etil acetato (2 x 25 mL). Los extractos orgánicos combinados fueron lavados con salmuera saturada (50 mL), secados ($MgSO_4$), filtrados y evaporados para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano, para dar el material deseado (402 mg).

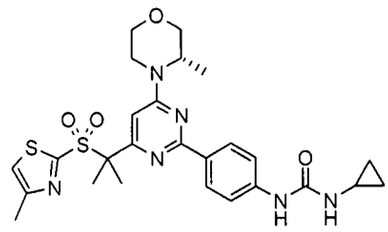
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 – 1.32 (6H, m), 1.38 – 1.50 (2H, m), 1.64 – 1.70 (1H, m), 1.85 – 1.92 (2H, m), 2.20 – 2.27 (2H, m), 3.19 (1H, td), 3.31 – 3.40 (1H, m), 3.48 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.10 – 4.18 (1H, m), 4.38 (2H, s), 4.40 – 4.48 (1H, m), 5.57 (2H, s), 6.61 (2H, d), 6.66 (1H, s), 8.04 (2H, d).

Espectro LCMS: MH+ 431, tiempo de retención 2.33 min.

La preparación de 2-cloro-4-(ciclohexilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

Ejemplo 69:

3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[2-[(4-metil-1,3-tiazol-2-il)sulfonil]propan-2-il]pirimidin-2-il]fenil]urea

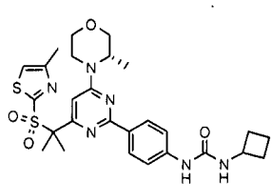
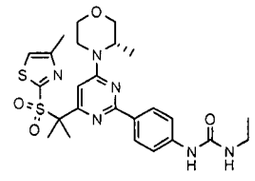
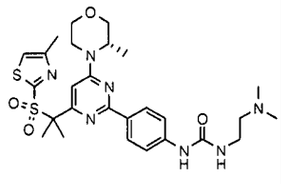
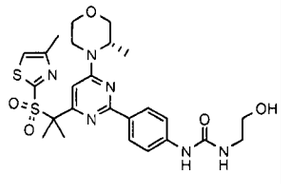
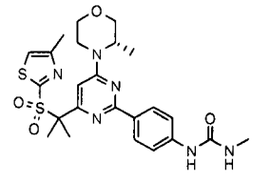


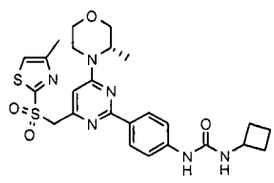
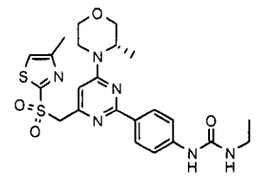
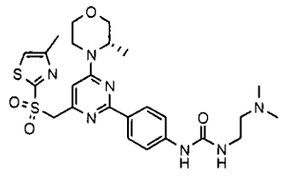
A ciclopropilamina (53 mg, 0.93 mmol) fue añadida una solución de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]carbamato (54 mg, 0.09 mmol) en DMA (2 mL) y trietilamina (0.045 mL, 0.32 mmol). La mezcla resultante fue calentada hasta 50°C durante 16 horas. La mezcla de reacción fue enfriada y vertida en agua (30 mL). El precipitado resultante fue recogido por filtración por succión y secado por succión para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano. Las fracciones que contienen el producto fueron evaporadas hasta secarse, trituradas con isohexano/dietil éter y secadas al vacío, a 50°C, durante 1 hora para proporcionar el material deseado como un sólido blanco (38 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.40 – 0.44 (2H, m), 0.63 – 0.67 (2H, m), 1.21 (3H, d), 1.92 (6H, s), 2.42 (3H, s), 2.53 – 2.59 (1H, m), 3.16 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 – 4.20 (1H, m), 4.52 – 4.58 (1H, m), 6.40 – 6.42 (1H, m), 6.69 (1H, s), 7.42 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.51 (1H, s)

Espectro LCMS: MH+ 557, tiempo de retención 2.33 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
69a		3–ciclobutil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]urea	571	2.53
69b		3–etil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]urea	545	2.3
69c		3–(2–dimetilaminoetil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]urea	588	2.44
69d		3–(2–hidroxietil)–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]urea	561	1.99
69e		3–metil–1–[4–[4–[(3S)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]urea	531	2.15

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
69f		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidin-2-il]fenil]urea	543	2.28
69g		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidin-2-il]fenil]urea	517	2.04
69h		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidin-2-il]fenil]urea	560	2.14

Ejemplo 69a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 – 1.68 (2H, m), 1.80 – 1.92 (2H, m), 1.92 (6H, s), 2.18 – 2.25 (2H, m), 2.41 – 2.42 (3H, m), 3.16 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 – 4.19 (2H, m), 4.51 – 4.58 (1H, m), 6.44 (1H, d), 6.69 (1H, s), 7.39 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.53 (1H, s).

Ejemplo 69b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.92 (6H, s), 2.41 – 2.42 (3H, m), 3.09 – 3.20 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.14 – 4.19 (1H, m), 4.52 – 4.58 (1H, m), 6.14 (1H, t), 6.69 (1H, s), 7.41 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.63 (1H, s).

Ejemplo 69c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.20 (6H, s), 2.33 – 2.40 (2H, m), 2.42 (3H, s), 3.12 – 3.22 (3H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H,

d), 3.97 (1H, dd), 4.16 (1H, d), 4.51 – 4.57 (1H, m), 6.15 (1H, t), 6.69 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.87 (1H, s).

Ejemplo 69d: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.41 (3H, s), 3.13 – 3.21 (3H, m), 3.44 – 3.52 (3H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.13 – 4.19 (1H, m), 4.52 – 4.57 (1H, m), 4.72 (1H, t), 6.24 (1H, t), 6.69 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.78 (1H, s).

Ejemplo 69e: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.21 (3H, d), 1.92 (6H, s), 2.41 – 2.42 (3H, m), 2.66 (3H, d), 3.12 – 3.20 (1H, m), 3.49 (1H, td), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 – 4.19 (1H, m), 4.51 – 4.57 (1H, m), 6.05 (1H, q), 6.69 (1H, s), 7.42 (2H, d), 7.68 (1H, d), 7.87 (2H, d), 8.72 (1H, s).

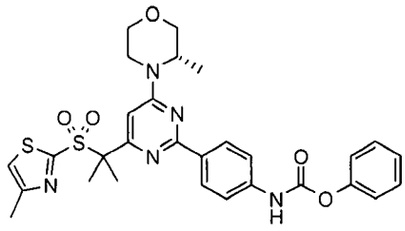
Ejemplo 69f: Ningún Espectro NMR

Ejemplo 69g: Ningún Espectro NMR

Ejemplo 69h: Ningún Espectro NMR

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]fenil]carbamato



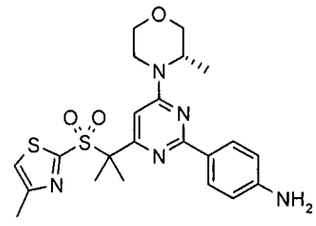
A una solución de 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]anilina (340 mg, 0.72 mmol) en 1,4–dioxano (4 mL) fue añadido bicarbonato de sodio (90 mg, 1.08 mmol). Fenil cloroformato (0.104 mL, 0.83 mmol) fue luego añadido en forma de gotas y la mezcla resultante fue agitada a RT durante 6 horas. La mezcla de reacción fue luego evaporada y el residuo fue particionado entre DCM (5 mL) y agua (5 mL). La capa orgánica fue separada y la acuosa extraída de nuevo con más DCM (5 mL). Las capas orgánicas combinadas fueron combinadas y evaporadas hasta secarse para proporcionar una goma ámbar, la cual fue adsorbida en dietil éter (5 mL) y triturada con

sonicación. El sólido resultante fue recogido por filtración por succión y secado para proporcionar el material deseado (334 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 1.93 (6H, s), 2.41 (3H, s), 3.17 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.15 – 4.22 (1H, m), 4.53 – 4.59 (1H, m), 6.73 (1H, s), 7.24 – 7.30 (3H, m), 7.45 (2H, t), 7.55 (2H, d), 7.68 (1H, m), 7.97 (2H, d), 10.39 (1H, s).

Espectro LCMS: MH+ 594, tiempo de retención 2.91 min.

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidin–2–il]anilina

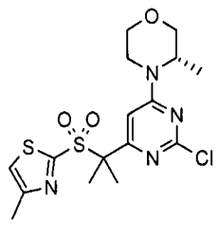


Una mezcla de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidina (480 mg, 1.15 mmol), 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (378 mg, 1.73 mmol) y solución acuosa 2M de carbonato de sodio (2.8 mL, 5.60 mmol) en una mezcla de DMF (2 mL), 1,2–dimetoxietano (2 mL), etanol (2 mL) y agua (5 mL) fue purgada con nitrógeno durante 10 minutos antes de la adición de bis(trifenilfosfina)paladio(II) cloruro (54 mg, 0.08 mmol). La mezcla de reacción fue calentada hasta 85°C y agitada a esa temperatura, bajo nitrógeno durante 3 horas. La mezcla de reacción fue luego enfriada y particionada entre etil acetato (50 mL) y agua (30 mL). La capa orgánica fue separada y la capa acuosa extraída nuevamente con etil acetato (25 mL). Las capas orgánicas combinadas fueron lavadas con salmuera (50 mL), secadas ($MgSO_4$), filtradas y evaporadas para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano, para dar el material deseado (367 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.19 (3H, d), 1.90 (6H, s), 2.43 (3H, s), 3.13 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.09 – 4.15 (1H, m), 4.47 – 4.54 (1H, m), 5.50 (2H, s), 6.52 (1H, d), 6.58 (2H, s), 7.68 – 7.72 (3H, m).

Espectro LCMS: MH+ 474, tiempo de retención 2.31 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[2–[(4–metil–1,3–tiazol–2–il)sulfonil]propan–2–il]pirimidina

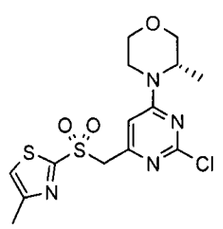


A una solución enfriada (baño de hielo/agua) de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidina (612 mg, 1.57 mmol) en DMF (8 mL) fue añadido tert–butóxido de sodio (157 mg, 1.63 mmol). La mezcla fue agitada durante 5 minutos, bajo nitrógeno, antes de la adición de yodometano (0.100 mL, 1.61 mmol). La mezcla de reacción se dejó agitar, en el baño de enfriamiento, durante unos 10 minutos adicionales antes de la adición de más tert–butóxido de sodio (157 mg, 1.63 mmol). Después de unos 5 minutos adicionales de agitación más yodometano (0.100 mL, 1.61 mmol) fue añadido y la mezcla de reacción agitada, bajo nitrógeno, en el baño de enfriamiento durante 20 minutos. En el baño de enfriamiento fue luego retirado y la agitación se continuó durante unas 2 horas adicionales. Agua (25 mL) fue luego añadida y el precipitado resultante recogido por filtración, lavado con agua (50 mL) y secado al vacío, a 50°C, durante 2 horas para proporcionar el material deseado (487 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.19 (3H, d), 1.79 (6H, d), 2.46 (3H, s), 3.15 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.96 – 4.03 (1H, m), 4.35 – 4.44 (1H, m), 6.78 (1H, s), 7.89 (1H, s).

Espectro LCMS: MH+ 417, tiempo de retención 2.28 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil] pirimidina

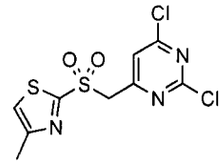


A una solución enfriada (baño de hielo/agua) de 2,4–dicloro–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidina (901 mg, 2.78 mmol) en DCM (12 mL) fue añadido trietilamina (0.45 mL, 3.23 mmol). La solución resultante fue tratada en forma de gotas, durante 3 minutos, con una solución de (3S)–3–metilmorfolina (319 mg, 3.15 mmol) en DCM (2.5 mL). La mezcla de reacción fue agitada, bajo nitrógeno durante 24 horas, dejándose calentar la reacción hasta RT. Agua (20 mL) fue añadida a la mezcla de reacción y agitada durante 15 minutos. La capa orgánica fue luego separada, secada ($MgSO_4$) y evaporada para dar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 75% etil acetato en isohexano, para dar el material deseado (615 mg).

Espectro NMR : ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.18 (3H, d), 2.49 (3H, s), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.86 – 3.96 (2H, m), 4.16 – 4.28 (1H, m), 4.82 (2H, s), 6.80 (1H, s), 7.89 (1H, d).

Espectro LCMS: MH+ 389, tiempo de retención 1.89 min.

2,4–Dicloro–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidina

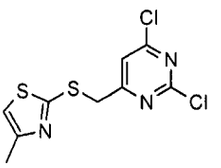


A una solución enfriada (baño de hielo/agua) de 2,4–dicloro–6–[(4–metil–1,3–tiazol–2–il)sulfanilmetil]pirimidina (867 mg, 2.97 mmol) en DCM (15 mL) fue añadido en forma de porciones, durante 10 minutos, ácido 3–cloroperoxibenzoico (1.42 g, 6.34 mmol). La suspensión resultante fue agitada en el baño de enfriamiento durante 15 minutos. El baño de enfriamiento fue luego retirado y la mezcla de reacción se dejó calentar hasta RT y fue agitada durante 22 horas. La reacción fue incompleta y ácido 3–cloroperoxibenzoico adicional (162 mg, 0.72 mmol) fue añadido y la mezcla agitada durante una hora adicional. Solución acuosa saturada de bicarbonato de sodio (20 mL) fue añadida a la mezcla de reacción y agitada durante 30 minutos. La capa orgánica fue separada, secada ($MgSO_4$), filtrada y evaporada para proporcionar el material deseado (912 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 2.48 (3H, d), 5.19 (2H, s), 7.84 (1H, s), 7.94 – 7.95 (1H, m).

Espectro LCMS: M–H– 322, tiempo de retención 1.47 min.

2,4–Dicloro–6–[(4–metil–1,3–tiazol–2–il)sulfanilmetil]pirimidina

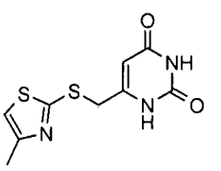


Una suspensión de 6–[(4–metil–1,3–tiazol–2–il)sulfanilmetil]–1*H*–pirimidina–2,4–diona (1.4 g, 5.48 mmol) en oxicloruro de fósforo (6 mL, 64.37 mmol) fue calentada hasta 100°C y agitada durante 6 horas. La mezcla de reacción fue enfriada antes de evaporarse y el residuo fue particionado entre DCM (30 mL) y agua helada (30 mL). Hidrógeno carbonato de sodio fue luego añadido cuidadosamente y en forma de porciones, durante 30 minutos, de manera de controlar la efervescencia. Una vez que la efervescencia había cesado y el pH había sido ajustado a 8, la mezcla fue tratada con más DCM (30 mL) y agua (20 mL), transferida a un embudo de separación y la capa orgánica fue separada. La capa acuosa fue extraída nuevamente con DCM adicional (2 x 25 mL) y los extractos orgánicos combinados lavados con salmuera, secados ($MgSO_4$) y evaporados hasta secarse para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 20% etil acetato en isohexano, para dar el material deseado (0.90 g).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 2.31 (3H, d), 4.55 (2H, s), 7.23 – 7.24 (1H, m), 7.83 (1H, s).

Espectro LCMS: MH+ 292, tiempo de retención 2.33 min.

6–[(4–Metil–1,3–tiazol–2–il)sulfanilmetil]–1*H*–pirimidina–2,4–diona



A una solución de 4–metiltiazol–2–tiol (1.01 g, 7.70 mmol) en DMF (15 mL) fue añadido 1,8–diazabiciclo[5.4.0]undec–7–eno (1.4 mL, 9.38 mmol). La solución resultante fue agitada a RT durante 30 minutos. 6–(clorometil)pirimidina–2,4(1H,3H)–diona (1 g, 6.23 mmol) fue luego añadida en forma de porciones, durante un período de 10 minutos, bajo nitrógeno. La solución resultante fue agitada a RT durante 19 horas. La mezcla de reacción fue luego

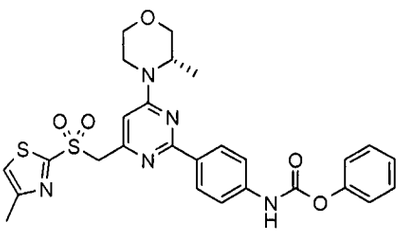
evaporada hasta secarse y el residuo particionado entre DCM (20 mL) y agua (20 mL). Un precipitado sólido el cual fue recogido por filtración por succión, fue lavado con agua (20 mL) y secado, al vacío, a 60°C, durante 2 horas para proporcionar el material deseado (1.07 g, 67 %). Material deseado adicional (0.330 g) fue obtenido ajustando el filtrado a pH2 con ácido clorhídrico 2M, filtrando el precipitado, lavándolo con agua (20 mL) y secándolo en un horno de vacío.

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 2.34 (3H, d), 4.08 (2H, s), 5.43 (1H, s), 7.27 (1H, m), 11.01 (2H, s).

Espectro LCMS: MH+ 256, tiempo de retención 0.53 min.

La preparación de fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil] pirimidin–2–il]fenil]carbamato

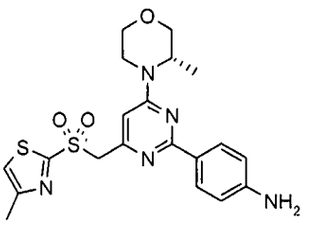


Fenil cloroformato (0.190 mL, 1.51 mmol) fue añadido a 4–[4–[(3S)–3–metilmorfolin–4–il]–6–[(4–metil–1,3–tiazol–2–il)sulfonilmetil]pirimidin–2–il]anilina (450 mg, 1.01 mmol), hidrógeno carbonato de sodio (127 mg, 1.51 mmol) en dioxano (10 mL) a 5°C bajo nitrógeno. La mezcla resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue diluida con etil acetato (200 mL), y lavada con agua (125 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo, la cual fue triturada con una mezcla de dietil éter e isohexano para proporcionar el material deseado (360 mg).

Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.22 (3H, d), 2.53 (3H, s) [oscurecido por DMSO], 3.20 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.45 (1H, s), 4.93 (2H, s), 6.77 (1H, s), 7.22 – 7.32 (3H, m), 7.43 – 7.47 (2H, m), 7.56 (2H, d), 7.84 (1H, s), 7.97 (2H, d), 10.43 (1H, s).

Espectro LCMS: MH+ 566, tiempo de retención 2.66 min

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidin-2-il]anilina



Bis(trifenilfosfina)paladio(II) cloruro (54.4 mg, 0.08 mmol) fue añadido a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (600 mg, 1.55 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (510 mg, 2.33 mmol) y carbonato de sodio (5 mL, 10.00 mmol) en una mezcla de DMF (6 mL), DME (12 mL), etanol (3 mL) y agua (3.5 mL) a RT bajo nitrógeno. La mezcla de reacción fue evacuada y rellenada con nitrógeno varias veces y la mezcla resultante agitada a 95°C durante 18 horas. La mezcla de reacción fue diluida con etil acetato (250 mL), y lavada con agua (2 x 150 mL). La capa orgánica fue secada (Na_2SO_4), filtrada y evaporada para proporcionar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente de elución 10 a 70% etil acetato en isohexano, para dar el material deseado (450 mg).

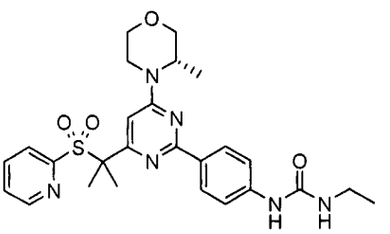
Espectro NMR: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.53 (3H, s), 3.15 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.09 (1H, d), 4.40 (1H, s), 4.83 (2H, s), 5.54 (2H, s), 6.52 (2H, d), 6.60 (1H, s), 7.70 (2H, d), 7.81 (1H, s).

Espectro LCMS: MH+ 446, tiempo de retención 2.0 min

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina fue descrita anteriormente.

Ejemplo 70:

3-Etil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]urea



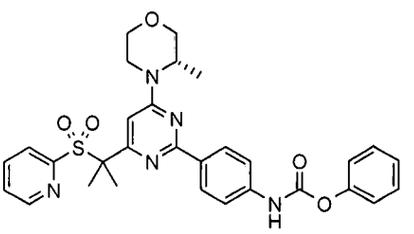
Una solución de 2M de etilamina en metanol (0.471 mL, 0.94 mmol) fue añadida en una porción a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]carbamato (120 mg, 0.21 mmol), en DMF (2 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 60 minutos. La mezcla de reacción fue evaporada hasta secarse y el producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 7% metanol en DCM, para dar el material deseado como una espuma blanca (103 mg).

Espectro NMR: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (t, 3H), 1.21 (d, 3H), 1.88 (s, 6H), 3.09 – 3.21 (m, 3H), 3.45 – 3.53 (m, 1H), 3.61 – 3.66 (m, 1H), 3.77 (d, 1H), 3.95 – 4.00 (m, 1H), 4.15 (d, 1H), 4.53 (s, 1H), 6.15 (t, 1H), 6.66 (s, 1H), 7.35 (d, 2H), 7.61 – 7.66 (m, 2H), 7.71 (d, 2H), 7.88 – 7.93 (m, 1H), 8.61 (s, 1H), 8.74 – 8.76 (m, 1H)

Espectro LCMS: MH+ 525.56, tiempo de retención 2.14 min.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-2-ilsulfonilpropan-2-il)pirimidin-2-il]fenil]carbamato



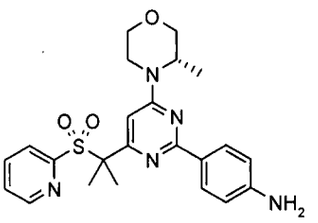
Fenil cloroformato (0.432 mL, 3.44 mmol) fue añadido a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(2-piridin-2-ilsulfonilpropan-2-il)pirimidin-2-il]anilina (1.3 g, 2.87 mmol) e hidrógeno carbonato de sodio (0.482 g, 5.73 mmol) en dioxano (20 mL) a RT. La lechada resultante fue agitada a RT durante 1 hora y luego la mezcla de reacción fue particionada entre etil acetato y

agua. La solución orgánica fue secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue cromatografiado en sílice, eluyendo con 0%–20% etil acetato en DCM, para dar el material deseado como una película seca amarilla (1.62 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.27 (d, 3H), 1.90 (s, 6H), 3.25 (m, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 4.03 (m, 2H), 4.39 – 4.46 (m, 1H), 6.60 (s, 1H), 6.93 (s, 1H), 7.12 – 7.22 (m, 12H), 7.32 (m, 5H), 7.57 (m, 2H), 7.82 (d, 2H).

Espectro LCMS: MH+ 574.52, tiempo de retención 2.85 min. (Monitor Ácido).

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(2–piridin–2–ilsulfonilpropan–2–il)pirimidin–2–il]anilina

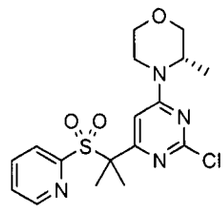


Tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.773 g, 3.53 mmol) y 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–2–ilsulfonilpropan–2–il)pirimidina (1.4 g, 3.53 mmol) fueron suspendidas en una mezcla de DME (10 mL), etanol (10.00 mL), DMF (10.00 mL) y agua (10 mL) a RT bajo nitrógeno. La mezcla fue purgada con nitrógeno y bis(trifenilfosfina)paladio(II) cloruro (0.124 g, 0.18 mmol) fue añadido. La suspensión resultante fue agitada a 80°C durante 90 minutos bajo una atmósfera de nitrógeno. La mezcla de reacción fue concentrada y diluida con etil acetato (150 mL), y lavada con agua (2 x 150 mL) y salmuera saturada (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 40% etil acetato en DCM, para dar el material deseado como una espuma amarilla (1.210 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.25 (d, 3H), 1.89 (s, 6H), 3.22 (m, 1H), 3.54 (m, 1H), 3.66 – 3.80 (m, 4H), 3.97 (m, 1H), 4.05 (m, 1H), 4.42 (s, 1H), 6.46 – 6.53 (m, 3H), 7.28 (m, 1H), 7.55 (m, 2H), 7.64 (d, 2H), 8.61 (d, 1H).

Espectro LCMS: MH+ 454.58, tiempo de retención 1.88 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(2–piridin–2–ilsulfonilpropan–2–il)pirimidina

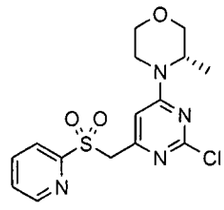


Yodometano (1.266 mL, 20.33 mmol) fue añadido a una solución de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidina (2.5 g, 6.78 mmol) y *tert*–butóxido de sodio (1.954 g, 20.33 mmol) en DMF (50 mL) a 0°C bajo nitrógeno. La solución se dejó calentar lentamente hasta RT y fue agitada a RT durante 1 hora. Agua y etil acetato fueron añadidos y la solución fue agitada y separada. Las capas de etil acetato combinadas fueron secadas ($MgSO_4$) y filtradas. El filtrado fue evaporado y el producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 60% etil acetato en DCM, para dar el material deseado como un aceite amarillo el cual se solidificó en reposo (1.77 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.26 (d, 3H), 1.77 (s, 6H), 3.22 (m, 1H), 3.49 (m, 1H), 3.64 (m, 1H), 3.74 (d, 1H), 3.89 – 3.98 (m, 2H), 4.27 (s, 1H), 6.67 (s, 1H), 7.46 (m, 1H), 7.73 (m, 1H), 7.80 (d, 1H), 7.82 (m, 1H).

Espectro LCMS: MH+ 397.38, tiempo de retención 2.04 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidina



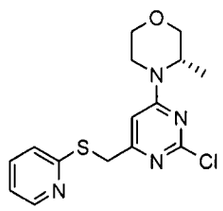
Una solución acuosa 35% de peróxido de hidrógeno (8.26 mL, 93.53 mmol) fue añadida en forma de gotas a una solución agitada de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfanilmetil)pirimidina (10.5g, 31.17 mmol), tungstato dihidrato de sodio (0.206 g, 0.62 mmol) y ácido sulfúrico 2N (0.6 mL) en dioxano (300 mL) y luego la solución fue calentada hasta 55°C. La solución fue agitada a 55°C durante 4 horas. Peróxido de hidrógeno adicional (8.26 mL) fue añadido y la mezcla agitada a 50°C durante 18 horas. Ácido 3–cloroperoxibenzoico (5.38 g, 31.17 mmol) fue añadido y la mezcla agitada a RT durante 2 horas. La solución fue diluida con agua (500 mL) y enfriada hasta 20°C. Una solución 10% de

metabisulfito de sodio fue añadida para destruir cualquier peróxido remanente y la solución fue extraída con etil acetato. La capa orgánica fue secada ($MgSO_4$) y filtrada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 50% etil acetato en DCM, para dar el material deseado como una goma amarilla (10.5 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 3H), 3.20 (m, 1H), 3.46 (m, 1H), 3.61 (d, 1H), 3.71 (d, 1H), 3.90 – 3.98 (m, 2H), 4.21 (s, 1H), 4.51 (s, 2H), 6.50 (s, 1H), 7.51 – 7.53 (m, 1H), 7.86 – 7.95 (m, 2H), 8.72 – 8.74 (m, 1H)

Espectro LCMS: MH+ 369.37, tiempo de retención 1.73 min.

2–Cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfanilmetil)pirimidina



DIPEA (8.77 ml, 50.71 mmol) fue añadida a 2–mercaptopiridina (3.80 g, 34.22 mmol), en DMF (300 mL) a RT en una atmósfera de nitrógeno. La solución resultante fue agitada a RT durante 15 minutos. 2–Cloro–4–(yodometil)–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (11 g, 31.11 mmol) fue añadida en forma de porciones durante 5 minutos y la mezcla agitada a RT durante 3 horas. La mezcla de reacción fue evaporada hasta secarse y redisuelta en DCM (200 mL) y lavada secuencialmente con solución de hidrógeno carbonato de sodio saturada (100 mL) y salmuera saturada (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 20% etil acetato en DCM, para dar el material deseado como un aceite color canela (10.50 g). La NMR muestra la presencia de 0.6 eq. de ácido m–clorobenzoico. Este material fue usado en el paso subsiguiente sin purificación adicional.

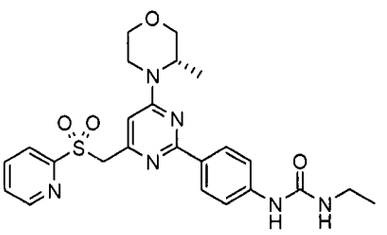
Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.17 – 3.25 (m, 1H), 3.46 – 3.54 (m, 1H), 3.62 – 3.67 (m, 1H), 3.74 (d, 1H), 3.93 – 4.01 (m, 2H), 4.20 (s, 1H), 4.29 – 4.38 (m, 2H), 6.60 (s, 1H), 6.99 – 7.02 (m, 1H), 7.20 (d, 1H), 7.47 – 7.51 (m, 1H), 8.40 – 8.42 (m, 1H).

Espectro LCMS: MH+ 337.48, tiempo de retención 2.19 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

Ejemplo 71:

3-Etil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidin-2-il]fenil]urea



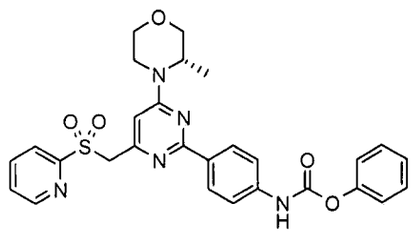
Una solución 2M de etilamina en metanol (0.495 mL, 0.99 mmol) fue añadida en una porción a una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidin-2-il]fenil]carbamato (120 mg, 0.22 mmol) en DMF (2 mL) a RT bajo nitrógeno. La solución resultante fue agitada a RT durante 60 minutos. La mezcla de reacción fue evaporada hasta secarse y el producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 7% metanol en DCM, para dar el material deseado como una espuma blanca (83 mg).

Espectro NMR: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (t, 3H), 1.20 (d, 3H), 3.09 – 3.22 (m, 3H), 3.44 – 3.52 (m, 1H), 3.61 – 3.65 (m, 1H), 3.76 (d, 1H), 3.95 – 4.00 (m, 1H), 4.12 (d, 1H), 4.40 (s, 1H), 4.85 (q, 2H), 6.14 (t, 1H), 6.69 (s, 1H), 7.35 (d, 2H), 7.66 (d, 2H), 7.79 – 7.82 (m, 1H), 7.90 (d, 1H), 8.08 – 8.13 (m, 1H), 8.62 (s, 1H), 8.93 (d, 1H).

Espectro LCMS: MH+ 497.49, tiempo de retención 1.66 min.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidin-2-il]fenil]carbamato es descrita a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidin-2-il]fenil]carbamato

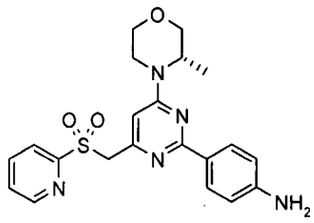


Fenil cloroformato (0.390 mL, 3.10 mmol) fue añadido a 4–[4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidin–2–il]anilina (1.1 g, 2.59 mmol) e hidrógeno carbonato de sodio (0.434 g, 5.17 mmol) en dioxano (25 mL) a RT. La lechada resultante fue agitada a RT durante 1 hora. La mezcla fue particionada entre etil acetato y agua. La solución orgánica fue separada, secada ($MgSO_4$) y concentrada a presión reducida. El residuo fue purificado por cromatografía flash en sílice usando elución en gradiente 0%–20%, etil acetato en DCM, para dar el material deseado como una espuma amarilla (1.130 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.25 (d, 3H), 3.23 (m, 1H), 3.52 (m, 1H), 3.65 – 3.68 (m, 1H), 3.75 (d, 1H), 3.95 – 3.99 (m, 1H), 4.05 – 4.11 (m, 2H), 4.31 – 4.38 (m, 1H), 4.63 (q, 2H), 6.39 (s, 1H), 6.95 (s, 1H), 7.13 (m, 2H), 7.17 – 7.21 (m, 1H), 7.34 (m, 4H), 7.48 (m, 1H), 7.75 – 7.85 (m, 4H), 8.77 – 8.79 (m, 1H).

Espectro LCMS: MH+ 546.49, tiempo de retención 2.54 min.

4–[4–[(3*S*)–3–Metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidin–2–il]anilina



Carbonato de sodio (7.32 mL, 14.64 mmol) fue añadido a 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.891 g, 4.07 mmol) y 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidina (1.5 g, 4.07 mmol) en una mezcla de DME (10 mL), etanol (10.00 mL), DMF (10.00 mL) y agua (10 mL) a RT bajo nitrógeno. La mezcla fue purgada con nitrógeno tres veces, bis(trifenilfosfina)paladio(II) cloruro (0.143 g, 0.20 mmol) fue añadido y la mezcla purgada con nitrógeno nuevamente. La suspensión resultante fue agitada a 80°C durante 90 minutos. La mezcla de reacción fue evaporada hasta secarse y suspendida en etil acetato (150 mL), y lavada con agua (2 x 150 mL) y salmuera saturada

(100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 0 a 40% etil acetato en DCM, para dar el material deseado como una espuma amarilla (1.21 g).

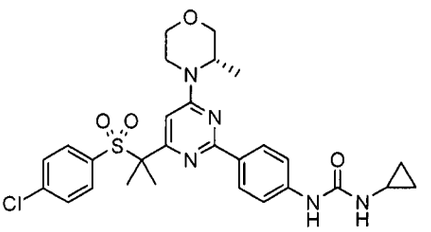
Espectro NMR: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.16 – 3.24 (m, 1H), 3.47 – 3.55 (m, 1H), 3.63 – 3.68 (m, 1H), 3.71 – 3.80 (m, 3H), 3.92 – 3.98 (m, 1H), 4.02 – 4.09 (m, 1H), 4.30 – 4.37 (m, 1H), 4.59 (q, 2H), 6.32 (s, 1H), 6.48 – 6.53 (m, 2H), 7.44 – 7.49 (m, 1H), 7.67 (d, 2H), 7.73 – 7.83 (m, 2H), 8.77 – 8.79 (m, 1H).

Espectro LCMS: MH+ 426.48, tiempo de retención 1.24 min. (Monitor Ácido).

La preparación de 2–cloro–4–[(3*S*)–3–metilmorfolin–4–il]–6–(piridin–2–ilsulfonilmetil)pirimidina fue descrita anteriormente.

Ejemplo 72:

1–[4–[4–[2–(4–Clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–ciclopropil–urea



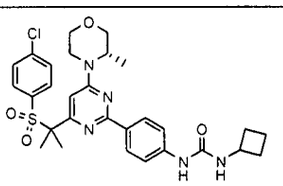
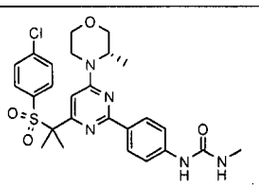
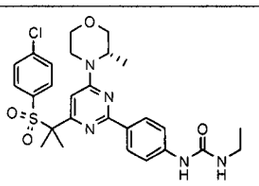
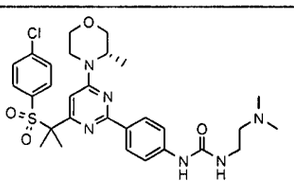
Ciclopropilamina (0.139 mL, 1.98 mmol) fue añadida a fenil *N*–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato (150 mg, 0.25 mmol) en DMF (2 mL). La solución resultante fue agitada a 60°C durante 5 horas. La mezcla fue evaporada hasta secarse y el residuo fue particionado entre etil acetato (30 mL) y agua (30 mL). La capa orgánica fue lavada con agua (2 x 30 mL) y salmuera saturada (30 mL), secada ($MgSO_4$), filtrada y evaporada hasta secarse. El residuo fue purificado por cromatografía flash en sílice, gradiente de elución 30 a 60% etil acetato en isohexano. Las fracciones puras fueron evaporadas hasta secarse y el residuo triturado con dietil éter para dar el material deseado como un sólido blanco (92 mg).

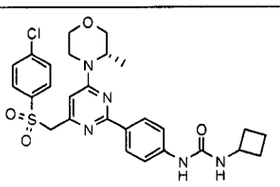
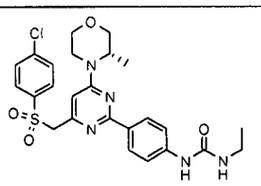
Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 0.70 (2H, s), 0.88 (2H, s), 1.34 (3H, d), 1.86 (6H, s), 2.63 (1H, t), 3.33 (1H, td), 3.63 (1H, td), 3.78 (2H, dd), 3.85 (2H, d), 4.06 (1H,

dd), 4.14 (1H, d), 4.49 (1H, d), 4.88 (1H, s), 6.63 (1H, s), 6.93 (1H, s), 7.30 (4H, d), 7.39 (2H, d), 7.47 (2H, d), 7.87 (2H, d).

Espectro LCMS: MH+ 570, 572, tiempo de retención 2.63 min.

Los siguientes compuestos fueron hechos de una forma análoga a partir de fenil *N*–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato o fenil *N*–[4–[4–[(4–clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
72a		1–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–ciclobutil–urea	584, 586	2.86
72b		1–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–metil–urea	544, 546	2.46
72c		1–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea	558, 560	2.63
72d		1–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–(2–	601, 603	2.51

		dimetilaminoetil)urea		
72e		(S)–1–(4–(4–((4–clorofenilsulfonil)metil)–6–(3–metilmorfolino)pirimidin–2–il)fenil)–3–ciclobutilurea	556, 558	2.56
72f		1–[4–[4–[(4–clorofenil)sulfonilmetil]–6–[(3S)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]–3–etil–urea	530, 532	2.38

Ejemplo 72a: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.72 (2H, m), 1.86 (2H, m), 1.86 (6H, s), 2.39 (2H, m), 3.32 (1H, ddd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.85 (1H, d), 4.06 (1H, dd), 4.14 (1H, d), 4.31 (1H, dtt), 4.49 (1H, br.d), 4.86 (1H, d), 6.29 (1H, s), 6.63 (1H, s), 7.27 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.86 (2H, d).

Ejemplo 72b: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.86 (6H, s), 2.86 (3H, d), 3.32 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.13 (1H, d), 4.48 (1H, br.d), 4.81 (1H, q), 6.52 (1H, s), 6.62 (1H, s), 7.28 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.87 (2H, d).

Ejemplo 72c: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.17 (3H, t), 1.34 (3H, d), 1.86 (6H, s), 3.32 (2H, dq), 3.32 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.13 (1H, d), 4.49 (1H, br.d), 4.78 (1H, t), 6.46 (1H, s), 6.62 (1H, s), 7.28 (2H, d), 7.29 (2H, d), 7.47 (2H, d), 7.86 (2H, d).

Ejemplo 72d: ^{1}H NMR (399.90 MHz, CDCl3) δ 1.34 (3H, d), 1.85 (6H, s), 2.32 (6H, s), 2.53 (2H, t), 3.31 (1H, ddd), 3.33 (2H, dt), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.14 (1H, d), 4.49 (1H, br.d), 5.29 (1H, br.s), 6.61 (1H, s), 7.29 (2H, d), 7.33 (2H, d), 7.47 (2H, d), 7.83 (2H, d), 8.41 (1H, v.br.s).

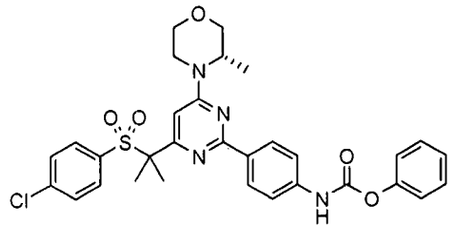
Ejemplo 72e: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 1.71 (2H, m), 1.84 (2H, m), 2.37 (2H, m), 3.30 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.14

(1H, d), 4.30 (2H, dtt), 4.38 (2H, s), 4.39 (1H, d), 4.97 (1H, d), 6.44 (1H, s), 6.49 (1H, s), 7.31 (2H, d), 7.43 (2H, d), 7.70 (2H, d), 7.87 (2H, d).

Ejemplo 72f: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.17 (3H, t), 1.33 (3H, d), 3.30 (1H, ddd), 3.32 (2H, dq), 3.60 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (1H, d), 4.38 (2H, s), 4.42 (1H, br.d), 4.77 (1H, t), 6.44 (1H, s), 6.47 (1H, s), 7.31 (2H, d), 7.43 (2H, d), 7.70 (2H, d), 7.88 (2H, d).

La preparación de fenil *N*–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

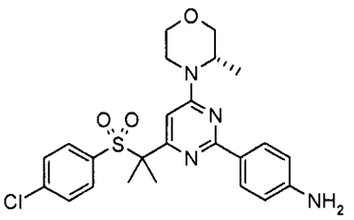


Fenil cloroformato (0.256 mL, 2.04 mmol) fue añadido en forma de gotas a 4–[4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (850 mg, 1.85 mmol) e hidrógeno carbonato de sodio (233 mg, 2.78 mmol) en dioxano (20 mL) a RT. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue diluida con etil acetato (100 mL) y lavada con agua (2 x 100 mL) y salmuera saturada (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 30 a 50% etil acetato en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar el material deseado como un sólido blanco (955 mg).

Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 3.32 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, br.d), 4.38 (2H, s), 4.43 (1H, br.d), 6.46 (1H, s), 7.03 (1H, s), 7.21 (2H, d), 7.25 (1H, dd), 7.40 (2H, d), 7.43 (2H, dd), 7.45 (2H, d), 7.70 (2H, d), 7.92 (2H, d)

Espectro LCMS: MH+ 579, 581, tiempo de retención 2.94 min.

4–[4–[2–(4–Clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina

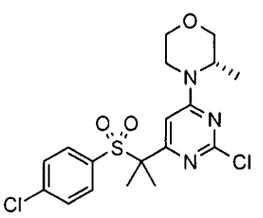


Carbonato de sodio (2M en agua, 6.69 mL, 13.38 mmol) fue añadido a 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.815 g, 3.72 mmol) y 2–cloro–4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3S)–3–metilmorfolin–4–il]pirimidina (1.60 g, 3.72 mmol) en una mezcla de DME (10 mL), etanol (10.00 mL), DMF (10.00 mL) y agua (20 mL) a RT bajo nitrógeno. La mezcla fue desgasificada y purgada con nitrógeno tres veces. Bis(trifenilfosfina)paladio(II) cloruro (0.130 g, 0.19 mmol) fue añadido y la mezcla fue desgasificada y purgada con nitrógeno unas tres veces adicionales. La suspensión resultante fue agitada bajo nitrógeno a 80°C durante 90 minutos. La mezcla de reacción fue concentrada y diluida con etil acetato (150 mL) y lavada con agua (2 x 150 mL) y salmuera saturada (100 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 30 a 45% etil acetato en isohexano, para dar el material deseado como un sólido blanco (1.502 g).

Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 1.84 (6H, s), 3.31 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 3.86 (2H, s), 4.05 (1H, dd), 4.13 (1H, br.d), 4.48 (1H, br.d), 6.57 (1H, s), 6.60 (2H, d), 7.30 (2H, d), 7.47 (2H, d), 7.72 (2H, d).

Espectro LCMS: MH+ 487, 489, tiempo de retención 2.64 min.

2–Cloro–4–[2–(4–clorofenil)sulfonilpropan–2–il]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina



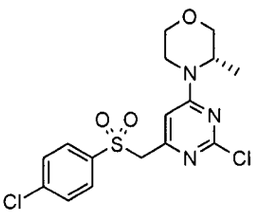
Metil yoduro (0.310 mL, 4.97 mmol) fue añadido en forma de gotas a 2–cloro–4–[(4–clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidina (2.00 g, 4.97 mmol) y tert–butóxido de sodio (0.478 g, 4.97 mmol) en DMF (50 mL) a 0°C durante un período de 5

minutos bajo nitrógeno. La solución resultante fue agitada a 0°C durante 15 minutos. *Tert*-butóxido de sodio (0.478 g, 4.97 mmol) fue añadido a 0°C, seguido por metil yoduro (0.310 mL, 4.97 mmol) y la mezcla agitada durante una hora adicional a 0°C. La mezcla fue vertida en agua agitada rápidamente (700 mL); el precipitado resultante fue recogido por filtración, lavado con agua y secado al vacío para dar el material deseado como un sólido blanco (1.79 g)

Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 1.74 (6H, s), 3.30 (1H, ddd), 3.57 (1H, ddd), 3.72 (dd, 1H), 3.81 (1H, d), 4.02 (2H, m), 4.33 (1H, br.s), 6.71 (1H, s), 7.45 (2H, d), 7.50 (2H, d).

Espectro LCMS: MH+ 430, 432, tiempo de retención 2.68 min.

2-Cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Sal sódica del ácido 4-clorobencenosulfínico (5.39 g, 27.15 mmol) fue añadida en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (8.00 g, 22.63 mmol) en acetonitrilo (400 mL) a RT. La suspensión resultante fue agitada a 85°C bajo reflujo durante 5 horas. La mezcla de reacción fue concentrada y diluida con DCM (400 mL) y lavada con agua (400 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 25 a 40% etil acetato en isohexano, para dar el material deseado como un sólido blanco (6.90 g).

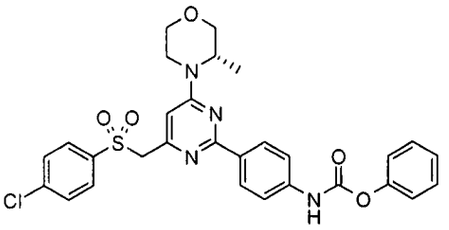
Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.55 (1H, ddd), 3.70 (1H, dd), 3.80 (1H, d), 4.02 (2H, m), 4.28 (1H, br.s), 4.29 (2H, s), 6.55 (1H, s), 7.51 (2H, d), 7.70 (2H, d).

Espectro LCMS: MH+ 402, 404, tiempo de retención 2.26 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

La preparación de fenil *N*–[4–[4–[(4–clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato es descrita a continuación.

Fenil *N*–[4–[4–[(4–clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]fenil]carbamato

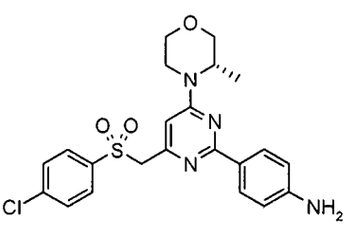


Fenil cloroformato (0.256 mL, 2.04 mmol) fue añadido en forma de gotas a 4–[4–[(4–clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina (850 mg, 1.85 mmol) e hidrógeno carbonato de sodio (233 mg, 2.78 mmol) en dioxano (20 mL) a RT. La suspensión resultante fue agitada a RT durante 2 horas. La mezcla de reacción fue diluida con etil acetato (100 mL), lavada con agua (2 x 100 mL) y salmuera saturada (50 mL). La capa orgánica fue secada ($MgSO_4$), filtrada y evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 30 a 50% etil acetato en isohexano, para dar el material deseado como un sólido blanco (955 mg).

Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.34 (3H, d), 3.32 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, br.d), 4.38 (2H, s), 4.43 (1H, br.d), 6.46 (1H, s), 7.03 (1H, s), 7.21 (2H, d), 7.25 (1H, dd), 7.40 (2H, d), 7.43 (2H, dd), 7.45 (2H, d), 7.70 (2H, d), 7.92 (2H, d).

Espectro LCMS: MH+ 579, 581, tiempo de retención 2.94 min.

4–[4–[(4–Clorofenil)sulfonilmetil]–6–[(3*S*)–3–metilmorfolin–4–il]pirimidin–2–il]anilina



Carbonato de sodio (2M en agua, 4.47 mL, 8.95 mmol) fue añadido a 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)anilina (0.572 g, 2.61 mmol) y 2–cloro–4–[(4–

clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1.00 g, 2.49 mmol) en una mezcla de DME (6.00 mL), DMF (6.00 mL), etanol (6.00 mL) y agua (14.00 mL) a RT. La mezcla fue desgasificada y purgada con nitrógeno tres veces. Bis(trifenilfosfina)paladio(II) cloruro (0.087 g, 0.120 mmol) fue añadido y la mezcla fue desgasificada y purgada con nitrógeno unas tres veces adicionales. La suspensión resultante fue agitada bajo nitrógeno a 80°C durante 90 minutos. La mezcla de reacción fue concentrada y diluida con etil acetato (100 mL) y lavada con agua (2 x 100 mL). La capa orgánica fue secada sobre ($MgSO_4$), filtrada y evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente de elución 30 a 60% etil acetato en isohexano, para dar el material deseado como un sólido blanco (0.980 g).

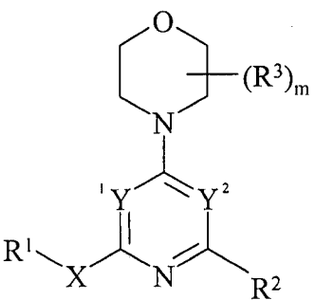
Espectro NMR: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.60 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 3.87 (2H, s), 4.04 (1H, dd), 4.15 (1H, m), 4.36 (2H, s), 4.42 (1H, br.s), 6.39 (1H, s), 6.62 (2H, d), 7.44 (2H, d), 7.69 (2H, d), 7.73 (2H, d).

Espectro LCMS: MH+ 459, 461, tiempo de retención 2.34 min.

La preparación de 2-cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina fue descrita anteriormente.

REIVINDICACIONES

1. Un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; donde

m es 0, 1, 2, 3 ó 4;

^{1}Y y **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y y Y^2 es N y el otro es CR^8;

X es un grupo de enlace seleccionado de $–CR^4=CR^5–$, $–CR^4=CR^5CR^6R^7–$, $–CR^6R^7CR^5=CR^4–$, $–C\equiv C–$, $–C\equiv CCR^6R^7–$, $–CR^6R^7C\equiv C–$, $–NR^4CR^6R^7–$, $–OCR^6R^7–$, $–SCR^6R^7–$, $–S(O)CR^6R^7–$, $–S(O)_2CR^6R^7–$, $–C(O)NR^4CR^6R^7–$, $–NR^4C(O)CR^6R^7–$, $–NR^4C(O)NR^5CR^6R^7–$, $–NR^4S(O)_2CR^6R^7–$, $–S(O)_2NR^4CR^6R^7–$, $–C(O)NR^4–$, $–NR^4C(O)–$, $–NR^4C(O)NR^5–$, $–S(O)_2NR^4–$ y $–NR^4S(O)_2–$;

R^1 es un grupo seleccionado de hidrógeno, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil, estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $–OR^9$, $–SR^9$, $–SOR^9$, $–SO_2R^9$, $–COR^9$, $–CO_2R^9$, $–CONR^9R^{10}$, $–NR^9R^{10}$, $–NR^9COR^{10}$, $–NR^9CO_2R^{10}$, $–NR^9CONR^{10}R^{15}$, $–NR^9COCONR^{10}R^{15}$ y $–NR^9SO_2R^{10}$;

R^2 es un grupo seleccionado de C_{1-6}alquil, carbociclil y heterociclil estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $–R^{11}$, $–OR^{11}$, $–SR^{11}$, $–SOR^{11}$, $–SO_2R^{11}$, $–COR^{11}$, $–CO_2R^{11}$, $–CONR^{11}R^{12}$, $–NR^{11}R^{12}$, $–NR^{11}COR^{12}$, y $–NR^{11}COCONR^{12}R^{16}$;

cada R^3, cuando está presente, es independientemente seleccionado de halo, ciano, nitro, $–R^{13}$, $–OR^{13}$, $–SR^{13}$, $–SOR^{13}$, $–SO_2R^{13}$, $–COR^{13}$, $–CO_2R^{13}$, $–CONR^{13}R^{14}$, $–NR^{13}R^{14}$, $–NR^{13}COR^{14}$, $–NR^{13}CO_2R^{14}$ y $–NR^{13}SO_2R^{14}$;

R^4 y R^5 son independientemente hidrógeno o C_{1-6}alquil;

o R^1 y R^4 junto con el átomo o átomos a los cuales están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros donde 1, 2 ó 3 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^6 y R^7 son independientemente seleccionados de hidrógeno, halo, ciano, nitro y C_{1-6}alquil;

R^8 es seleccionado de hidrógeno, halo, ciano y C_{1-6}alquil;

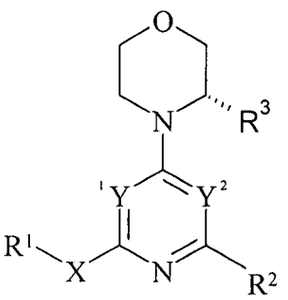
R^9 y R^{10} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil;

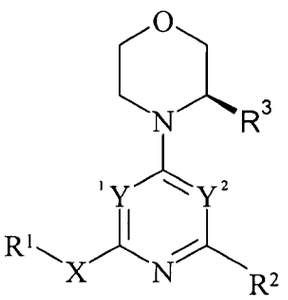
R^{13}, R^{14}, R^{15}, R^{16} y R^{19} son independientemente hidrógeno o un grupo seleccionado de C_{1-6}alquil, carbociclil, carbociclilC_{1-6}alquil, heterociclil y heterociclilC_{1-6}alquil estando dicho

grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil; o $\mathbf{R}^{18}$ y $\mathbf{R}^{19}$ junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico de 3 a 10 miembros donde 1 ó 2 átomos de carbono del anillo son opcionalmente reemplazados con N, O o S y estando dicho anillo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, oxo, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

2. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 1 donde el compuesto de fórmula (I) es un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo, donde R^1, R^2, R^3, X, Y^1 y Y^2 son como los definidos para el compuesto de fórmula (I) como se reivindicó en la Reivindicación 1.

3. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 1 ó 2 donde R^3 es metil.

4. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 1 a 3 donde Y^1 es CR^8 y Y^2 es N.

5. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 4 donde Y^1 es CH y Y^2 es N.

6. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 1 a 5 donde X es un grupo de enlace seleccionado de –$NR^4CR^6R^7$–, –OCR^6R^7–, –SCR^6R^7–, –$S(O)CR^6R^7$–, –$S(O)_2CR^6R^7$–, –$C(O)NR^4CR^6R^7$–, –$NR^4C(O)NR^5CR^6R^7$–, –$S(O)_2NR^4CR^6R^7$, –$C(O)NR^4$– y –$NR^4C(O)$–.

7. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 6 donde X es un grupo de enlace seleccionado de –$NR^4CR^6R^7$–, –OCR^6R^7–, –SCR^6R^7–, –$S(O)CR^6R^7$–, –$S(O)_2CR^6R^7$–, –$C(O)NR^4$–, y –$NR^4C(O)$–.

8. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 6 donde X es un grupo de enlace seleccionado de –NR^4CH_2–, –OCH_2–, –$OCH(CH_3)$–, –$OC(CH_3)_2$–, –SCH_2–, –$SCH(CH_3)$–, –$SC(CH_3)_2$–, –$S(O)CH_2$–, –$S(O)CH(CH_3)$–, –$S(O)C(CH_3)_2$–, –$S(O)_2CH_2$–, –$S(O)_2CH(CH_3)$–, –$S(O)_2C(CH_3)_2$–, –$C(O)NR^4$– y –$NR^4C(O)$–.

9. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 6 donde X es –$S(O)_2CH_2$–, –$S(O)_2CH(CH_3)$– o –$S(O)_2C(CH_3)_2$–.

10. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 6 donde X es –$S(O)_2C(CH_3)_2$–.

11. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 1 a 10 donde R^1 es un grupo seleccionado de adamantil, metil, etil, propil, butil, isobutil, *tert*–butil, ciclopentil, ciclohexil, fenil, bencil, oxetanil, fenetil, pirrolidinil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, pirazinil,

pirrolidinilmetil, pirrolidiniletil, pirrolilmetil, pirroliletil, imidazolilmetil, imidazoliletil, pirazolilmetil, pirazoliletil, furanilmetil, furaniletil, tienilmetil, tieniletil, piridinilmetil, piridiniletil, pirimidinilmetil, pirimidiniletil, pirazinilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1, 2 ó 3 grupos sustituyentes seleccionados de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$.

12. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 11 donde R^1 es un grupo seleccionado de metil, etil, propil, butil, isobutil, *tert*–butil, ciclopropil, ciclopentil, ciclohexil, fenil, bencil, fenetil, piridinil, pirrolidinil, pirazoliletil, furanilmetil, oxetanil, imidazolilmetil, tienilmetil, tiazolilmetil, tiadiazolilmetil y piraziniletil, estando dicho grupo opcionalmente sustituido por 1 ó 2 grupos sustituyentes seleccionados de amino, halo, ciano, metil, metoxi, trifluorometil, trifluorometoxi, $–NMe_2$, $–NHCOCH_3$, $–CONH_2$ y $–CONHCH_3$.

13. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 11 donde R^1 es un grupo seleccionado de metil, etil, isopropil, tert–butil, ciclopropil, ciclopentil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2OMe$, $–CH_2CH_2NMe_2$, $–CH_2CH_2NC(O)CH_3$, $–CH_2CONH_2$, fenil, 3,5–difluorofenil, 4–fluorofenil, 2–clorofenil, 4–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, oxetan–3–il, 2–oxopirolidin–3–il, 1–metilimidazol–5–ilmetil , 1–metilpirrolidin–3–il , tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il.

14. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 11 donde R^1 es un grupo seleccionado de metil, isopropil, ciclopropil, ciclohexil, $–CH_2CH_2OH$, $–CH_2CH_2NC(O)CH_3$, fenil, 4–fluorofenil, 2–clorofenil, 2–trifluorometilfenil, 2–metoxifenil, 2–metilfenil, 4–acetamidofenil, 4–aminofenil, piridin–4–il, piridin–2–il, 2–oxopirolidin–3–il, tiazol–2–il, 4–metiltiazol–2–il, y 3–metil–1,3,4–tiadiazol–2–il.

15. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 11 donde R^1 es metil, etil, isopropil, tert–butil, 4–fluorofenil, 3,5–difluorofenil, piridin–4–il o ciclopropil.

16. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 11 donde R^1 es metil, etil, isopropil, *tert*–butil, 4–fluorofenil, piridin–4–il o ciclopropil.

17. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 1 a 16 donde R^2 es seleccionado de carbociclil o heterociclil de 5 ó 6 miembros estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $–R^{11}$, $–OR^{11}$, $–COR^{11}$, $–CONR^{11}R^{12}$, $–NR^{11}R^{12}$ y $–NR^{11}COR^{12}$.

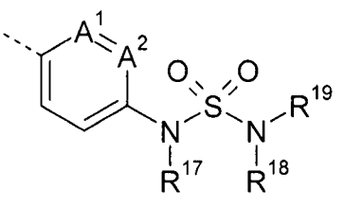
18. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 17 donde R^2 es seleccionado de un aril de 6 miembros y un heteroaril de 5 ó 6 miembros estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $–R^{11}$, $–OR^{11}$, $–COR^{11}$, $–CONR^{11}R^{12}$, $–NR^{11}R^{12}$ y $–NR^{11}COR^{12}$.

19. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 17 donde R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil, tiazolil estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de halo, ciano, nitro, $–R^{11}$, $–OR^{11}$, $–COR^{11}$, $–CONR^{11}R^{12}$, $–NR^{11}R^{12}$ y $–NR^{11}COR^{12}$.

20. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 17 donde R^2 es seleccionado de fenil, pirrolil, imidazolil, pirazolil, furanil, tienil, piridinil, pirimidinil, piridazinil, tiazolil estando dicho grupo sustituido por $–NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $–CONH_2$, $–CONHCH_3$ y $–CON(CH_3)_2$.

21. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 17 donde R^2 es fenil o piridil sustituido por $-NR^{17}CONR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes independientemente seleccionados de fluoro, metil, metoxi, hidroximetil, cianometil, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

22. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 17 donde R^2 es



donde A^1 y A^2 son seleccionados de CH o N siempre que al menos uno de A^1 o A^2 es CH.

23. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 17 a 22 donde R^{17} es hidrógeno.

24. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 17 a 23 donde R^{18} es hidrógeno.

25. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las Reivindicaciones 1 a 24 donde R^{19} es hidrógeno o un grupo seleccionado de C_{1-6}alquil, C_{3-6}cicloalquil, aril, heteroaril, arilC_{1-6}alquil y heteroarilC_{1-6}alquil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

26. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 25 donde R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, fenil, tienil, imidazoilmetil, isoxazolil, pirazolil, pirazolilmetil, piridinil y pirimidinil estando dicho grupo opcionalmente sustituido por uno o más grupos sustituyentes seleccionados de halo, ciano, nitro, hidroxi, C_{1-6}alquil, C_{1-6}alcoxi, haloC_{1-6}alquil, haloC_{1-6}alcoxi, hidroxiC_{1-6}alquil, hidroxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alquil, C_{1-6}alcoxiC_{1-6}alcoxi, amino, C_{1-6}alquilamino, bis(C_{1-6}alquil)amino, aminoC_{1-6}alquil, (C_{1-6}alquil)aminoC_{1-6}alquil, bis(C_{1-6}alquil)aminoC_{1-6}alquil, cianoC_{1-6}alquil, C_{1-6}alquilsulfonil, C_{1-6}alquilsulfonilamino, C_{1-6}alquilsulfonil(C_{1-6}alquil)amino, sulfamoil, C_{1-6}alquilsulfamoil, bis(C_{1-6}alquil)sulfamoil, C_{1-6}alcanoilamino, C_{1-6}alcanoil(C_{1-6}alquil)amino, carbamoil, C_{1-6}alquilcarbamoil y bis(C_{1-6}alquil)carbamoil.

27. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 25 donde R^{19} es hidrógeno o un grupo seleccionado de metil, etil, propil, i–propil, butil, i–butil, t–butil, pentil, ciclopropil, ciclobutil, ciclopentil, ciclohexil, –CH_2(ciclopropil), –$CH_2CH_2NMe_2$, –$CH(CH_3)CH_2OH$, –$C(CH_3)_2CH_2OH$, –CH_2CH_2OH, –$CH_2CH_2CH_2OH$, 4–metilfenil, 4–clorofenil, 4–trifluorometilfenil, 4–fluorofenil, 4–metoxifenil, 3,4–difluorofenil, tien–2–il, –CH_2(imidazol–2–il), –CH_2(imidazol–3–il), isoxazol–3–il, 6–oxo–1H–piridin–2–il, 5–metilisoxazol–3–il, 1–metilpirazol–4–il, –CH_2(1–metilpirazol–4–il), 6–metoxipiridin–3–il, 5–fluoropiridin–2–il, piridinil–2–il, pirimidin–2–il, y 1H–pirazol–3–il.

28. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 25 donde R^{19} es un grupo seleccionado de metil, etil, propil, ciclopropil, ciclobutil, –CH_2CH_2OH, –$CH_2CH_2NMe_2$, –$C(Me)_2CH_2OH$ y 1H–pirazol–3–il.

29. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la Reivindicación 1 seleccionado de cualquiera de los Ejemplos, o una sal farmacéuticamente aceptable de los mismos.

30. Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las Reivindicaciones 1 a 29 para el uso como un medicamento en el tratamiento de una enfermedad proliferativa.

31. El uso de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo definido en cualquiera de las Reivindicaciones 1 a 29 en la fabricación de un medicamento para el uso en el tratamiento de una enfermedad proliferativa.

32. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, definido en cualquiera de las Reivindicaciones 1 a 29 para la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

33. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, definido en cualquiera de las Reivindicaciones 1 a 29 en la fabricación de un medicamento para el uso en la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

34. Un método para producir un efecto antiproliferativo en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, definido en cualquiera de las Reivindicaciones 1 a 29.

35. Un método para tratar cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, definido en cualquiera de las Reivindicaciones 1 a 29.

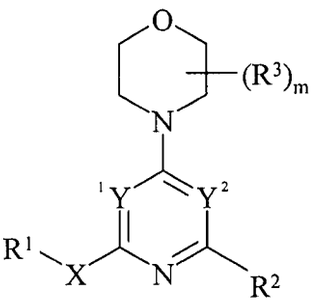
36. Una composición farmacéutica que comprende un compuesto de fórmula (I) definido en cualquiera de las Reivindicaciones 1 a 29, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluente o portador farmacéuticamente aceptable.

37. Un compuesto de fórmula (I) definido en cualquiera de las Reivindicaciones 1 a 29, o una sal farmacéuticamente aceptable del mismo, para el uso como un medicamento.

38. Un método para tratar cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares en un animal de sangre caliente tal como el hombre que está necesitado de tal tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, definido en cualquiera de las Reivindicaciones 1 a 29 concurrentemente o secuencialmente o como una preparación combinada con otro tratamiento utilizado en el control de la enfermedad oncológica.

RESUMEN

Un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en terapia, por ejemplo en el tratamiento de una enfermedad proliferativa tal como el cáncer y particularmente en enfermedades mediadas por una quinasa mTOR y/o una o más enzimas PI3K.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003173

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D239/42 C07D401/12 C07D401/14 C07D403/04
C07D403/12 C07D405/12 C07D409/12 C07D413/12 C07D417/12
A61K31/506 A61K31/5377 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2007/042806 A (LUDWIG INST CANCER RES [CH]; CANCER REC TECH LTD [GB]; INST OF CANCER) 19 April 2007 (2007-04-19) examples	1-38
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2007	20/12/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fazzi, Raffaella

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003173

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/053227 A (SYNTA PHARMACEUTICALS CORP [US]; SUN LIJUN [US]; KOSTIK ELENA [US]; PR) 18 May 2006 (2006-05-18) examples	1-38
P,X	WO 2006/125554 A (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; WUNDER FRANK [DE]; TERS) 30 November 2006 (2006-11-30) examples	1-38
P,X	WO 2006/124662 A (SYNTA PHARMACEUTICALS CORP [US]; DEMKO ZACHARY [US]; SUN LI JUN [US];) 23 November 2006 (2006-11-23) examples	1-38
Y	WO 2004/048365 A (CHIRON CORP [US]; NUSS JOHN M [US]; PECCHI SABINA [US]; RENHOWE PAUL A) 10 June 2004 (2004-06-10) cited in the application examples	1-38
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P,X	DOTZAUER ET AL: "2,4-Diamino-9H-pyrimido[4,5-b]indol-5-ols : Synthesis, in vitro cytotoxic activity, and QSAR investigations" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 14, no. 21, 1 November 2006 (2006-11-01), pages 7282-7292, XP005661674 ISSN: 0968-0896 page 7284; examples 9-11	1-38
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003173

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHANDRA N ET AL: "Antileishmanial agents part-IV: synthesis and antileishmanial activity of novel terpenyl pyrimidines" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 40, no. 6, June 2005 (2005-06), pages 552-556, XP004911366 ISSN: 0223-5234 page 553	1-38
X	"4-PYRIMIDINECARBOXAMIDE, 2,6-DI-4-MORPHOLINYL-N-(2-PHENYLETHYL)-" CHEMCATS, 2004, XP002348927 the whole document	1-38
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X	KUMAR ET AL.: "A Novel and Convenient Synthesis of 2-Amino-4-(N-alkyl-N-arylamino)-pyrimidines using Polarized Ketene S,S- and S,N-Acetals" SYNTHESIS, vol. 9, 1980, pages 748-751, XP002432317 page 749	1-38
X	SCHMIDT R R: "NEUE SYNTHESE VON PYRIMIDINDERIVATEN" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 98, no. 2, 1965, pages 346-351, XP009042438 ISSN: 0009-2940 page 347; example XIIa	1-38
X	WO 02/38551 A (HOFFMANN LA ROCHE [CH]) 16 May 2002 (2002-05-16) page 10	1-38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/003173

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32, 34-35 and 38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/003173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-017337- -00000-0000

Fecha: 2009-02-20 17:09:26 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 925

Industria y Comercio
SUPERINTENDENCIA

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 [ ]

Claudio Nieto Cortés
Firma Responsable

Fecha_____

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