-CSA045280

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

Organizacion y
Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-62879

SOLICITUD DE PATENTE DE INVENCIÓN

TÍTULO: ACILAMINOPIRAZOLES COMO INHIBIDORES DE FGFR

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-151 85 Södertalje, Suecia

APODERADO: J. IAN RAISBECK

BOGOTÁ 17 de Junio de 2009

P2009/000103

OLARTE RAISBECK

OLARTE RAISBECK M

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-062879- -00000-0000
Fecha: 2009-06-17 17:21:30 Dep.:2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 827

PETITORIO - FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000103**

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/GB2007/004917 Fecha Diciembre 20, 2007

Publicación Internacional No. WO 2008/075068 Fecha Junio 26, 2008

(6) **Título (54)** **ACILAMINOPIRAZOLES COMO INHIBIDORES DE FGFR**

Clasificación Internacional (51) C07D 231/40, C07D 401/06, C07D 401/12, C07D 401/14, C07D 403/12, C07D 405/06, C07D 409/12, C07D 413/12, C07D 471/04, C07D 487/04, A61K 31/415, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 21, 2006	60/871.190
US	Noviembre 5, 2007	60/985.542

(9) **Comprobante de pago No.** 09- _____ **Fecha** Junio 17 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).
[ ]	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

LISTA DE INVENTORES

PCT/GB2007/004917

Kevin Michael FOOTE,
AstraZeneca R & D Alderley,
Arderley Park,
Macclesfield Cheshire SK10 4TG
Gran Bretaña
Nacionalidad: Británica

Maria-Elena THEOCLITOU,
AstraZeneca R & D Alderley,
Arderley Park,
Macclesfield Cheshire SK10 4TG
Gran Bretaña
Nacionalidad: Griega

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AstraZeneca R & D Alderley,
Arderley Park,
Macclesfield Cheshire SK10 4TG
Gran Bretaña
Nacionalidad: Británica

David BUTTAR,
AstraZeneca R & D Alderley,
Arderley Park,
Macclesfield Cheshire SK10 4TG
Gran Bretaña
Nacionalidad: Británica

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-062879- -00000-0000
Fecha: 2009-06-17 17:21:30 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 44,585
FECHA : JUNIO 16 DE 2009

***** 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	105800155	16/06/2009	6,975,000.00

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

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

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial de un documento cuyo original está en inglés

No. 11426

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

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

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

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

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

Certificación Notarial

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

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

Ex oficio:

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

Traducción certificada
JORGE E. SERRA Jr.
Matrícula [illegible]

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 de Justicia

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:



OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Delgado
Simón Arbeláez
Alexander Agudelo
Camilo A. Rodríguez
Lina Moreno
Catalina Barbosa

Of Counsel
Guillermo Olarte
Gerardo Patel
Jacqueline Chaparro
Cruz E. de Monasterio

Power of Attorney

Poder

The undersigned,

El suscrito,

AstraZeneca AB

domiciled in

domiciliado en

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.

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

NOTARIAS PUBLICAS ESTOCOLMO
ANNE-MARIE BOOK

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

Andrea Burén
Authorised Signatory

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

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

3. That ASTRAZENECA AB
having its principal place of business located in SODERTALJE, SWEDEN
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

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

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

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

NOTARIUS PUBLICUS LEGALIS
ANNE-MARIE BONET

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

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. SIERRA [illegible]

- 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 [illegible]
Licencia 376 - ISPI Alejandría

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 376 - 1993 Ministerio

14

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

Certificate of Good Standing

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

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

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

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 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

The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Ms. Anna-Karin Eneström

Swedish Companies Registration Office, Sundsvall

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

For Stockholm this 17th day of August
MFA PAID 2007

Agneta Rosenlund

SIGNATURE OF Agneta Rosenlund
AND STAMP OF : Ec MFA
SIGNATURE : Mohamed Hussein
DATE : 29-08-07

09/103

Official translation of a document originally in Spanish

El Traspaso adjunto a AstraZeneca AB lleva la siguiente certificación notarial:

Se informa que yo, RICHARD PHILIP GODFREY CRAIK, de First Floor, 15/17 Broadway West Ealing, London, W13 9DA, Reino Unido, es un Notario Público debidamente autorizado.

Solamente certifico que Blair Consular Services Limited, en nombre de su cliente ASTRAZENECA AB

este día me ha presentado el documento anexo a éste que se describe como

Cesión firmada por David Buttar, Kevin Michael Foote, Maria-Elana Theoclitou y Andrew Peter Thomas

y que dicho Blair Consular Services Limited ha declarado ante mí por medio de dicha presentación que dicho cliente suyo les ha declarado que el mencionado documento anexo es un documento auténtico original.

Firmado y sellado en First Floor, 15/17 Broadway West Ealing, London, W13 9DA, Reino Unido, el día 12 de mayo de 2009.

(Firmado) Richard Philip Godfrey Craik, Notario Público

Hay un sello.

Apostilla adjunta:

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

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País:	Reino Unido de Gran Bretaña e Irlanda del Norte

El presente documento público

2. Ha sido firmado por:	Richard Philip Godfrey Craik
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	De dicho Notario Público

Certificado

5. En:	Londres
6. El:	15 de mayo de 2009
7. Por:	Secretario de Estado Principal de su Majestad para las Relaciones Exteriores y la Commonwealth.
8. Bajo el No.:	I150060
9. Sello / estampilla:	"Oficina de Relaciones Exteriores y de la Commonwealth – Londres"
10. Firma:	G. Barrie-Shilson. Por el Secretario de Estado

Si este documento va a ser usado en un país que no haga parte de la convención de La Haya del 5 de Octubre de 1961, debe presentarse a la sección consular de la misión que representa a ese país. Una Apostilla o certificado de legalización sólo confirma que la firma, sello o estampilla que lleva el documento es genuina. No significa que el contenido del documento sea correcto o que la Oficina de Relaciones Exteriores y de la Commonwealth apruebe el contenido.

MINISTERIO DE RELACIONES EXTERIORES
JEFE DE LEGALIZACIONES
BOGOTÁ D.C.
2009 JUN -2 P 2:31

FIN DE LA TRADUCCIÓN

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "Certificación Notarial y Apostilla"
Fecha: 2 de junio 2009.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registradas ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: tresser1@yahoo.com
Traducción # 13-256@

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

B009/103

[redacted]

BE IT KNOWN that I, RICHARD PHILIP GODFREY CRAIK of First Floor, 15/17 Broadway West Ealing, London, W13 9DA, United Kingdom, a duly authorised Notary Public

CERTIFY ONLY that Blair Consular Services Limited on behalf of their client

ASTRAZENECA AB

have this day presented to me the hereto annexed document describing itself as

ASSIGNMENT signed by David Buttar, Kevin Michael Foote, Maria-Elana Theoclitou and Andrew Peter Thomas

and that the said Blair Consular Services Limited have represented to me by such presentation that their said client has represented to them that the said annexed document is a authentic original document.

SIGNED AND SEALED at First Floor, 15/17 Broadway West Ealing, London, W13 9DA, United Kingdom, on 12th May 2009.

[redacted]

First Floor
15/17 Broadway
West Ealing
London W13 9DA
Tel: 020 8840 9524

Richard Philip Godfrey Craik
Notary Public

Richard Philip Godfrey Craik Notary Public

401536

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
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4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres

   Certified/Attesté
6. the/le **14 May 2009**

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

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9. Stamp: / timbre:

10. Signature: **G Barrie-Shilson**
    GBS

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LONDON

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

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102601-1P CO

ASSIGNMENT

The undersigned,

BUTTAR David; FOOTE Kevin, Michael;
THEOCLITOU Maria-Elena and THOMAS Andrew, Peter

domiciled in
AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom

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

ACYLAMINOPYRAZOLES AS FGFR INHIBITORS

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

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

SE-151 85 Södertälje, Sweden

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

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abajo firmado

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

organizada y existente de conformidad con la leves de

domiciliada en

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

BUTTAR David

FOOTE Kevin, Michael

THEOCLITOU Maria-Elena

THOMAS Andrew, Peter

102601-1P CO

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A los días del mes de , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

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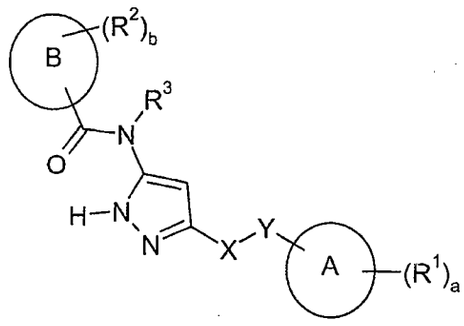
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(54) Title: NOVEL COMPOUNDS



(I)

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

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NOVEL COMPOUNDS

The present invention relates to pyrazole derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

Protein kinases are a class of proteins (enzymes) that regulate a variety of cellular functions. This is accomplished by the phosphorylation of specific amino acids on protein substrates resulting in conformational alteration of the substrate protein. The conformational change modulates the activity of the substrate or its ability to interact with other binding partners. The enzyme activity of the protein kinase refers to the rate at which the kinase adds phosphate groups to a substrate. It can be measured, for example, by determining the amount of a substrate that is converted to a product as a function of time. Phosphorylation of a substrate occurs at the active-site of a protein kinase.

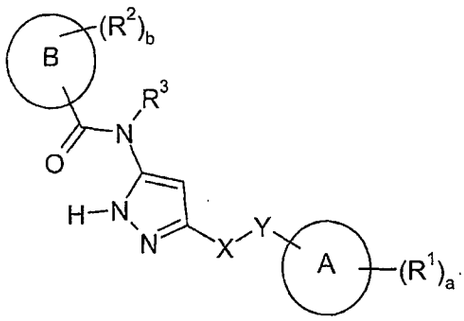
Tyrosine kinases are a subset of protein kinases that catalyze the transfer of the terminal phosphate of adenosine triphosphate (ATP) to tyrosine residues on protein substrates. These kinases play an important part in the propagation of growth factor signal transduction that leads to cellular proliferation, differentiation and migration.

Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as morphogenesis during development and angiogenesis. There are currently over 25 known members of the FGF family. The fibroblast growth factor receptor (FGFR) family consists of four members with each composed of an extracellular ligand binding domain, a single transmembrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Upon stimulation with FGF, FGFRs undergo dimerisation and transphosphorylation, which results in receptor activation. Receptor activation is sufficient for the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse process such as cell growth, cell metabolism and cell survival (Reviewed in Eswarakumar, V.P. et. al., Cytokine & Growth Factor Reviews 2005, 16, p139-149). Consequently, FGF and FGFRs have the potential to initiate and/ or promote tumorigenesis.

There is now considerable evidence directly linking FGF signalling to human cancer. The elevated expression of various FGFs has been reported in a diverse range of tumour types such as bladder, renal cell and prostate (amongst others). FGF has also been described as a powerful angiogenic factor. The expression of FGFRs in endothelial cells has also been

reported. Activating mutations of various FGFRs have been associated with bladder cancer and multiple myeloma (amongst others) whilst receptor expression has also been documented in prostate and bladder cancer amongst others (Reviewed in Grose, R. et. al., Cytokine & Growth Factor Reviews 2005, 16, p179-186 and Kwabi-Addo, B. et. al., Endocrine-Related Cancer 2004, 11, p709-724). For these reasons, the FGF signalling system is an attractive therapeutic target, particularly since therapies targeting FGFRs and/ or FGF signalling may affect both the tumour cells directly and tumour angiogenesis.

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



(I)

or a pharmaceutically acceptable salt thereof

wherein

ring **A** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

ring **B** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

$\mathbf{R^1}$ each independently represents

a halogen,

a hydroxyl group,

a cyano group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy,

C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_{3-5}cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -NR^6R^7 (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_3alkenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -NR^8R^9 (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a phenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{10}R^{11}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 6-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{12}R^{13}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-

C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a $-NR^{16}R^{17}$ group,

a $-OCOR^{18}$ group,

a $-CO_2R^{19}$ group,

a $-CONR^{20}R^{21}$ group,

a $-NR^{22}COR^{23}$ group,

a $-NR^{24}CO_2R^{25}$ group.

a $-OSO_2R^{26}$ group,

or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^2 each independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more

substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{45}R^{46}$, -CO_2R^{47} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl,

a C_3-C_6cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{48}R^{49}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{50}R^{51}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_6alkenyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{52}R^{53}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy,

C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{54}R^{55}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, -$NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{64}R^{65}$ (each of which may be

optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or two adjacent R^2 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{66}R^{67}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

$\mathbf{R^3}$ represents hydrogen,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{68}R^{69}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

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

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

$\mathbf{R^4}$ and $\mathbf{R^5}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^6}$ and $\mathbf{R^7}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^8}$ and $\mathbf{R^9}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{10} and R^{11} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{12} and R^{13} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{14} and R^{15} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{16} and R^{17} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{18} represents C_1-C_4alkyl, or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{19} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{20} and R^{21} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{22} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{23}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl(each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{24}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{25}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{26}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{27}}$ and $\mathbf{R^{28}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{27} and R^{28} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{29}}$ represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{30} and R^{31} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{32} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{33} represents hydrogen, C_1-C_4alkyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{34} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{35} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{36} and R^{37} each independently represent hydrogen, C_1-C_4alkyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, or R^{36} and R^{37} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl and 4- to 7-membered carbocyclyl or heterocycly group which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl);

R^{38} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{39} and R^{40} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{39} and R^{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{41} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{42} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{43} and R^{44} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{43} and R^{44} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{45} and R^{46} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{47} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{48} and R^{49} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{48} and R^{49} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{50} and R^{51} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{50} and R^{51} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{52} and R^{53} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{52} and R^{53} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{54} and R^{55} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{56} and R^{57} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{56} and R^{57} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{58} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{59} and R^{60} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{59} and R^{60} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{61} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{62} and R^{63} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{62} and R^{63} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{64} and R^{65} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{64} and R^{65} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

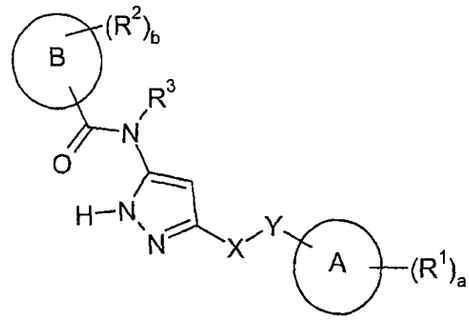
R^{66} and R^{67} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{66} and R^{67} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{68} and R^{69} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{68} and R^{69} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and where

when **Y** represents CH_2, **X** represents CH_2, O, NR^{70} or $S(O)_x$ wherein R^{70} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **x** is 0, 1 or 2; or

when **X** represents CH_2, **Y** represents CH_2, O, NR^{71} or $S(O)_y$ wherein R^{71} respresents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **y** is 0, 1 or 2.

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



(I)

or a pharmaceutically acceptable salt thereof

wherein

ring **A** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

ring **B** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

$\mathbf{R^1}$ each independently represents

a halogen,

a hydroxyl group,

a cyano group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_{3-5}cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^6R^7$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_3alkenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^8R^9$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a phenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{10}R^{11}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 6-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{12}R^{13}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a $-NR^{16}R^{17}$ group,

a $-OCOR^{18}$ group,

a $-CO_2R^{19}$ group,

a $-CONR^{20}R^{21}$ group,

a $-NR^{22}COR^{23}$ group,

a $-NR^{24}CO_2R^{25}$ group.

a $-OSO_2R^{26}$ group,

or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^2 each independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally

substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl,

a C_3-C_6cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{48}R^{49}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{50}R^{51}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_6alkenyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{52}R^{53}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{54}R^{55}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or two adjacent R^2 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{66}R^{67}$ (each of which may be optionally substituted by one or more

substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{68}R^{69}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

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

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

R^4 and R^5 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^6 and R^7 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^8 and R^9 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{10} and R^{11} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{12} and R^{13} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{14} and R^{15} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{16} and R^{17} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a 4- to

6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{18}}$ represents C_1-C_4alkyl, or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{19}}$ represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{20}}$ and $\mathbf{R^{21}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{22}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{23}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl(each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{24}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{25}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{26}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{27}}$ and $\mathbf{R^{28}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{27} and R^{28} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{29}}$ represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{30}}$ and $\mathbf{R^{31}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{30} and R^{31} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{32}}$ represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{33}}$ represents hydrogen, C_1-C_4alkyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{34}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{35} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{36} and R^{37} each independently represent hydrogen, C_1-C_4alkyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, or R^{36} and R^{37} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl and 4- to 7-membered carbocyclyl or heterocycly group which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl);

R^{38} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{39} and R^{40} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{39} and R^{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{41} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{42} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{43}}$ and $\mathbf{R^{44}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{43} and R^{44} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{45}}$ and $\mathbf{R^{46}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{47}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl;

$\mathbf{R^{48}}$ and $\mathbf{R^{49}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{48} and R^{49} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{50}}$ and $\mathbf{R^{51}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{50} and R^{51} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{52}}$ and $\mathbf{R^{53}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{52} and R^{53} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{54}}$ and $\mathbf{R^{55}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{56}}$ and $\mathbf{R^{57}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{56} and R^{57} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{58}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

$\mathbf{R^{59}}$ and $\mathbf{R^{60}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{59} and R^{60} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{61}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

$\mathbf{R^{62}}$ and $\mathbf{R^{63}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{62} and R^{63} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{64} and R^{65} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{64} and R^{65} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{66} and R^{67} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{66} and R^{67} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{68} and R^{69} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{68} and R^{69} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and where

when **Y** represents CH_2, **X** represents CH_2, O, NR^{70} or $S(O)_x$ wherein R^{70} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **x** is 0, 1 or 2; or

when **X** represents CH_2, **Y** represents CH_2, O, NR^{71} or $S(O)_y$ wherein R^{71} respresents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **y** is 0, 1 or 2; and

provided that the compound is not

4-benzamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

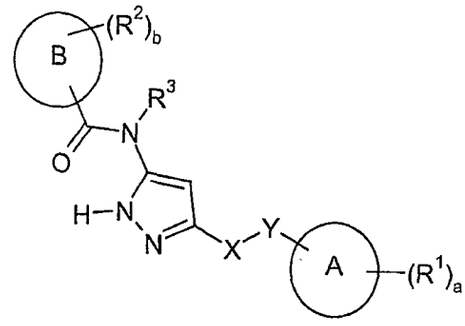
6-anilino-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

prop-2-enyl N-[5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridin-2-yl]carbamate,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide,

or methyl 6-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-3-carboxylate.

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



(I)

or a pharmaceutically acceptable salt thereof

wherein

ring **A** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

ring **B** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

$\mathbf{R^1}$ each independently represents

a halogen,

a hydroxyl group,

a cyano group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_{3-5}cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^6R^7$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_3alkenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^8R^9$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a phenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{10}R^{11}$ (each of which may be optionally substituted by one or more

substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 6-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{12}R^{13}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a –$NR^{16}R^{17}$ group,

a –$OCOR^{18}$ group,

a –CO_2R^{19} group,

a –$CONR^{20}R^{21}$ group,

a –$NR^{22}COR^{23}$ group,

a –$NR^{24}CO_2R^{25}$ group.

a –OSO_2R^{26} group,

or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^2 each independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl,

a C_3-C_6cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{48}R^{49}$ (each of which may be optionally substituted

by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{50}R^{51}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_6alkenyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{52}R^{53}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{54}R^{55}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more

substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or two adjacent R^2 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{66}R^{67}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{68}R^{69}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy,

C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

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

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

$\mathbf{R^4}$ and $\mathbf{R^5}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^6}$ and $\mathbf{R^7}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^8}$ and $\mathbf{R^9}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{10}}$ and $\mathbf{R^{11}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{12}}$ and $\mathbf{R^{13}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{16}}$ and $\mathbf{R^{17}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{18}}$ represents C_1-C_4alkyl, or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{19} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{20} and R^{21} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{22} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{23} represents C_1-C_4alkyl or C_3-C_6cycloalkyl(each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{24} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{25} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{26} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{27} and R^{28} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{27} and R^{28} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{29} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{30} and R^{31} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{30} and R^{31} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{32} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{33} represents hydrogen, C_1-C_4alkyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{34} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{35} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{36} and R^{37} each independently represent hydrogen, C_1-C_4alkyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least

one ring heteroatom selected from nitrogen, oxygen and sulphur, or R^{36} and R^{37} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl and 4- to 7-membered carbocyclyl or heterocycly group which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl);

$\mathbf{R^{38}}$ represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{39}}$ and $\mathbf{R^{40}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{39} and R^{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{41}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{42}}$ represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

$\mathbf{R^{43}}$ and $\mathbf{R^{44}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{43} and R^{44} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{45} and R^{46} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{47} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{48} and R^{49} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{48} and R^{49} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{50} and R^{51} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{50} and R^{51} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{52} and R^{53} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{52} and R^{53} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{54} and R^{55} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{56} and R^{57} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{56} and R^{57} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{58} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{59} and R^{60} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{59} and R^{60} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{61} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{62} and R^{63} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{62} and R^{63} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{64} and R^{65} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{64} and R^{65} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

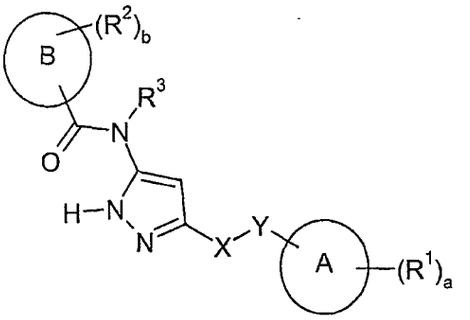
R^{66} and R^{67} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{66} and R^{67} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{68} and R^{69} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{68} and R^{69} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and where

when **Y** represents CH_2, **X** represents CH_2, O, NR^{70} or $S(O)_X$ wherein R^{70} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **x** is 0, 1 or 2; or

when **X** represents CH_2, **Y** represents CH_2, O, NR^{71} or $S(O)_y$ wherein R^{71} respresents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **y** is 0, 1 or 2.

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



(I)

or a pharmaceutically acceptable salt thereof

wherein

ring **A** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

ring **B** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

R^1 each independently represents

a halogen,

a hydroxyl group,

a cyano group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_{3-5}cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^6R^7$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_3alkenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^8R^9$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a phenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{10}R^{11}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 6-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{12}R^{13}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a $-NR^{16}R^{17}$ group,

a $-OCOR^{18}$ group,

a $-CO_2R^{19}$ group,

a $-CONR^{20}R^{21}$ group,

a $-NR^{22}COR^{23}$ group,

a $-NR^{24}CO_2R^{25}$ group.

a $-OSO_2R^{26}$ group,

or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

$\mathbf{R^2}$ each independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_3-C_6cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{48}R^{49}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{50}R^{51}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_6alkenyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{52}R^{53}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{54}R^{55}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl

and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or two adjacent R^2 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{66}R^{67}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{68}R^{69}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

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

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

R^4 and R^5 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^6 and R^7 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^8 and R^9 each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{10} and R^{11} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{12} and R^{13} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{14} and R^{15} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{16} and R^{17} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{18} represents C_1-C_4alkyl, or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{19} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{20} and R^{21} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{22} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{23} represents C_1-C_4alkyl or C_3-C_6cycloalkyl(each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{24} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{25} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{26} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{27} and R^{28} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{27} and R^{28} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{29} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{30} and R^{31} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{30} and R^{31} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy,

C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{32} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{33} represents hydrogen, C_1-C_4alkyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{34} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{35} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{36} and R^{37} each independently represent hydrogen, C_1-C_4alkyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, or R^{36} and R^{37} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl and 5- or 6-membered aryl group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur);

R^{38} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{39} and R^{40} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{39} and R^{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{41} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{42} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{43} and R^{44} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{43} and R^{44} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{45} and R^{46} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{47} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{48} and R^{49} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{48} and R^{49} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{50} and R^{51} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{50} and R^{51} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{52} and R^{53} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{52} and R^{53} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{54} and R^{55} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{56} and R^{57} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{56} and R^{57} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{58} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{59} and R^{60} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{59} and R^{60} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{61} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{62} and R^{63} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{62} and R^{63} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{64} and R^{65} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{64} and R^{65} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{66} and R^{67} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{66} and R^{67} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{68} and R^{69} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{68} and R^{69} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and where

when **Y** represents CH_2, **X** represents CH_2, O, NR^{70} or $S(O)_x$ wherein R^{70} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **x** is 0, 1 or 2; or

when **X** represents CH_2, **Y** represents CH_2, O, NR^{71} or $S(O)_y$ wherein R^{71} respresents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **y** is 0, 1 or 2.

In the context of the present specification, unless otherwise indicated, the term "alkyl" includes both linear and branched chain alkyl groups, but references to individual groups such as "*n*-propyl" are specific for the linear version only, and references to individual branch chained versions, for example "*i*-propyl", are specific for the branched version only. A similar convention applies to other radicals.

For example, examples of "C_1-C_6alkyl" and "C_1-C_4alkyl" include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl and *t*-butyl. Examples of "C_1-C_6alkoxy" and "C_1-C_3alkoxy" include methoxy, ethoxy, *n*-propoxy and *i*-propoxy. Examples of "C_2-C_6alkenyl" include vinyl, allyl and 1-propenyl. Examples of "C_3-C_6cycloalkyl" include cyclopropyl, cyclopentyl and cyclohexyl. Example of "mono- and di-C_1-C_6alkylamino" include methylamino, dimethylamino, ethylamino, diethylamino and ethylmethylamino. Examples of "C_1-C_6alkylthio" include methylthio, ethylthio and propylthio.

Examples of halogen include fluorine, chlorine, bromine and iodine.

A "4- to 7-membered carbocyclyl group", unless otherwise stated, includes saturated and fully or partially unsaturated, monocyclic rings containing 4, 5, 6 or 7 carbon atoms. A "4- to 7-membered carbocyclyl group" includes groups such as C_4-C_7cycloalkyl, C_4-C_7cycloalkenyl and C_6aryl.

A "5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" or "5- or 6-membered aryl group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably a "5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl and triazolyl rings.

A "4- to 7-membered heterocyclyl group", unless otherwise stated, includes saturated and fully or partially unsaturated, monocyclic rings containing 4, 5, 6 or 7 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, and which may, unless otherwise specified, be carbon or nitrogen linked. Suitable "4- to 7-membered heterocyclyl group" which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur include azetidine, *gamma*-butyrolactone, diazepine, dioxolane, dioxane, dihydro-oxazine, dihydrothiophene, dithiolan, furan, hexahydroazepine, imidazole, imidazoline, imidazolidine, isothiazole, isoxazole, morpholine, oxadiazole, oxazine, oxazole, oxetane, piperidine, piperazine, *alpha*-pyran, *gamma*-pyran, pyrazine, pyrazolidine, pyrazole, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, tetrahydrofuran,

tetrahydrofuranone, tetrahydropyran, tetrazine, tetrazole, thiadiazole, thiazole, thiolan, thiomorpholine, thiomorpholine S,S-dioxide, thiophene and triazine.

When R^4 and R^5, or R^6 and R^7, or R^8 and R^9, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, or R^{27} and R^{28}, or R^{43} and R^{44}, or R^{45} and R^{46}, or R^{48} and R^{49}, or R^{50} and R^{51}, or R^{52} and R^{53}, or R^{54} and R^{55}, or R^{56} and R^{57}, or R^{59} and R^{60}, or R^{62} and R^{63}, or R^{64} and R^{65}, or R^{66} and R^{67}, or R^{68} and R^{69} represent a 4- to 6-membered saturated heterocycle, it should be understood that when only one heteroatom is present it is the nitrogen atom to which R^4 and R^5, or R^6 and R^7, or R^8 and R^9, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, or R^{27} and R^{28}, or R^{43} and R^{44}, or R^{45} and R^{46}, or R^{48} and R^{49}, or R^{50} and R^{51}, or R^{52} and R^{53}, or R^{54} and R^{55}, or R^{56} and R^{57}, or R^{59} and R^{60}, or R^{62} and R^{63}, or R^{64} and R^{65}, or R^{66} and R^{67}, or R^{68} and R^{69} are attached. The "4- to 6-membered saturated heterocycle", unless otherwise stated, includes saturated monocyclic rings containing 4, 5 or 6 atoms wherein at least one atom is nitrogen and the remaining atoms are selected from carbon, nitrogen, oxygen and sulphur. Suitable "4- to 6-membered saturated heterocycle" include pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine, morpholine, thiomorpholine and thiomorpholine S,S-dioxide.

A "4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group", unless otherwise stated, includes saturated and fully or partially unsaturated, monocyclic or bicyclic rings, each ring containing 4, 5, 6 or 7 atoms and at least one ring atom of one ring is a heteroatom selected from nitrogen, oxygen and sulphur, and which may, unless otherwise specified, be carbon or nitrogen linked. Suitable "4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group" which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur include azetidine, benzfuran, benzimidazole, benzthiophene, *gamma*-butyrolactone, diazepine, dioxolane, dioxane, dihydro-oxazine, dihydrothiophene, dithiolan, furan, hexahydroazepine, imidazole, imidazoline, imidazolidine, indazole, indole, isothiazole, isoxazole, morpholine, oxadiazole, oxazine, oxazole, oxetane, piperidine, piperazine, *alpha*-pyran, *gamma*-pyran, pyrazine, pyrazolidine, pyrazole, pyrazoline, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrroline, quinazoline, quinoline, tetrahydrofuran, tetrahydrofuranone, tetrahydropyran, tetrahydroquinoline, tetrazine, tetrazole, thiadiazole, thiazole, thiolan, thiomorpholine, thiomorpholine S,S-dioxide, thiophene and triazine.

For the aviodance of doubt, where it is indicated that substituents may carry further substituents for example in definitions of terms such as "a C_1-C_3alkyl group optionally

substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -NR^4R^5 (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl)", it is understood that atoms, such as carbon atoms that may be capable of carrying optionally substituents by replacement of hydrogen radicals, in the groups C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio and -NR^4R^5 (irrespective of any additional substituents defined in the definitions of R^4 or R^5) may be substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl. For example, R^4 or R^5 may also be substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl.

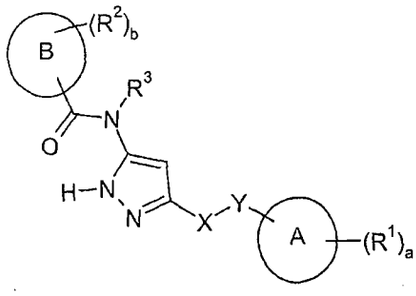
A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. 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.

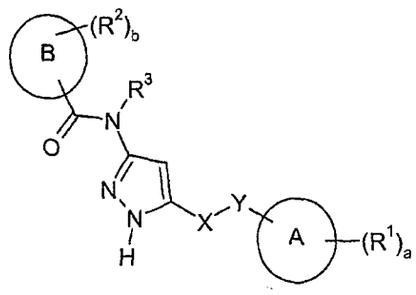
An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula **(I)** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess FGFR inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula **(I)** that possess FGFR inhibitory activity. For example, the compound of formula (IA) is a tautomer of the compound of formula (I).



(I)



(IA)

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms that possess FGFR inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In a further embodiment of the invention, A represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring.

In a further embodiment of the invention, A represents a furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring.

In a further embodiment of the invention, A represents a furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring.

In a further embodiment of the invention, A represents a furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, or pyrimidinyl ring.

In a further aspect of the invention, A represents a furyl, phenyl, pyridyl or pyrimidinyl ring.

In a further aspect of the invention, A represents a furyl, phenyl or pyridyl ring.

In a further aspect of the invention, A represents a furyl or phenyl ring.

In a further aspect of the invention, A represents a phenyl ring.

In a further embodiment of the invention B represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring.

In a further embodiment of the invention B represents a furyl, isothiazolyl, isoxazolyl, oxadiazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl or thienyl ring.

In a further embodiment of the invention, B represents a furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring.

In a further embodiment of the invention, B represents a furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring.

In a further embodiment of the invention B represents a phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl or pyrimidinyl ring.

In a further embodiment of the invention B represents a phenyl, pyrazinyl, pyridyl, thienyl or pyrimidinyl ring.

In a further aspect of the invention B represents a pyridyl, pyrimidinyl or phenyl ring.

In a further embodiment of the invention B represents a phenyl, pyrazinyl, thienyl or pyrimidinyl ring.

In a further aspect of the invention B represents a phenyl ring.

In one embodiment of the invention, each R^1 independently represents a halogen; a hydroxyl group; a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a $-CONR^{20}R^{21}$ group.

In a further embodiment of the invention, each R^1 independently represents a halogen; a hydroxyl group; a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; a $-CONR^{20}R^{21}$ group; or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further embodiment of the invention, each R^1 independently represents a halogen; a hydroxyl group; a C_1-C_3alkoxy group optionally substituted by one or more substituents

selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a –$CONR^{20}R^{21}$ group.

In a further embodiment of the invention, each R^1 independently represents a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further embodiment of the invention, each R^1 independently represents a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from methoxy, -$N(Me)_2$ and hydroxyl.

In a further additional aspect of the invention each R^1 independently represents a -$CONR^{20}R^{21}$ group.

In a further additional aspect of the invention each R^1 independently represents a methoxy group; -OCH_2CH_2OMe; -CH_2NMe_2 or or two adjacent R^1 groups together form an -OCH_2O- bridge.

In a further additional aspect of the invention each R^1 independently represents a hydroxyl group; -$CONH_2$; –CONHMe; -$CONMe_2$ or a methoxy group.

In a further additional aspect of the invention each R^1 indpendently represents -CONHMe or a methoxy group.

In a further additional aspect of the invention R^1 represents –CONHMe.

In a further additional aspect of the invention R^1 represents methoxy.

In another embodiment of the invention, each R^2 independently represents a -$NR^{36}R^{37}$ group; a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally

fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In another embodiment of the invention, each R^2 independently represents a $-NR^{36}R^{37}$ group; a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio,

C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{45}R^{46}$, -CO_2R^{47} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, -$NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a hydroxyl group; a halogen; a cyano group; a -CO_2R^{29} group; a –$CONR^{30}R^{31}$ group; a –$NR^{32}COR^{33}$ group; a –$NR^{34}CO_2R^{35}$ group; a –$NR^{36}R^{37}$ group; a -SO_2R^{38} group; a -$SO_2NR^{39}R^{40}$ group; a –$NR^{41}SO_2R^{42}$ group; a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{45}R^{46}$, -CO_2R^{47} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl; a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, -$NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a hydroxyl group; a halogen; a cyano group; a $-CO_2R^{29}$ group; a $-CONR^{30}R^{31}$ group; a $-NR^{32}COR^{33}$ group; a $-NR^{34}CO_2R^{35}$ group; a $-NR^{36}R^{37}$ group; a $-SO_2R^{38}$ group; a $-SO_2NR^{39}R^{40}$ group; a $-NR^{41}SO_2R^{42}$ group; a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl; a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or

more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a $-NR^{36}R^{37}$ group; a C_1-C_6alkyl group optionally substituted by one or more substituents selected from $-NR^{43}R^{44}$ (which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl; or a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a methyl or a methoxy group optionally substituted by a morpholine, piperidine or piperazine group each optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy,

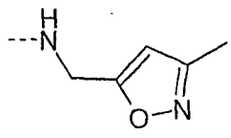
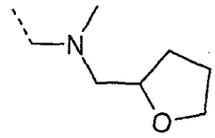
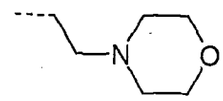
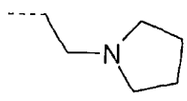
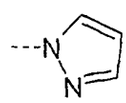
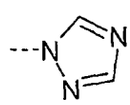
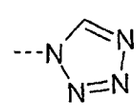
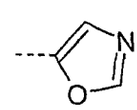
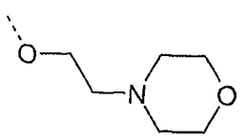
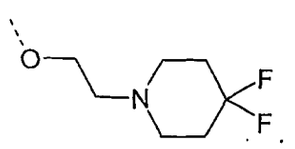
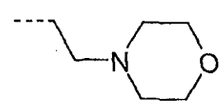
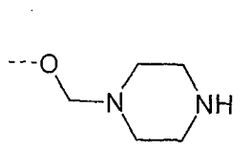
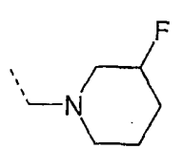
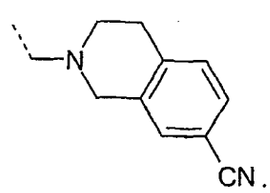
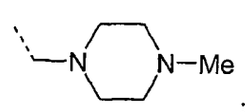
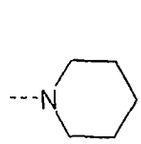
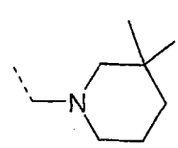
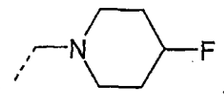
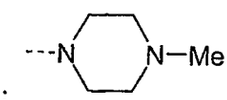
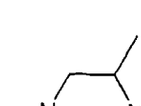
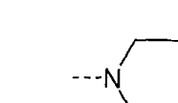
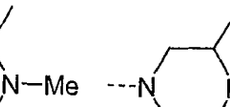
C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

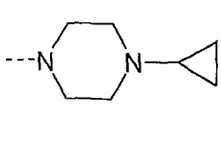
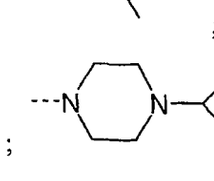
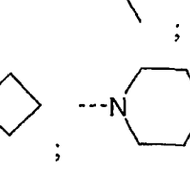
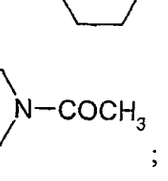
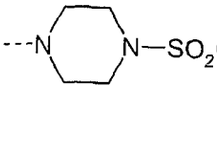
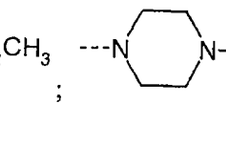
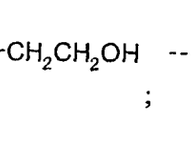
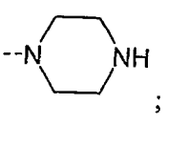
In a further aspect of the invention, each R^2 independently represents a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl.

In a further aspect of the invention, each R^2 independently represents a –Cl; -F; -I; -OH; -CN; -CH_3; -CH_2OH; -$CH_2N(CH_3)_2$; -$CH_2CH(CH_3)NH_2$; -OCH_3; -OCH_2CH_2OH; -$OCH_2CH_2OCH_2CH_3$; -SO_2CH_3; -$N(CH_3)_2$; -NHPh; -$NHCH_2C{\equiv}CH$; -$NHCH_2CH_3$;

$-NHCH_2CH_2N(CH_3)_2$; $-NHCO_2CH_2CH{=}CH_2$; $-NHCOCH_3$; -NHCOH; -NHCOPh; $-CONH_2$; $-NHSO_2Me$; $-SO_2N(CH_3)_2$; $-CO_2H$; $-CO_2CH_3$; $-CO_2CH_2CH_3$;


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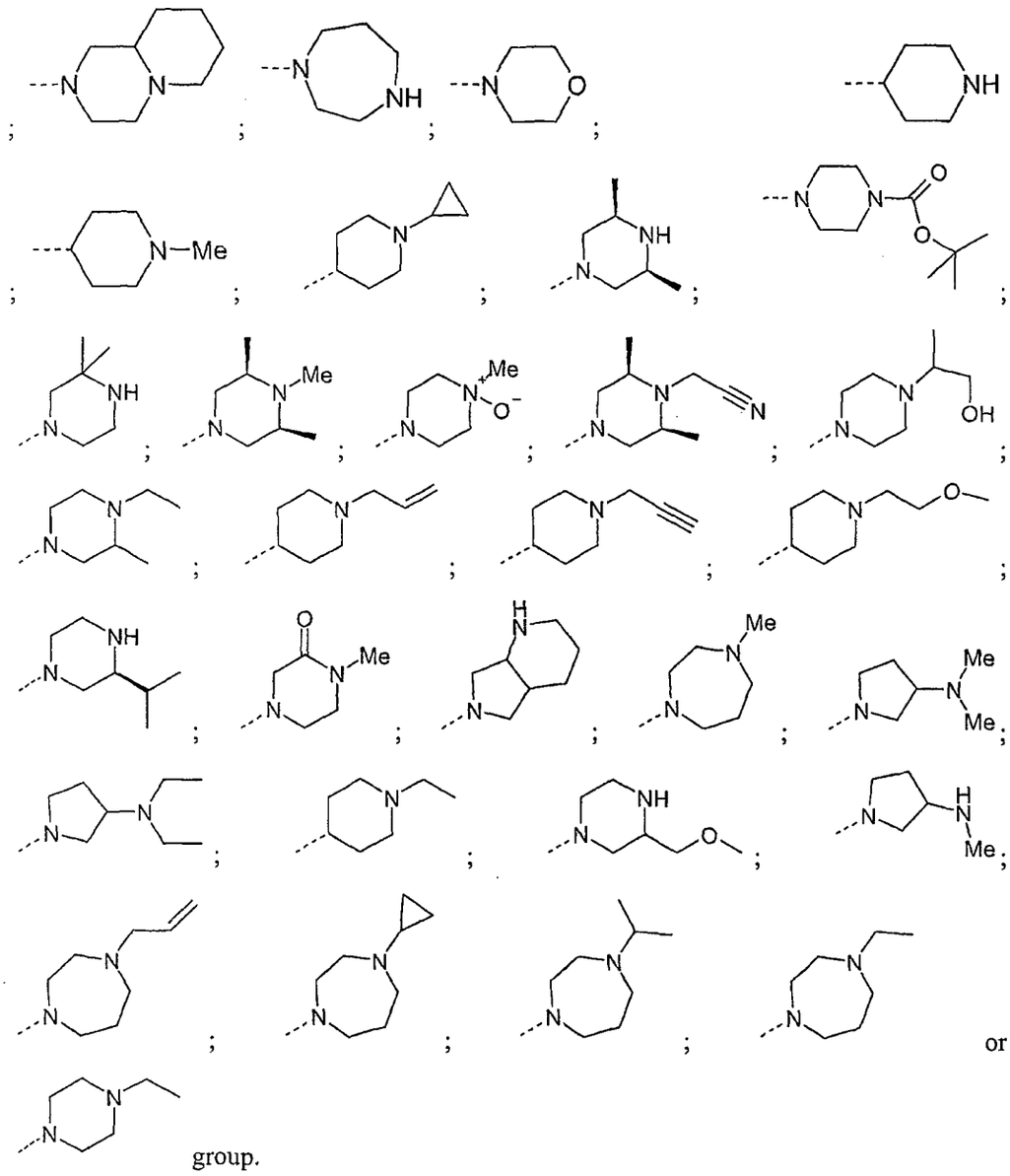
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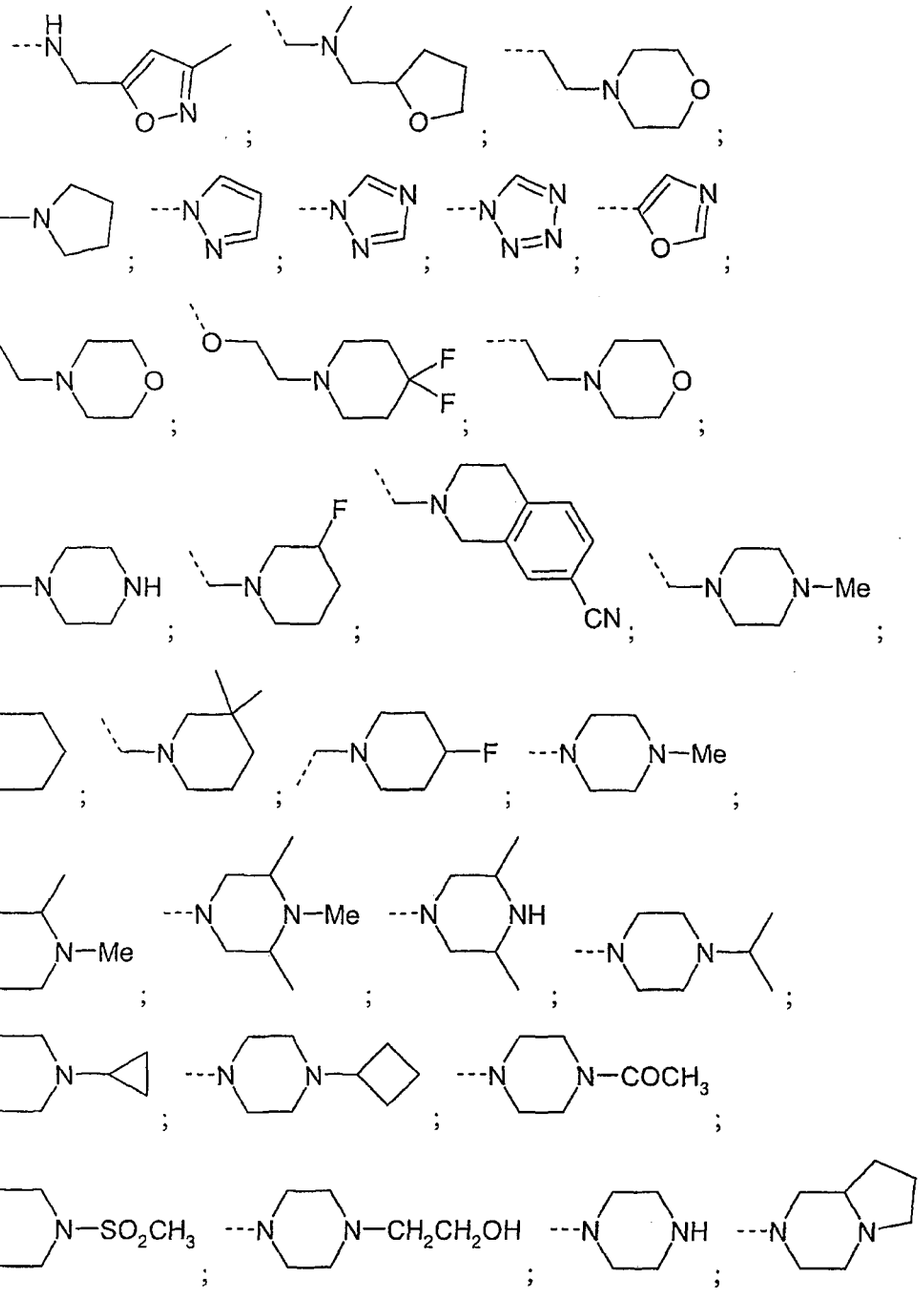
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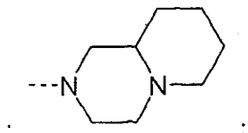
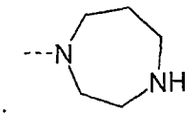
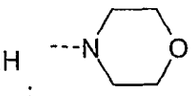
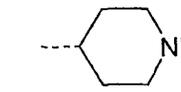
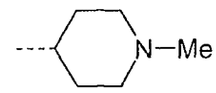
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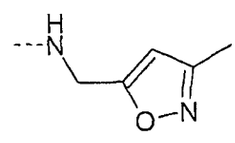
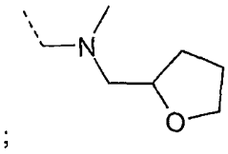
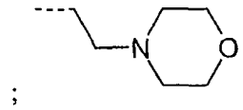
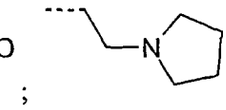
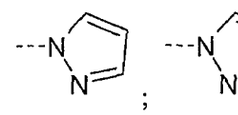
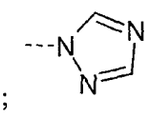
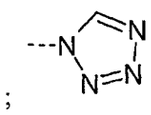
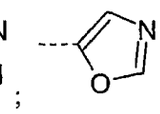
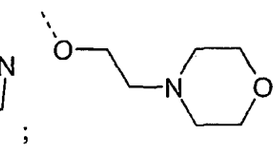
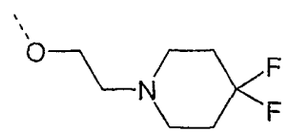
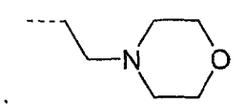
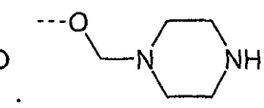
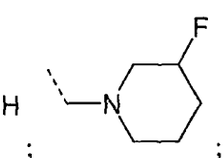
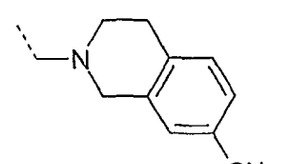
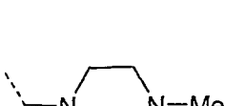
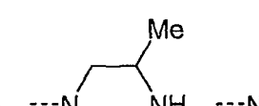
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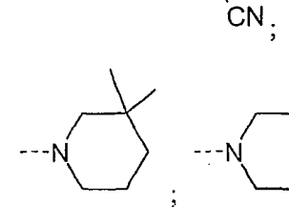
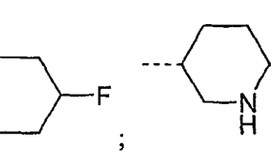
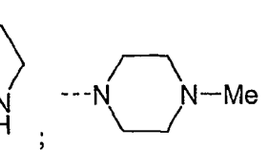
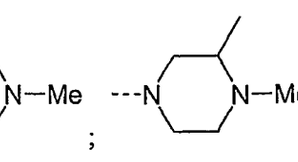
In a further aspect of the invention, each R^2 independently represents a –Cl; -F; -I; -OH; -CN; $-CH_3$; $-CH_2OH$; $-CH_2N(CH_3)_2$; $-CH_2CH(CH_3)NH_2$; $-OCH_3$; $-OCH_2CH_2OH$; $-OCH_2CH_2OCH_2CH_3$; $-SO_2CH_3$; $-OCH_2CH_2OH$; $-N(CH_3)_2$; -NHPh; $-NHCH_2C{\equiv}CH$; $-NHCH_2CH_3$; $-NHCH_2CH_2N(CH_3)_2$; $-NHCO_2CH_2CH{=}CH_2$; $-NHCOCH_3$; -NHCOH; -NHCOPh; $-CONH_2$; $-NHSO_2Me$; $-SO_2N(CH_3)_2$; $-CO_2H$; $-CO_2CH_3$; $-CO_2CH_2CH_3$;




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or group.

In a further aspect of the invention, each R^2 independently represents a –Cl; -F; -I; -OH; -CN; $-CH_3$; $-CH_2OH$; $-CH_2N(CH_3)_2$; $-CH_2CH(CH_3)NH_2$; $-OCH_3$; $-OCH_2CH_2OH$; $-OCH_2CH_2OCH_2CH_3$; $-SO_2CH_3$; $-OCH_2CH_2OH$; $-N(CH_3)_2$; -NHPh; $-NHCH_2C{\equiv}CH$; $-NHCH_2CH_3$; $-NHCH_2CH_2N(CH_3)_2$; $-NHCO_2CH_2CH{=}CH_2$; $-NHCOCH_3$; -NHCOH; -NHCOPh; $-CONH_2$; $-NHSO_2Me$; $-SO_2N(CH_3)_2$; $-CO_2H$; $-CO_2CH_3$; $-CO_2CH_2CH_3$;


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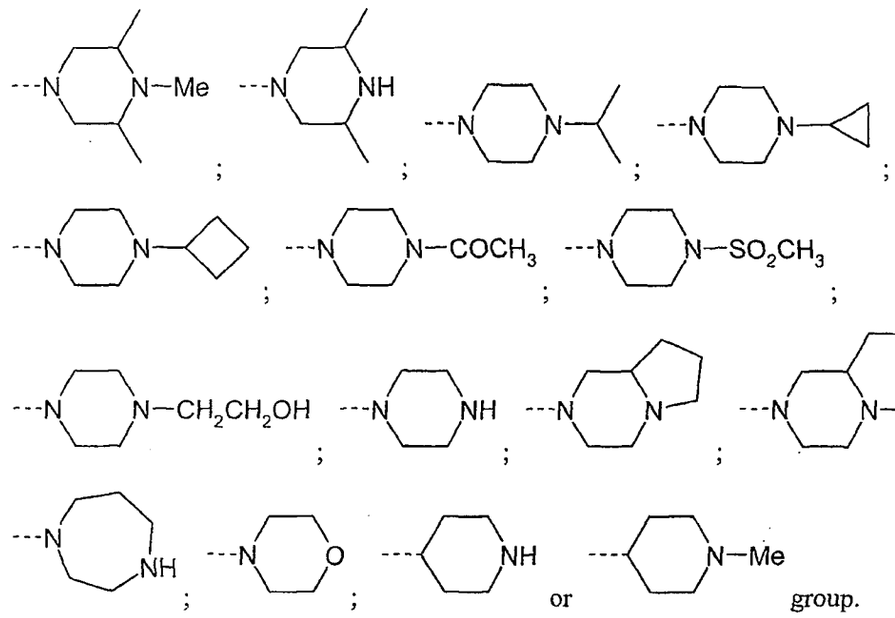
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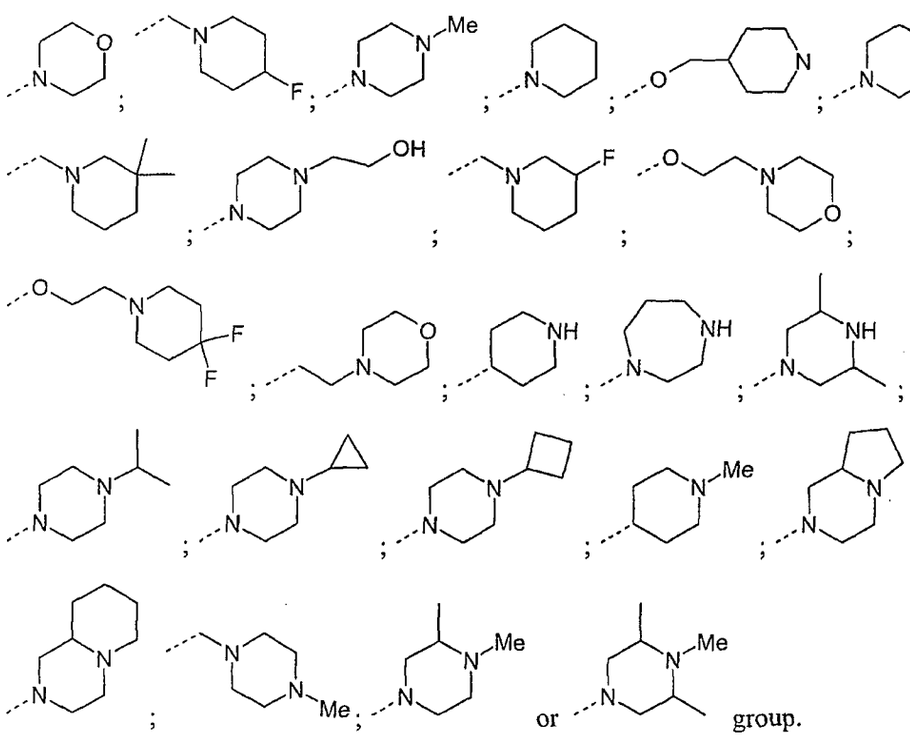
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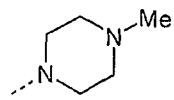
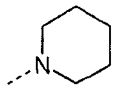
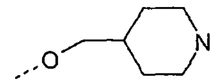
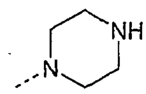
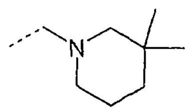
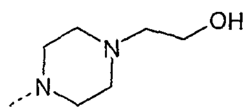
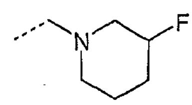
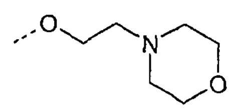
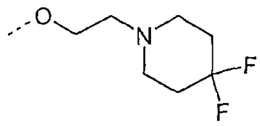
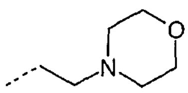
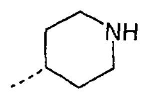
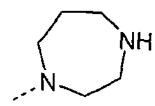
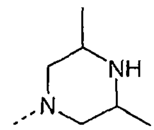
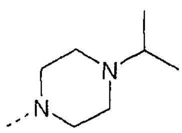
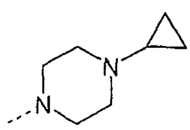
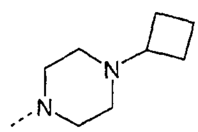
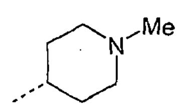
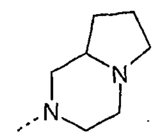
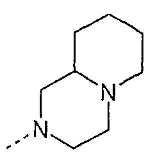
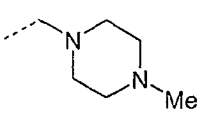
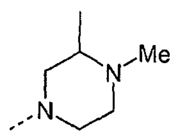
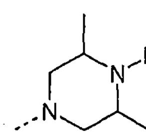
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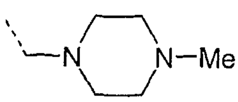
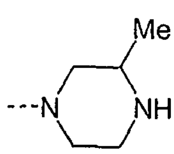
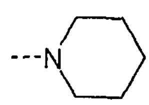
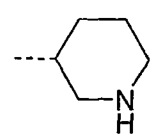
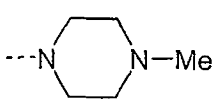
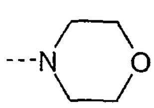
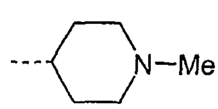
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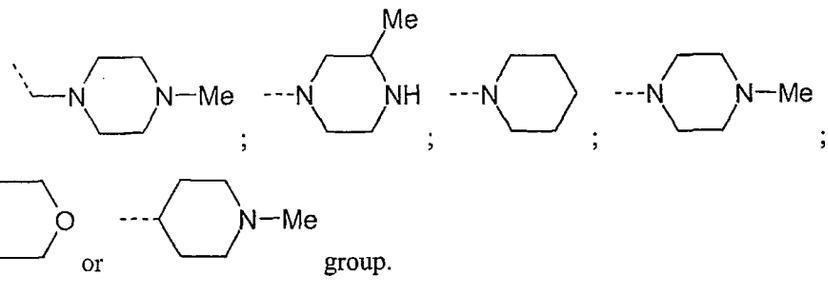
In a further aspect of the invention, each R^2 independently represents a –OMe; $-OCH_2CH_2OCH_2CH_3$; $-OCH_2CH_2OH$; $-CH_2N(CH_3)_2$; $-NHCH_2CH_2N(CH_3)_2$;



In a further aspect of the invention, each R^2 independently represents a $-NHCH_2CH_2N(CH_3)_2$;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; or  group.

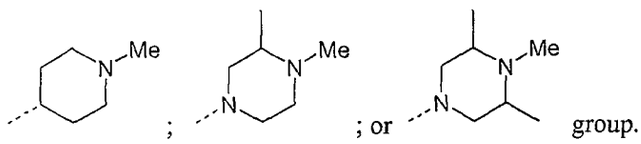
In a further aspect of the invention, each R^2 independently represents a  ;  ;  ;  ;  ;  or  group.

In a further aspect of the invention, each R^2 independently represents a



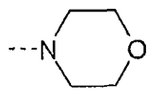
or group.

In a further aspect of the invention, each R^2 independently represents a



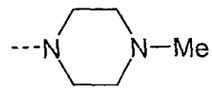
group.

In a further aspect of the invention, R^2 represents a



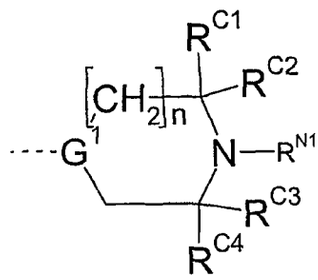
group.

In a further aspect of the invention, R^2 represents a



group.

In a further aspect of the invention, R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

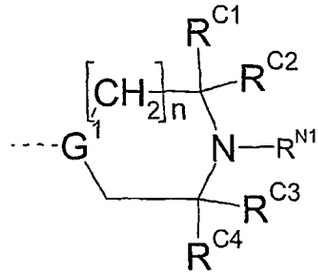
R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from cyano, halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected fromC_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl.

In a further aspect of the invention, R^2 independently represents



wherein

G^1 is C or N,

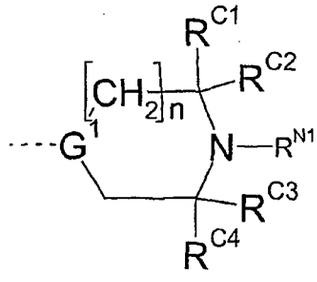
n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 5-membered carbocyclic ring, and

R^{N1} is selected from selected from C_1-C_2alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl) and hydrogen, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring.

In a further aspect of the invention, R^2 independently represents



wherein

G^1 is C or N,

n is 1 or 2,

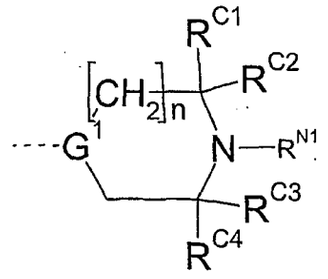
R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring, and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl propenyl, propynyl, propyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring.

In a further aspect of the invention, R^2 independently represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring, and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl propenyl, propynyl, propyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring.

In a further aspect of the invention R^3 represent hydrogen.

In a further embodiment of the invention X represents CH_2 or O.

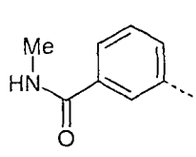
In a further embodiment of the invention Y represents CH_2.

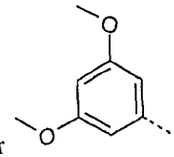
In a further embodiment of the invention a is 0, 1 or 2.

In a further embodiment of the invention b is 0, 1 or 2.

In a further aspect of the invention, b is 1.

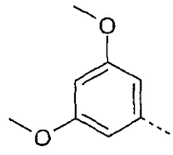
In a further aspect of the invention, -A-$(R^1)_a$ represents a



or 

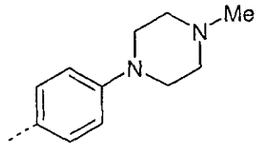
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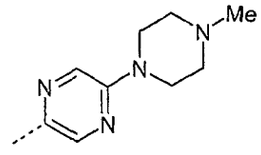
In a further aspect of the invention, -A-$(R^1)_a$ represents a

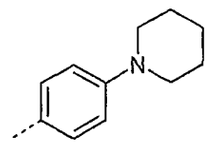


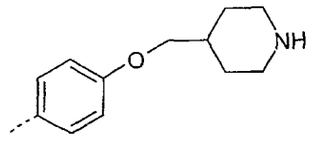
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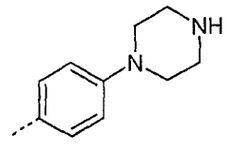
In a further aspect of the invention, -B-$(R^2)_b$ represents a

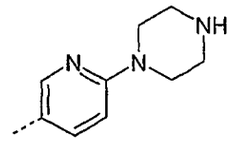


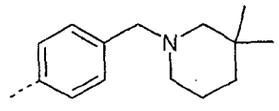
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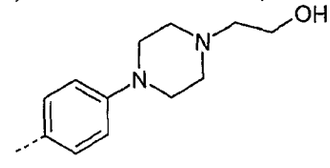
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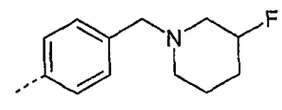
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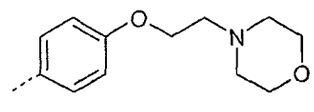
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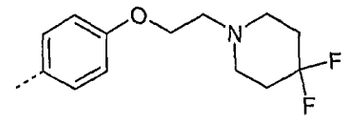
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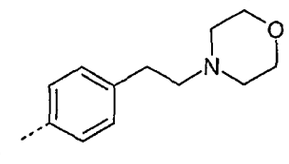
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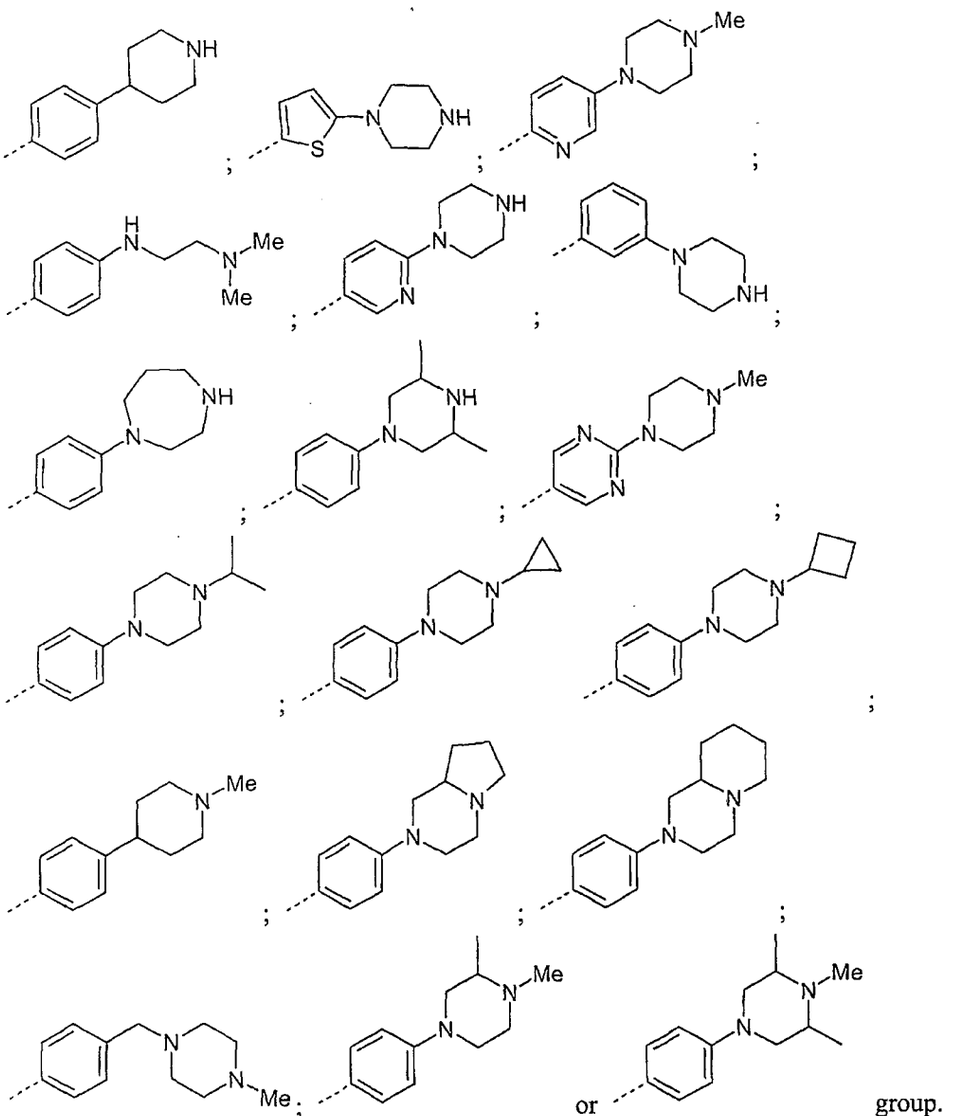
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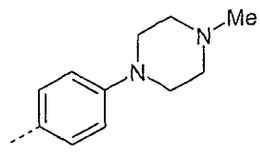
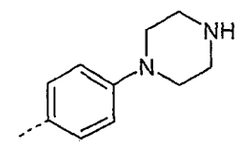
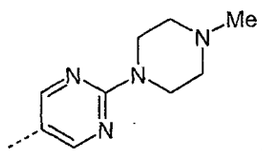
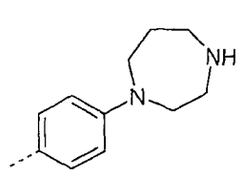
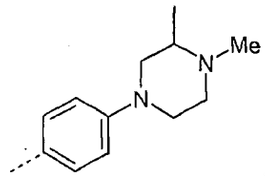
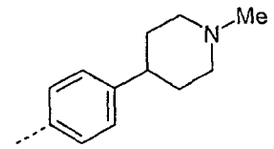
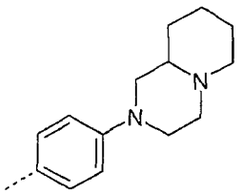
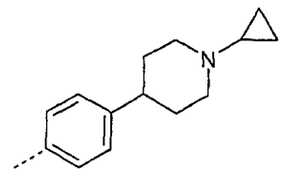
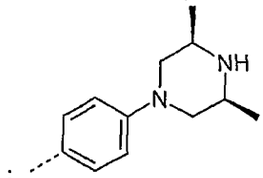
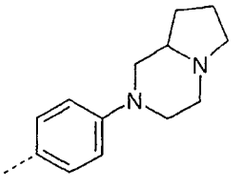
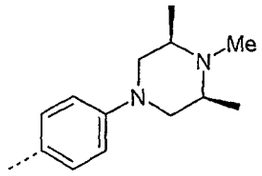
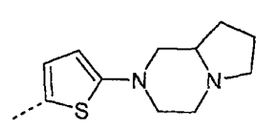
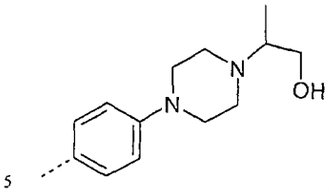
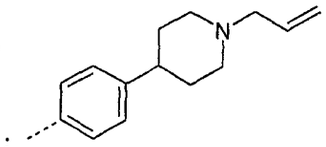
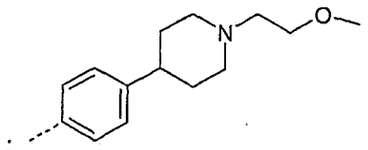
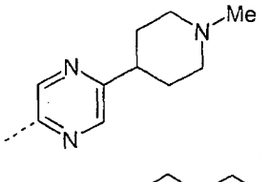
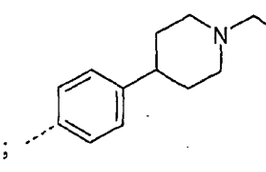
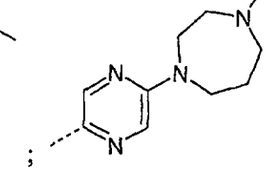
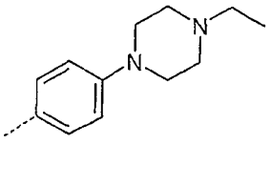
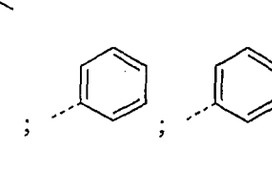
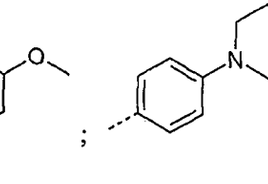
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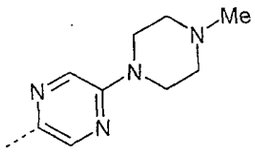
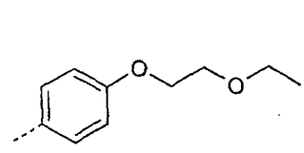
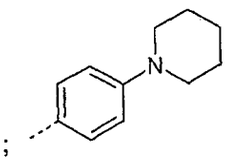
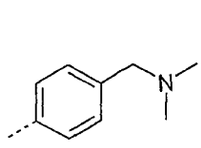
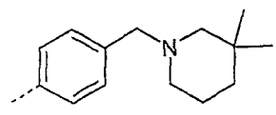
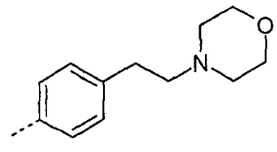
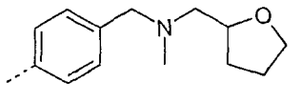
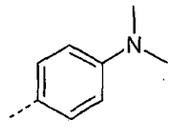
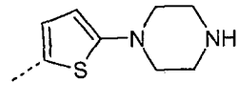
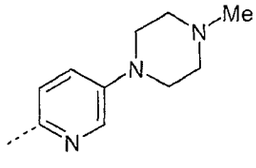
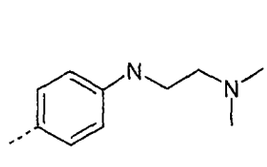
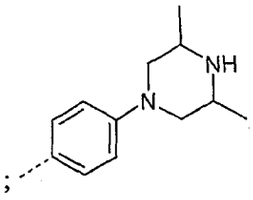
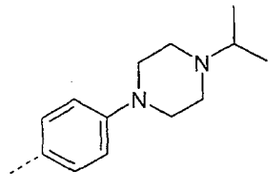
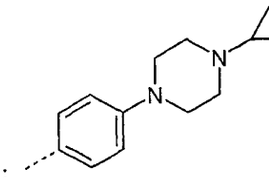
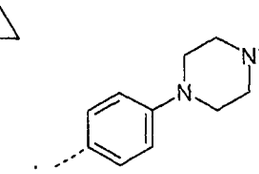
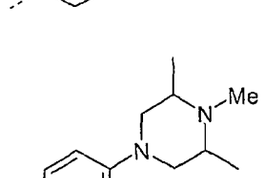
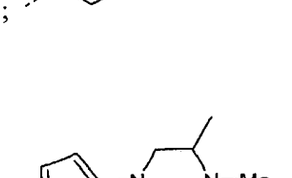
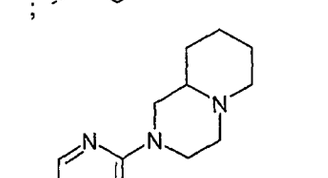
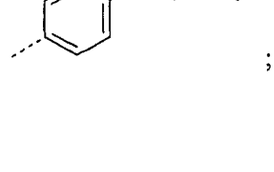
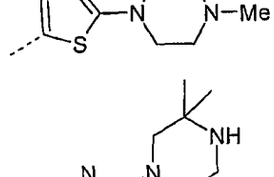
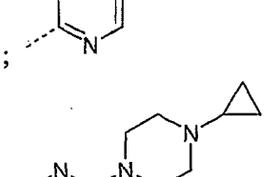
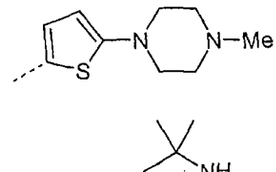
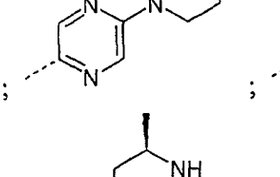
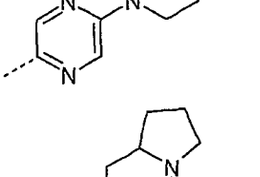
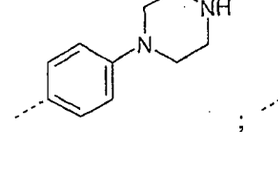
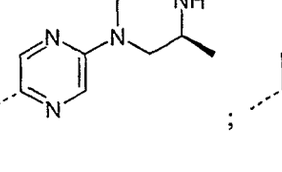
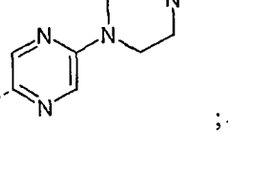
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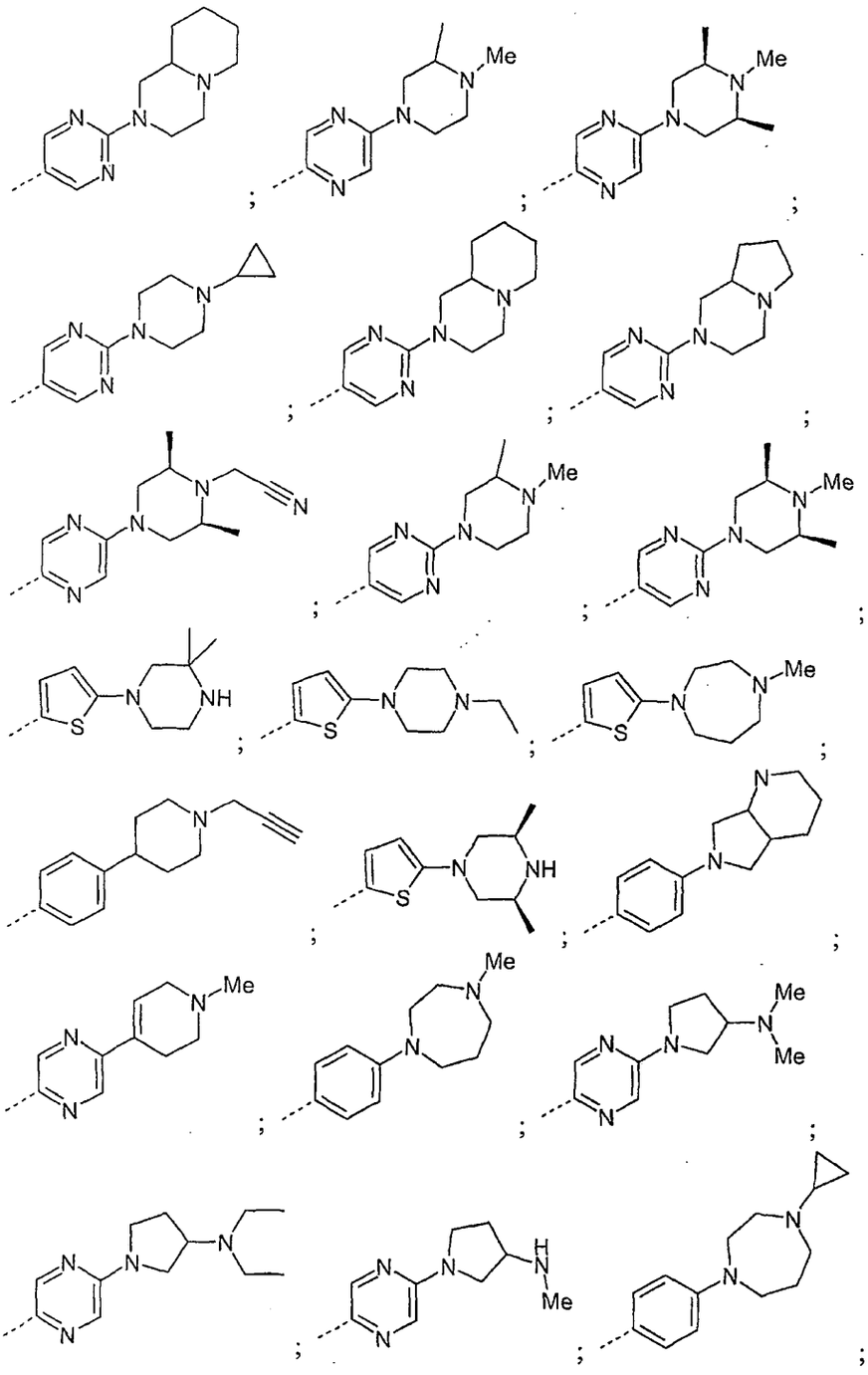
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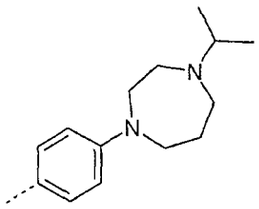
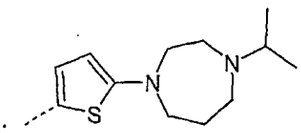
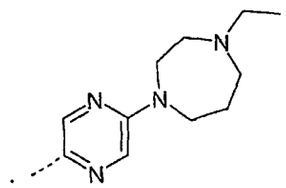
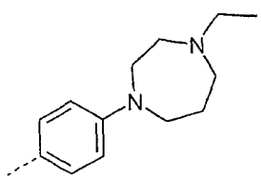
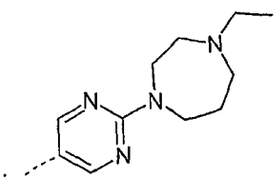
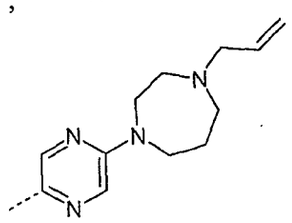
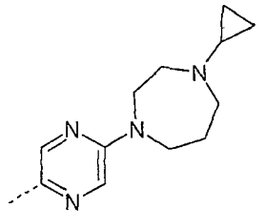
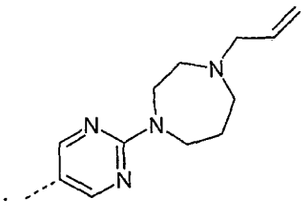
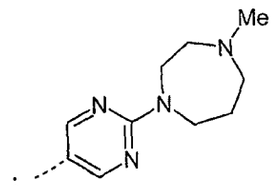
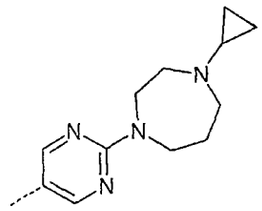


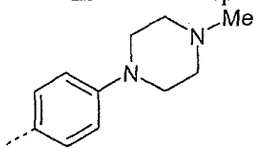
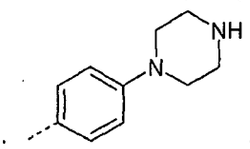
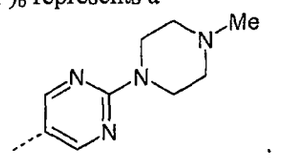
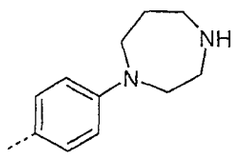
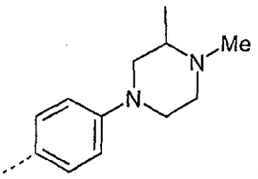
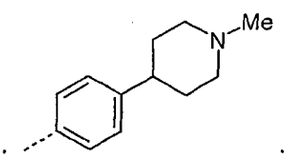
In a further aspect of the invention, -B-$(R^2)_b$ represents a group.

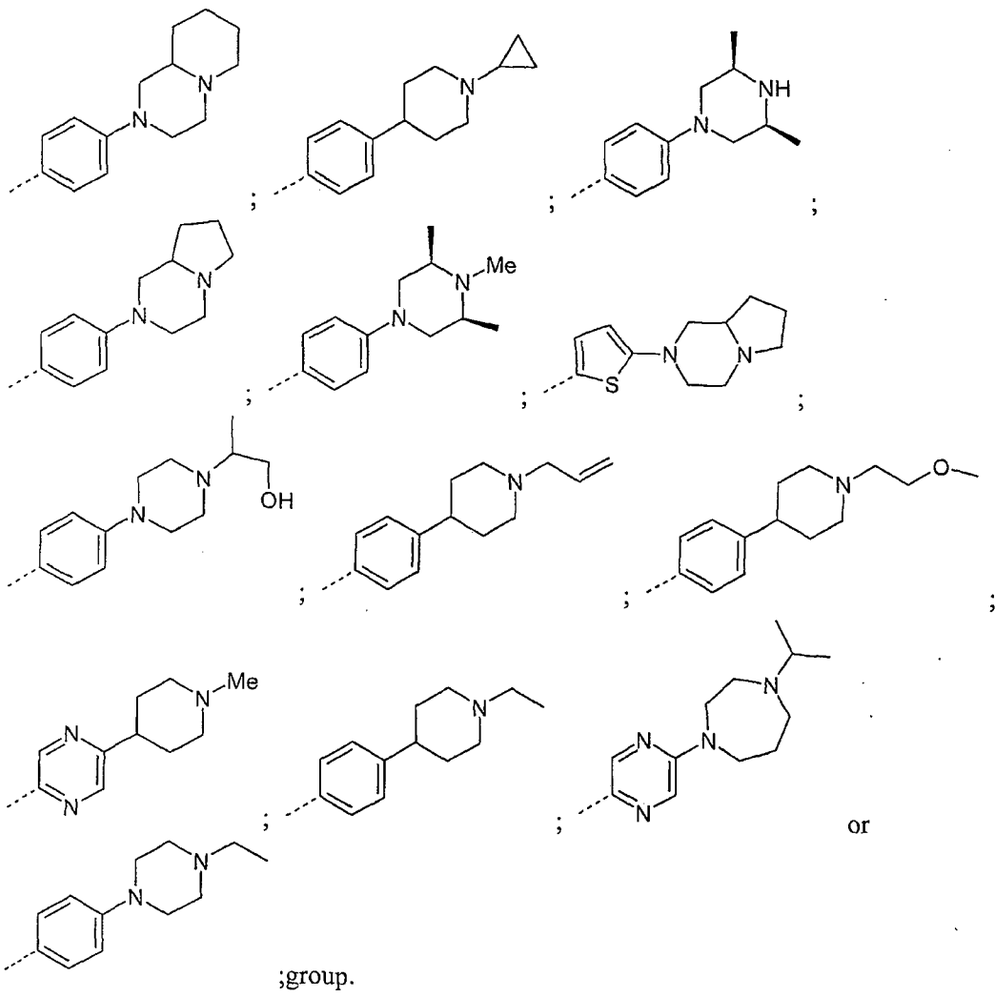

























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or

group.

In a further aspect of the invention, -B-$(R^2)_b$ represents a

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;group.

In an embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

ring B represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl,

pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

each R^1 independently represents

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

each R^2 independently represents

a $-NR^{36}R^{37}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally

substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy,

C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

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

ring A represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

ring B represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

each R^1 independently represents

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -NR^4R^5 (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a –$CONR^{20}R^{21}$ group;

each R^2 independently represents

a –$NR^{36}R^{37}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino (-NH_2), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{45}R^{46}$, -CO_2R^{47} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-

C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

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

ring A represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl,

pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

ring B represents a furyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, trazinyl or triazolyl ring;

each R^1 independently represents

a halogen,

a hydroxyl group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a $-CONR^{20}R^{21}$ group, or

two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

each R^2 independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, $-NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

each R^2 independently represents

a $-NR^{36}R^{37}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from $-NR^{43}R^{44}$ (which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from

halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

In another embodiment of the invention, there is provided a subset of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

each R^2 independently represents

a $-NR^{36}R^{37}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from $-NR^{43}R^{44}$ (which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl), and a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a morpholine, piperidine or piperazine optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-

C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

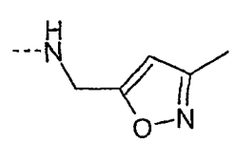
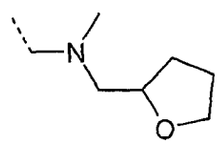
ring A represents furyl, phenyl or pyridyl ring;

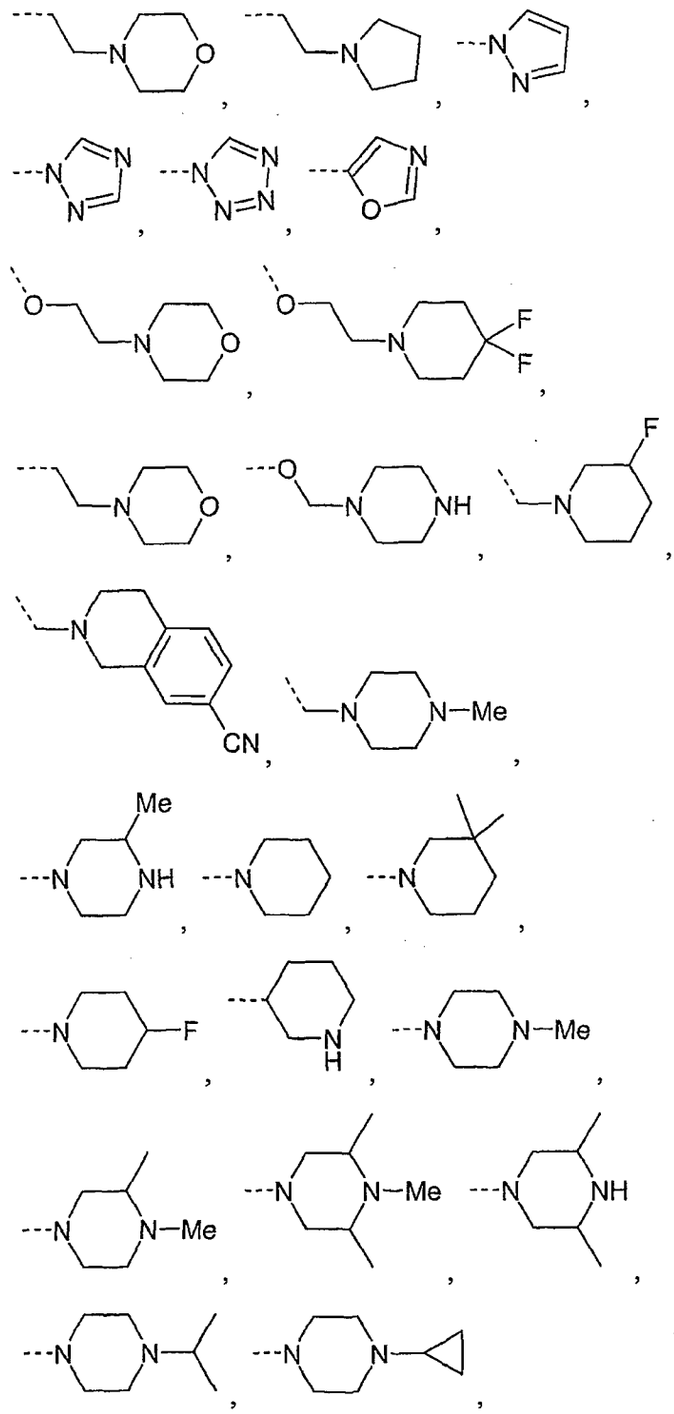
ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

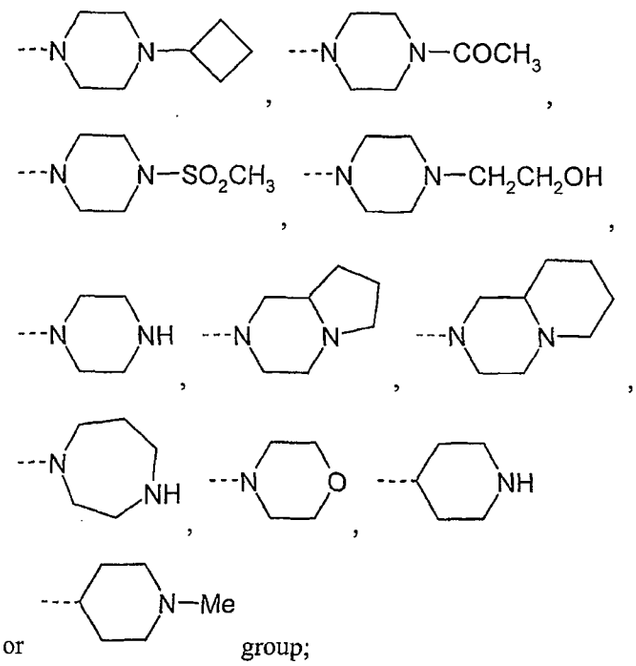
each R^1 independently represents

a methoxy group, $-OCH_2CH_2Ome$, $-CH_2NMe_2$ or or two adjacent R^1 groups together form an $-OCH_2O-$ bridge;

each R^2 independently represents

a –Cl, -F, -I, -OH, -CN, $-CH_3$, $-CH_2OH$, $-CH_2N(CH_3)_2$, $-CH_2CH(CH_3)NH_2$, $-OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2OCH_2CH_3$, $-SO_2CH_3$, $-N(CH_3)_2$, -NHPh, $-NHCH_2C{\equiv}CH$, $-NHCH_2CH_3$, $-NHCH_2CH_2N(CH_3)_2$, $-NHCO_2CH_2CH{=}CH_2$, $-NHCOCH_3$, -NHCOH, -NHCOPh, $-CONH_2$, $-NHSO_2Me$, $-SO_2N(CH_3)_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$,  ,  ,





or group;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 0, 1 or 2.

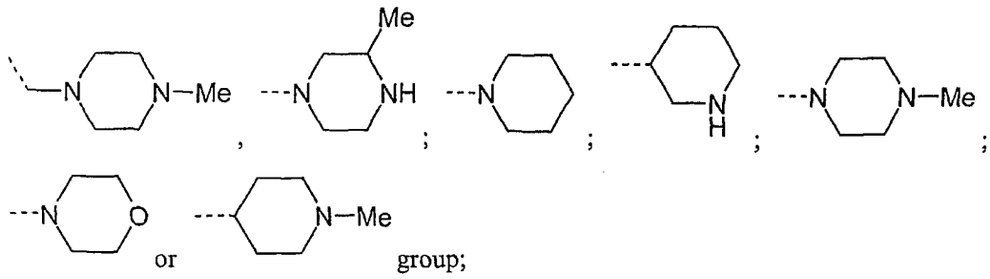
In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents a furyl, phenyl, pyridyl or pyrimidinyl ring;

ring B represents a phenyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents –CONHMe or a methoxy group;

R^2 represents a



or group;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

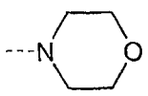
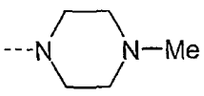
b is 1.

In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

ring A represents furyl, phenyl, pyridyl or pyrimidinyl ring;

ring B represents a phenyl, pyridyl or pyrimidinyl ring;

R^1 represents methoxy;

R^2 represents a  or  group;

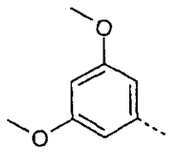
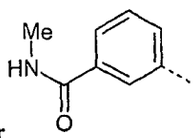
X represents CH_2 or O;

a is 0, 1 or 2; and

b is 1,

or a pharmaceutically acceptable salt thereof.

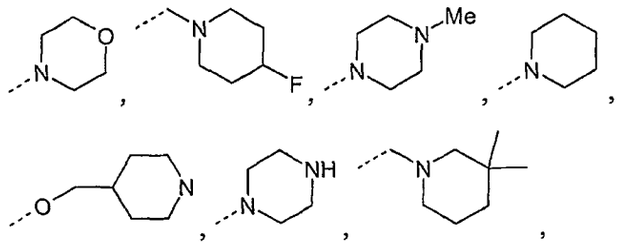
In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

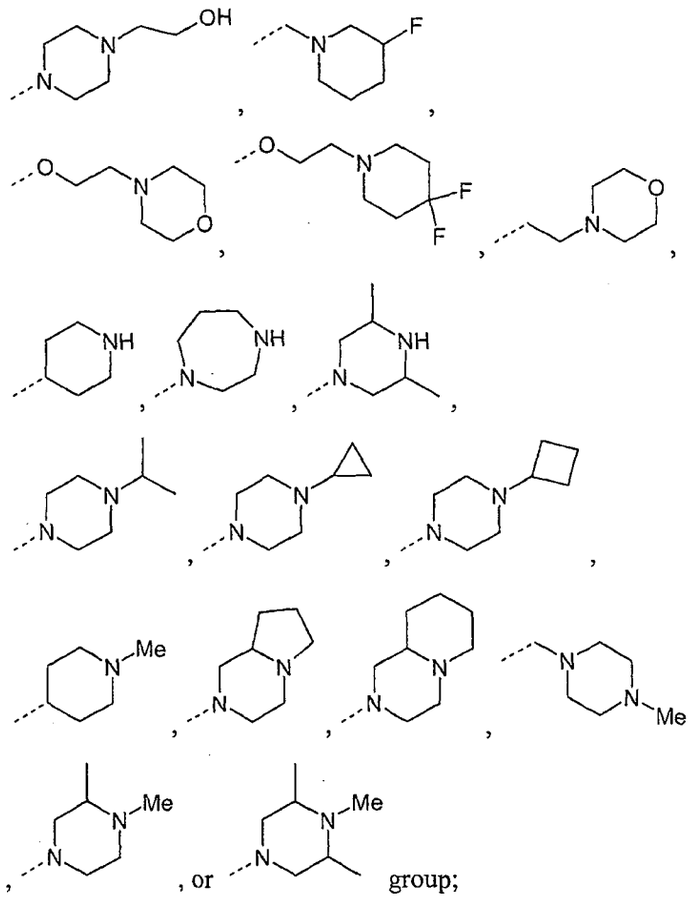
-A-$(R^1)_a$ represents a  or  group;

ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^2 independently represents

a –OMe, $-OCH_2CH_2OCH_2CH_3$, $-OCH_2CH_2OH$, $-CH_2N(CH_3)_2$, $-NHCH_2CH_2N(CH_3)_2$,





group;

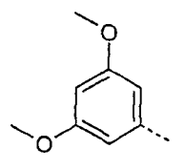
R^3 represents hydrogen;

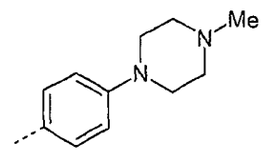
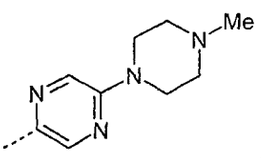
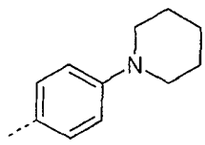
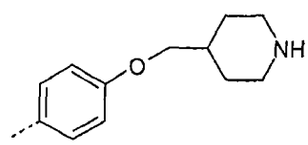
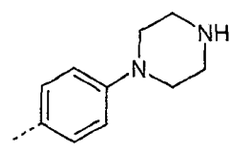
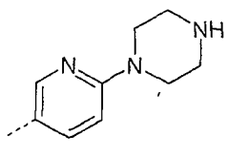
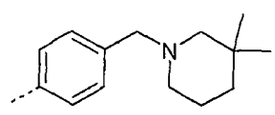
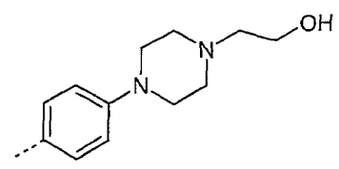
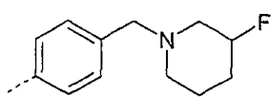
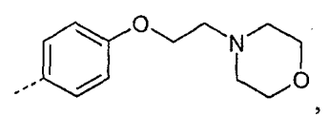
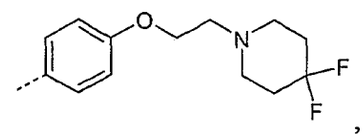
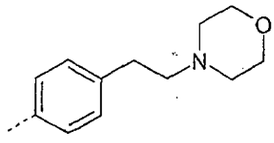
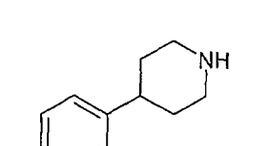
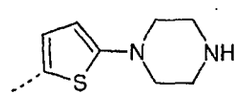
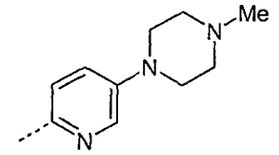
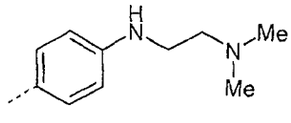
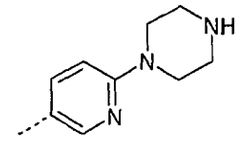
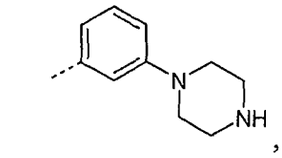
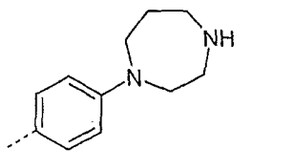
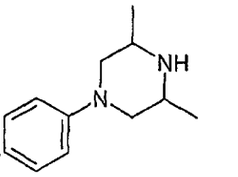
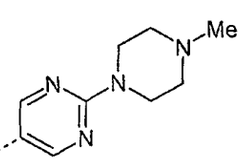
X represents CH_2 or O;

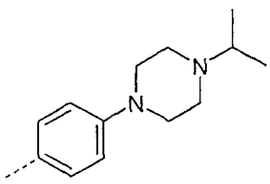
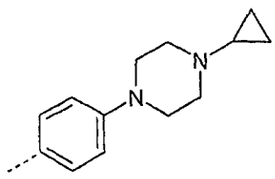
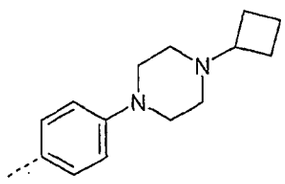
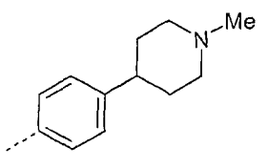
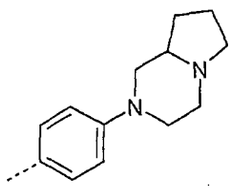
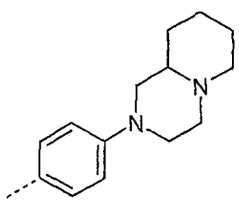
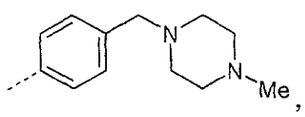
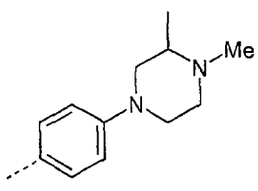
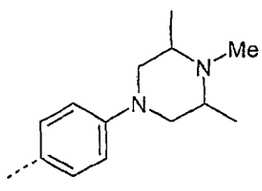
Y represents CH_2;

b is 1.

In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

-A-$(R^1)_a$ represents a  group;

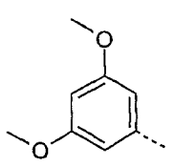
-B-$(R^2)_b$ represents a  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , ,  ,  ,  ,  ,  ,  ,  ,  , , , .

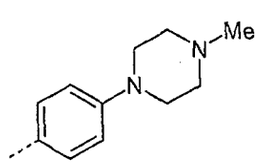
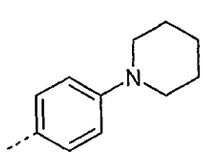
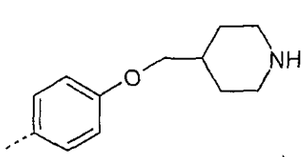
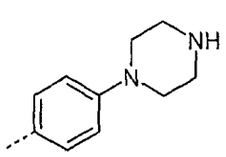
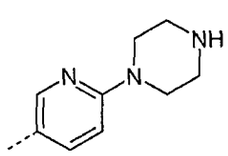

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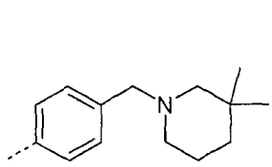
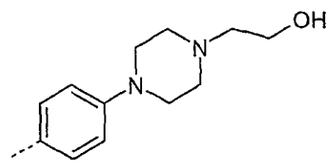
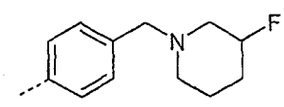
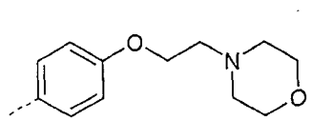
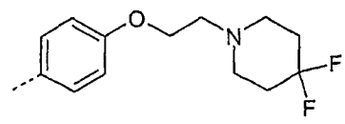
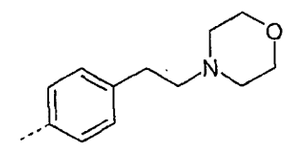
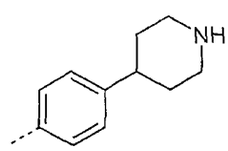
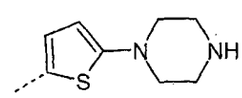
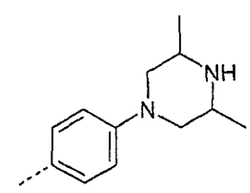
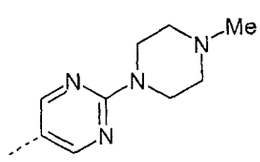
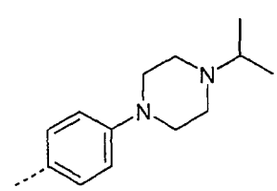
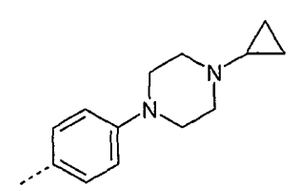
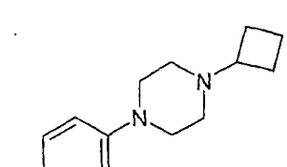
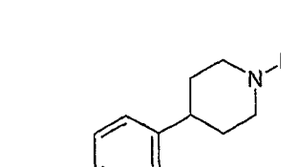
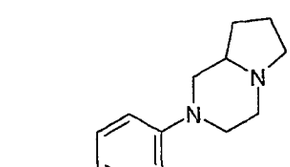
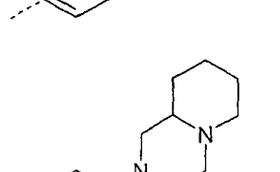
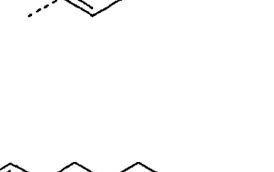
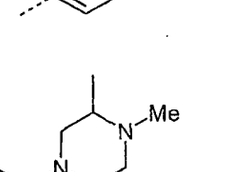
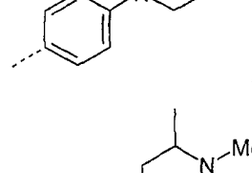
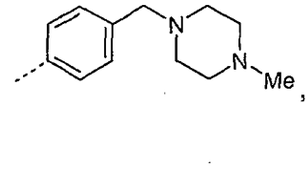
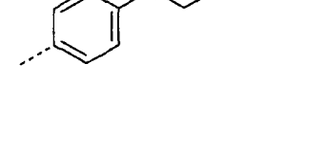
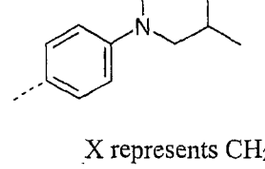
X represents CH_2 or O,

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

-A-$(R^1)_a$ represents a  group;

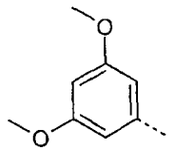
-B-$(R^2)_b$ represents a 
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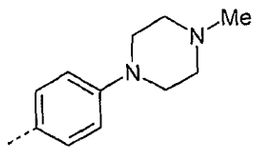
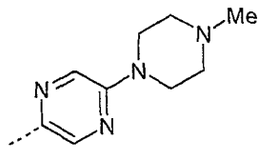
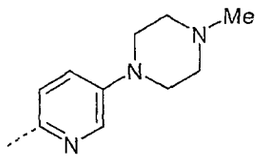
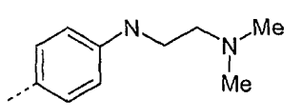
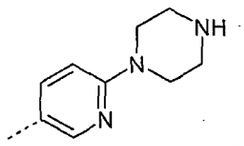
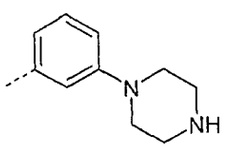
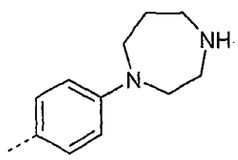
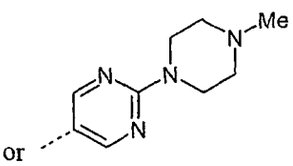

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or

group; and

X represents CH_2,

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

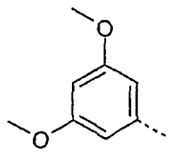
-A-$(R^1)_a$ represents a  group;

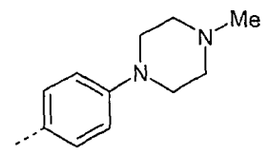
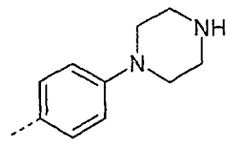
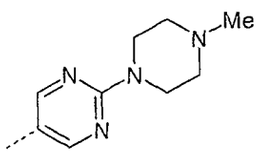
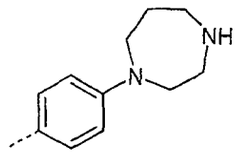
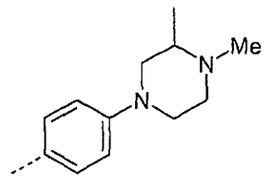
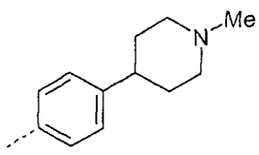
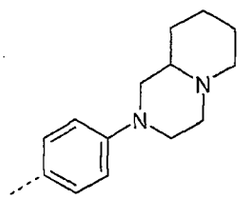
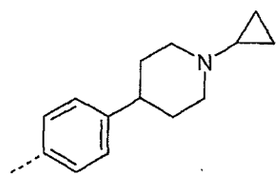
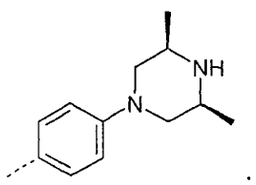
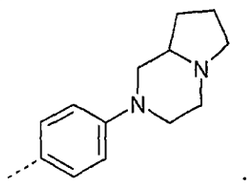
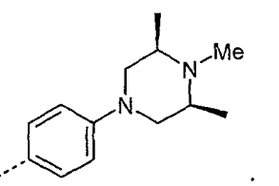
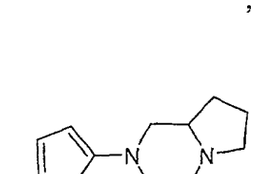
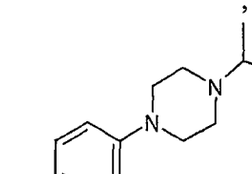
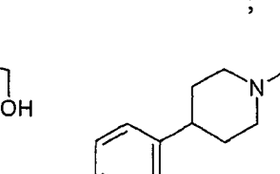
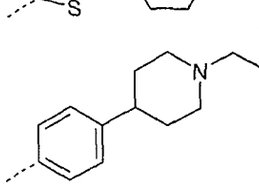
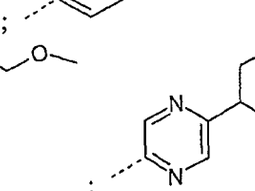
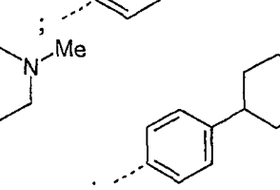
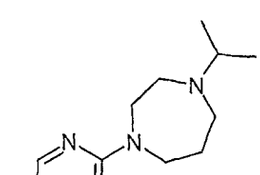
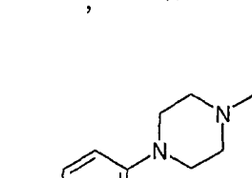
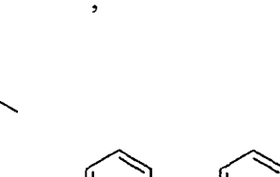
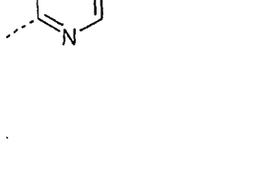
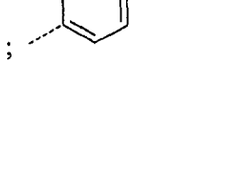
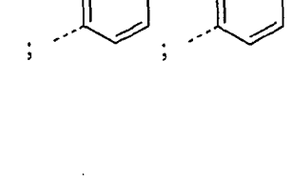
-B-$(R^2)_b$ represents a  ,  ,  ,  ,  ,  ,  ,  or , group; and

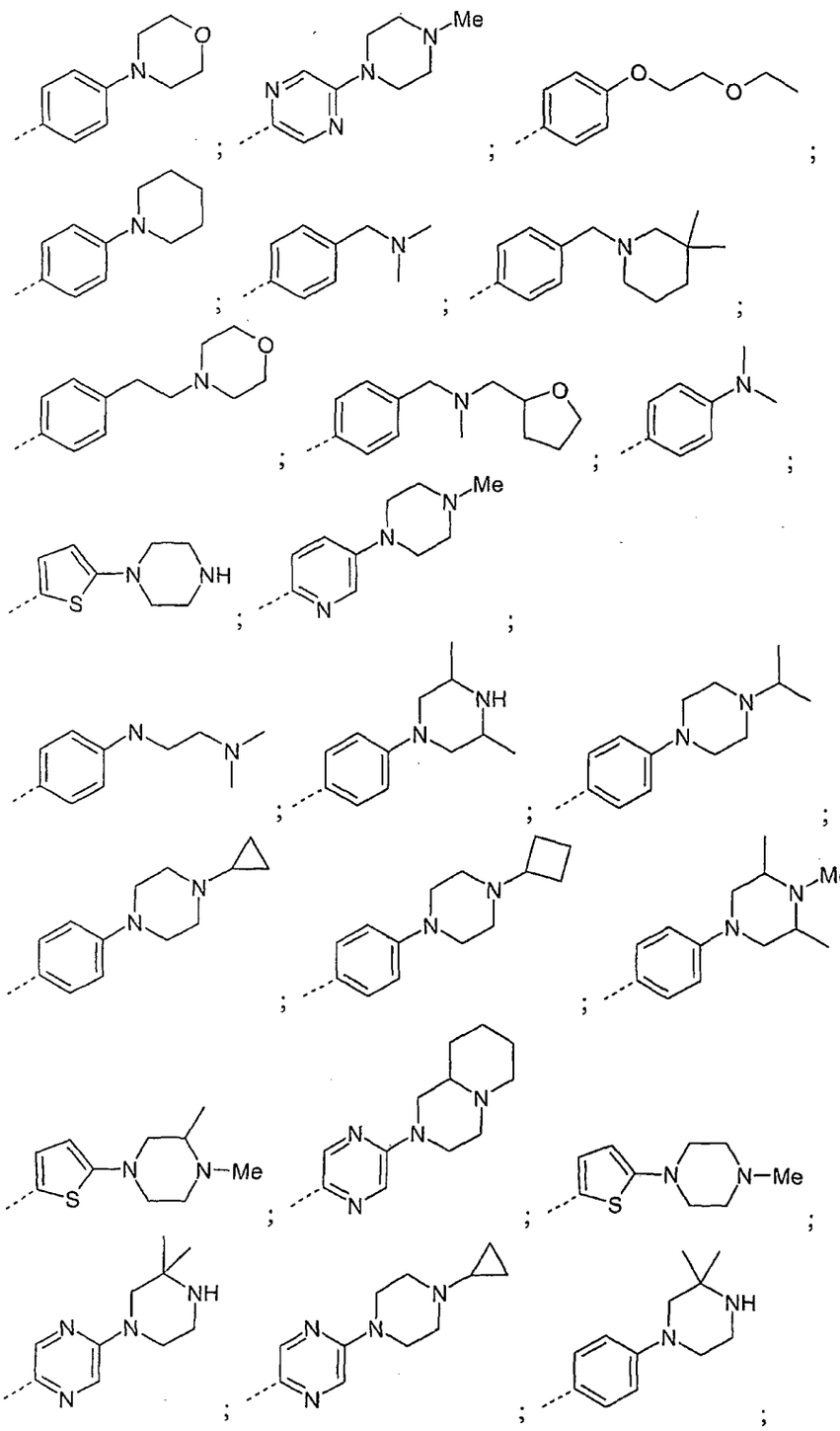
X represents O,

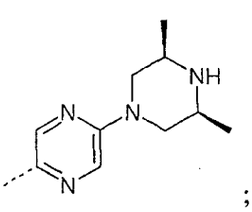
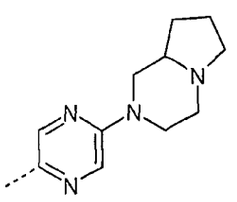
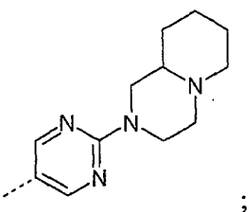
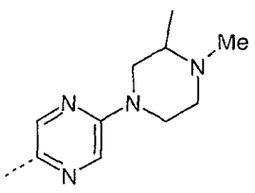
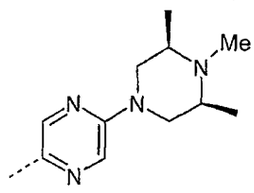
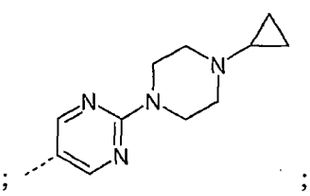
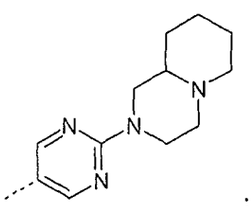
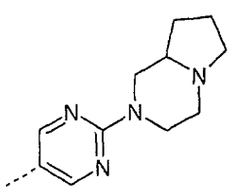
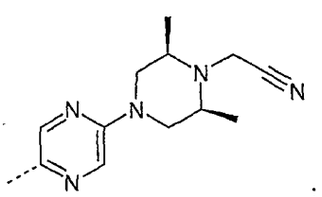
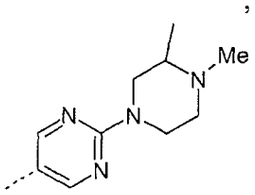
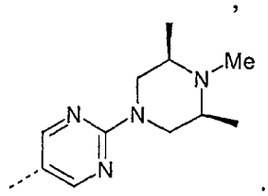
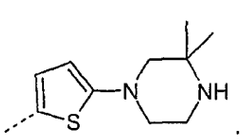
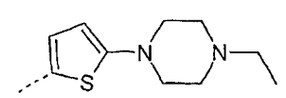
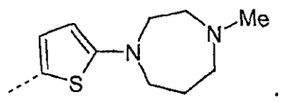
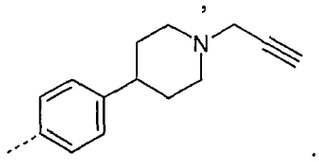
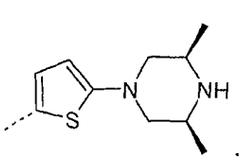
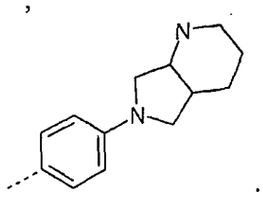
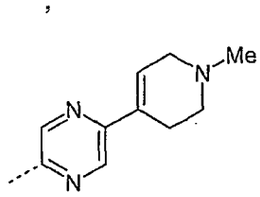
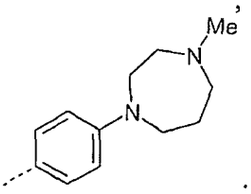
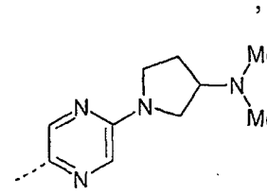
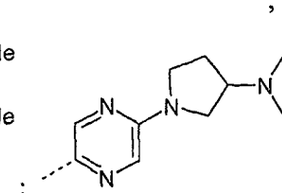
or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

-A-$(R^1)_a$ represents a  group; and

-B-$(R^2)_b$ represents a  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; ; ; ; ; ; ; ; ;

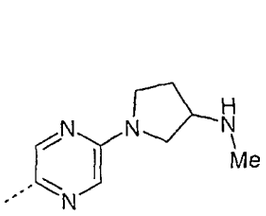
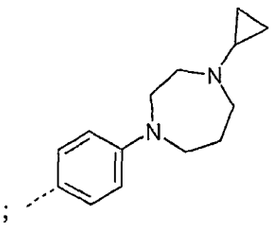
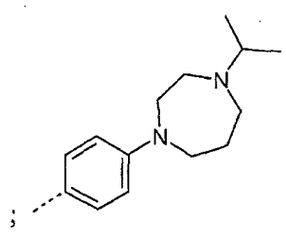
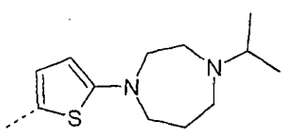
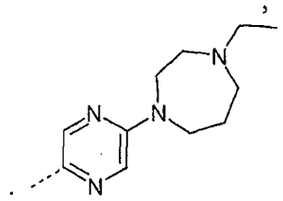
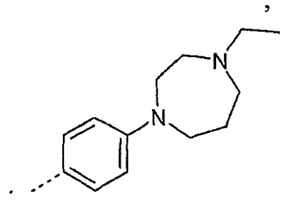
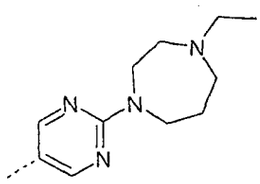
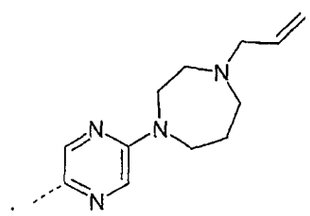
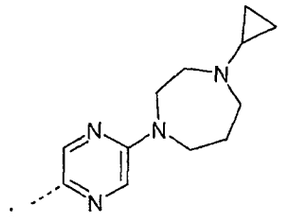
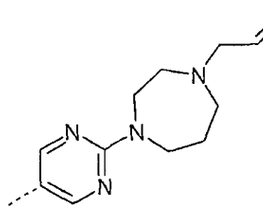
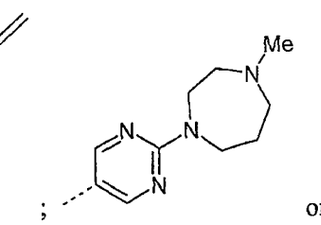
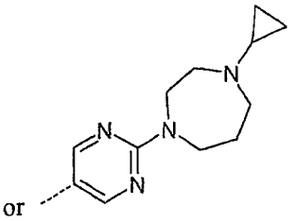
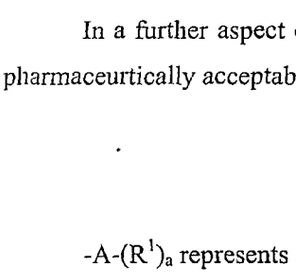
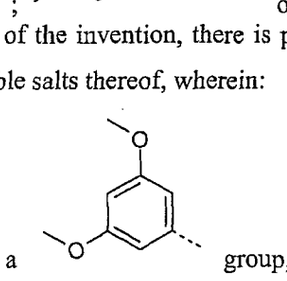
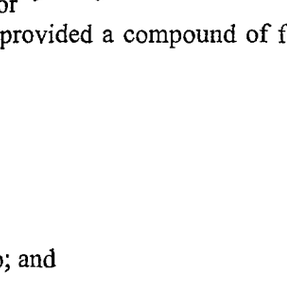



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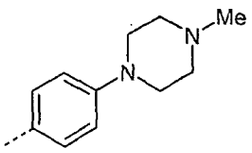
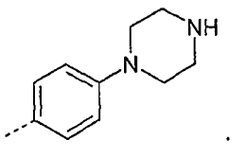
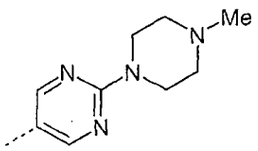
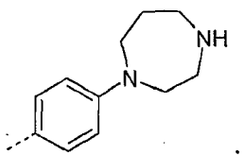
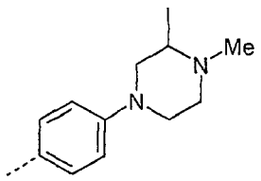
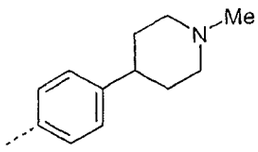
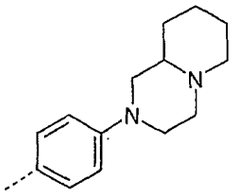
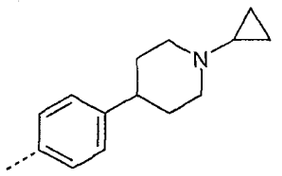
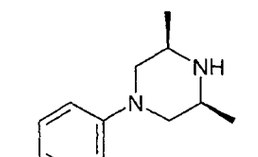
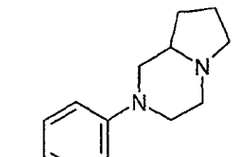
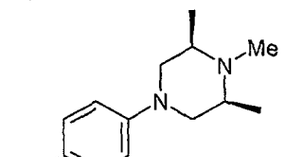
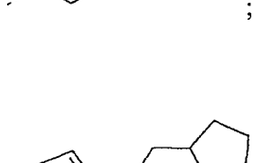
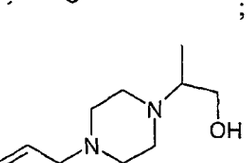
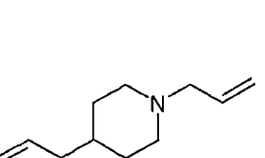
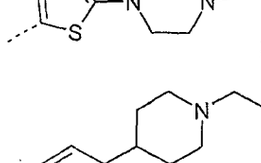
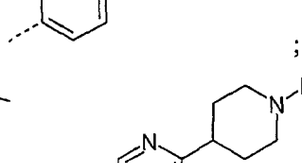
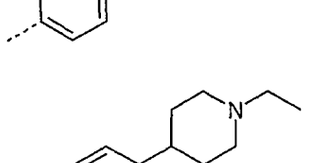
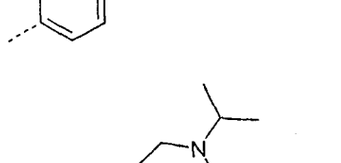
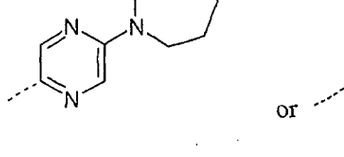
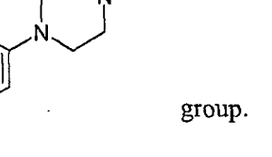
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In a further aspect of the invention, there is provided a compound of formula **(I)**, or pharmaceurtically acceptable salts thereof, wherein:

-A-$(R^1)_a$ represents a group; and

-B-$(R^2)_b$ represents a  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; or group.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring;

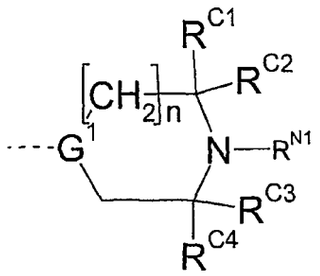
ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from cyano, halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy,

C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

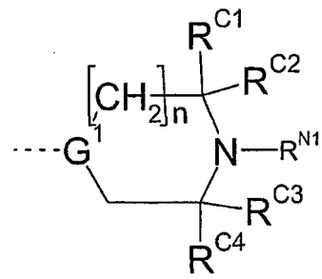
ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a –$CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents furyl, phenyl or pyridyl ring;

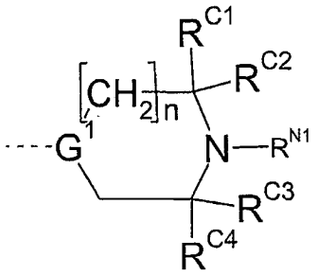
ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from

halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

ring A represents phenyl ring;

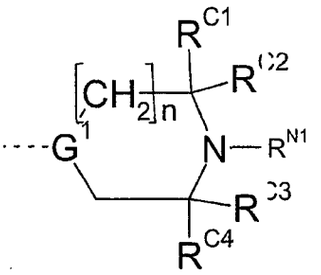
ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one

or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen,

C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

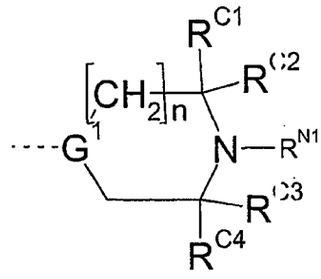
ring A represents phenyl ring;

ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 5-membered carbocyclic ring,

and

R^{N1} is selected from selected from C_1-C_2alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl) and hydrogen, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

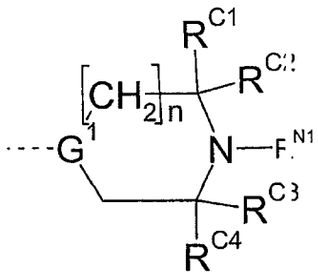
b is 1.

In another embodiment of the invention, there is provided a subset of compounds of formula (I), or pharmaceutically acceptable salts thereof, wherein:

$A(R^1)_a$ represents 3,5-dimethoxyphenyl;

ring B represents phenyl, pyrazinyl, pyrimidinyl or thienyl ring;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring,

and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl, propenyl, propynyl, propyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2; and

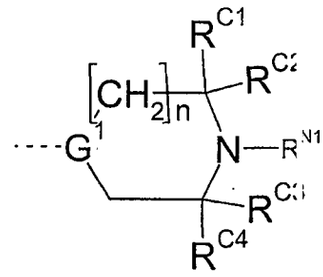
b is 1.

In another embodiment of the invention, there is provided a subset of compounds of formula **(I)**, or pharmaceutically acceptable salts thereof, wherein:

$A(R^1)_a$ represents 3,5-dimethoxyphenyl;

ring B represents phenyl, pyrazinyl, pyrimidinyl or thienyl ring;

R^2 represents



wherein

G^1 is C or N,

n is 1,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring,

and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl, propenyl, propynyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2; and

b is 1.

In a further embodiment of the invention, only one of R^{C1} and R^{C2} or R^{C1} and R^{C3} or R^{C3} and R^{C4} or R^{N1} and R^{C4} together with the atoms to which they are attached form a ring.

In a further embodiment of the invention, R^{C1} and R^{C2} together with the atoms to which they are attached form a ring, and only one of either R^{C3} and R^{C4} or R^{N1} and R^{C4} may together with the atoms to which they are attached form a ring.

In a further embodiment of the invention R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen and methyl.

Examples of compounds of the invention include:

4-(4-methylpiperazin-1-yl)-N-(5-phenethyl-2H-pyrazol-3-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-methoxy-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-morpholin-4-yl-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3-fluoro-1-piperidyl)methyl]benzamide,

N-[5-[2-[3-(2-Methoxyethoxy)phenyl]ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

4-(4-Methylpiperazin-1-yl)-N-[5-(2-pyridin-3-ylethyl)-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(2-furyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(3-furyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-methyl-pyridine-3-carboxamide,

6-Methoxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-methylsulfonyl-benzamide,

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-methyl-pyrazine-2-carboxamide,

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(prop-2-ynylamino)pyridine-2-carboxamide,

6-Ethylamino-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

4-Acetamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)pyrazine-2-carboxamide,

4-benzamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

6-(2-methoxyethoxy)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

4-cyano-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzene-1,4-dicarboxamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-pyrazol-1-yl-benzamide,

6-anilino-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

4-methanesulfonamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

4-(hydroxymethyl)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

5-formamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-2-carboxamide,

4-(dimethylsulfamoyl)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

6-hydroxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-morpholin-4-yl-pyridine-3-carboxamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1,3-oxazol-5-yl)benzamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(tetrazol-1-yl)benzamide,

prop-2-enyl N-[5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridin-2-yl]carbamate,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1,2,4-triazol-1-yl)benzamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluoro-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-3-methoxy-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-3-morpholin-4-yl-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-2-methoxy-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-ethoxyethoxy)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(1-piperidyl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-piperidylmethoxy)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-piperazin-1-yl-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-6-piperazin-1-yl-pyridine-3-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(dimethylaminomethyl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-hydroxyethoxy)benzamide,
4-(2-aminopropyl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3,3-dimethyl-1-piperidyl)methyl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[4-(2-hydroxyethyl)piperazin-1-yl]benzamide,
4-[(7-cyano-3,4-dihydro-1H-isoquinolin-2-yl)methyl]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3-fluoro-1-piperidyl)methyl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-morpholin-4-ylethoxy)benzamide,
4-[2-(4,4-difluoro-1-piperidyl)ethoxy]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-morpholin-4-ylethyl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(methyl-(oxolan-2-ylmethyl)amino)methyl]benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-piperidyl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-dimethylamino-benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-5-piperazin-1-yl-thiophene-2-carboxamide,
methyl 6-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-3-carboxylate,
6-chloro-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,
6-cyano-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide,
4-hydroxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-2-carboxamide,
N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-(2-pyrrolidin-1-ylethyl)pyridine-3-carboxamide,
5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid,
methyl 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylate,
ethyl 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylate,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl] 5-(4-methylpiperazin-1-yl)pyridine-2-carboxamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl] 4-(2-dimethylaminoethylamino)benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl] 4-methoxy-benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl] 6-piperazin-1-yl-pyridine-3-carboxamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl] 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl] 3-piperazin-1-yl-benzamide,

4-(1,4-diazepan-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl]benzamide,

N-[5-[2-[5-(dimethylaminomethyl)-2-furyl]ethyl]-1H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-(2-benzo[1,3]dioxol-5-ylethyl)-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(2,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(4-methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-iodo-benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-2-[(3-methyl-1,2-oxazol-5-yl)methylamino]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-methylpiperazine-1-carbonyl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-propan-2-ylpiperazin-1-yl)benzamide,

4-(4-cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxy phenyl)ethyl]-1H-pyrazol-3-yl]benzamide,

4-(4-cyclobutylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyp enyl)ethyl]-1H-pyrazol-3-yl]benzamide,

4-(4-acetylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide,

N-[5-[2-(3-methoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-methylsulfonylpiperazin-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(1-methyl-4-piperidyl)benzamide,

4-(3,4,6,7,8,8a-Hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

4-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(3,4,5-trimethylpiperazin-1-yl)benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)thiophene-2-carboxamide,

4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide,

4-(1-Cyclopropylpiperidin-4-yl)-N-[5-[2-(3,5-dimethoxy phenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide,

tert-Butyl 4-[5-[[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H- pyrazol-3-yl]carbamoyl]thiophen-2-yl]piperazine-1-carboxylate,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(1-methylpiperidin-4-yl)benzamide,

4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide,
5-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)thiophene-2-carboxamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)thiophene-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3,3-dimethylpiperazin-1-yl)pyrazine-2-carboxamide,
5-(4-Cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]benzamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(3,3-dimethylpiperazin-1-yl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrazine-2-carboxamide,
5-(4-Cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
5-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
4-(4-cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide,
N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methyl-4-oxidopiperazin-4-ium-1-yl)benzamide,
4-(4-Cyclobutylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide,
2-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,

5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]thiophene-2-carboxamide,
5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]thiophene-2-carboxamide,
5-(3,4,6,7,8,8a-Hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)pyrazine-2-carboxamide,
N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)pyrazine-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrazine-2-carboxamide,
2-(4-cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
5-[(3R,5S)-4-(cyanomethyl)-3,5-dimethylpiperazin-1-yl]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrazine-2-carboxamide,
5-[(3R,5S)-4-(cyanomethyl)-3,5-dimethylpiperazin-1-yl]-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxamide,
2-(4-cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[4-(1-hydroxypropan-2-yl)piperazin-1-yl]benzamide,

N-(3-(3,5-dimethoxybenzyloxy)-1H-pyrazol-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,3-dimethylpiperazin-1-yl)benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,3-dimethylpiperazin-1-yl)thiophene-2-carboxamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-ethylpiperazin-1-yl)thiophene-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methyl-1,4-diazepan-1-yl)thiophene-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-ethyl-3-methylpiperazin-1-yl)pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-enylpiperidin-4-yl)benzamide,

4-(1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-ynylpiperidin-4-yl)benzamide,

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-[(3S,5R)-3,5-dimethylpiperazin-1-yl]thiophene-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[1-(2-methoxyethyl)piperidin-4-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[(3S)-3-propan-2-ylpiperazin-1-yl]pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide,

4-(1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridin-6-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(1-methylpiperidin-4-yl)pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3-dimethylaminopyrrolidin-1-yl)pyrazine-2-carboxamide,

5-(3-diethylaminopyrrolidin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-ethylpiperidin-4-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[3-(methoxymethyl)piperazin-1-yl]pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3-methylaminopyrrolidin-1-yl)pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(1-methylpiperidin-4-yl)pyrimidine-5-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-prop-2-enyl-1,4-diazepan-1-yl)benzamide,

4-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-propan-2-yl-1,4-diazepan-1-yl)benzamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-propan-2-yl-1,4-diazepan-1-yl)pyrazine-2-carboxamide,

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-propan-2-yl-1,4-diazepan-1-yl)thiophene-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-ethyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-ethyl-1,4-diazepan-1-yl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-ethyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-propan-2-yl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide,
5-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide,
2-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide,
N-[5-[2-[3-(methylcarbamoyl)phenyl]ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide,
N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(4-ethylpiperazin-1-yl)benzamide,
N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-ethylpiperazin-1-yl)benzamide
and pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of the Examples 1 to 20 or pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of the Examples or pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of Examples 1, 2, 3, 4, 5, 10, 11, 12, 20, 42, 43, 44, 45, 46, 47, 48, 50, 51, 53, 54, 55, 56, 57,

58, 59, 60, 69, 70, 71, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, or 96, or pharmaceutically acceptable salts of any one thereof.

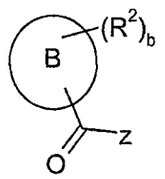
In another aspect of the invention, particular compounds of the invention are any one of Examples 2, 3, 4, 5, 10, 11, 12, 20, 42, 43, 44, 45, 46, 47, 48, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 71, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, or 96, or pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of Examples 10, 11, 12, 20, 43, 44, 45, 46, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, or 96, or pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of Examples 2, 3, 4, 10, 11, 12, 20, 42, 43, 45, 47, 50, 56, 57, 59, 60, 69, 70, 71, 73, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 151, 152, 153, 154, 155, 156, 157, 158, 159, 161, 165, 166, 167, 168, 169, 170, 171, 172, 174, 175, 176, 177, 179 or 180, or pharmaceutically acceptable salts of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of Examples 12, 45, 73, 75, 81, 92, 98, 99, 100, 103, 104, 110, 121, 137, 144, 148, 152, 154, 155, 159, 167, 179 or 180, or pharmaceutically acceptable salts of any one thereof.

The present invention further provides a process for the preparation of a compound of formula **(I)** as defined herein, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula **(II)**

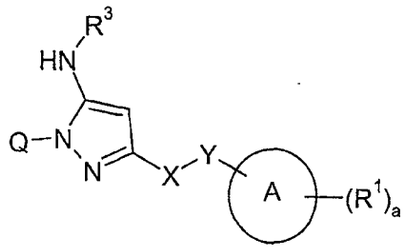


(II)

wherein Z represents a leaving group (e.g. halogen, for example chlorine, -CN, $-N_3$, -OH or a –OR, -OC(O)R, $-OCR(NR^aR^b)_2$ or $-OC(=NR)NR^aR^b$ group where R is an optionally substituted alkyl, aryl, heteroaryl or alkaryl and each R^a, R^b independently

is hydrogen or an optionally substituted alkyl, aryl or alkaryl), and B, R^2 and b are as hereinbefore defined for a compound formula **(I)**,

with a compound of formula **(III)**



(III)

wherein Q is hydrogen or a protecting group (for example t-Bu or BOC group or as described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991)), and A, R^1, R^3, X, Y and a are as defined hereinbefore for a compound of formula **(I)**

to give a compound of formual **(I)**,

and optionally carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

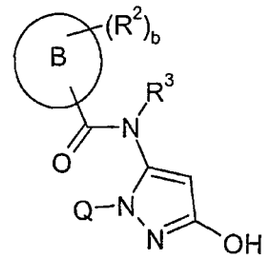
Suitable compounds of Formula (II) include carboxylic acids or reactive derivatives of a carboxylic acid. Carboxylic acids or reactive derivatives of a carboxylic acid include acyl halides, such as an acyl chloride formed by the reaction of the acid with an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of a carboxylic acid with a phenol such as pentafluorophenol, with an ester, such as pentafluorophenyl trifluoroacetate, or with an alcohol such as methanol, ethanol, isopropanol, butanol or *N*-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid with an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid with a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid with a carbodiimide such as dicyclohexylcarbodiimide or with a uronium compound such as 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V).

The reaction may conveniently be carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene. The reaction can also be carried out in the presence of a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, –20°C to 100°C, preferably between 0°C to ambient temperature, dependant upon the reaction being carried out and the nature of the leaving group Z.

The reaction typically can be carried out in the presence of a base. Suitable bases include organic amine bases, such as pyridine, 2,6-lutidine, *N,N*-diisopropylethylamine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, alkali or alkaline earth metal carbonates or hydroxides, such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, alkali metal amides, such as sodium hexamethyldisilazide (NaHMDS), or alkali metal hydrides, such as sodium hydride, dependant upon the reaction being carried out and the nature of the leaving group Z.

The reaction can also be carried out in the presence of a Lewis acid, for example trimethylaluminium, dependant upon the reaction being carried out and the nature of the leaving group Z.

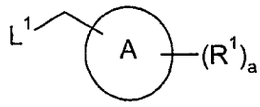
Alternatively, the present invention further provides a process for the preparation of a compound of formula **(I)** as defined herein, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula **(IV)**



(IV)

wherein Q is hydrogen or a protecting group (for example t-Bu or BOC group or as described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991)); and B, R^2, R^3 and b are as defined hereinbefore for a compound of formula **(I)**,

with a compound of formula **(V)**



(V)

wherein L^1 represents OH or a leaving group such as halogen or OTs; and A, R^1 and a are as defined hereinbefore for a compound of formula **(I)**

to give a compound of formual **(I)**

and optionally carrying out one or more of the following:

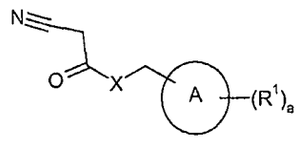
- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

The reaction may conveniently be carried out in a suitable solvent such as dichloromethane at temperature in the range from 0°C to room temperature. When L^1 is OH, the reaction typically may be carried out in the presence of diisopropylazidocarboxylate and triphenylphosphine. When L^1 is a halogen or OTs, the reaction may conveniently be carried out in a suitable solvent such as N,N-dimethylformamide or acetonitrile at temperature in the range from room temperature to 100°C. The reaction typically may be carried out in the presence of an inorganic base such as potassium carbonate or sodium hydride.

Compounds of formula **(II)**, **(III)**, **(IV)** or **(V)** are either commercially available, are known in the literature or may be prepared using known techniques.

Compounds of formula **(II)**, wherein Z is halogen or –OR, may be prepared from compounds of formula (II) wherein Z is -OH by methods known in the literature. For example, methods known for the preparation of acid chlorides or esters from carboxylic acids may be employed.

Compounds of formula **(III)** where **X** represents CH_2 may be prepared by reacting a compound of formula (VI)

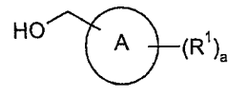


with a hydrazine of formula (VII)

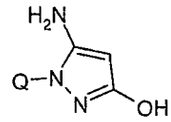


The reaction may be conveniently carried out in a solvent, such as ethanol, at temperature range of 60 to 80°C.

Alternatively, compounds of formula **(III)** where **X** represents O may be prepared by reacting a compound of formula (VIII)

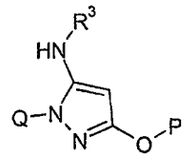


with a compound of formula (IX)

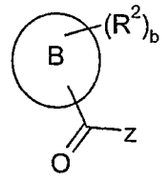


The reaction may be conveniently carried out in a solvent, such as dichloromethane, at temperature range of 0°C to room temperature. The reaction typically may be carried out in the presence of diisopropylazidocarboxylate and triphenylphosphine.

Compounds of formulae **(IV)** may be prepared by reacting a compound of formula (X)



with a compound of formula (II)



wherein Z represents a leaving group (e.g. halogen, for example chlorine, -CN, -N_3, -OH or a –OR, -OC(O)R, –OCR(NR^aR^b)$_2$ or –OC(=NR)NR^aR^b

group where R is an optionally substituted alkyl, aryl, heteroaryl or alkaryl and each R^a, R^b independently is hydrogen or an optionally substituted alkyl, aryl or alkaryl);

P represents H or a protecting group (for example as described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991));

Q is hydrogen or a protecting group (for example t-Bu or BOC group or as described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991)); and

B, R^2, R^3 and b and wherein are as defined hereinbefore for a compound of formula **(I)**,

and, when P is a protecting group, removing protecting group P.

Compounds of formula **(VI)**, **(VII)**, **(VIII)** and **(IX)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula **(I)** can be converted into further compounds of formula **(I)** using standard procedures. Examples of the types of conversion reactions that may be used include 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. 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 aryl group, for example, using an aryl halide under Suzuki conditions; the introduction of an amino group using, for example, an aryl halide and an amine under Buchwald 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. Examples of reduction reactions include the reduction of a nitro group to an amino group by catalytic hydrogenation with a nickel catalyst or by treatment with iron in the presence of hydrochloric acid with heating; and particular examples of oxidation reactions include oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl. These reagents and reaction condtions described above are well known in the art.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula **(I)** may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula **(I)** above may be converted to a pharmaceutically acceptable salt, for example an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula **(I)** are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula **(I)** and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

Certain compounds of formula **(I)**, a pharmaceutically acceptable salt thereof, may be isolated as an amorphous solid or as a crystalline solid. If the compound is in crystalline form, it may exist in a number of different polymorphic forms. Examples of compounds that have been isolated as either amorphous or crystalline solids include: Example 10 isolated as a crystalline form (2-Theta° 3.521 (100%), 7.025 (14.8%), 9.274 (16.9%), 9.654 (15.2%), 10.162 (14.8%), 10.508 (19.3%), 11.628 (49.8%), 12.047 (19.3%), 14.516 (21%), 16.242 (26.3%), 17.682 (18.5%), 18.099 (31.3%), 18.615 (92.6%), 19.315 (56.8%), 20.353 (16%), 20.581 (17.3%), 21.192 (10.3%), 22.467 (23%), 23.057 (88.1%), 23.28 (52.3%), 24.261 (34.2%), 25.363 (10.7%), 27.546 (15.6%), 28.285 (14%) and 29.862 (11.9 %); Example 75 isolated as an amorphous solid; Example 81 isolated as an amorphous solid; Example 144 isolated as a crystalline form (2-Theta° 3.62 (100%), 7.247 (4.6%), 10.013 (5.1%), 10.889 (8.1%), 11.294 (7.7%), 12.185 (8.6%), 14.091 (19%), 18.2 (12.7%), 19.102 (8.9%), 19.789 (15.2%) and 20.608 (32.7%); Example 99 isolated as a crystalline form (2-Theta° 4.293 (100%), 8.498 (14%), 10.694 (8.1%), 13.078 (4.5%), 15.056 (49.4%), 16.14 (8.1%), 16.298

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Patente de invención

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(11.1%), 17.425 (34.6%), 17.812 (23.1%), 18.157 (9.6%), 19.224 (15%), 20.931 (20.2%), 21.819 (27.9%), 22.248 (16.2%), 22.593 (23.7%), 23.416 (8.8%), 24.726 (26%), 25.295 (11.6%), 25.859 (5.6%), 27.001 (5.9%), 27.754 (5.3%), 28.442 (4.8%), 29.861 (4.3%), 30.89 (3.8%), 32.264 (5.9%) and 32.896 (5.4%); Example 147 isolated as a crystalline form (2-Theta° 4.492 (91.3%), 12.465 (23.1%), 13.862 (26.3%), 14.56 (14.4%), 15.811 (16.3%), 17.226 (24.4%), 17.886 (20%), 18.3 (15%), 18.9 (100%), 21.328 (20%), 21.705 (28.1%), 23.263 (27.5%), 23.699 (19.4%), 24.005 (53.8%), 24.333 (37.5%), 25.184 (11.9%), 26.114 (11.3%), 26.573 (10.6%) and 27.803 (16.9%); Example 151 isolated as a crystalline form (2-Theta° 3.754 (29.6%), 8.495 (13.9%), 10.235 (19.1%), 10.98 (29.6%), 12.014 (23.5%), 13.38 (18.3%), 14.591 (33%), 15.924 (41.7%), 17.057 (26.1%), 17.379 (30.4%), 18.219 (32.2%), 18.791 (36.5%), 19.201 (100%), 19.577 (47.8%), 20.788 (33%), 21.394 (27%), 22.07 (33%), 23.285 (25.2%), 23.922 (29.6%) and 25.533 (33%); Example 154 isolated as a crystalline form (2-Theta° 5.833 (89.6%), 9.786 (21.9%), 10.784 (32.8%), 12.121 (30.7%), 13.394 (35.4%), 13.709 (45.3%), 14.939 (28.1%), 16.799 (35.4%), 17.664 (25%), 18.223 (21.9%), 18.646 (50%), 19.29 (25.5%), 20.563 (35.4%), 21.32 (100%), 22.747 (37.5%), 24.154 (38.5%), 25.197 (23.4%), 25.704 (15.1%), 26.752 (16.7%) and 31.134 (12%); and Example 155 isolated as an amorphous solid. Unless otherwise stated, the X-ray powder diffraction patterns were determined by mounting a sample of the crystalline material on Siemens single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40 kV and 40 mA with a wavelength of 1.5418 Angstroms using a Siemens Diffraktometer 5000. The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 2 mm antiscatter slit and a 0.2 mm detector slit. The sample was exposed for 1 second per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ software.

A person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996). Therefore, it

shall be understood that the crystalline form is not intended to be limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction patterns described herein. The present invention also includes any crystals providing X-ray powder diffraction patterns substantially the same as those described herein. A person skilled in the art of X-ray powder diffraction is able to judge the substantial similarity of X-ray powder diffraction patterns and will understand that differences may be the result of various factors for example measurement errors resulting from measurement conditions (such as equipment, sample preparation or the machine used); intensity variations resulting from measurement conditions and sample preparation; relative intensity variations of peaks resulting from variations in size or non-unitary aspect ratios of cyrstals; and the position of reflections which can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer, and surface planarity of the sample.

The compounds of formula **(I)** have activity as pharmaceuticals, in particular as modulators or inhibitors of FGFR activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

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

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

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

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

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

In one embodiment the compounds of the invention are useful in the treatment of tumors of the bladder, breast and prostate and multiple myeloma.

Thus, the present invention provides a compound of formula **(I)**, or a pharmaceutically-acceptable salt thereof, as herein defined for use in therapy.

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

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In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, as herein defined in the manufacture of a medicament for use in therapy.

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

The invention also provides a method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as herein defined.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective anti-cancer agents which property is believed to arise from modulating or inhbiting FGFR activity. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by FGFR, i.e. the compounds may be used to produce a FGFR inhibitory effect in a warm-blooded animal in need of such treatment.

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

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

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

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

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

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

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

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

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

According to a further feature of this aspect of the invention there is provided a method for producing a FGFR inhibitory effect in a warm-blooded animal, such as man, in

need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

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

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, multiple myeloma, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined herein.

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

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

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

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical

composition in which the formula (I) compound or salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition may comprise from 0.01 to 99 %w (per cent by weight), from 0.05 to 80 %w, from 0.10 to 70 %w, and or even from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

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

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as herein defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

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.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for

use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

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

In general, a compound of the invention will be administered so that a daily dose in the range, for example, from 0.1 mg to 1000 mg active ingredient per kg body weight is received, given if required in divided doses. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. 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, from 0.1 mg to 30 mg active ingredient per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, from 0.1 mg to 25 mg active ingredient per kg body weight will generally be used. Oral administration is however preferred. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.1 mg to 2 g of active ingredient.

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

The anti cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or

radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:-

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of

5*-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54,

pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI 774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

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

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene directed enzyme pro drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a

bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex vivo and in vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches to decrease T cell anergy, approaches using transfected immune cells such as cytokine transfected dendritic cells, approaches using cytokine transfected tumour cell lines and approaches using anti idiotypic antibodies.

Examples

The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz, in DMSO-d_6 unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra (MS) data was generated on an LC/MS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment

and was run on a Phemonenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ spectrometer. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is the $(M+H)^+$ for positive ion mode and $(M-H)^-$ for negative ion mode;

(xi) Preparative HPLC was performed on C18 reversed-phase silica, for example on a Waters 'Xterra' preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example decreasingly polar mixtures of water (containing 1% acetic acid or 1% aqueous ammonium hydroxide (d=0.88) and acetonitrile;

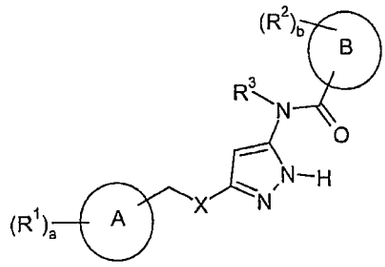
(xii) the following abbreviations have been used:

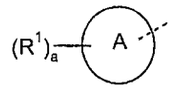
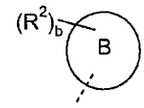
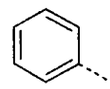
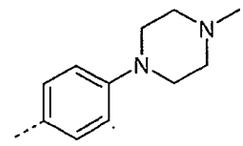
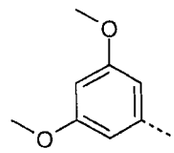
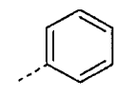
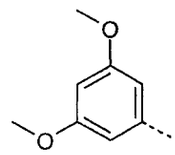
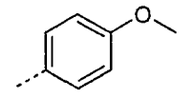
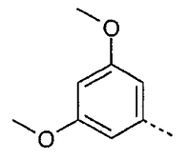
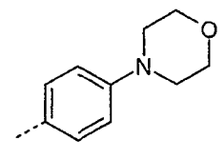
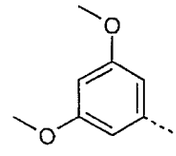
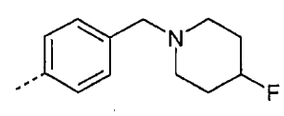
THF	tetrahydrofuran;
DMF	*N,N*-dimethylformamide;
EtOAc	ethyl acetate;
DCM	dichloromethane; and
DMSO	dimethylsulphoxide
DIPEA	*N,N*-diisopropylethylamine (also known as N-ethyl-N-propan-2-yl-propan-2-amine)
PBS	phosphate buffered saline
HEPES	*N*-[2-Hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]
DTT	dithiothreitol
ATP	Adenosine Triphosphate
BSA	bovine serum albumin
DMEM	Dulbecco's modified Eagle's Medium
MOPS	3-(N-morpholino)propanesulfonic acid

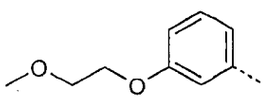
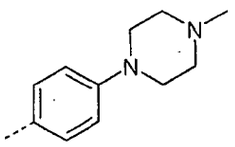
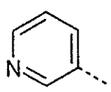
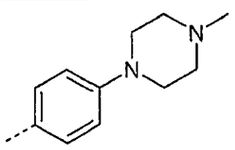
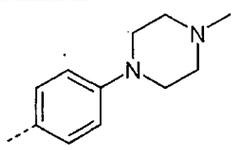
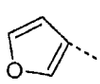
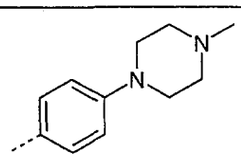
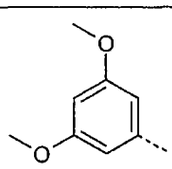
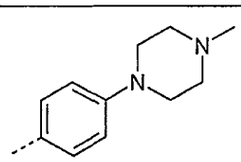
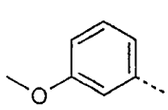
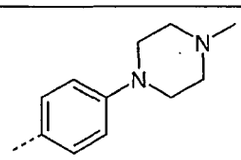
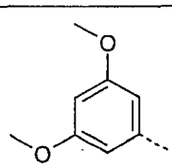
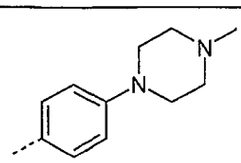
(xiii) compounds are named using proprietary naming software: Openeye Lexichem version 1.4, using IUPAC naming convention;

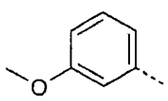
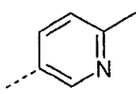
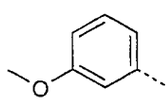
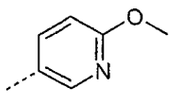
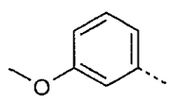
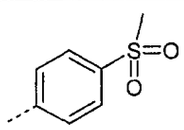
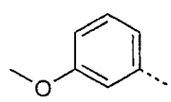
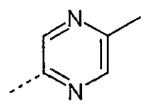
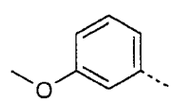
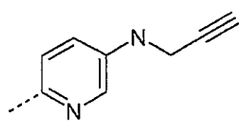
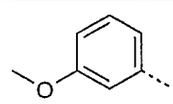
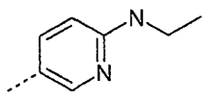
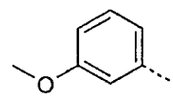
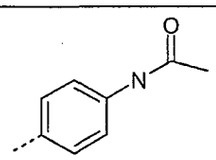
(xiv) unless otherwise specified, starting materials are commercially available.

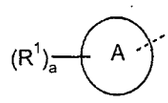
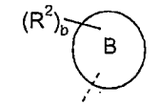
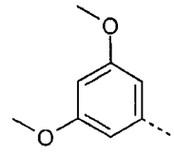
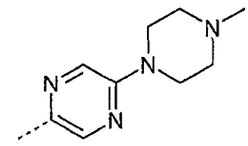
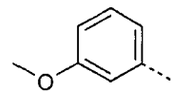
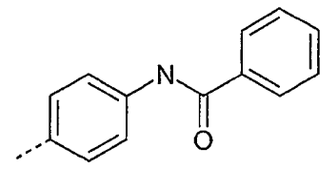
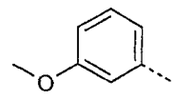
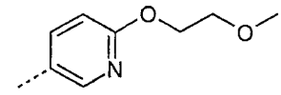
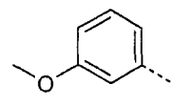
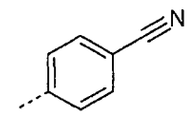
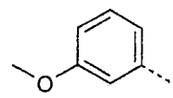
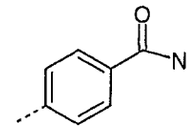
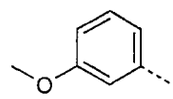
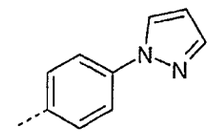
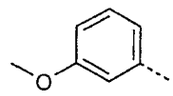
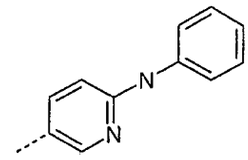
Table 1

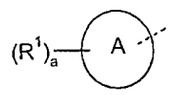
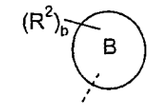
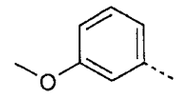
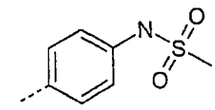
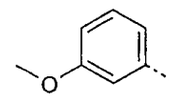
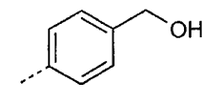
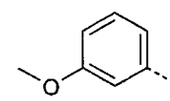
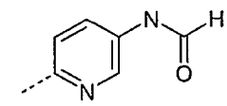
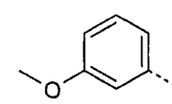
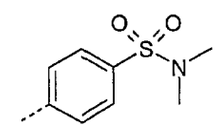
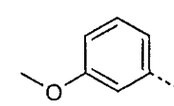
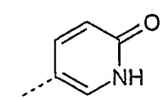
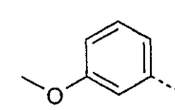
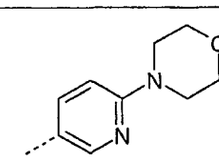
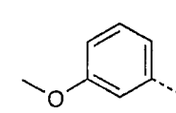
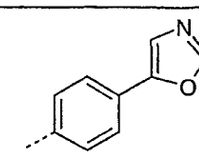


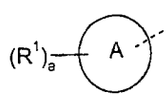
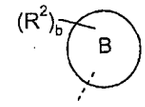
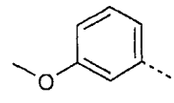
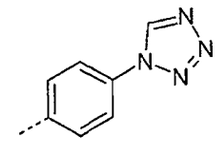
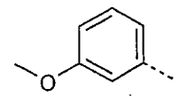
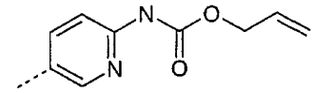
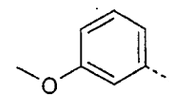
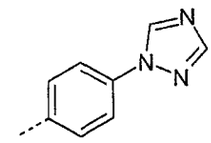
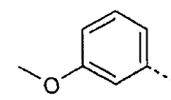
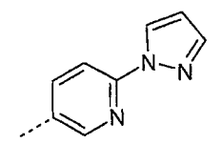
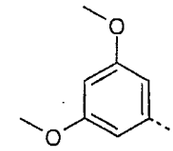
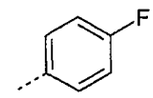
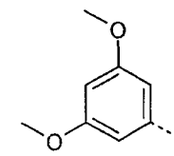
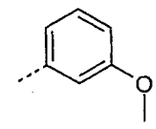
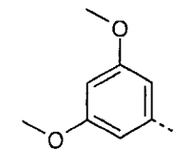
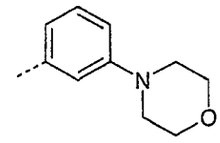
Example		X		R^3
1		CH_2		H
2		CH_2		H
3		CH_2		H
4		CH_2		H
5		CH_2		H

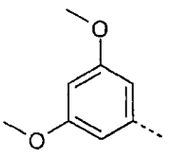
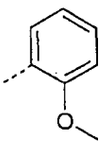
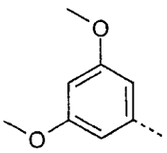
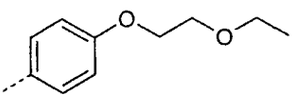
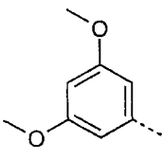
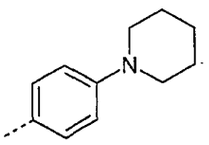
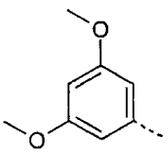
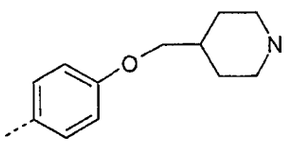
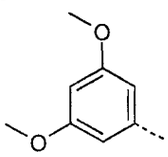
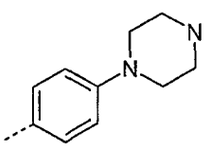
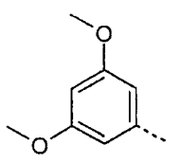
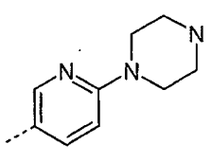
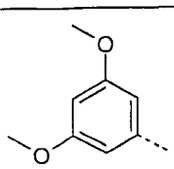
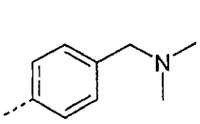
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
6		CH_2		H
7		CH_2		H
8		CH_2		H
9		CH_2		H
10		CH_2		H
11		CH_2		H
12		O		H

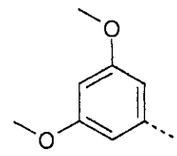
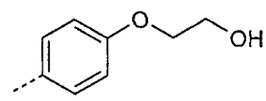
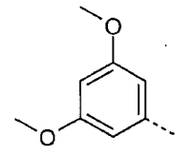
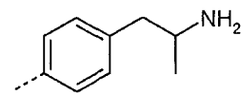
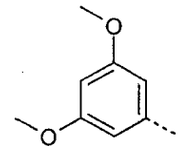
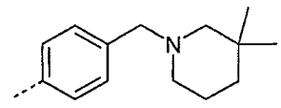
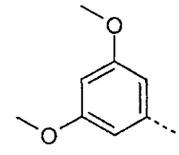
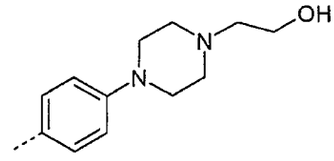
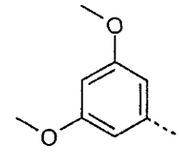
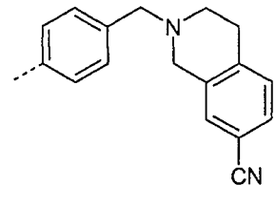
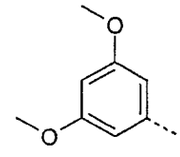
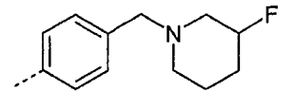
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
13		CH_2		H
14		CH_2		H
15		CH_2		H
16		CH_2		H
17		CH_2		H
18		CH_2		H
19		CH_2		H

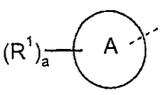
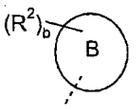
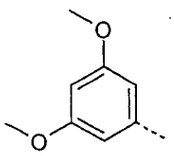
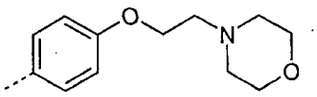
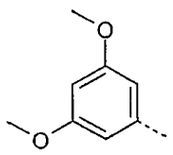
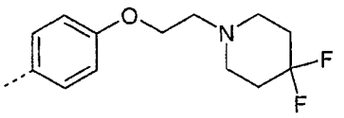
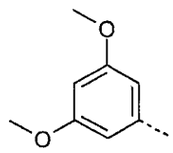
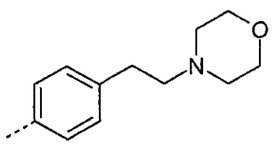
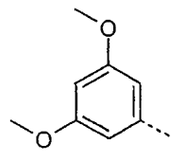
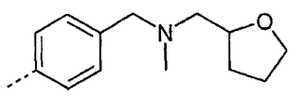
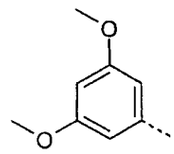
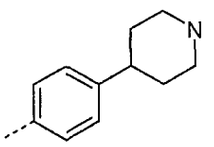
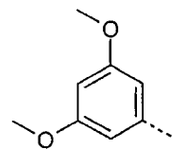
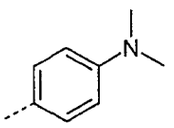
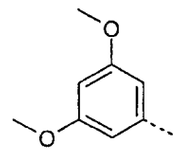
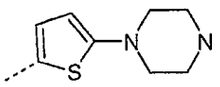
Example		X		R^3
20		O		H
21		CH_2		H
22		CH_2		H
23		CH_2		H
24		CH_2		H
25		CH_2		H
26		CH_2		H

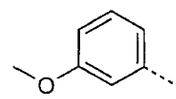
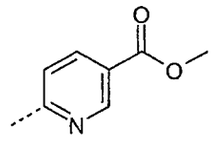
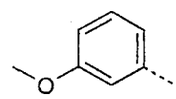
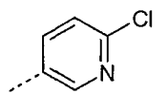
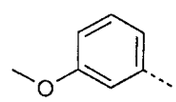
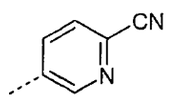
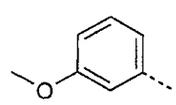
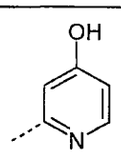
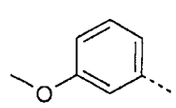
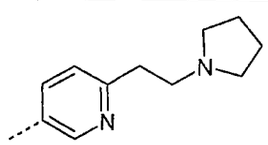
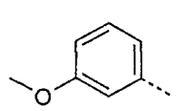
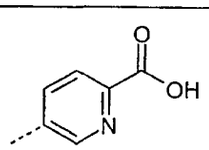
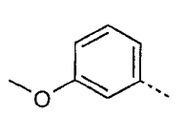
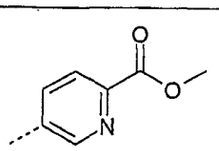
Example		X		R^3
27		CH_2		H
28		CH_2		H
29		CH_2		H
30		CH_2		H
31		CH_2		H
32		CH_2		H
33		CH_2		H

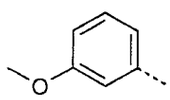
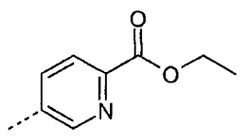
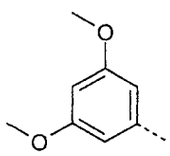
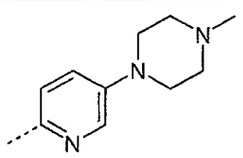
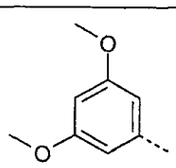
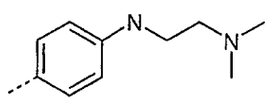
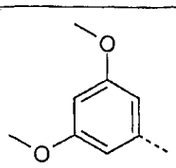
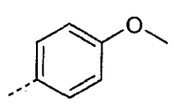
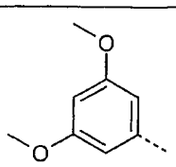
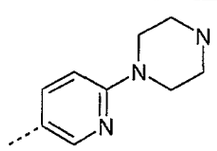
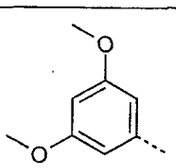
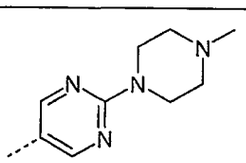
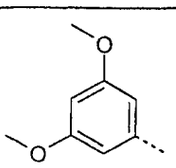
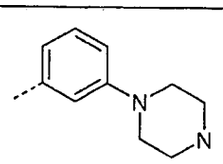
Example		X		R^3
34		CH_2		H
35		CH_2		H
36		CH_2		H
37		CH_2		H
38		CH_2		H
39		CH_2		H
40		CH_2		H

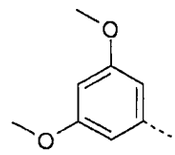
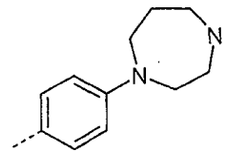
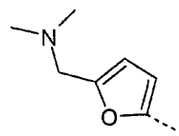
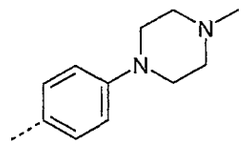
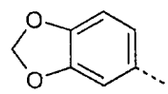
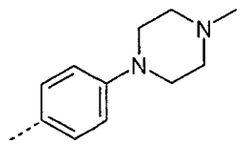
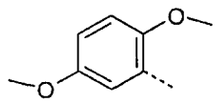
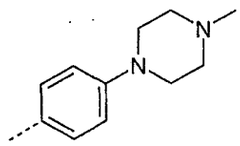
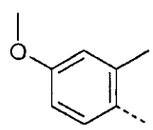
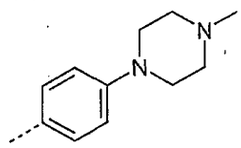
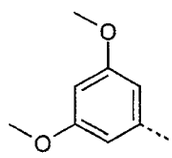
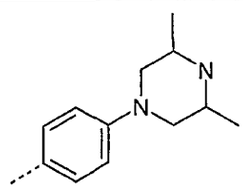
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
41		CH_2		H
42		CH_2		H
43		CH_2		H
44		CH_2		H
45		CH_2		H
46		CH_2		H
47		CH_2		H

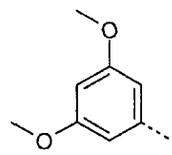
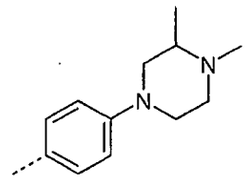
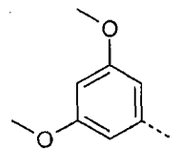
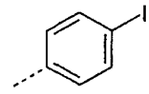
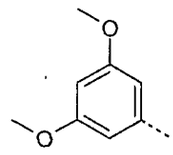
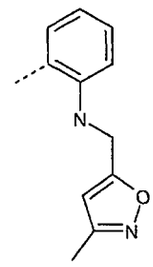
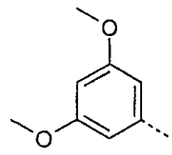
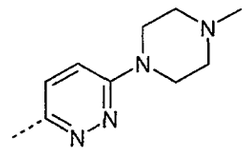
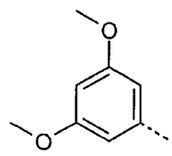
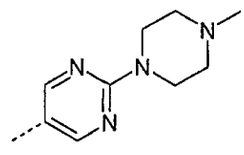
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
48		CH_2		H
49		CH_2		H
50		CH_2		H
51		CH_2		H
52		CH_2		H
53		CH_2		H

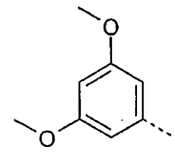
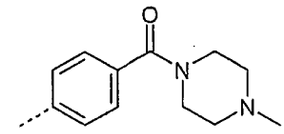
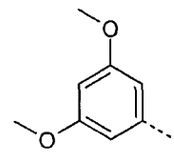
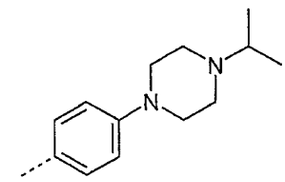
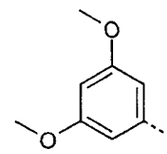
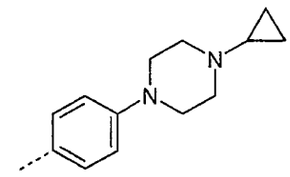
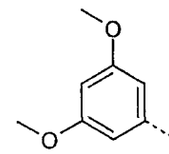
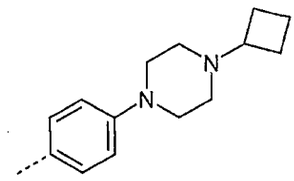
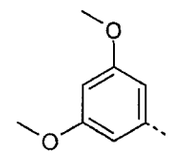
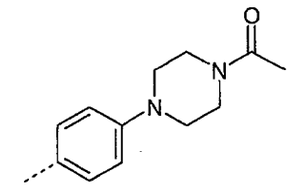
Example		X		R^3
54		CH_2		H
55		CH_2		H
56		CH_2		H
57		CH_2		H
58		CH_2		H
59		CH_2		H
60		CH_2		H

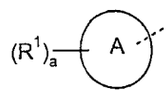
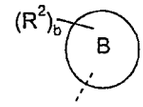
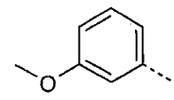
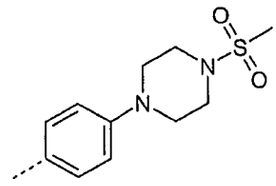
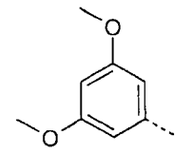
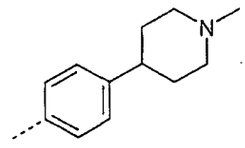
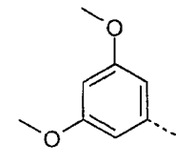
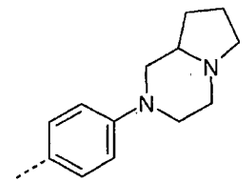
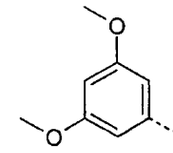
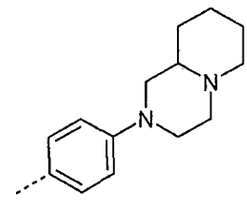
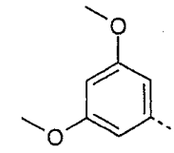
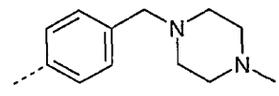
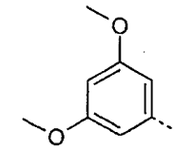
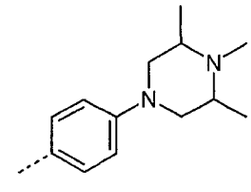
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
61		CH_2		H
62		CH_2		H
63		CH_2		H
64		CH_2		H
65		CH_2		H
66		CH_2		H
67		CH_2		H

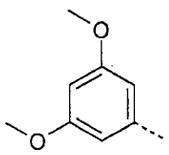
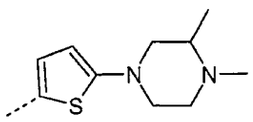
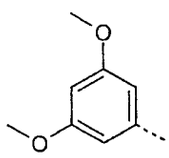
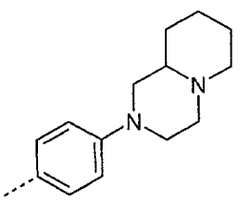
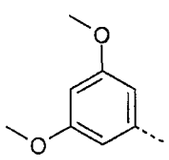
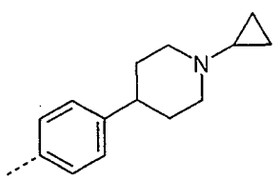
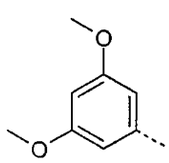
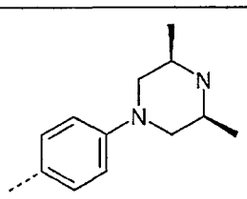
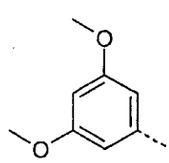
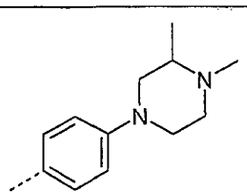
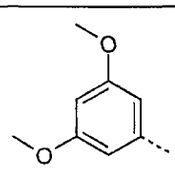
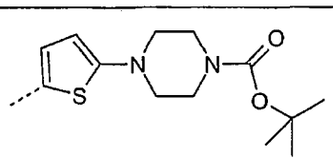
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
68		CH_2		H
69		O		H
70		O		H
71		O		H
72		O		H
73		O		H
74		O		H

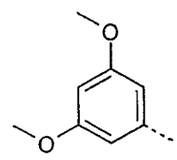
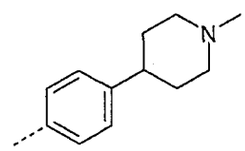
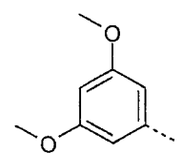
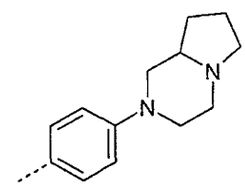
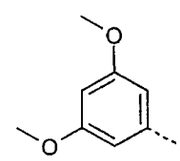
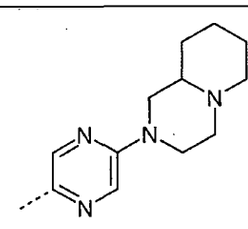
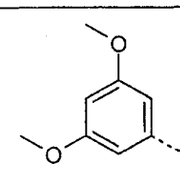
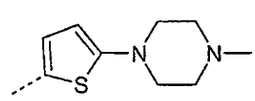
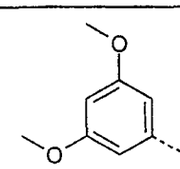
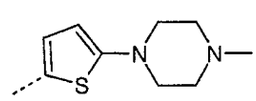
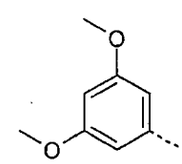
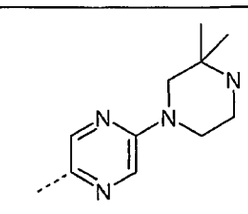
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
75		O		H
76		CH_2		H
77		CH_2		H
78		CH_2		H
79		CH_2		H
80		CH_2		H

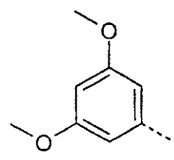
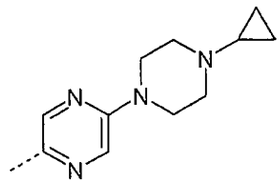
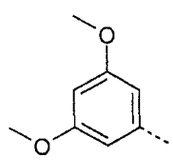
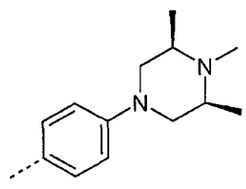
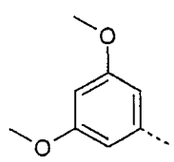
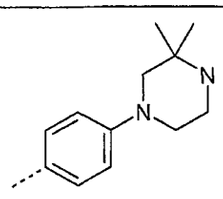
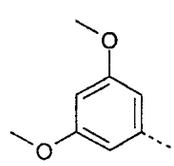
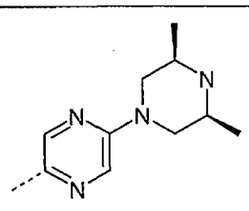
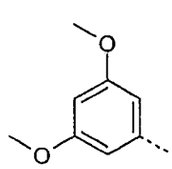
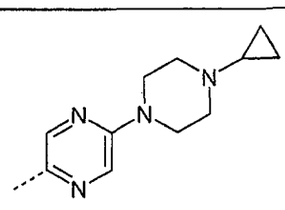
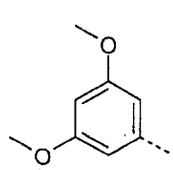
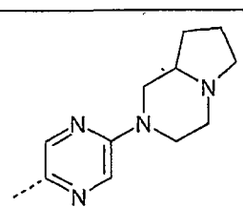
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
81		CH_2		H
82		CH_2		H
83		CH_2		H
84		CH_2		H
85		CH_2		H

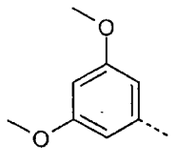
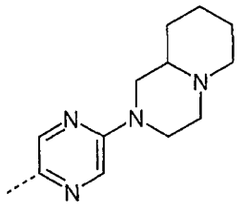
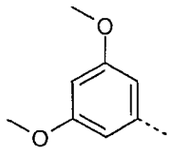
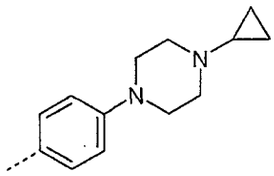
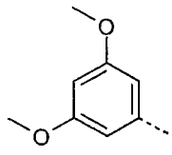
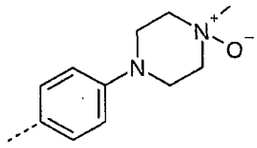
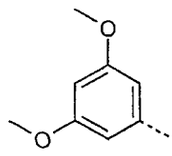
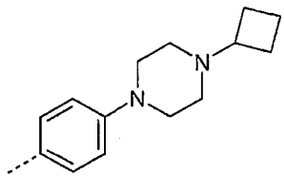
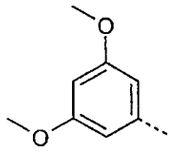
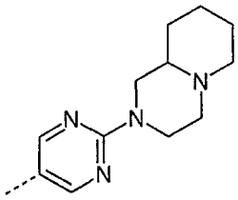
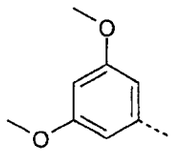
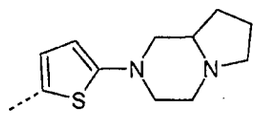
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
86		CH_2		H
87		CH_2		H
88		CH_2		H
89		CH_2		H
90		CH_2		H

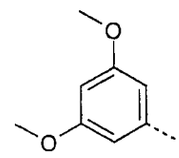
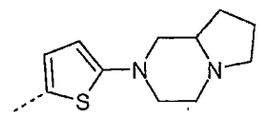
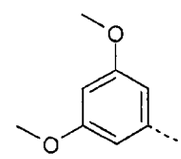
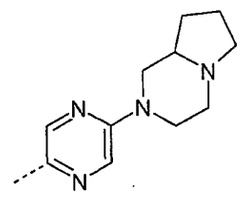
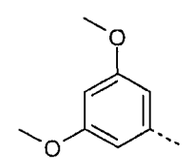
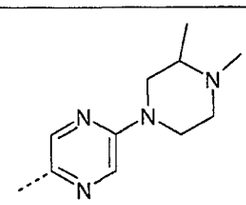
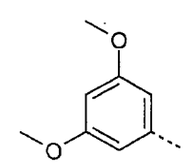
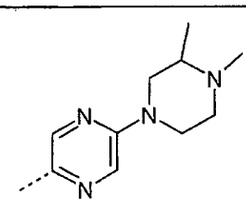
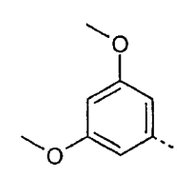
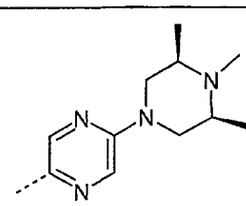
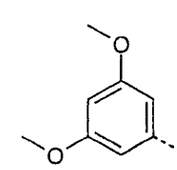
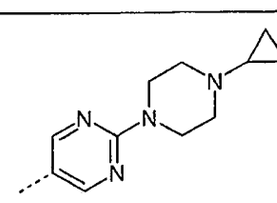
Example		X		R^3
91		CH_2		H
92		CH_2		H
93		CH_2		H
94		CH_2		H
95		CH_2		H
96		CH_2		H

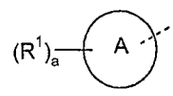
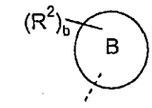
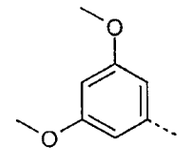
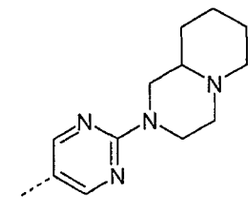
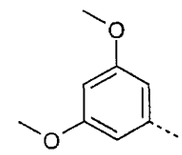
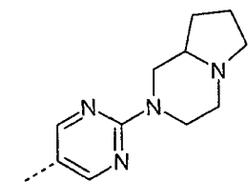
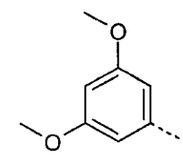
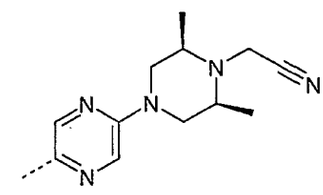
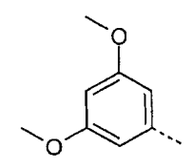
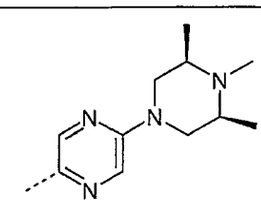
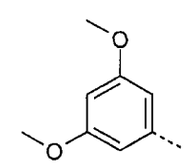
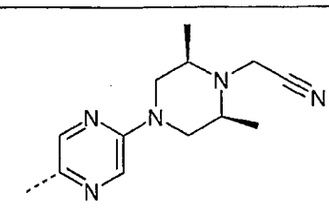
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
97		O		H
98		O		H
99		CH_2		H
100		O		H
101		O		H
102		CH_2		H

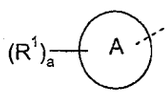
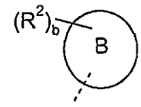
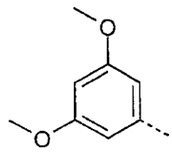
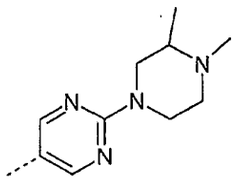
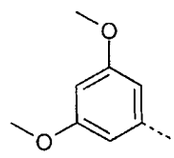
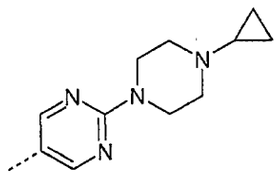
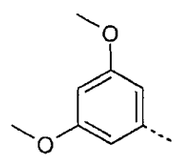
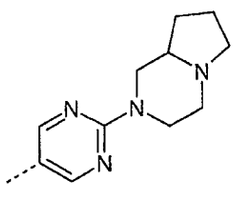
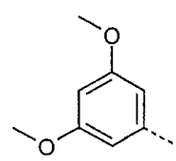
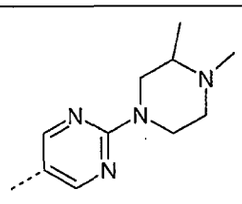
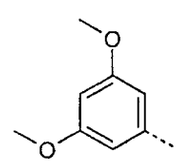
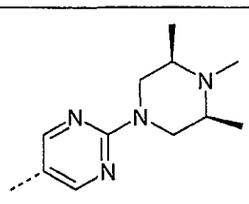
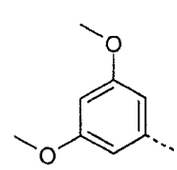
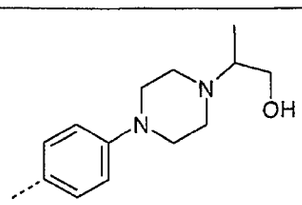
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
103		O		H
104		O		H
105		CH_2		H
106		CH_2		H
107		O		H
108		CH_2		H

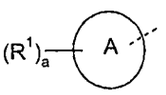
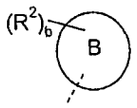
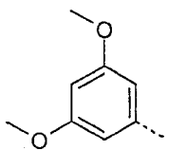
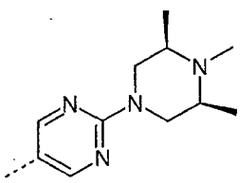
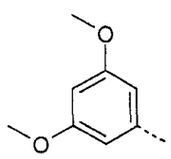
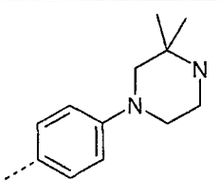
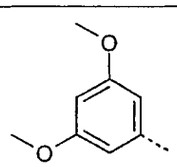
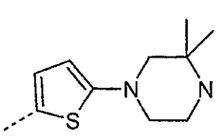
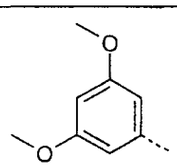
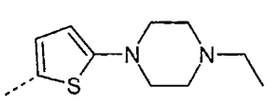
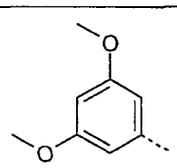
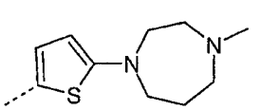
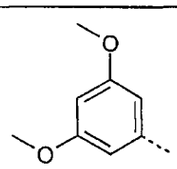
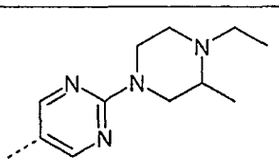
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
109		O		H
110		O		H
111		O		H
112		CH_2		H
113		CH_2		H
114		CH_2		H

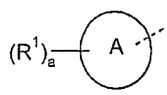
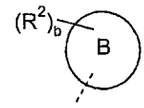
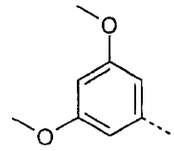
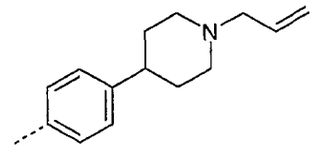
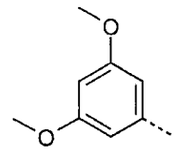
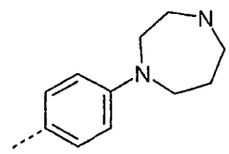
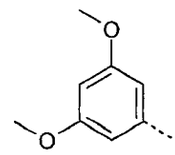
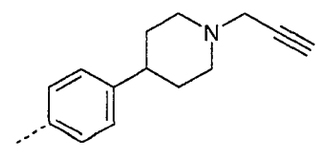
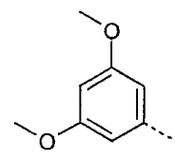
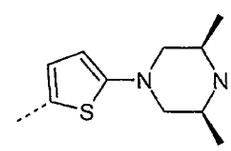
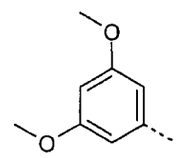
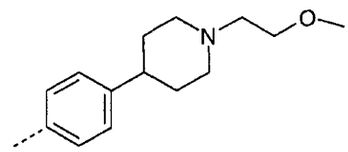
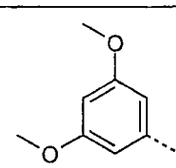
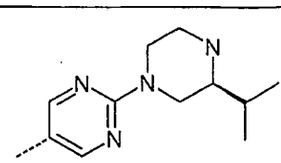
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
115		O		H
116		O		H
117		CH_2		H
118		O		H
119		O		H
120		CH_2		H

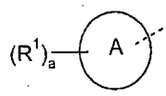
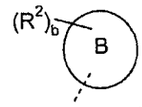
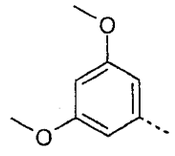
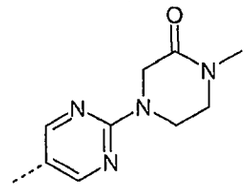
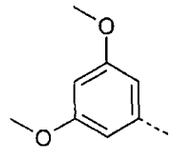
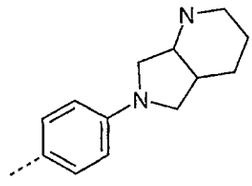
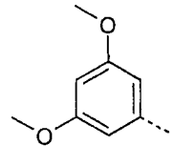
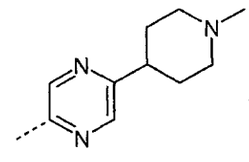
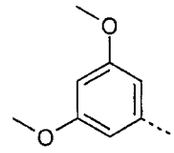
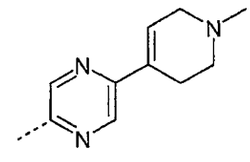
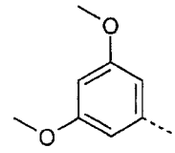
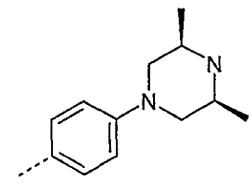
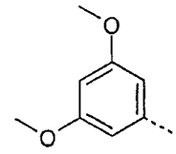
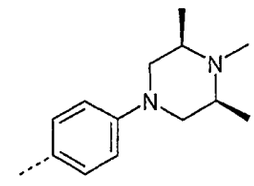
Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
121		O		H
122		O		H
123		CH_2		H
124		O		H
125		CH_2		H
126		CH_2		H

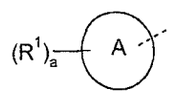
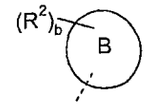
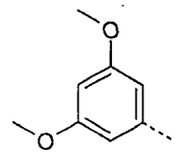
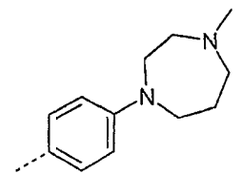
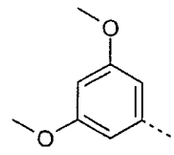
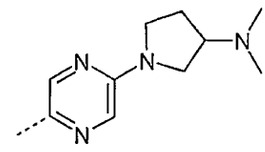
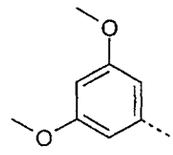
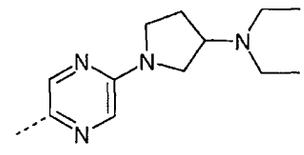
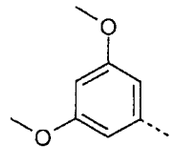
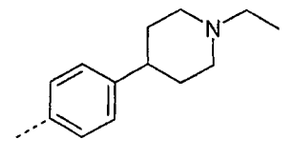
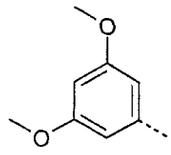
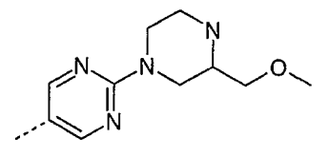
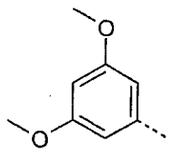
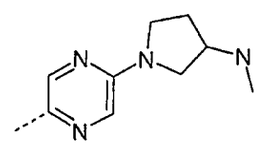
Example		X		R^3
127		CH_2		H
128		CH_2		H
129		CH_2		H
130		O		H
131		O		H

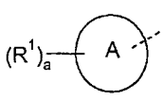
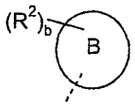
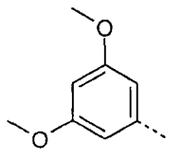
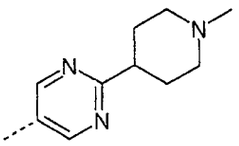
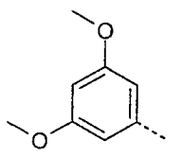
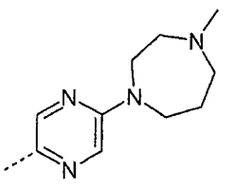
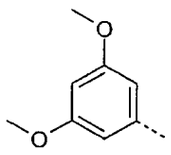
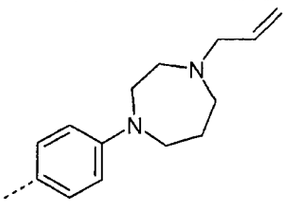
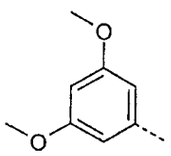
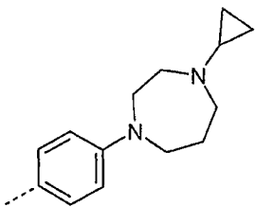
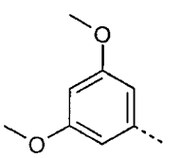
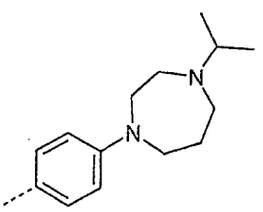
Example		X		R^3
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133		O		H
134		O		H
135		CH_2		H
136		CH_2		H
137		CH_2		H

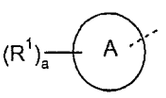
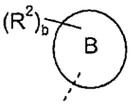
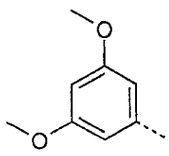
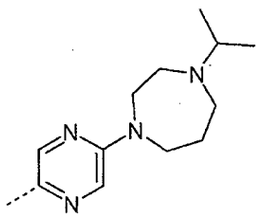
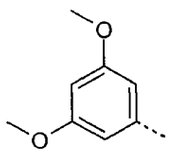
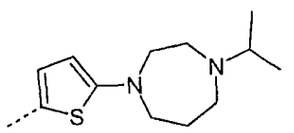
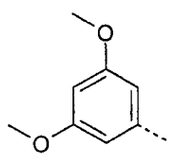
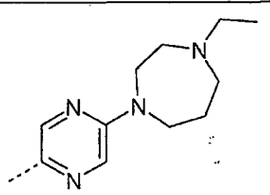
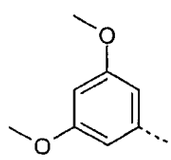
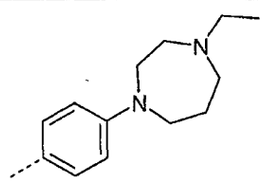
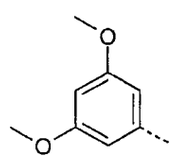
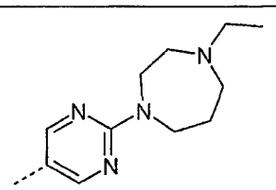
Example		X		R^3
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140		O		H
141		O		H
142		CH_2		H
143		CH_2		H

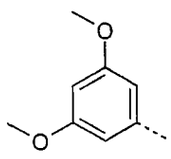
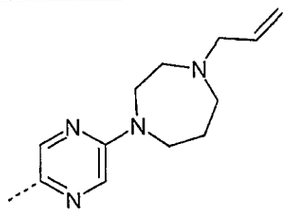
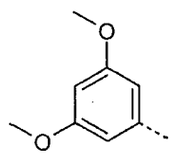
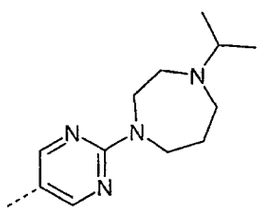
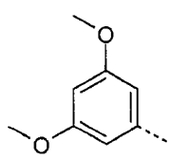
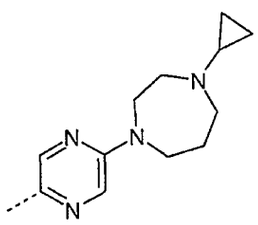
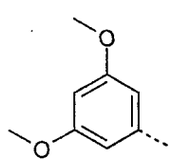
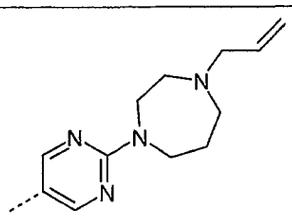
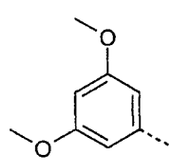
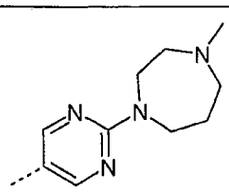
Example		X		R^3
144		CH_2		H
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146		CH_2		H
147		O		H
148		CH_2		H
149		CH_2		H

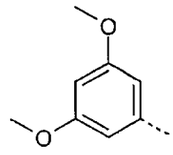
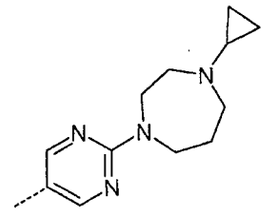
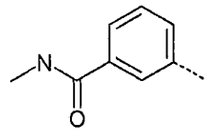
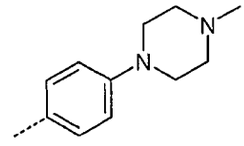
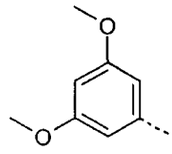
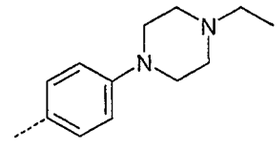
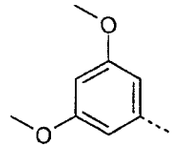
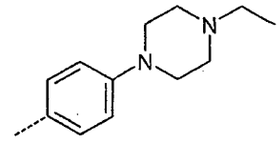
Example		X		R^3
150		CH_2		H
151		O		H
152		CH_2		H
153		CH_2		H
154		CH_2		H
155		CH_2		H

Example		X		R^3
156		CH_2		H
157		CH_2		H
158		CH_2		H
159		CH_2		H
160		CH_2		H
161		CH_2		H

Example		X		R^3
162		CH_2		H
163		CH_2		H
164		CH_2		H
165		CH_2		H
166		CH_2		H

Example		X		R^3
167		CH_2		H
168		CH_2		H
169		CH_2		H
170		CH_2		H
171		CH_2		H

Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
172		CH_2		H
173		CH_2		H
174		CH_2		H
175		CH_2		H
176		CH_2		H

Example	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
177		CH_2		H
178		CH_2		H
179		O		H
180		CH_2		H

Example 1

4-(4-methylpiperazin-1-yl)-N-(5-phenethyl-2H-pyrazol-3-yl)benzamide

Oxalyl chloride (2M in DCM, 250µl, 0.50mmol, 1.1eq) was added dropwise to a mixture of 4-(4-methylpiperazin-1-yl)benzoic acid (100mg, 0.45mmol, 1eq) in DCM (5ml, containing a few drops of DMF) and DIPEA (171µl, 0.95mmol, 2.1eq) at 0°C. After stirring for 1h at 0°C, a solution of 5-phenethyl-2H-pyrazol-3-amine (128mg, 0.68mmol, 1.5eq) in DCM (2ml) was added dropwise. The mixture was maintained at 0°C for 2 h, then gradually allowed to warm to room temperature overnight. The mixture was diluted with DCM (50 ml), washed with aq. $NaHCO_3$ solution (50 ml) and the aqueous layer was extracted with DCM (50 ml). The combined organic layers were concentrated. The crude product was purified by reverse-phase

prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water (containing 1% ammonium hydroxide) to yield the title compound (8mg, 3% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 2.84 - 2.95 (4H, m), 3.26 - 3.30 (4H, m), 6.41 (1H, s), 6.96 (2H, d), 7.15 - 7.33 (5H, m), 7.89 (2H, d), 10.30 (1H, s), 12.08 (1H, s). MS m/z 390 (MH+)

FGFR Kinase assay – Elisa, IC_{50} 0.22μM.

Example 2

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2*H*-pyrazol-3-yl]benzamide

Benzoyl chloride (56μl, 0.47mmol, 1.1eq) was added dropwise to a mixture of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (150mg, 0.43mmol, 1 eq) and pyridine (104μl, 1.29mmol, 3eq) in DCM (1.5ml) at ambient temperature. After stirring at ambient temperature for 2 h, a solution of TFA (321μl, 4.32mmol, 10eq) in DCM (2.7ml) was added dropwise and stirring was continued for a further 1 h. The reaction mixture was concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a 33-53% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless foamy solid (100mg, 66% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 2.81 (4H, s), 3.65 (6H, s), 6.26-6.25 (1H, m), 6.35 (2H, d), 6.41 (1H, s), 7.50-7.39 (3H, m), 7.91 (2H, d), 10.56 (1H, s), 12.07 (1H, s). MS: m/z 352 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.140 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as follows:

A solution of di-*tert*-butyl dicarbonate (464mg, 2.12mmol, 1.05eq) in DCM (2ml) was added dropwise to a mixture of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (500mg, 2.02mmol, 1eq) in DCM (18ml) containing aq. KOH solution (4.5 N, 3.6ml, ca. 16mmol, 8eq). The reaction mixture was transferred to a separating funnel and the layers separated. The organic layer was washed with water (10ml), brine (10ml) and dried over sodium sulfate.

After filtering the solvent was evaporated under reduced pressure to yield a pale yellow oil which solidified on standing overnight to afford a cream solid (704mg, 100% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 1.56 (9H, s), 2.68-2.63 (2H, m), 2.80-2.75 (2H, m), 3.73 (6H, s), 5.22 (1H, s), 6.23 (2H, br.s), 6.32-6.31 (1H, m), 6.44 (2H, d). MS: m/z 370 ([M+Na]+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as follows:

Acetonitrile (2.29ml, 43.61mmol, 1.2eq) was added to a slurry of sodium hydride (1.75g dispersion in mineral oil, 43.61mmol, 1.2eq) in anhydrous toluene (70ml) and the mixture stirred at room temperature for 30 mins. Ethyl 3-(3,5-dimethoxyphenyl)propanoate (8.66g, 36.34mmol, 1eq) in toluene (60ml) was added and the reaction was refluxed for 18h. After cooling, the reaction mixture was quenched with water and the solvent was evaporated under reduced pressure. The residue was dissolved in 2M HCl (50ml). The acidic solution was extracted with ethyl acetate. The organic extracts were combined and washed with water, brine and dried over magnesium sulphate. After filtering, the solvent was evaporated under reduced pressure to yield the crude product as a yellow oil. The oil was purified by silica column chromatography (eluting with DCM) and the desired fractions were combined and evaporated to yield a cream solid (3.76g, 44% yield).

To the cream solid (3.72g, 15.96mmol, 1eq) in ethanol (55ml) was added hydrazine hydrate (852µl, 17.56mmol, 1.1eq). The reaction was refluxed for 24h before allowing to cool. After evaporation under reduced pressure, the residue was extracted into DCM. The organic layers were washed with water, brine, dried with magnesium sulphate, filtered and evaporated under reduced pressure to afford 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine as a pale yellow solid (3.76g. 42% over 2 steps).

^{1}H NMR (300.132 MHz, DMSO) δ 2.64 - 2.82 (4H, m), 3.71 (6H, s), 4.07 - 4.72 (2H, m), 5.20 (1H, s), 6.31 (1H, t), 6.38 (2H, d). MS: m/z 248 (MH+)

Example 3

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-methoxy-benzamide

1-Chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (89 µl, 0.63mmol, 1.05eq) was added dropwise to 4-methoxybenzoic acid (97mg, 0.63mmol, 1eq) in DCM (1.5ml) at ambient temperature. After stirring at ambient temperature for 1.5 h, a solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (199mg, 0.57mmol, 0.9eq) and pyridine (142µL, 1.74mmol, 2.75 eq) in DCM (2ml) was added to the reaction mixture and stirring was continued at ambient temperature for a further 3 h. A solution of TFA (386µL, 5.2mmol, 8.25eq) in DCM (3.5ml) was then added and stirring was continued at ambient temperature for 18 h. The reaction mixture was concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a 33-53% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless foamy solid (113mg, 52% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 2.88 (4H, s), 3.73 (6H, s), 3.84 (3H, s), 6.34–6.32 (1H, m), 6.42 (2H, d), 6.47 (1H, s), 7.01 (2H, d), 7.99 (2H, d), 10.48 (1H, br.s), 12.12 (1H, br.s).
MS: m/z 382 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.132 µM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 4

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-morpholin-4-yl-benzamide

Prepared in an analogous way to Example 3 to give the title compound as a solid (125 mg, 50% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 2.88 (4H, s), 3.26-3.24 (4H, m), 3.76-3.72 (10H, m), 6.34-6.32 (1H, m), 6.46-6.42 (3H, m), 6.98 (2H, d), 7.92 (2H, d), 10.35 (1H, br.s), 12.10 (1H, br.s).
MS: m/z 437 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.068 µM.

Example 5

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2*H*-pyrazol-3-yl]-4-[(4-fluoropiperidin-1-yl)methyl]benzamide

A solution of NaHMDS in THF (1 M, 0.65ml, 0.65mmol, 1.5eq) was added dropwise at ambient temperature to a mixture of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl) ethyl]pyrazole-1-carboxylate (150mg, 0.43mmol, 1eq) and methyl 4-[(4-fluoropiperidin-1-yl)methyl]benzoate (131 mg, 0.52mmol, 1.2eq) in THF (0.5ml). The reaction mixture was stirred at ambient temperature for 1 h. It was then concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a 39-49% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless solid (33mg, 16% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 1.78-1.67 (2H, m), 1.94-1.80 (2H, m), 2.35-2.29 (2H, m), 2.57-2.55 (2H, m), 2.89 (4H, s), 3.55 (2H, s), 3.73 (6H, s), 4.79-4.61 (1H, m), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.48 (1H, s), 7.40 (2H, d), 7.95 (2H, d), 10.59 (1H, br.s), 12.15 (1H, br.s).

MS: m/z 467 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.063 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Methyl 4-[(4-fluoropiperidin-1-yl)methyl]benzoate, used as starting material was prepared as follows:

4-Fluoropiperidine hydrochloride (366mg, 2.62mmol, 1.2eq) was added in one portion to a mixture of methyl 4-(bromomethyl)benzoate (500mg, 2.18mmol, 1eq) and MP-carbonate (2.74mmol/g, 1.912g, 5.24mmol, 2.4eq) in MeCN (10ml). The reaction mixture was stirred at ambient temperature for 18 h. Polymer-supported isocyanate (1 mmol/g, 500mg, 0.5mmol, 0.5eq) was added in one portion and stirring continued for 4 h. The reaction mixture was filtered, the resins washed with MeCN and the combined filtrate was concentrated to afford a clear oil, 478 mg, 87% yield at 80% purity.

^{1}H NMR (399.902 MHz, CDCl3) δ 1.98-1.83 (4H, m), 2.40-2.34 (2H, m), 2.61-2.54 (2H, m), 3.55 (2H, s), 3.91 (3H, s), 4.77-4.60 (1H, m), 7.40 (2H, d), 8.00-7.98 (2H, m). MS: m/z 252 (MH+).

Example 6

N-[5-[2-[3-(2-methoxyethoxy)phenyl]ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

To 4-(4-methylpiperazin-1-yl)benzoic acid (440mg, 2mmol, 1eq) in dichloromethane (10ml) at 0°C was added a few drops of N,N-dimethylformamide followed by the dropwise addition of a 2M solution of oxalyl chloride in dichloromethane (1.1ml, 2.2mmol, 1.1eq). The reaction was maintained at 0°C for 1h. 5-[2-[3-(2-Methoxyethoxy)phenyl]ethyl]-2H-pyrazol-3-amine (628mg, 2.4mmol, 1.2eq) in dichloromethane (10ml) was then added dropwise followed by DIPEA (750µl, 4.20mmol, 2.1eq). The reaction was maintained at 0°C for a further hour before allowing to warm to room temperature overnight. The mixture was diluted with DCM (50 ml) and washed with aq. $NaHCO_3$ solution (50 ml). The aqueous layer was extracted with DCM (50 ml). The organic extracts were combined, washed with brine, dried with magnesium sulphate and evaporated under reduced pressure. The crude product was purified by acidic reverse-phase prep. HPLC. Fractions containing product were captured onto a SCX-2 column. After washing with methanol, the crude product was released with 10% ammonia in methanol. After evaporation under reduced pressure, the crude product was re-purified on the basic reverse-phase prep. HPLC using a 20-45% gradient of acetonitrile in water containing 1% ammonium hydroxide to yield, after evaporation, a white solid (22.9mg, 2.5%).

^{1}H NMR (300.132 MHz, DMSO) δ 2.22 (3H, s), 2.44 (4H, t),2.88 (4H, s),3.27 (4H, t),3.30 (3H, s),3.64 (2H, dd),4.06 (2H, dd),6.41 (1H, s),6.72 - 6.84 (3H, m),6.95 (2H, d),7.18 (1H, t),7.88 (2H, d),10.30 (1H, s),12.06 (1H, s) MS: m/z 464 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.058 µM.

5-[2-[3-(2-methoxyethoxy)phenyl]ethyl]-2H-pyrazol-3-amine used as starting material was prepared as follows:

To sodium hydride (1.065g, 26.57mmol, 1.1eq) was added anhydrous 1,4-dioxane (40ml) followed by anhydrous acetonitrile (1.52ml, 29mmol, 1.2eq). 2-Methoxyethyl 3-[3-(2-

methoxyethoxy)phenyl]propanoate (6.82g, 24.16mmol, 1eq) in anhydrous 1,4-dioxane (35ml) was then added. The reaction was refluxed for 18h. After cooling, the brown solution was quenched with water. The solvent was evaporated under reduced pressure and the aqueous residue was acidified with 2M HCl and extracted with ethyl acetate. The organic layers were combined, washed with 2M HCl, water and brine. After drying (magnesium sulphate), the solution was filtered and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with 0-50% ethyl acetate in hexanes. The desired intermediate was obtained, after evaporation, as a yellow oil (3.24g, 54%). To this intermediate (3.24g, 13.10mmol, 1eq) in ethanol (65ml) was added hydrazine.monohydrate (700ul, 14.41mmol, 1.1eq). The reaction was refluxed at 85°C for 18h. The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with water and brine, dried (magnesium sulphate), filtered and evaporated under reduced pressure to yield a yellow oil (2.78g, 81%).

^{1}H NMR (300.132 MHz, DMSO) δ 2.68 - 2.84 (4H, m),3.31 (3H, s),3.65 (2H, dd),4.06 (2H, dd),4.40 (2H, s),5.19 (1H, s),6.71 - 6.81 (3H, m),7.17 (1H, t),11.08 (1H, s); MS: m/z 262 (MH+).

2-Methoxyethyl 3-[3-(2-methoxyethoxy)phenyl]propanoate used as starting material was prepared as follows:

To 3-(3-hydroxyphenyl)propionic acid (8.31g, 50mmol, 1eq) in N,N-dimethylformamide (150ml) was added potassium carbonate (17.28g, 125mmol, 3eq) followed by 2-bromoethyl methyl ether (10.34ml, 110mmol, 2.20eq). The reaction mixture was stirred overnight at room temperature. The reaction mixture was evaporated to dryness. The residue was extracted into ethyl acetate, washed with water and brine, dried with magnesium sulphate, filtered and evaporated to yield a yellow oil ~ 11.38g. The reaction mixture was purified by column chromatography using a gradient of 0-30% ethyl acetate in hexanes. To this intermediate (9.82g, 43.76mmol, 1eq) was added N,N-dimethylformamide (50ml) followed by potassium carbonate (9.1g, 65.64mmol, 2.5eq) and 2-bromoethyl methyl ether (4.94ml, 52.5mmol, 1:2eq). The reaction mixture was heated at 60 °C for 18h. The reaction mixture was diluted with N,N-dimethylformamide (50ml) and a further 4.55g of potassium carbonate was added followed by 2-bromoethyl methyl ether (2.45ml). The reaction mixture was heated overnight at 60 °C for a further 20h. After cooling to room temperature, the inorganics were filtered and

the solvent was evaporated under reduced pressure. The residue was extracted into ethyl acetate and the organic layers was washed with water, saturated sodium hydrogen carbonate and brine. After drying (magnesium sulphate) and filtration, the organic layers were evaporated under reduced pressure to yield a yellow oil. The crude product was purified by column chromatography, eluting with a gradient of 0-50% ethyl acetate in hexanes. The desired product was obtained as a clear yellow oil (8.755g, 71%).

^{1}H NMR (300.132 MHz, DMSO) δ 2.63 (2H, t), 2.82 (2H, t), 3.25 (3H, s), 3.31 (3H, s), 3.50 (2H, m), 3.65 (2H, m), 4.06 (2H, m), 4.13 (2H, dd), 6.73 - 6.82 (3H, m), 7.18 (1H, t); MS: m/z 283 (MH+).

Example 7

4-(4-methylpiperazin-1-yl)-N-[5-(2-pyridin-3-ylethyl)-2H-pyrazol-3-yl]benzamide

Prepared in an analogous way to Example 1 but starting with 5-(2-pyridin-3-ylethyl)-2H-pyrazol-3-amine (189mg, 1mmol, 1.5eq) to give the above titled compound as a white solid (15mg, 6% yield)

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 2.89 - 2.98 (4H, m), 3.28 (4H, t), 6.40 (1H, s), 6.96 (2H, d), 7.28 - 7.33 (1H, m), 7.65 (1H, dt), 7.89 (2H, d), 8.40 (1H, dd), 8.45 (1H, d), 10.31 (1H, s), 12.09 (1H, s). MS m/z 391 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.047 μM.

5-(2-pyridin-3-ylethyl)-2H-pyrazol-3-amine, used as starting material was prepared as follows:

Acetonitrile (2.9ml, 54.8mmol, 1.3eq) was added to a slurry of sodium hydride (2.2g, 54.8mmol, 1.3eq) in anhydrous 1,4-dioxane (50ml). To this was then added a solution of methyl 3-pyridin-3-ylpropanoate (6.96g, 42mmol, 1eq) in anhydrous 1,4-dioxane (50ml). The reaction was heated under reflux for 18h. After cooling, ethanol (5ml) was added, followed by hydrazine.HCl (3181mg, 46.43mmol, 1.1eq). The reaction mixture was heated at 100°C for 20h, allowed to cool to room temperature and then evaporated under reduced pressure. The orange residue was dissolved in water (50ml) and partioned with ethyl acetate (2x75ml) The organic layers were combined and washed with 2M HCl. The aqueous acidic layers were combined and washed with ethyl acetate. The aqueous layer was separated, basified by the

addition of 8N ammonia solution and extracted with ethyl acetate. The organic layer was washed with brine, dried with magnesium sulphate, filtered and evaporated under reduced pressure to yield the title compound as an orange oil. The oil was dissolved in acetonitrile (10ml) and purified on basic reverse-phase hplc using a 2-20% gradient of acetonitrile in water (containing 1% ammonium hydroxide). Desired fractions were combined and evaporated to yield the title compound (348mg , 5% yield).

^{1}H NMR (400.132 MHz, DMSO) δ 2.74 (2H, t), 2.87 (2H, t), 4.43 (2H, s), 5.17 (1H, s), 7.29 (1H, ddd), 7.61 (1H, dddd), 8.39 (1H, dd), 8.42 (1H, d), 11.08 (1H, s). MS; m/z 189 (MH+).

Further product was obtained from the basified aqueous layer by purification using basic reverse-phase prep. HPLC. After evaporation of the desired fractions under reduced pressure to low volume, the solution was acidified using 2M HCl. The product was captured onto a SCX-2 column. The product was column was eluted using 10% ammonia solution in methanol. After evaporation under reduced pressure a yellow oil was obtained (657mg, 9% yield).

Example 8

N-[5-[2-(2-furyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Prepared in an analogous way to Example 1 but starting with 5-[2-(2-furyl)ethyl]-2H-pyrazol-3-amine (178mg, 1mmol, 1.5eq) to give the above titled compound as a tan solid (24.8mg, 10% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 2.89 - 2.98 (4H, m), 3.28 (4H, t), 6.40 (1H, s), 6.96 (2H, d), 7.28 - 7.33 (1H, m), 7.65 (1H, dt), 7.89 (2H, d), 8.40 (1H, dd), 8.45 (1H, d), 10.31 (1H, s), 12.09 (1H, s). MS; m/z 380 (MH+).

Mean of n=1, FGFR Kinase assay – Elisa, IC_{50} 0.0795 μM.

5-[2-(2-furyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as follows:

a) A mixture of ethyl 2-triphenylphosphoranylideneacetate (34.84g, 100mmol, 1eq) and furan-2-carbaldehyde (9609mg, 100mmol,1eq) in anhydrous THF (200ml) was stirred at room temperature for 24h. The solvent was evaporated under reduced pressure and the residue triturated with ether to produce a brown solution and a precipitate. The solid was filtered, washed and removed. The filtrate was then evaporated. The product was purified by column

chromatography on silica eluting with 0-20% ethyl acetate in hexanes. The desired fractions were evaporated to yield a cis/trans mixture of ethyl (E)-3-(2-furyl)prop-2-enoate as a pale yellow oil (NMR suggested mainly trans product) (15.5g, 93%).

b) A cis/trans mixture of ethyl (E)-3-(2-furyl)prop-2-enoate (15.5g, 93.27mmol, 1eq) was stirred in ethanol (120ml) containing 10% palladium on charcoal (775mg, 5% by w). The reaction mixture was stirred under hydrogen for 4h. A further quantity of 10% Pd/C (775mg, 5% by w) was added. The reaction was stirred under hydrogen for an additional 95 mins. The reaction was filtered and evaporated under reduced pressure. The crude product was purified by silica column chromatography eluting with 20% ethyl acetate in hexanes. The desired fractions were evaporated under reduced pressure and ethyl 3-(2-furyl)propanoate was obtained as a clear oil (3.69g, 24% yield).

^{1}H NMR (300.132 MHz, CDCl3) δ 1.25 (3H, t), 2.64 (2H, t), 2.97 (2H, t), 4.15 (2H, q), 6.02 (1H, td), 6.27 (1H, dd), 7.30 (1H, dd)

5-[2-(2-furyl)ethyl]-2H-pyrazol-3-amine (2.09g, 54% over 2steps) was then prepared in an analogous manner to that described for the starting material for example 2 (5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine) using ethyl 3-(2-furyl)propanoate (6.33g, 37.64mmol, 1eq) as starting material.

^{1}H NMR (300.132 MHz, CDCl3) δ 2.98 (4H, t), 3.45 (2H, s), 6.04 (1H, d), 6.28 (1H, dd), 7.30 (1H, dd). MS m/z 178 (MH+).

Example 9

N-[5-[2-(3-furyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Prepared in an analogous way to Example 1 but starting with 5-[2-(3-furyl)ethyl]-2H-pyrazol-3-amine (178mg, 1mmol, 1.5eq) to give the title compound as a tan solid (17.3mg, 7% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.45 (4H, t), 2.67 - 2.89 (4H, m), 3.28 (4H, t), 6.39 (1H, d), 6.43 (1H, s), 6.96 (2H, d), 7.45 (1H, s), 7.56 (1H, t), 7.89 (2H, d), 10.29 (1H, s), 12.07 (1H, s). MS m/z 380 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.137 μM.

5-[2-(3-furyl)ethyl]-2H-pyrazol-3-amine (3.94g, 59% over final 2 steps), used as starting material was prepared in an analogous manner to the synthesis of 5-[2-(2-furyl)ethyl]-2H-pyrazol-3-amine shown in example 8.

Example 10

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Prepared in an analogous way to Example 1, but starting with 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (566mg, 2.30mmol, 1.5eq) to give the title compound as a beige solid (183.5mg, 27% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 2.86 (4H, s), 3.27 (4H, t), 3.72 (6H, s), 6.32 (2H, t), 6.35 - 6.42 (3H, m), 6.96 (2H, d), 7.89 (2H, d), 10.31 (1H, s), 12.08 (1H, s). MS: m/z 450 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00085 μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 11

N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Prepared in an analogous way to Example 1, but starting with 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine (148mg, 0.68mmol, 1.5eq) to give the title compound as a solid (8.2mg, 4% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 2.89 (4H, s), 3.26 - 3.31 (4H, m), 3.73 (3H, s), 6.16 (1H, s), 6.69 - 6.86 (3H, m), 6.96 (2H, d), 7.20 (1H, t), 7.89 (2H, d), 10.31 (1H, s), 12.08 (1H, s). MS m/z 420 (MH+)

Mean of n=1, FGFR Kinase assay – Elisa, IC_{50} 0.0828 μM.

5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine used as starting material was prepared as follows:-

Acetonitrile (3.36ml, 64.25mmol, 1eq) was added to a slurry of sodium hydride (2.57g dispersion in mineral oil, 64.25mmol, 1eq) in anhydrous 1,4-dioxane (50ml) and the mixture was stirred at room temperature for 20 mins. Methyl 3-(3-methoxyphenyl)propanoate (10.4g, 53.54mmol, 1eq) in 1,4-dioxane (25ml) was added and the reaction was refluxed for 2h. The reaction mixture was cooled and quenched with water. The residue was dissolved in 2M HCl and extracted into ethyl acetate. The organic layer was separated, washed with 2M HCl, water and brine and dried over magnesium sulphate. Evaporation under reduced pressure gave yield to a yellow oil, which was purified by silica column chromatography, eluting with a mixture of 0-50% ethyl acetate in hexanes. Fractions containing the product were combined and evaporated to leave 5-(3-methoxyphenyl)-3-oxo-pentanenitrile (5.37g, 49% yield).

^{1}H NMR (300.132 MHz, CDCl3) δ 2.86 (4H, s), 3.32 (2H, s), 3.73 (3H, s), 6.64 - 6.72 (3H, m), 7.14 (1H, t)

To 5-(3-methoxyphenyl)-3-oxo-pentanenitrile (5.37g, 26.42mmol, 1eq) in ethanol (80ml) was added hydrazine hydrate (1.41ml, 29.06mmol, 1.1eq). The reaction was refluxed for 3.5 h then allowed to cool. The mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine, dried with magnesium sulphate, filtered and evaporated to yield a yellow oil (which solidified on standing). This was acidified and purified by SCX-3 column chromatography. The compound was eluted with 10% ammonia in methanol. After evaporation 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine was obtained (5.48g, 96% yield).

^{1}H NMR (300.132 MHz, DMSO): δ 2.64 - 2.87 (4H, m), 3.73 (3H, s), 4.40 (1H, s), 5.19 (1H, s), 6.71 - 6.82 (3H, m), 7.18 (1H, t), 11.07 (1H, s). MS; m/z 218 (MH+)

Example 12

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Prepared in an analogous way to Example 1 but starting with 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride to give the title compound as a beige solid (34mg, 13% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (3H, s), 2.44 (4H, t), 3.27 - 3.32 (4H, m), 3.75 (6H, s), 5.07 (2H, s), 5.57 (1H, s), 6.44 - 6.45 (1H, m), 6.59 (2H, d), 7.01 (2H, d), 7.85 (2H, d), 10.64 (1H, s), 11.54 (1H, s). MS m/z 452 (MH+)

Mean of n=3, FGFR Kinase assay – Elisa, IC_{50} 0.06μM.

5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as follows:

3-Amino-5-hydroxypyrazole (8g, 80.74mmol) and triphenylphosphine (25.45g, 96.88mmol) were stirred in DCM (110ml) under nitrogen and the mixture was cooled in an ice-bath. Diisopropylazodicarboxylate (19.08ml, 96.88mmol) was added dropwise (temperature <10°C) and the reaction mixture was stirred in the ice-bath for 1h. 3,5-Dimethoxybenzyl alcohol (16.30g, 96.88mol) in DCM (35ml) was added dropwise, the reaction mixture was allowed to warm to room temperature and stirred under nitrogen for 4 days. The mixture was filtered, washed with DCM and the filtrate was extracted with 1M HCl (aq) (3 x 50ml). The combined aqueous extracts were washed with DCM (50ml), resulting in precipitation of the product. The product was collected by filtration, washed with water, DCM and dried under vacuum to afford the title compound as a white solid (358mg, 1.8% yield). A further crop of product was obtained following precipitation from the initial DCM layer on allowing to stand at room temperature. The solid product was collected by filtration, washed with DCM and dried under vacuum to give an off-white solid (1.127g, 5.6% yield).

^{1}H NMR (300.132 MHz, DMSO) δ 3.75 (s, 6H), 5.18 (s, 2H), 5.26 (s, 1H), 6.50 (t, 1H), 6.60 (d, 2H). MS:m/z 250 (MH+)

Example 13

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-methyl-pyridine-3-carboxamide

5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine (0.2 g, 0.73 mmol) was dissolved in toluene (10 ml) and to this was added methyl 6-methylpyridine-3-carboxylate (122 mg, 0.73 mmol) and $AlMe_3$ (0.93 ml, 1.8 mmol). The reaction mixture was stirred overnight. The reaction mixture was diluted with DCM (15 ml) and quenched with damp sodium sulfite (care); the reaction was stirred for 20 mins before being filtered and the solvent removed *in vacuo* to yield a yellow gum. This was dissolved in formic acid (12 ml) and heated at 82°C

overnight. The reaction mixture was evaporated to dryness and the resulting product was passed through a SCX column, eluting initially with methanol followed by 2N ammonia/methanol.After removal of the solvent a yellow solid was obtained which was triturated with hot acetonitrile to afford a white solid. The solid was filtered and dried (117 mg, 48%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.54 (s, 3H), 2.91 (s, 4H), 3.74 (s, 3H), 6.45 (s, 1H), 6.76 (d, 1H), 6.83-6.82 (m, 2H), 7.20 (t, 1H), 7.36 (d, 1H), 8.21 (dd, 1H), 9.01 (s, 1H), 10.81 (s, 1H), 12.21 (s, 1H); MS: m/z 409 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.95 μM.

5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine, used as starting material was prepared as follows:

The crude 5-(3-methoxy-phenyl)-3-oxo-pentanenitrile (10 g, 0.049 mol), *t*-butylhydrazine HCl (7.29 g, 0.059 mol) and TEA (8.20 ml, 0.059 mol) were dissolved in ethanol (300 ml) and heated at reflux for 3 h. The reaction mixture was cooled and solvent removed *in vacuo* to yield a viscous brown oil; this was quenched with water (100 ml), extracted with diethyl ether (3 x 200 ml), dried ($MgSO_4$) and solvent removed *in vacuo* to yield a dark orange oil. This was purified via distillation at 165°C @ 0.40 mbar to afford a clear viscous oil which solidified on standing.

^{1}H NMR (400.132 MHz, CDCl3) δ 1.55 (s, 9H), 2.76-2.71 (m, 2H), 2.85-2.80 (m, 2H), 3.40 (brs, 2H), 3.72 (s, 3H), 5.31 (s, 1H), 6.66 (dd, 1H), 6.71 (s, 1H), 6.76 (d, 1H), 7.11 (t, 1H); MS: m/z 274 (MH+).

5-(3-Methoxy-phenyl)-3-oxo-pentanenitrile, used as starting material was prepared as follows:

LDA (34 ml, 0.068 mol) was added to THF (300 ml) and cooled to –78°C under a nitrogen atmosphere, to this was slowly added acetonitrile (2.8 g, 0.068 mol) in THF (20 ml). The reaction was stirred for 10 mins at –78°C before the rapid addition of methyl 3-(3-methoxyphenyl)propanoate (10 g, 0.052 mol). The reaction was stirred for 30 mins before being allowed to warm up to room temperature. The reaction was quenched with 1.0 N HCl (100 ml), extracted with diethyl ether (2 x 200 ml), dried ($MgSO_4$) and solvent removed *in*

vacuo to yield a yellow gum. This appeared to slowly decompose and was used immediately in the next step.

Example 14

6-Methoxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

Prepared in an analogous manner to Example 13 except using methyl 6-methoxypyridine-3-carboxylate as a starting material (168 mg, 65%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.74 (s, 3H), 3.93 (s, 3H), 6.45 (s, 1H), 6.77-6.75 (m, 1H), 6.83-6.81 (m, 2H), 6.90 (d, 1H), 7.20 (t, 1H), 8.25 (dd, 1H), 8.81 (d, 1H), 10.70 (s, 1H), 12.17 (s, 1H); MS: m/z 353 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.61 μM.

Example 15

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-methylsulfonyl-benzamide

Prepared in an analogous manner to Example 13 except using ethyl 4-methylsulfonylbenzoate as a starting material (82 mg, 28%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.91 (s, 4H), 3.28 (s, 3H), 3.74 (s, 3H), 6.49 (s, 1H), 6.78-6.75 (m, 1H), 6.84-6.81 (m, 2H), 7.20 (t, 1H), 8.03 (d, 2H), 8.20 (d, 2H), 10.96 (s, 1H), 12.23 (s, 1H); MS: m/z 400 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.11 μM.

Example 16

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-methyl-pyrazine-2-carboxamide

Prepared in an analogous manner to Example 13 except using methyl 5-methylpyrazine-2-carboxylateas a starting material (63 mg, 26%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.62 (s, 3H), 2.91 (s, 4H), 3.73 (s, 3H), 6.48 (s, 1H), 6.77-6.75 (m, 1H), 6.85-6.80 (m, 2H), 7.20 (t, 1H), 8.67 (s, 1H), 9.13 (s, 1H), 10.26 (s, 1H), 12.28 (s, 1H); MS: m/z 338 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.75 μM.

Example 17

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(prop-2-ynylamino)pyridine-2-carboxamide

Prepared in an analogous manner Example 13 except using methyl 5-(prop-2-ynylamino)pyridine-2-carboxylate as a starting material (39 mg, 14%).

^{1}H NMR (400.132 MHz, CDCl3) δ 2.28 (t, 1H), 2.96 (s, 4H), 3.77 (s, 3H), 4.00 (s, 2H), 4.56 (s, 1H), 6.47 (s, 1H), 6.76-6.73 (m, 2H), 6.78 (d, 1H), 7.04 (dd, 1H), 7.21-7.17 (m, 1H), 7.96 (d, 1H), 8.09 (d, 1H), 10.14 (s, 1H), NH missing; MS: m/z 376 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.66 μM.

Example 18

6-Ethylamino-*N*-{5-[2-(3-methoxy-phenyl)-ethyl]-2*H*-pyrazol-3-yl}-nicotinamide

Prepared in an analogous manner to Example 13 except using 6-ethylamino-nicotinic acid methyl ester as a starting material (44 mg, 16%).

^{1}H NMR (400.132 MHz, DMSO) δ 1.15 (t, 3H), 2.89 (s, 4H), 3.35-3.30 (m, 2H), 3.74 (s, 3H), 6.46-6.42 (m, 2H), 6.77-6.75 (m, 1H), 6.82-6.81 (m, 2H), 7.06 (s, 1H), 7.20 (t, 1H), 7.93 (d, 1H), 8.65 (s, 1H), 10.28 (s, 1H), 12.06 (s, 1H); MS: m/z 366 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.54 μM.

Example 19

4-Acetamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine (0.2 g, 0.73 mmol) was dissolved in THF/pyridine (5 ml/1ml), to this was added 4-acetamidobenzoyl chloride (190 mg, 0.95 mmol) and the reaction mixture was stirred overnight. The reaction mixture was evaporated to dryness, purified by column chromatography, eluting with 0-5% MeOH in DCM, and evaporated to afford a white foam. The residue was dissolved in formic acid (12 ml) and heated at 82°C overnight. The reaction mixture was evaporated to dryness and the product was purified by a SCX column. Removal of the solvent gave a yellow solid, which was triturated with hot acetonitrile to afford a white solid. The solid was filtered and dried *in vacuo* (16 mg, 6%); MS: m/z 378 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.40 μM.

5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine used as starting material was prepared as indicated in Example 13.

Example 20

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)pyrazine-2-carboxamide

NaHMDS (1M solution in THF, 0.645ml, 0.644mmol, 1.5eq) was added dropwise to a stirred suspension of *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (150mg, 0.429mmol, 1eq) and methyl 5-(4-methylpiperazin-1-yl)pyrazine-2-carboxylate (122mg, 0.515mmol, 1.2eq) in dry THF (2.5ml) under nitrogen. The reaction mixture was stirred at room temperature for 50min, then neutralised with satd aq NH_4Cl and diluted with water (5ml). The aqueous phase was extracted with ethyl acetate (3 x 8ml) and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The residual solid was purified by reverse-phase prep. HPLC using a gradient of 31-51% acetonitrile in water containing 1% ammonium hydroxide to afford the product as a white solid (88mg, 45%).

^1H NMR (399.902 MHz, DMSO) δ 2.24 (s, 3H), 2.41 - 2.46 (m, 4H), 3.72 - 3.78 (m, 4H), 3.75 (s, 6H), 5.08 (s, 2H), 5.84 (s, 1H), 6.44 (t, 1H), 6.59 (d, 2H), 8.33 (s, 1H), 8.72 (s, 1H), 10.81 (s, 1H), 11.35 (s, 1H). MS: m/z 454 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.046 μM.

Methyl 5-(4-methylpiperazin-1-yl)pyrazine-2-carboxylate, used as starting material was prepared as follows:

Methyl 5-chloropyrazine-2-carboxylate (100mg, 0.579mmol, 1eq), 1-methylpiperazine (65μl, 0579mmol, 1eq) and potassium carbonate (161mg, 1.159mmol, 2eq) were heated in DMSO in a microwave reactor at 120°C for 5min. The reaction mixture was poured onto an SCX column (10g), washed with methanol then eluted with 2M ammonia in methanol. The reaction was repeated as above with methyl 5-chloropyrazine-2-carboxylate (150mg), 1-methylpiperazine (98μl) and potassium carbonate (241mg) in DMSO (3ml). The product

fractions from both reactions were combined and evaporated under vacuum to afford the product as a yellow solid (283mg, 83%).

^{1}H NMR (399.902 MHz, DMSO) δ 2.23 (s, 3H), 2.42 (t, 4H), 3.73 (t, 4H), 3.82 (s, 3H), 8.38 (d, 1H), 8.66 (d, 1H). MS: m/z 237 (MH+).

Example 21

4-Benzamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

5-[2-(3-Methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine (0.2 g, 0.73 mmol) was dissolved in toluene (10 ml) and to this was added methyl 4-benzamidobenzoate (200 mg, 0.80 mmol) and $AlMe_3$ (0.93 ml, 1.8 mmol). The reaction was stirred overnight. The reaction was diluted with DCM (15 ml) and quenched with damp sodium sulfite. The reaction mixture was stirred for 20 mins before being filtered and the solvent removed *in vacuo* to yield a yellow gum. This gum was dissolved in formic acid (12 ml) and heated at 82°C overnight. The reaction was evaporated to dryness and the resulting product was passed through a SCX column, eluting initially with methanol followed by 2N ammonia/methanol. After removal of the solvent, a yellow solid was obtained which was triturated with hot acetonitrile to afford a white solid. The solid was filtered and dried (66 mg, 21%); 1H NMR (400.132 MHz, DMSO) δ 2.91 (s, 4H), 3.74 (s, 3H), 6.46 (brs, 1H), 6.77 (d, 1H), 6.83 (s, 2H), 7.20 (t, 1H), 7.64-7.54 (m, 3H), 7.90 (d, 2H), 8.02-7.97 (m, 4H), 10.46 (s, 1H), 10.55 (s, 1H), 12.15 (s, 1H); MS: m/z 441 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 231 μM.

Example 22

6-(2-Methoxyethoxy)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

6-Chloro-N-[5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-yl]pyridine-3-carboxamide (0.15 g, 0.36 mmol) was added to a tube and dissolved in 2-methoxyethanol (15 ml). NaH (51 mg, 1.0 mmol) was added and the reaction was heated at 80°C overnight. The reaction mixture was evaporated to dryness and passed through a SCX column, eluting initially with methanol followed by 2N ammonia/methanol. The eluant was evaporated to dryness. The obtained gum was then dissolved in formic acid and heated at 80°C overnight. The reaction

was evaporated to dryness and passed through a SCX column, eluting initially with methanol followed by 2N ammonia/methanol. The eluant was evaporated to dryness and the resulting gum was purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The product was obtained as solid (19 mg, 13%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.31 (s, 3H), 3.69 - 3.67 (m, 2H), 3.74 (s, 3H), 4.47 - 4.44 (m, 2H), 6.45 (s, 1H), 6.76 (d, 1H), 6.82 (s, 2H), 6.90 (d, 1H), 7.20 (t, 1H), 8.25 (d, 1H), 8.78 (s, 1H), 10.69 (s, 1H), 12.17 (s, 1H); MH+ 397.
Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.72 μM.

6-Chloro-N-[5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-yl]pyridine-3-carboxamide, used as starting material was prepared as per Example 21 using methyl 6-chloropyridine-3-carboxylate (1.02 g, 33%); ^{1}H NMR (400.132 MHz, CDCl3) δ 1.65 (s, 9H), 2.98 - 2.88 (m, 4H), 3.79 (s, 3H), 6.20 (brs, 1H), 6.73 (dd, 1H), 6.79 (s, 1H), 6.83 (d, 1H), 7.19 (t, 1H), 7.52 - 7.47 (m, 2H), 8.12 (brs, 1H), 8.83 (brs, 1H); MS: m/z 413 (MH+).

Example 23

4-Cyano-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

tert-Butyl 5-[(4-cyanobenzoyl)amino]-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate was added to acetonitrile (5 ml) and 6.0 N HCl in propan-2-ol (10 ml). The reaction mixture was stirred overnight to afford a white solid, which was filtered and dissolved in methanol/water. The solution was then passed through a SCX column. On removal of the solvent *in vacuo* a white solid was obtained (0.29 g, 67%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.91 (s, 4H), 3.74 (s, 3H), 6.48 (s, 1H), 6.76 (d, 1H), 6.83 (s, 2H), 7.20 (t, 1H), 7.97 (d, 2H), 8.12 (d, 2H), 10.95 (s, 1H), 12.24 (s, 1H); MH+ 347.
Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 28.6 μM.

tert-Butyl 5-[(4-cyanobenzoyl)amino]-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as follows:
tert-Butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate (0.4 g, 1.26 mmol) was dissolved in DCM/pyridine (6 ml, 5:1) and to this was added 4-cyanobenzoyl chloride (0.27 g, 0.95 mmol). The reaction mixture was stirred overnight. The reaction mixture was

evaporated to dryness to afford a black gum which was used in the next step without any further purification.

tert-butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as follows:

5-[2-(3-Methoxy-phenyl)-ethyl]-2*H*-pyrazol-3-ylamine (5 g, 23 mmol) and Boc anhydride (6.5 g, 30 mmol) were dissolved in DCM (200 ml) and stirred overnight at room temperature. The reaction mixture was evaporated to dryness and dissolved in diethyl ether. To this was added iso-hexane and the solvent was slowly removed *in vacuo* until a solid was visible. The solution was scratched and sonicated to afford *tert*-butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate (6.3 g, 86%) as a white solid; ^{1}H NMR (400.132 MHz, CDCl3) δ 7.20 (t, 1H), 6.82 (d, 1H), 6.79 (s, 1H), 6.74 (d, 1H), 5.22 (s, 1H), 3.79 (s, 3H), 2.93 - 2.88 (m, 2H), 2.86 - 2.81 (m, 2H), 1.65 (s, 9H); MH+ 318.

Example 24

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzene-1,4-dicarboxamide

4-Cyano-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide (Example 23) (0.2 g, 0.58 mmol) and NaOH (69 mg, 1.73 mmol) were added to a solution of ethanol/water (20 ml, 3:1) and heated at 80°C until complete consumption of starting material was observed. Care was required as the amide further hydrolysed to the carboxylic acid. The reaction was extracted with DCM (3 x 50 ml), dried and the solvent was removed *in vacuo* to yield a white solid. This was triturated with DCM to afford a white solid (20 mg, 10%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.75 (s, 3H), 6.42 (s, 1H), 6.82 - 6.75 (m, 3H), 7.20 (t, 1H), 7.46 (s, 1H), 7.95 (d, 2H), 8.16 - 8.03 (m, 3H), 10.82 (s, 1H), 12.18 (s, 1H); MH+ 366.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.43 μM.

Example 25

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-pyrazol-1-yl-benzamide

5-[2-(3-Methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine (0.2 g, 0.73 mmol) was dissolved in toluene (10 ml) and to this was added methyl 4-pyrazol-1-ylbenzoate (177 mg, 0.88 mmol) and $AlMe_3$ (0.93 ml, 1.8 mmol). The reaction mixture was stirred overnight. The reaction

mixture was diluted with DCM (15 ml), quenched with damp sodium sulfite and further stirred for 20 mins before being filtered. The solvent was removed *in vacuo* to yield a yellow gum. This gum was dissolved in formic acid (12 ml) and heated at 82°C overnight. The reaction mixture was evaporated to dryness and the resulting product was passed through a SCX column, eluting initially with methanol followed by 2N ammonia/methanol. After solvent removal, a yellow solid was obtained which was triturated with hot acetonitrile to afford a white solid. The solid was filtered and dried (155 mg, 55%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.92 (s, 4H), 3.74 (s, 3H), 6.48 (s, 1H), 6.60 (s, 1H), 6.77 (d, 1H), 6.84 - 6.82 (m, 2H), 7.20 (t, 1H), 7.81 (s, 1H), 7.96 (d, 2H), 8.14 (d, 2H), 8.63 (s, 1H), 10.69 (s, 1H), 12.18 (s, 1H); MS: m/z 388 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.94 μM.

Example 26

6-Anilino-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

Prepared using an analogous method to example 25, but starting with methyl 6-anilinopyridine-3-carboxylate (200mg, 0.88mmol) to give the title compound (106 mg, 35%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.74 (s, 3H), 6.44 (s, 1H), 6.76 (d, 1H), 6.87 - 6.82 (m, 3H), 6.97 (t, 1H), 7.20 (t, 1H), 7.31 (t, 2H), 7.70 (d, 2H), 8.11 (d, 1H), 8.79 (s, 1H), 9.41 (s, 1H), 10.51 (s, 1H), 12.13 (s, 1H); MH+414

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 64 μM.

Example 27

4-Methanesulfonamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-methanesulfonamidobenzoate (200mg, 0.88mmol) to give the title compound (125 mg, 41%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.06 (s, 3H), 3.74 (s, 3H), 6.42 (s, 1H), 6.76 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 7.24 (d, 2H), 7.97 (d, 2H), 10.54 (s, 1H), 12.09 (vbrs, 1H); MH+ 416

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.26 μM.

Example 28

4-(Hydroxymethyl)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-(hydroxymethyl)benzoate (146mg, 0.88mmol) to give the title compound (136 mg, 53%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.74 (s, 3H), 4.57 (d, 2H), 5.28 (t, 1H), 6.45 (s, 1H), 6.76 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 7.41 (d, 2H), 7.95 (d, 2H), 10.58 (s, 1H), 12.14 (s, 1H); MH+ 352.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.074 μM.

Example 29

5-Formamido-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-2-carboxamide

Prepared using an analogous method to example 25, but starting with methyl 5-[(2-methylpropan-2-yl)oxycarbonylamino]pyridine-2-carboxylate (222mg, 0.88mmol) to give the title compound (72 mg, 27%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.91 (s, 4H), 3.73 (s, 3H), 6.47 (s, 1H), 6.76 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 8.12 (d, 1H), 8.26 (dd, 1H), 8.44 (s, 1H), 8.87 (s, 1H), 10.13 (vbrs, 1H), 10.74 (s, 1H), 12.23 (s, 1H); MH+ 366

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.87 μM.

Example 30

4-(Dimethylsulfamoyl)-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-(dimethylsulfamoyl)benzoate (214mg, 0.88mmol) to give the title compound (126 mg, 40%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.66 (s, 6H), 2.91 (s, 4H), 3.74 (s, 3H), 6.49 (s, 1H), 6.77 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 7.85 (d, 2H), 8.20 (d, 2H), 10.93 (s, 1H), 12.23 (s, 1H); MH+ 429.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.80 μM.

Example 31

6-Hydroxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

Prepared using an analogous method to example 25, but starting with methyl 6-hydroxypyridine-3-carboxylate (147mg, 0.88mmol) to give the title compound (28 mg, 11%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.89 (s, 4H), 3.73 (s, 3H), 6.37 - 6.34 (m, 2H), 6.76 (d, 1H), 6.82 - 6.80 (m, 2H), 7.19 (t, 1H), 7.97 (dd, 1H), 8.18 (d, 1H), 10.44 (s, 1H), 12.03 (vbrs, 1H); MH+ 339

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 1.05 μM.

Example 32

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-morpholin-4-yl-pyridine-3-carboxamide

Prepared using an analogous method to example 25, but starting with methyl 6-morpholin-4-ylpyridine-3-carboxylate (195mg, 0.88mmol) to give the title compound (140 mg, 47%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.59 - 3.57 (m, 4H), 3.71 - 3.69 (m, 4H), 3.74 (s, 3H), 6.44 (s, 1H), 6.76 (d, 1H), 6.82 - 6.81 (m, 2H), 6.86 (d, 1H), 7.20 (t, 1H), 8.13 (d, 1H), 8.76 (s, 1H), 10.45 (s, 1H), 12.11 (s, 1H); MH+ 408

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.027 μM.

Methyl 6-morpholin-4-ylpyridine-3-carboxylate, used as starting material was prepared as follows:

6-Morpholin-4-ylpyridine-3-carboxylic acid (2.56 g, 13.6 mmol) and potassium carbonate (2.8 g, 20.4 mmol) were added to DMF (40 ml) and to this was added MeI (0.97 ml, 15 mmol). The reaction mixture was heated at 50°C for 3 h. The solvent was removed *in vacuo* to yield a dark solid, which was quenched with 2.0N NaOH (100 ml), extracted with DCM (3 X 100 ml), dried ($MgSO_4$) and solvent removed *in vacuo* to yield a brown solid. This solid was dissolved in hot acetonitrile and allowed to cool to afford a white solid, which was filtered and the process repeated on the mother liquor to obtain the title compound (1.8 g, 60%); 1H NMR (400.132 MHz, CDCl3) 3.65 (t, 4H), 3.81 (t, 4H), 3.87 (s, 3H), 6.53 (d, 1H), 8.04 (dd, 1H), 8.80 (d, 1H); MH+ 223.

Example 33

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1,3-oxazol-5-yl)benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-(1,3-oxazol-5-yl)benzoate (177mg, 0.88mmol) to give the title compound (28 mg, 10%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.91 (s, 4H), 3.74 (s, 3H), 6.48 (s, 1H), 6.77 (d, 1H), 6.82 (m, 2H), 7.20 (t, 1H), 7.87 - 7.83 (m, 3H), 8.10 (d, 2H), 8.51 (s, 1H), 10.73 (s, 1H), 12.18 (s, 1H); MH+ 389.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 1.2 μM.

Example 34

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(tetrazol-1-yl)benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-(tetrazol-1-yl)benzoate (179mg, 0.88mmol) to give the title compound (16 mg, 6%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.92 (s, 4H), 3.74 (s, 3H), 6.50 (s, 1H), 6.77 (d, 1H), 6.84 - 6.82 (m, 2H), 7.21 (t, 1H), 8.06 (d, 2H), 8.25 (d, 2H), 10.19 (s, 1H), 10.89 (s, 1H), 12.22 (s, 1H); MH+ 390.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 1 μM.

Example 35

Prop-2-enyl N-[5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridin-2-yl]carbamate

Prepared using an analogous method to example 25, but starting with methyl 6-(prop-2-enoxycarbonylamino)pyridine-3-carboxylate (208mg, 0.88mmol) to give the title compound (38 mg, 12%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.90 (s, 4H), 3.74 (s, 3H), 4.66 (d, 2H), 5.25 (d, 1H), 5.40 (d, 1H), 6.02 - 5.95 (m, 1H), 6.46 (s, 1H), 6.76 (d, 1H), 6.84 - 6.80 (m, 2H), 7.20 (t, 1H), 7.91 (d, 1H), 8.32 (d, 1H), 8.87 (s, 1H), 10.56 (s, 1H), 10.74 (s, 1H), 12.17 (s, 1H); MH+ 422.

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 76 μM.

Methyl 6-(prop-2-enoxycarbonylamino)pyridine-3-carboxylate, used as starting material was prepared in an analogous manner to the synthesis of methyl 6-morpholin-4-ylpyridine-3-carboxylate in Example 32, but starting with 6-(prop-2-enoxycarbonylamino)pyridine-3-carboxylic acid carboxylate (880mg, 3.96mmol) to give the title compound (0.35 g, 37%); 1H

NMR (400.132 MHz, CDCl3) 3.93 (s, 3H), 4.75 (dt, 2H), 5.32 (dq, 1H), 5.41 (dq, 1H), 6.09-5.99 (m, 1H), 8.07 (d, 1H), 8.30 (dd, 1H), 8.97 (d, 1H), 9.45 (brs, 1H); MH+ 237.

Example 36

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1,2,4-triazol-1-yl)benzamide

Prepared using an analogous method to example 25, but starting with methyl 4-(1,2,4-triazol-1-yl)benzoate (177mg, 0.88mmol) to give the title compound (83 mg, 29%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.92 (s, 4H), 3.74 (s, 3H), 6.48 (s, 1H), 6.77 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 8.00 (d, 2H), 8.19 (d, 2H), 8.29 (s, 1H), 9.42 (s, 1H), 10.79 (s, 1H), 12.20 (s, 1H); MH+ 389.

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.66 μM.

Example 37

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-pyrazol-1-yl-pyridine-3-carboxamide

Prepared using an analogous method to example 25, but starting with methyl 6-pyrazol-1-ylpyridine-3-carboxylate (177mg, 0.88mmol) to give the title compound (151 mg, 54%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.92 (s, 4H), 3.74 (s, 3H), 6.49 (s, 1H), 6.63 (dd, 1H), 6.77 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 7.90 (s, 1H), 8.01 (d, 1H), 8.52 (d, 1H), 8.70 (s, 1H), 9.03 (s, 1H), 10.95 (s, 1H), 12.23 (s, 1H); MH+ 389.

Mean of n=3, FGFR Kinase assay – Caliper, IC_{50} 69 μM.

Methyl 6-pyrazol-1-ylpyridine-3-carboxylate, used as starting material was prepared as follows:

Pyrazole (2.4 g, 35.4 mmol) was added to DMA (100 ml) and to this was slowly added NaH (1.85 g, 38.6 mmol). The reaction mixture was stirred for 10 mins under a nitrogen atmosphere. To the resulting anion was added methyl 6-chloropyridine-3-carboxylate (5.5 g, 32.2 mmol) and the reaction was heated at 95°C overnight. The reaction mixture was evaporated to dryness, quenched with 2.0 N NaOH (100 ml), extracted with DCM (3 x 100 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown solid. This solid was purified via silica column chromatography, eluting with 0-40% diethyl ether in iso-hexane. A

white solid was obtained, which was dissolved in hot iso-hexane. On cooling a white solid was obtained which was filtered and dried (2.6 g, 40%); ^{1}H NMR (400.132 MHz, CDCl3) δ 3.96 (s, 3H), 6.50 (s, 1H), 7.77 (s, 1H), 8.05 (d, 1H), 8.40 (dd, 1H), 8.62 (d, 1H), 9.02 (d, 1H); MH+ 203.

Example 38

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluoro-benzamide

Oxalyl chloride (2M in DCM, 1.40ml, 2.75mmol, 1.1eq) was added dropwise to a mixture of 4-fluorobenzoic acid (350mg, 2.50mmol, 1eq) in dichloromethane (15ml) at 0°C containing a few drops of DMF (10ul, 0.12mmol, 0.05eq) and DIPEA (937µl, 5.25mmol, 2.1eq). After stirring for 60 mins at 0°C a solution of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (742mg, 3mmol, 1.2eq) in DCM (10ml) was added dropwise over 15mins. The mixture was maintained at 0°C for a further 2 h, then gradually allowed to warm to room temperature overnight. The mixture was diluted with DCM (50 ml) and washed with aqueous $NaHCO_3$ solution (50 ml). The aqueous layer was extracted with DCM (50 ml). The combined organic layers were collected and concentrated. The crude product was purified by reverse-phase prep HPLC using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The desired fractions were evaporated to afford the title compound as a beige solid. (31.5mg, 3% yield)

^{1}H NMR (300.132 MHz, DMSO) δ 2.87 (4H, s),3.72 (6H, s),6.32 (1H, t),6.42 (2H, d),6.46 (1H, s),7.31 (2H, t),8.06 (2H, m),10.69 (1H, s),12.16 (1H, s). MS: m/z 370 (MH+) Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.165 µM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as shown in the starting material preparation in Example 2.

Example 39

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-3-methoxy-benzamide

1-Chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (89 µl, 0.67mmol, 1.05eq) was added dropwise to 3-methoxybenzoic acid (97mg, 0.63mmol, 1eq) in DCM (1.5ml) at ambient temperature. After stirring at ambient temperature for 1.5 h, a solution of *tert*-butyl 5-amino-3-[2-(3,5-

dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (199mg, 0.57mmol, 0.9eq) and pyridine (142μL, 1.74mmol, 2.75 eq) in DCM (2ml) was added to the reaction mixture and stirring was continued at ambient temperature for a further 3 h. A solution of TFA (386μL, 5.2mmol, 8.25eq) in DCM (3.5ml) was then added and stirring was continued at ambient temperature for 18 h. The reaction mixture was concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless solid (129mg, 59% yield). ^{1}H NMR (399.902 MHz, DMSO) δ 2.89 (4H, s), 3.73 (6H, s), 3.84 (3H, s), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.48 (1H, s), 7.12-7.10 (1H, m), 7.42-7.37 (1H, m), 7.59-7.56 (2H, m), 10.65 (1H, br.s), 12.16 (1H, br.s). MS: m/z 382 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.37 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 40

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-3-morpholin-4-yl-benzamide

Prepared in an analogous way to Example 39, starting with 3-morpholin-4-ylbenzoic acid (130mg, 0.63mmol) to give the title compound as a solid (105mg, 42% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.89 (4H, s), 3.21-3.19 (4H, m), 3.73 (6H, s), 3.79-3.76 (4H, m), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.48 (1H, s), 7.12 (1H, d), 7.35-7.31 (1H, m), 7.43 (1H, d), 7.57 (1H, s), 10.62 (1H, br.s), 12.15 (1H, br.s). MS: m/z 437 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.71 μM.

Example 41

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-2-methoxy-benzamide

Prepared in an analogous way to Example 39, starting with 2-methoxybenzoic acid (95.8mg, 0.63mmol) to give the title compound as a solid (100mg, 46% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.89 (4H, s), 3.73 (6H, s), 3.97 (3H, s), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.49

(1H, s), 7.12-7.07 (1H, m), 7.21 (1H, d), 7.56-7.51 (1H, m), 7.85-7.82 (1H, m), 10.16 (1H, br.s), 12.14 (1H, br.s). MS: m/z 382 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 2.61 μM.

Example 42

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-ethoxyethoxy)benzamide

Prepared in an analogous way to Example 39, starting with 4-(2-ethoxyethoxy)benzoic acid (132mg, 0.63mmol) to give the title compound as a solid (126mg, 50% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 1.15 (3H, t), 2.88 (4H, s), 3.52 (2H, q), 3.73 (8H, s), 4.19-4.16 (1H, m), 6.34-6.32 (1H, m), 6.43 (2H, d), 6.46 (1H, s), 7.02 (2H, d), 7.98 (2H, d), 10.47 (1H, br.s), 12.11 (1H, br.s). MS: m/z 440 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.075μM.

Example 43

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(1-piperidyl)benzamide

Prepared in an analogous way to Example 39, starting with 4-(1-piperidyl)benzoic acid (129 mg, 0.63mmol) to give the title compound as a solid (97.5mg, 39% yield);

^{1}H NMR (399.902 MHz, DMSO) δ 1.60 (6H, s), 2.88 (4H, s), 3.33-3.31 (6H, m), 3.73 (1H, s), 6.33-6.32 (2H, m), 6.42 (1H, d), 6.45 (2H, s), 6.94 (2H, d), 10.26 (1H, br.s), 12.07 (1H, br.s). MS: m/z 435 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.438 μM.

Example 44

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-piperidylmethoxy)benzamide

Prepared in an analogous way to Example 39, starting with 4-[[1-[(2-methylpropan-2-yl)oxycarbonyl]-4-piperidyl]methoxy]benzoic acid (211mg, 0.63mmol) to give the title compound as a solid (40mg, 15% yield); ^{1}H NMR (399.902 MHz, DMSO) δ1.72-1.67 (2H, m), 1.87-1.79 (2H, m), 2.48-2.45 (1H, m), 2.88 (4H, s), 2.98-2.94 (2H, m), 3.73 (6H, s), 3.88 (2H, d), 6.34 (1H, s), 6.46-6.42 (3H, m), 7.00 (2H, d), 7.97 (2H, d), 10.48 (1H, br.s), 12.14 (1H, br.s). MS: m/z 465 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.025 μM.

Example 45

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-piperazin-1-yl-benzamide

Prepared in an analogous way to Example 39, starting with 4-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]benzoic acid (193mg, 0.63mmol) to give the title compound as a solid (100mg, 40% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.84-2.82 (4H, m), 2.88 (4H, s), 3.21-3.15 (4H, m), 3.73 (6H, s), 6.33 (1H, s), 6.46-6.42 (3H, m), 6.94 (2H, d), 7.89 (2H, d), 10.30 (1H, br.s), 12.09 (1H, br.s). MS: m/z 436 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.026 μM.

Example 46

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-6-piperazin-1-yl-pyridine-3-carboxamide

Prepared in an analogous way to Example 39, starting with 6-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]pyridine-3-carboxylic acid (193mg, 0.63mmol) to give the title compound as a solid (96mg, 39% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.79-2.76 (4H, m), 2.88 (4H, s), 3.56-3.53 (4H, m), 3.73 (6H, s), 6.34-6.32 (1H, m), 6.45-6.42 (3H, m), 6.82 (1H, d), 8.10-8.07 (1H, m), 8.73 (1H, d), 10.43 (1H, br.s), 12.12 (1H, br.s). MS: m/z 437 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.040 μM.

Example 47

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(dimethylaminomethyl)benzamide

Oxalyl chloride (61 μl, 0.69mmol, 1.1eq) was added dropwise to 4-(dimethylaminomethyl)benzoic acid (113mg, 0.63mmol, 1eq) in DCM (2.5ml) containing 1 drop of DMF. After stirring at ambient temperature for 1.5 h, a solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (196mg, 0.56mmol, 0.9eq) and pyridine (137μL, 1.69mmol, 2.70 eq) in DCM (2ml) was added to the reaction mixture and stirring was continued at ambient temperature for a further 2 h. A solution of TFA (384μL, 5.16mmol, 8.25eq) in DCM (3.5ml) was then added and stirring was continued at

ambient temperature for 18 h. The reaction mixture was concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless solid (65mg, 25% yield).; ^{1}H NMR (399.902 MHz, DMSO) δ 2.09 (6H, s), 2.81 (4H, s), 3.38 (2H, s), 3.65 (6H, s), 6.26-6.25 (1H, m), 6.35 (2H, d), 6.40 (1H, s), 7.31 (2H, d), 7.87 (2H, d), 10.51 (1H, br.s), 12.07 (1H, br.s). MS: m/z 409 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.019 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

1H NMR (399.902 MHz, DMSO) δ1.56 (9H, s), 2.68-2.63 (2H, m), 2.80-2.75 (2H, m), 3.73 (6H, s), 5.22 (1H, s), 6.23 (2H, br.s), 6.32-6.31 (1H, m), 6.44 (2H, d). MS: m/z 370 ([M+Na]+).

Example 48

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-hydroxyethoxy)benzamide

A solution of NaHMDS in THF (1 M, 1.15ml, 1.15mmol, 2eq) was added dropwise at ambient temperature to a mixture of *tert*-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (200mg, 0.58mmol, 1eq) and methyl 4-(2-hydroxyethoxy)benzoate (136mg, 0.69mmol, 1.2eq) in THF (1ml). The reaction mixture was stirred at ambient temperature for 1 h. It was then concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a colourless solid (29mg, 12% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.89 (4H, s), 3.77-3.72 (8H, m), 4.07 (2H, t), 4.88 (1H, t), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.46 (1H, s), 7.01 (2H, d), 7.98 (2H, d), 10.46 (1H, br.s), 12.12 (1H, br.s). MS: m/z 412 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.039 μM.

tert-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 49

4-(2-Aminopropyl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

A solution of NaHMDS in THF (1 M, 0.86ml, 0.86mmol, 1.5eq) was added dropwise at ambient temperature to a mixture of *tert*-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (200mg, 0.58mmol, 1eq) and methyl 4-(2-aminopropyl)benzoate (133mg, 0.69mmol, 1.2eq) in THF (1ml). The reaction mixture was stirred at ambient temperature for 2 h. It was then concentrated and the crude product was purified by reverse-phase prep. HPLC (basic) using a gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a pale yellow gum (10 mg, 4% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 0.89 (3H, d), 2.53-2.47 (2H, m), 2.80 (4H, s), 3.01-2.93 (1H, m), 3.65 (6H, s), 6.25-6.24 (1H, m), 6.34 (2H, d), 6.40 (1H, s), 7.21 (2H, d), 7.84 (2H, d), 10.47 (1H, br.s), 12.06 (1H, br.s). MS: m/z 409 (MH+)

Cell FGFR1, IC_{50} 1.47μM.

tert-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 50

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3,3-dimethyl-1-piperidyl)methyl]benzamide

Prepared in an analogous way to Example 49, starting with methyl 4-[(3,3-dimethyl-1-piperidyl)methyl]benzoate (180mg, 0.69mmol) to give the title compound as a colourless solid (44mg, 16% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 0.92 (3H, s), 1.23-1.20 (2H, m), 1.59-1.52 (2H, m), 2.01-1.99 (2H, m), 2.35-2.29 (2H, m), 2.89 (4H, s), 3.48 (2H, s), 3.73 (6H, s), 6.34-6.32 (1H, m), 6.43 (2H, d), 6.48 (1H, s), 7.40 (2H, d), 7.94 (2H, d), 10.57 (1H, br.s), 12.14 (1H, br.s). MS: m/z 477 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.001 μM.

Methyl 4-[(3,3-dimethyl-1-piperidyl)methyl]benzoate, used as starting material was prepared as follows:

3,3-Dimethylpiperidine (170mg, 1.5mmol, 1.5eq) was added in one portion to a mixture of methyl 4-(bromomethyl)benzoate (230mg, 1mmol, 1eq) and MP-carbonate (2.74mmol/g, 1.46g, 4mmol, 4eq) in MeCN (5ml). The reaction mixture was stirred at ambient temperature for 18 h. Polymer-supported isocyanate (1 mmol/g, 1g, 1mmol, 1eq) was added in one portion and stirring continued for 4 h. The reaction mixture was filtered, the resins washed with MeCN and the combined filtrate was concentrated to afford a clear liquid (216 mg, 83% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 0.91 (6H, s), 1.22-1.19 (2H, m), 1.58-1.52 (2H, m), 1.99 (2H, s), 2.33-2.28 (2H, m), 3.49 (2H, s), 3.85 (3H, s), 7.46 (2H, d), 7.92 (2H, d). MS: m/z 262 (MH+)

Example 51

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[4-(2-hydroxyethyl)piperazin-1-yl]benzamide

Prepared in an analogous way to Example 49, starting with methyl 4-[4-(2-hydroxyethyl)piperazin-1-yl]benzoate (182mg, 0.69mmol) to give the title compound as a colourless solid (11mg, 4% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.45 (2H, t), 2.58-2.55 (4H, m), 2.88 (4H, s), 3.29-3.26 (4H, m), 3.58-3.53 (2H, m), 3.73 (6H, s), 4.42 (1H, t), 6.34-6.32 (1H, m), 6.42 (2H, d), 6.45 (1H, s), 6.96 (2H, d), 7.90 (2H, d), 10.30 (1H, br.s), 12.08 (1H, br.s). MS: m/z 480 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.081 μM.

Methyl 4-[4-(2-hydroxyethyl)piperazin-1-yl]benzoate, used as starting material was prepared as follows:

Trimethylsilyldiazomethane solution (2M in hexanes, 1.2ml, 2.4mmol, 1.2eq) was added dropwise to 4-(4-[2-hydroxyethyl]piperazin-1-yl)benzoic acid (501mg, 2mmol, 1eq) in toluene (14ml) and methanol (4ml) at ambient temperature. The reaction mixture was allowed to stir for 5 h, the solvent removed under reduced pressure and the residue dried under high vacuum to afford methyl 4-(2-bromoethoxy)benzoate as a cream solid (342mg, 65% yield). MS: m/z 265 (MH+)

Example 52

4-[(7-Cyano-3,4-dihydro-1H-isoquinolin-2-yl)methyl]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-[(7-cyano-3,4-dihydro-1H-isoquinolin-2-yl)methyl]benzoate (211mg, 0.69mmol) to give the title compound as a pale yellow gum (45mg, 15% yield);^{1}H NMR (399.902 MHz, DMSO) δ 2.67-2.64 (2H, m), 2.81 (4H, s), 2.86-2.83 (2H, m), 3.54 (2H, s), 3.67-3.64 (8H, m), 6.26-6.24 (1H, m), 6.35 (2H, d), 6.41 (1H, s), 7.26 (1H, d), 7.39 (2H, d), 7.51-7.47 (2H, m), 7.91 (2H, d), 10.53 (1H, br.s), 12.07 (1H, br.s). MS: m/z 522 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.486 μM.

Methyl 4-[(7-cyano-3,4-dihydro-1H-isoquinolin-2-yl)methyl]benzoate, used as starting material was prepared as follows:

1,2,3,4-tetrahydroisoquinoline-7-carbonitrile hydrochloride (292mg, 1.5mmol, 1.5eq) was added in one portion to a mixture of methyl 4-(bromomethyl)benzoate (230mg, 1mmol, 1eq) and MP-carbonate (2.74mmol/g, 1.46g, 4mmol, 4eq) in MeCN (5ml). The reaction mixture was stirred at ambient temperature for 18 h. Polymer-supported isocyanate (1 mmol/g, 1g, 1mmol, 1eq) was added in one portion and stirring continued for 4 h. The reaction mixture was filtered, the resins washed with MeCN and the combined filtrate was concentrated to afford a pale yellow oil which solidified on standing overnight (292mg, 95% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.70–2.63 (2H, m), 2.89–2.82 (2H, m), 3.53 (2H, s), 3.68 (2H, s), 3.78 (3H, s), 7.25 (1H, d), 7.51-7.38 (4H, m), 7.89-7.86 (2H, m). MS: m/z 307 (MH+)

Example 53

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(3-fluoro-1-piperidyl)methyl]benzamide

A solution of NaHMDS in THF (1 M, 0.86ml, 0.86mmol, 1.5eq) was added dropwise at ambient temperature to a mixture of *tert*-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (200mg, 0.58mmol, 1eq) and methyl 4-[(3-fluoro-1-piperidyl)methyl]benzoate (174mg, 0.69mmol, 1.2eq) in THF (1ml). The reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was then concentrated and the crude product was purified by reverse-phase prep. HPLC (acidic) using a

gradient of acetonitrile in water containing 0.1% TFA. The clean fractions were taken and evaporated. The residue was dissolved in 3:1 DCM:MeCN mixture (4ml) and MP-carbonate (2.74 mmol/g, 1 g, 2.74 mmol) was added. The mixture was stirred for 4 h, filtered and the filtrate evaporated to afford the title compound as a pale yellow gum (43mg, 16% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 1.46-1.34 (2H, m), 1.82-1.61 (2H, m), 2.36-2.28 (2H, m), 2.66-2.56 (2H, m), 2.81 (4H, s), 3.50 (2H, s), 3.65 (6H, s), 4.66-4.47 (1H, m), 6.26-6.24 (1H, m), 6.35 (2H, d), 6.40 (1H, s), 7.32 (2H, d), 7.88 (2H, d), 10.51 (1H, br.s), 12.07 (1H, br.s). MS: m/z 467 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.090 μM.

Methyl 4-[(3-fluoro-1-piperidyl)methyl]benzoate, used as starting material was prepared as follows:

3-Fluoropiperidine hydrochloride (210mg, 1.5mmol, 1.5eq) was added in one portion to a mixture of methyl 4-(bromomethyl)benzoate (230mg, 1mmol, 1eq) and MP-carbonate (2.74mmol/g, 1.46g, 4mmol, 4eq) in MeCN (5ml). The reaction mixture was stirred at ambient temperature for 18 h. Polymer-supported isocyanate (1 mmol/g, 1g, 1mmol, 1eq) was added in one portion and stirring continued for 4 h. The reaction mixture was filtered, the resins washed with MeCN and the combined filtrate was concentrated to afford a clear oil, 217mg, 86% yield.

^{1}H NMR (399.902 MHz, DMSO) δ 1.59-1.42 (2H, m), 1.90-1.67 (2H, m), 2.42-2.36 (2H, m), 2.73-2.63 (2H, m), 3.59 (2H, s), 3.86 (3H, s), 4.73-4.56 (1H, m), 7.46 (2H, d), 7.93 (2H, d). MS: m/z 252 (MH+)

tert-butyl-5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 54

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-morpholin-4-ylethoxy)benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-(2-morpholin-4-ylethoxy)benzoate (183mg, 0.69mmol) to give the title compound as a pale yellow gum (21mg, 7.5% yield); ^{1}H NMR (399.902 MHz, CDCl3) δ 2.59-2.57 (4H, m), 2.81 (2H, t), 2.99-

2.90 (4H, m), 3.75-3.72 (4H, m), 3.77 (6H, s), 4.14 (2H, t), 6.36-6.32 (4H, m), 6.67 (1H, br.s), 6.96 (2H, d), 7.83 (2H, d), 8.53 (1H, br.s). MS: m/z 481 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.096 μM.

Methyl 4-(2-morpholin-4-ylethoxy)benzoate, used as starting material was prepared as follows:

MP-Carbonate (2.74mmol/g, 529mg, 1.45mmol, 1.5eq) was added to methyl 4-(2-bromoethoxy)benzoate (250mg, 0.96mmol, 1eq), morpholine (93μl, 1.06mmol, 1.1eq), sodium iodide (150mg, 1mmol, 1.05eq) and MeCN (5ml) were charged to a microwave reactor vessel and the reaction mixture heated to 120 °C in a microwave reactor for 10 minutes. The reaction mixture was transferred to a SCX-2 cartridge, eluted with MeOH followed by 3.5 N ammonia in MeOH solution. The latter fractions were combined and evaporated to afford a clear oil which solidified on standing to a cream solid (146mg, 57% yield). ^{1}H NMR (400.132 MHz, CDCl3) δ 2.59-2.57 (4H, m), 2.82 (2H, t), 3.74-3.72 (4H, m), 3.88 (3H, s), 4.16 (2H, t), 6.93-6.91 (2H, m), 7.99-7.97 (2H, m). MS: m/z 266 (MH+)

Example 55

4-[2-(4,4-Difluoro-1-piperidyl)ethoxy]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-[2-(4,4-difluoro-1-piperidyl)ethoxy]benzoate (104mg, 0.35mmol) to give the title compound as a clear gum (5mg, 1.7% yield); ^{1}H NMR (399.902 MHz, CDCl3) δ 2.06-1.96 (4H, m), 2.70-2.67 (4H, m), 2.88-2.85 (2H, m), 2.97-2.92 (4H, m), 3.77-3.76 (8H, m), 4.12 (2H, t), 6.33-6.32 (2H, m), 6.35-6.35 (2H, m), 6.65 (1H, br.s), 6.95 (2H, d), 7.83 (2H, d), 8.59 (1H, s). MS: m/z 515 (MH+)

Cell FGFR1, IC_{50} 0.46μM.

Methyl 4-[2-(4,4-difluoro-1-piperidyl)ethoxy]benzoate, used as starting material was prepared as follows:

MP-Carbonate (2.74mmol/g, 1.234g, 3.38mmol, 2.5eq) was added to methyl 4-(2-bromoethoxy)benzoate (350mg, 1.35mmol, 1eq), 4,4-difluoropiperidine hydrochloride (235mg, 1.49mmol, 1.1eq), sodium iodide (212mg, 1.42mmol, 1.05eq) and MeCN (6ml) were

charged to a microwave reactor vessel and the reaction mixture heated to 120 °C in a microwave reactor for 10 minutes. The reaction mixture was transferred to a SCX-2 cartridge, eluted with MeOH followed by 3.5 N ammonia in MeOH solution. The latter fractions were combined and evaporated to afford a colourless solid (104mg, 35% yield). ^{1}H NMR (400.132 MHz, CDCl3) δ 2.08-1.98 (4H, m), 2.74-2.71 (4H, m), 2.90 (2H, t), 3.89 (3H, s), 4.16 (2H, t), 6.93-6.91 (2H, m), 8.00-7.98 (2H, m). MS: m/z 300 (MH+)

Example 56

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(2-morpholin-4-ylethyl)benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-(2-morpholin-4-ylethyl)benzoate (172mg, 0.69mmol) to give the title compound as a clear gum (42mg, 15.6% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.37-2.35 (4H, m), 2.49-2.45 (2H, m), 2.73 (2H, t), 2.80 (4H, s), 3.50 (4H, t), 3.65 (6H, s), 6.26-6.24 (1H, m), 6.34 (2H, d), 6.40 (1H, s), 7.26 (2H, d), 7.83 (2H, d), 10.47 (1H, br.s), 12.06 (1H, br.s). MS: m/z 465 (MH+)
Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.120 μM.

4-(2-Morpholin-4-ylethyl)benzoic acid, used as starting material was prepared as follows: Trimethylsilyldiazomethane solution (2M in hexanes, 1.2ml, 2.4mmol, 1.2eq) was added dropwise to 4-(2-bromoethyl)benzoc acid (459mg, 2mmol, 1eq) in toluene (14ml) and methanol (4ml) at ambient temperature. The reaction mixture was allowed to stir for 5 h, the solvent removed under reduced pressure and the residue dried under high vacuum to afford methyl 4-(2-bromoethoxy)benzoate as a pale yellow liquid (487mg, 100% yield). ^{1}H NMR (399.902 MHz, DMSO) δ 3.20 (2H, t), 3.76 (2H, t), 3.83 (3H, s), 7.42 (2H, d), 7.89 (2H, d).
MP-carbonate (2.74mmol/g, 270mg, 0.74mmol, 0.6eq) was added to methyl 4-(2-bromoethoxy)benzoate (300mg, 1.23mmol, 1eq), morpholine (0.12ml, 1.36mmol, 1.1eq), sodium iodide (193mg, 1.29mmol, 1.05eq) and MeCN (6ml) were charged to a microwave reactor vessel and the reaction mixture heated to 120 °C in a microwave reactor for 10 minutes. The reaction mixture was transferred to an SCX-2 cartridge, eluted with MeOH

followed by 3.5 N ammonia in MeOH solution. The latter fractions were combined and evaporated to afford a pale yellow solid (130mg, 52% yield).

^{1}H NMR (399.902 MHz, CDCl3) δ 2.53-2.51 (4H, m), 2.64-2.60 (2H, m), 2.88-2.84 (2H, m), 3.75-3.72 (4H, m), 3.90 (3H, s), 7.28-7.26 (2H, m), 7.97-7.94 (2H, m). MS: m/z 250 (MH+)

Example 57

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(methyl-(oxolan-2-ylmethyl)amino)methyl]benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-[(methyl-(oxolan-2-ylmethyl)amino)methyl]benzoate (181mg, 0.69mmol) to give the title compound as a clear gum (56mg, 20% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 1.56-1.42 (1H, m), 1.81-1.74 (2H, m), 1.98-1.90 (1H, m), 2.20 (3H, s), 2.44 (2H, d), 3.31 (4H, s), 3.66-3.59 (3H, m), 3.73 (6H, s), 4.01-3.94 (2H, m), 6.34-6.33 (1H, m), 6.43 (2H, d), 6.48 (1H, s), 7.40 (2H, d), 7.95 (2H, d), 10.58 (1H, br.s), 12.15 (1H, br.s). MS: m/z 479 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0053 μM.

Methyl 4-[(methyl-(oxolan-2-ylmethyl)amino)methyl]benzoate, used as starting material was prepared as follows:

MP-carbonate (2.74mmol/g, 1.44g, 4mmol, 2eq) was added to methyl 4-(bromomethyl)benzoate (500mg, 2mmol, 1eq), *N*-methyl-1-(oxolan-2-yl)methanamine (231mg, 2mmol, 1eq) and MeCN (10ml). The reaction mixture was allowed to stir at ambient temperature for 18 h and was then transferred to a SCX-2 cartridge, eluted with MeOH followed by 3.5 N ammonia in MeOH solution. The latter fractions were combined and evaporated to afford a pale yellow solid (355mg, 64% yield).

1H NMR (399.902 MHz, CDCl3) δ 1.54-1.47 (1H, m), 1.87-1.80 (2H, m), 2.01-1.93 (1H, m), 2.28 (3H, s), 2.46-2.42 (1H, m), 2.55-2.50 (1H, m), 3.68-3.57 (2H, m), 3.76-3.71 (1H, m), 3.87-3.81 (1H, m), 3.91 (3H, s), 4.08-4.01 (1H, m), 7.41 (2H, d), 7.98 (2H, d). MS: m/z 264 (MH+)

Example 58

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-piperidyl)benzamide

Prepared in an analogous way to Example 53, starting with methyl 4-(4-piperidyl)benzoate hydrochloride (176mg, 0.69mmol) to give the title compound as a pale yellow gum (20mg, 8% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 1.69-1.57 (2H, m), 1.84-1.76 (2H, m), 2.76-2.68 (2H, m), 2.93 (4H, s), 3.17-3.12 (2H, m), 3.77-3.76 (7H, m), 6.38-6.37 (1H, m), 6.47 (2H, d), 6.53 (1H, s), 7.38 (2H, d), 7.98 (2H, d), 10.61 (1H, s), 12.20 (1H, s). MS: m/z 435 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.001 μM.

Example 59

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-dimethylamino-benzamide

Prepared in an analogous way to Example 39, starting with 4-dimethylaminobenzoic acid (102mg, 0.63mmol) to give the title compound as a solid (139mg, 63% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.87 (4H, s), 3.00 (6H, s), 3.73 (6H, s), 6.33-6.32 (1H, m), 6.42 (2H, d), 6.45 (1H, s), 6.72 (2H, d), 7.89 (2H, d), 10.21 (1H, brs), 12.06 (1H, br.s). MS: m/z 395 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.134 μM.

Example 60

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-5-piperazin-1-yl-thiophene-2-carboxamide (2,2,2-trifluoroacetic acid salt)

5-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]thiophene-2-carboxylic acid (150 mg, mmol) was dissolved in dry THF (10 ml) under nitrogen, 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (177 μl, mmol) was added and the mixture was stirred at room temperature for 3.5 h. *Tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl) ethyl]pyrazole-1-carboxylate (167 mg, mmol) and pyridine (47 μl, mmol) were added and the reaction was heated to 65 °C for 18 h. The reaction mixture was then cooled to room temperature and 4M HCl in dioxane (2.0 ml, 2.0 mmol) added. The mixture was stirred overnight at room temperature, evaporated and the residue was purified by acidic prep. HPLC, eluting with a gradient of 24-32% MeCN in 0.1% TFA in water. The clean fractions were taken and evaporated to give the title compound as a

pale green solid (28.7 mg, 11 %); ^{1}H NMR (399.902 MHz, DMSO) δ 2.79 (s, 4H), 3.21 (s, 4H), 3.34 (s, 4H), 3.64 (s, 6H), 6.29 (m, 5H), 7.77 (m, 1H), 8.71 (s, 1H), 10.37 (s, 1H) MS: m/z = 442 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.022 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

5-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]thiophene-2-carboxylic acid, , used as starting material was prepared as follows:-

A solution of tert-butyl 4-(5-formylthien-2-yl)piperazine-1-carboxylate (2.51 g, 8.50 mmol) in ethanol (85 ml) was added in one portion to a solution of silver (I) nitrate (10.0 g, 58.8 mmol) and sodium hydroxide (4.83 g, 120.6 mmol) in water (85 ml). This mixture was stirred and heated at 65°C for 22 h. The mixture was cooled by the addition of ice and then filtered to remove silver salts. The filtrate was carefully evaporated to remove the ethanol and the resulting aqueous solution was filtered again through a glass-fibre pad to remove tarry material. The filtrate was then diluted with water to a total volume of 400ml and then acidified to pH 5 with acetic acid. The precipitate was filtered off, washed with water and then dried in a vacuum oven at 45°C overnight to give 5-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]thiophene-2-carboxylic acid (1.88 g, 71%).

1H NMR (399.9 MHz, DMSO-d_6) δ 1.41 (9H, s), 3.18 (4H, m), 3.45 (4H, m), 6.20 (1H, d), 7.43 (1H, d)

MS: m/z 313 (MH+)

tert-Butyl 4-(5-formylthien-2-yl)piperazine-1-carboxylate, used as starting material was prepared as follows:-

A mixture of 5-bromothiophene-2-carboxaldehyde (3.82 g, 20.0 mmol), tert-butyl piperazine-1-carboxylate (4.1 g, 22.0 mmol), N-ethyl-N, N-diisopropylamine (7.0 ml, 40.0 mmol) and dimethylsulphoxide (5.0 ml) were stirred at 130°C under an atmosphere of nitrogen for 18 h. The cooled mixture was partitioned between ethyl acetate and water. The organics were washed with water, brine, dried over magnesium sulphate and evaporated. The resultant dark

red solid was purified by silica column chromatography, eluting with dichloromethane followed by ethyl acetate/dichloromethane (15%) to give tert-butyl 4-(5-formylthien-2-yl)piperazine-1-carboxylate (4.3 g, 73%).

1H NMR (399.9 MHz, DMSO-d_6) δ 1.41 (9H, s), 3.34 (4H, m), 3.47 (4H, m), 6.36 (1H, d), 7.70 (1H, d), 9.49 (1H, s)

MS: m/z 297 (MH+)

Example 61

Methyl 6-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-3-carboxylate

5-Methoxycarbonylpyridine-2-carboxylic acid (0.285 g, 1.58 mmol) was added to DCM (40 ml), to this was added oxayl chloride (0.165 ml, 1.90 mmol) and a few drops of anhydrous DMF. The reaction mixture was stirred for 30 mins before the addition of *tert*-butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate (0.50 g, 1.58 mmol) and pyridine (2.0 ml). The reaction was stirred overnight. The reaction was evaporated to dryness to give yield to a gum. To this gum was added formic acid. The reaction mixture was stirred for 1 h before being evaporated to dryness. The resulting gum was quenched with saturated potassium carbonate (30 ml), extracted with DCM (3 x 50 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a viscous gum. Trituration with acetonitrile gave the desired product as a slightly yellow solid (24 mg, 4%); ^{1}H NMR (400.132 MHz, DMSO) δ 2.92 (s, 4H), 3.74 (s, 3H), 3.95 (s, 3H), 6.50 (s, 1H), 6.76 (d, 1H), 6.83 - 6.82 (m, 2H), 7.20 (t, 1H), 8.26 (d, 1H), 8.53 (d, 1H), 9.17 (s, 1H), 10.38 (s, 1H), 12.31 (s, 1H); MH+ 381.

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 68 μM.

tert-butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was prepared as in Example 23.

4-(4-Methylpiperazin-1-yl)benzoyl chloride, used as starting material was prepared as follows:

To a suspension of 4-(4-methylpiperazin-1-yl)benzoic acid (500mg, 2.27mmol, 1eq) in DCM (20ml) was added DMF (1 drop) followed by oxalyl chloride (219μl, 2.50mmol, 1.1eq) added

dropwise. The mixture was allowed to stir for 18 hours after which time the mixture was concentrated to dryness and taken through to the next stage with no further purification or characterisation.

Example 62

6-Chloro-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

6-Bromopyridine-3-carboxylic acid (122mg, 0.82mmol, 1.3eq) was dissolved in DCM (5mL) and oxalyl chloride (72μL, 0.82mmol, 1.3eq) was added dropwise followed by a drop of DMF. The reaction was stirred for 1 h at ambient temperature, then N,N-diethylethanamine (1mL, 1.89mmol, 3eq) was added followed by tert-butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate (200mg, 0.63mmol, 1eq). The reaction was stirred for 2 h, then diluted with DCM and washed with water, brine, dried ($MgSO_4$), filtered and evaporated to give the crude Boc-protected compound as a yellow gum. The gum was dissolved in 2-propanol (5mL) and a solution of 6M HCl in 2-propanol (4mL) was added. The solution was stirred at ambient temperature overnight and was then evaporated to dryness and loaded onto a SCX-2 column. The column was washed with methanol and the product eluted with 2N ammonia in methanol to give an orange solid. Trituration with a small volume of methanol gave 6-chloro-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide (39mg, 17%) as a white solid; ^{1}H NMR (400.13MHz, DMSO) δ 2.89 (4H, s), 3.74 (3H, s), 6.46 (1H, s), 6.75 (1H, m), 6.81 (2H, m), 7.20 (1H, t), 7.65 (1H, d), 8.35 (1H, m), 8.95 (1H, d), 10.99 (1H, s), 12.23 (1H, s) MS m/z 357 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 4.54 μM.

tert-Butyl 5-amino-3-[2-(3-methoxyphenyl)ethyl]pyrazole-1-carboxylate used as starting material was prepared as outlined in Example 23.

Example 63

6-Cyano-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-3-carboxamide

Preparation was analogous to that described for Example 62, except using 6-cyanopyridine-3-carboxylic acid (122mg, 0.82mmol, 1.3eq) as starting material. After purification by SCX column, the material was further purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean

fractions were taken and evaporated to afford the title compound as a cream solid. (58mg, 27% yield); ^{1}H NMR (400.13MHz, DMSO) δ 2.9 (4H, s), 3.74 (3H, s), 6.48 (1H, s), 6.75 (1H, m), 6.8 (2H, m), 7.2 (1H, t), 8.15 (1H, d), 8.52 (1H, m), 9.22 (1H, d), 11.19 (1H, s), 12.26 (1H, s) MS m/z 348 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 3.77 μM.

Example 64

4-Hydroxy-N-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyridine-2-carboxamide

Preparation was analogous to that described for Example 62, except using 4-hydroxypyridine-2-carboxylic acid (114mg, 0.82mmol, 1.3eq) as starting material. After purification by SCX column, the material was further purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a white solid (10mg, 5% yield); ^{1}H NMR (400.13MHz, DMSO) δ 2.9 (4H, s), 3.73 (3H, s), 6.47 (1H, s), 6.75 (1H, m), 6.8 (2H, m), 6.92 (1H, s), 7.19 (1H, t), 7.47 (1H, s), 8.32 (1H, s), 10.2 (1H, s), 12.21 (1H, s) MS m/z 339 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 5 μM.

Example 65

N-[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-(2-pyrrolidin-1-ylethyl)pyridine-3-carboxamide

Preparation was analogous to that described for Example 62, except using 6-(2-pyrrolidin-1-ylethyl)pyridine-3-carboxylic acid (180mg, 0.82mmol, 1.3eq) as starting material. After purification by SCX column, the material was further purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a white solid (5mg, 2% yield); ^{1}H NMR (400.13MHz, DMSO) δ 1.66 (4H, m), 2.77 (2H, t), 2.89 (4H, s), 2.94 (2H, t), 3.27 (4H, m), 3.73 (3H, s), 6.46 (1H, s), 6.75 (1H, m), 6.82 (1H, m), 7.19 (1H, t), 7.40 (1H, d), 8.21 (1H, m), 9.01 (1H, d), 10.79 (1H, s), 12.17 (1H, s) MS m/z 420 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.24 μM.

Example 66

5-[[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid

Preparation was analogous to that described for Example 62, except using 6-methoxycarbonylpyridine-3-carboxylic acid (149mg, 0.82mmol, 1.3eq) as starting material. After purification by SCX column, the material was further purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. During this purification the ester hydrolysed to the acid product. The clean fractions were taken and evaporated to afford the title compound as a white solid (66mg, 40% yield); ^{1}H NMR (400.13MHz, DMSO) δ 2.90 (4H, s), 3.74 (3H, s), 6.46 (1H, s), 6.75 (1H, m), 6.83 (2H, m), 7.19 (1H, t), 8.01 (1H, d), 9.12 (1H, d), 11.01 (1H, s), 12.2 (1H, s) MS m/z 367 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 1.02 μM.

Example 67

Methyl 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylate

To a stirred suspension of 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid (55mg, 0.15mmol, 1eq) in methanol (0.5mL) was added thionyl chloride (23uL, 0.32mmol, 2.1eq) dropwise. The resulting solution was heated at 50°C for 3 h. Tthe mixture was concentrated *in vacuo* to yield an orange solid. This was dissolved in DCM and washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layers were dried over magnesium sulphate, filtered and concentrated to give the crude product as a yellow solid. Trituration with diethyl ether gave the title compound as a white solid 27mg (47%); ^{1}H NMR (400.13MHz, DMSO) δ 2.92 (4H, s), 3.74 (3H, s), 3.92 (3H, s), 6.49 (1H, s), 6.25 (1H, m), 6.82 (2H, m), 7.19 (1H, t), 8.14 (1H, d), 8.46 (1H, m), 9.20 (1H, d), 11.11 (1H, s), 12.25 (1H, s) MS m/z 381 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 2.86 μM.

5-[[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid used as starting material was prepared as outlined in Example 66.

Example 68

Ethyl 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylate

Preparation was analogous to that described for Example 67, except using 5-[[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid (55mg, 0.15mmol, 1eq) in ethanol (0.5mL) to give title compound as a white solid (9mg, 15% yield); ^{1}H NMR (400.13MHz, DMSO) δ 1.40 (3H, t), 2.97 (4H, s), 3.79 (3H, s), 4.44 (2H, q), 6.54 (1H, s), 6.8 (1H, m), 6.87 (2H, m), 7.25 (1H, t), 8.19 (1H, d), 8.52 (1H, m), 9.25 (1H, s), 11.17 (1H, s), 12.3 (1H, s) MS m/z 395 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.724 μM.

5-[[5-[2-(3-Methoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyridine-2-carboxylic acid used as starting material was prepared as outlined in Example 66.

Example 69

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)pyridine-2-carboxamide

NaHMDS (1M solution in THF, 0.45ml, 0.451mmol, 1.5eq) was added dropwise to a stirred suspension of *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (105mg, 0.301mmol, 1eq) and methyl 5-(4-methylpiperazin-1-yl)pyridine-2-carboxylate (85mg, 0.361mmol, 1.2eq) in dry THF (2.5ml) under nitrogen. The solution was stirred at room temperature for 1h. The solution was neutralised with satd. aq. NH_4Cl and diluted with water (5ml). The aqueous phase was extracted with ethyl acetate (3 x 8ml) and the combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The reaction was repeated as above on a 0.338mmol scale. The crude extracts were combined with those above and purified on by silica column chromatography, eluting with 0-6% MeOH in DCM, to afford the title compound as a pale brown solid (92mg, 35% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.25 (s, 3H), 2.45 - 2.50 (m, 4H), 3.37 - 3.43 (m, 4H), 3.75 (s, 6H), 5.08 (s, 2H), 5.88 (bs, 1H), 6.45 (t, 1H), 6.60 (d, 2H), 7.45 - 7.49 (m, 1H), 7.94 (d, 1H), 8.35 (d, 1H), 10.89 (bs, 1H), 11.36 (bs, 1H) MS: m/z 453 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.122 μM.

5-(4-Methylpiperazin-1-yl)pyridine-2-carboxylate, used as starting material was prepared as follows:-

Methyl 5-bromo 2-carboxylate (250mg, 1.16mmol, 1eq), potassium phosphate (334mg, 1.62mmol, 1.4eq), S-Phos (96mg, 0.231mmol, 0.2eq) and Pd_2dba_3 (13mg, 0.058mmol, 0.05eq) were stirred in toluene (5ml) under nitrogen. N-Methylpiperazine (155μl, 1.39mmol, 1.2eq) was added and the mixture was stirred at 100°C for 48h, then allowed to cool to room temperature and stirred for a further 48h. The reaction mixture was poured onto a SCX column and washed through with MeOH, then with 2M NH_3 in MeOH to elute the product. Product fractions were evaporated to afford 5-(4-methylpiperazin-1-yl)pyridine-2-carboxylate as an orange oil which crystallized on standing (194mg, 72% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 2.24 (s, 3H), 2.43 - 2.48 (m, 4H), 3.35 - 3.40 (m, 4H), 3.81 (s, 3H), 7.32 - 7.37 (m, 1H), 7.88 (d, 1H), 8.38 (d, 1H). MS: m/z 236 (MH+)

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate, used as a starting material was prepared as outlined in Example 70.

Example 70

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(2-dimethylaminoethylamino)benzamide hydrochloride

tert-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (150 mg, 0.429 mmol) and methyl 4-[2-dimethylaminoethyl-[*tert*-butoxycarbonyl]amino]benzoate (166 mg, 0.515 mmol) were dissolved in dry THF (2.5 ml). NaHMDS (1 M in THF, 0.645 ml) was added dropwise under nitrogen and the mixture was stirred for 1h at room temperature. The mixture was neutralised with NH_4Cl (aq), diluted with water and extracted with ethyl acetate. The extracts were combined, dried and evaporated. The crude product was purified by silica column chromatography, eluting with a gradient of 0-8 % MeOH in DCM. Pure fractions were combined and evaporated to give a brown oil (74 mg). The oil was dissolved in THF (10 ml) and 4 M HCl in dioxane (2 ml) was added. The reaction mixture was stirred at room temperature for 18h. The solid was collected by filtration, washed (hexane) and dried to give N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(2-

dimethylaminoethylamino)benzamide hydrochloride (38.6 mg, 20 % overall yield) as a white solid; ^{1}H NMR (399.902 MHz, DMSO) δ 2.84 (d, *J* = 4.0 Hz, 6H), 3.25 (m, 2H), 3.75 (s, 6H), 5.08 (s, 2H), 5.67 (s, 1H), 6.45 (t, *J* = 2.2 Hz, 1H), 6.60 (d, *J* = 2.2 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 9.85 (s, 1H), 10.53 (s, 1H). MS: m/z = 440 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.031 μM.

tert-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate, used as starting material, was prepared as follows:-

Potassium hydroxide (11.19g, 199.4 mmol) dissolved in water (44.8 ml) was added to a solution of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (7.121 g) dissolved in dichloromethane (40 ml). (2-Methylpropan-2-yl)oxycarbonyl tert-butyl carbonate (6.8 g, 31.2 mmol) dissolved in DCM (35 ml) was added and the reaction mixture was stirred vigorously at room temperature for 4 h. The reaction mixture was separated and the organic layer was washed with water (2 x 15 ml), brine (2 x 15 ml), dried over sodium sulphate, filtered, evaporated and dried *in vacuo* to give *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (8.70 g, 99%) as a cream solid.

^{1}H NMR (399.902 MHz, DMSO) δ 1.55 (s, 9H), 3.75 (s, 6H), 4.93 (s, 1H), 5.06 (s, 2H), 6.38 (s, 2H), 6.45 (t, *J* = 2.2 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 2H). MS: m/z = 350 (MH+)

Methyl 4-[2-dimethylaminoethyl-[*tert*-butoxycarbonyl]amino]benzoate, used as starting material, was prepared as follows:-

Methyl 4-(2-[dimethylamino]ethylamino)benzoate (1.00 g, 4.50 mmol) was dissolved in THF (30 ml). (2-Methylpropan-2-yl)oxycarbonyl tert-butyl carbonate (1.035 g, 4.72 mmol) was added and the solution was refluxed for 3h. The solvent was then evaporated, the residue was dissolved in DCM, washed with sat. aq. ammonium chloride solution, dried over sodium sulphate, filtered and evaporated to give methyl 4-[2-dimethylaminoethyl-[*tert*-butoxycarbonyl]amino]benzoate (1.07g, 74 %) as a brown oil.

^{1}H NMR (399.902 MHz, DMSO) δ 1.41 (s, 9H), 2.13 (s, 6H), 2.34 (t, *J* = 6.9 Hz, 2H), 3.73 (t, *J* = 6.8 Hz, 2H), 3.86 (s, 3H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H). MS: m/z = 323 (MH+)

Methyl 4-(2-[dimethylamino]ethylamino)benzoate, used as starting material, was prepared as follows:-

Methyl 4-iodobenzoate (1.19 g, 4.54 mmol, 1.0 eq) was dissolved in dry dimethylformamide (10 ml). *N,N*-dimethylethane-1,2-diamine (400 mg, 4.54 mmol, 1.0 eq), caesium carbonate (2.69 g, 9.08 mmol, 2.0 eq), 2-acetylcyclohexanone (120 µl, 0.908 mmol, 0.20 eq [20 mol%]) and copper (I) iodide (44 mg, 0.227 mmol, 0.05 eq [5 mol%]) were added and the mixture was stirred under nitrogen at 90 °C for 18 h. The reaction mixture was concentrated, dissolved in methanol and absorbed onto a SCX-2 cation exchange resin column. The column was washed with methanol and the product was eluted with 2M ammonia in methanol. Fractions were evaporated to give methyl 4-(2-[dimethylamino]ethylamino)benzoate (1.00 g, 99%) as a brown gum.

^{1}H NMR (399.902 MHz, DMSO) δ 2.19 (s, 6H), 2.44 (t, J = 6.3 Hz, 5H), 3.17 (m, 2H), 3.75 (s, 3H), 6.33 (t, J = 5.3 Hz, 1H), 6.62 (d, J = 8.9 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H). MS: m/z = 223 (MH+)

Example 71

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-methoxy-benzamide

4-Methoxybenzoyl chloride (54mg, 0.315mmol, 1.1eq) in THF (2ml) was added dropwise to a solution of *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (100mg, 0.286mmol, 1eq) in THF (3ml) under nitrogen and the solution was heated at reflux for a total of 14h, then stirred at room temperature for 16h. The solvent was evaporated and the residue was purified by prep. HPLC, using a gradient of 55-75% MeCN in H_2O (containing 1% ammonium hydroxide). The product fractions were evaporated to dryness and taken up in DCM (4ml). 4M HCl in dioxane (1ml) was added and the mixture stirred at room temperature for 1h, then evaporated to dryness. The residue was partitioned between ethyl acetate (6ml) and aqueous $NaHCO_3$ (6ml), the layers were separated and the aqueous layer was re-extracted with ethyl acetate (3 x 6ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to afford the title compound as an off-white solid (22mg, 20% yield); ^{1}H NMR (400.132 MHz, DMSO) δ 3.74 (s, 6H), 3.82 (s, 3H), 5.06 (s, 2H), 5.59 (s, 1H), 6.43 (t, 1H), 6.59 (d, 2H), 7.00 (d, 2H), 7.96 (d, 2H) MS: m/z 384 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.157 µM.

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate, used as a starting material was prepared as outlined in Example 70.

Example 72

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-6-piperazin-1-yl-pyridine-3-carboxamide

6-[4-[(2-Methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]pyridine-3-carboxylic acid (150 mg, 0.412 mmol) was dissolved in dry THF (10 ml), 1-chloro-N,N,2-trimethyl-prop-1-en-1-amine (65 µl, 0.412 mmol) was added and the mixture was stirred at room temperature under nitrogen overnight. Pyridine (40 µl, 0.412 mmol) and *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (142 mg, 0.343 mmol) were added and the mixture was stirred at 65 °C for 18h. The mixture was then cooled to room temperature and stirred overnight with 4 M HCl in dioxane (1.8 ml, 7.20 mmol). The mixture was then filtered and the solid was washed with hexane. The product was purified on acidic prep. HPLC, eluting with a gradient of 16-26 % MeCN in water (containing 0.1% TFA). The product containing fractions were neutralised with aq. $NaHCO_3$ and the acetonitrile removed under vacuum. The product precipitated out and was collected by filtration. This was further washed with water and dried *in vacuo* to give the title compound (39 mg, 26 %) as a white solid; ^{1}H NMR (399.902 MHz, DMSO) δ 2.82 (t, J = 5.1 Hz, 4H), 3.61 (t, J = 4.8 Hz, 4H), 3.80 (s, 6H), 5.13 (s, 2H), 5.62 (bs, 1H), 6.50 (s, 1H), 6.65 (d, J = 2.2 Hz, 2H), 6.92 (d, J = 8.9 Hz, 1H), 8.09 (d, J = 9.3 Hz, 1H), 8.76 (d, J = 2.3 Hz, 1H), 10.74 (bs, 1H), 11.64 (bs, 1H). MS: m/z = 439 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.025 µM.

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate, used as starting material, was prepared as follows:

Potassium hydroxide (11.19g, 199.4 mmol) dissolved in water (44.8 ml) was added to a solution of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (7.121 g) dissolved in dichloromethane (40 ml). A solution of (2-methylpropan-2-yl)oxycarbonyl tert-butyl carbonate (6.8 g, 31.2 mmol) in DCM (35 ml) was added and the reaction mixture was stirred

vigorously at room temperature for 4 h. The reaction mixture was separated and the organic layer was washed with water (2 x 15 ml) and brine (2 x 15 ml), dried over sodium sulphate, filtered, evaporated and dried *in vacuo* to give tert-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (8.70 g, 99%) as a cream solid.

^{1}H NMR (399.902 MHz, DMSO) δ 1.55 (s, 9H), 3.75 (s, 6H), 4.93 (s, 1H), 5.06 (s, 2H), 6.38 (s, 2H), 6.45 (t, J = 2.2 Hz, 1H), 6.60 (d, J = 2.3 Hz, 2H). MS: m/z = 350 (MH+)

Example 73

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide

NaHMDS (1M solution in THF, 0.39ml, 0.386mmol, 1.5eq) was added dropwise to a stirred solution of *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (90mg, 0.258mmol, 1eq) and methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate (74mg, 0.309mmol, 1.2eq) in dry THF (5ml) under nitrogen. The solution was stirred at room temperature for 1h, then neutralised with satd. aq. NH_4Cl, diluted with water (15ml) and extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to give an orange gum. The gum was purified by silica column chromatography, eluting with a gradient of 0-2.5% MeOH in DCM. The crude material, containing starting methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate, was re-dissolved in THF (5ml) under nitrogen. *tert*-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (50mg, 0.143mmol) was added followed by dropwise addition of NaHMDS (1M solution in THF, 0.32ml, 0.32mmol). The solution was stirred at room temperature for 45 mins, neutralised with satd. aq. NH_4Cl, diluted with water (10ml) and extracted with ethyl acetate (3 x 10ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. The gummy residue was purified by silica column chromatography, eluting with a gradient of 0-8% MeOH in DCM, to afford the title compound as a pale brown solid (16mg, 14% yield); ^{1}H NMR (399.9 MHz, DMSO-d_6 + d4-AcOD) δ 2.42 (3H, s), 2.67 - 2.70 (4H, m), 3.75 (6H, s), 3.91 - 3.94 (4H, m), 5.08 (2H, s), 5.75 (1H, s), 6.45 (1H, t), 6.59 (2H, d), 8.90 (2H, s). MS: m/z 454 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.044 μM.

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate, used as a starting material was prepared as outlined in Example 70.

Methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate, used as starting material was prepared as follows:

2-Chloropyrimidine 5-carboxylic acid (100mg, 0.631mmol, 1eq) was suspended in a mixture of toluene (3ml) and methanol (0.8ml) under nitrogen and cooled in an ice-bath. Trimethylsilyldiazomethane (2M solution in hexanes, 0.347ml, 0.694mmol, 1.1eq) was added dropwise. The solution was stirred at 0°C for 10min, then allowed to warm to room temperature and stirred for a further 1h. 1-Methylpiperazine (70µl, 0.631mmol, 1eq) and triethylamine (88µl, 0.631mmol, 1eq) were added dropwise and stirring continued at room temperature for 2h. The solvent was evaporated and the residue was taken up in ethyl acetate (20ml) and water (15ml). The layers were separated and the aqueous extracted with further portions of ethyl acetate (2 x 10ml). The combined extracts were dried over $MgSO_4$, filtered and evaporated. The reaction was repeated as above and the extracts combined with those above to afford methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate as a gummy yellow solid (76mg, 25% yield).

^{1}H NMR (399.902 MHz, DMSO) δ 2.12 (s, 3H), 2.27 (t, 4H), 3.70 (s, 3H), 3.75 (t, 4H), 8.68 (s, 2H). MS: m/z 237 (MH+)

Example 74

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl]-3-piperazin-1-yl-benzamide 1-Chloro-*N,N*-2-trimethyl-1-propenylamine (78µl, 0.588mmol, 1.2eq) was added dropwise to a stirred solution of 3-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]benzoic acid (150mg, 0.588mmol, 1.2eq) in THF (10ml) under nitrogen. The mixture was stirred at room temperature overnight. *tert*-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (172mg, 0.490mmol, 1eq) and pyridine (48µl, 0.588mol, 1.2eq) were added and the mixture was heated at 65 °C overnight. The mixture was allowed to cool to room temperature and 4M HCl in dioxane (2ml) was added. Stirring was continued at room temperature overnight. The precipitated yellow solid was collected by filtration and washed with THF. The solid was triturated with aq $NaHCO_3$ (4ml) and DCM (2ml). A small amount of a brown gum remained

out of solution. The gum was collected by filtration and washed with water and ether. The aqueous filtrate was extracted with ethyl acetate (3 x 10ml) and the combined extracts were dried over $MgSO_4$, filtered and evaporated. The extracted product was combined with the gum from filtration and purified by silica column chromatography, eluting with a gradient of 10-12% MeOH in DCM. Product fractions were evaporated to give the title compound as a white solid (27mg, 10% yield); ^{1}H NMR (399.902 MHz, DMSO + d4-AcOD) δ 3.13 - 3.21 (m, 4H), 3.33 - 3.40 (m, 4H), 3.68 (s, 6H), 5.02 (s, 2H), 5.71 (s, 1H), 6.38 (t, 1H), 6.52 (d, 2H), 7.12 - 7.17 (m, 1H), 7.33 (t, 1H), 7.37 - 7.41 (m, 1H), 7.46 - 7.49 (m, 1H). MS: m/z 438 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.130 μM.

Example 75

4-(1,4-Diazepan-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-1H-pyrazol-3-yl]benzamide hydrochloride

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (176 mg, 0.50 mmol) and *tert*-butyl 4-(4-methoxycarbonylphenyl)-1,4-diazepane-1-carboxylate (168 mg, 0.60 mmol) were dissolved in dry THF (5 ml). NaHMDS (1 M in THF, 0.754 ml) was added dropwise under nitrogen and the mixture was stirred for 1 h at room temperature. A further amount of NaHMDS (1M in THF, 0.754 ml) was added and the reaction mixture was stirred under nitrogen for 30 mins. The reaction mixture was neutralised with saturated NH_4Cl (aq), diluted with water (20 ml) and extracted with ethyl acetate (3 x 30 ml). The extracts were combined, dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica column chromatography, eluting with 0-3% MeOH in DCM. The fractions were evaporated to give a brown oil (51 mg) which was repurified by silica column chromatography, eluting with 0-1% MeOH in DCM. The pure fractions were combined, evaporated and the residue was dissolved in THF (10 ml). 4M HCl in dioxan (1.5 ml, 1.5 mmol) was added and the solution was stirred at room temperature overnight. The precipitate was collected by filtration, washed with hexane and dried *in vacuo* to give the title compound (18.7 mg, 6.5 %) as a white solid; ^{1}H NMR (399.902 MHz, DMSO) δ 2.01 (m, 2H), 3.08 (m, 2H), 3.20 (m, 2H), 3.53 (m, 2H), 3.68 (s, 6H), 3.72 (t, J = 5.2 Hz, 2H), 5.01 (s, 2H), 5.60 (s, 1H), 6.38 (t, J =

2.4 Hz, 1H), 6.52 (d, J = 2.3 Hz, 2H), 6.81 (d, J = 9.2 Hz, 2H), 7.82 (d, J = 8.9 Hz, 2H), 8.69 (s, 1H), 10.49 (s, 1H). MS: m/z = 452 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.0085 μM.

tert-Butyl 4-(4-methoxycarbonylphenyl)-1,4-diazepane-1-carboxylate used as starting material was prepared as follows:-

Methyl 4-iodobenzoate (1.00 g, 3.82 mmol, 1.0 eq) was dissolved in DMF and *tert*-butyl 1,4-diazepane-1-carboxylate (765 mg, 3.82 mmol, 1.0 eq), caesium carbonate (2.49 g, 7.63 mmol, 2.0 eq), 2-acetylcyclohexanone (101 μl, 0.76 mmol, 0.20 eq [20 mol%]) and copper iodide (37 mg, 0.19 mmol, 0.05 eq [5 mol%]) were added. The reaction mixture was stirred at 90 °C under nitrogen for 7 h. The reaction mixture was evaporated, dissolved in DCM (50 ml), washed with water (20 ml), saturated ammonium chloride solution (20 ml), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by silica column chromatography, eluting with 0-1 % MeOH in DCM. The product containing fractions were combined, evaporated and dried *in vacuo* to give *tert*-butyl 4-(4-methoxycarbonylphenyl)-1,4-diazepane-1-carboxylate (168 mg, 13%) as a yellow oil.

^{1}H NMR (399.902 MHz, DMSO) δ 1.12 (s, 5H), 1.24 (s, 4H), 1.72 (m, 2H), 3.12 (m, 1H), 3.42 (m, 1H), 3.49 (m, 3H), 3.59 (m, 2H), 3.69 (s, 3H), 6.72 (d, J = 9.1 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H) MS: m/z = 335 (MH+)

tert-Butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate was prepared as follows:

Potassium hydroxide (11.19g, 199.4 mmol) dissolved in water (44.8 ml) was added to a solution of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (7.121 g) dissolved in dichloromethane (40 ml). (2-Methylpropan-2-yl)oxycarbonyl tert-butyl carbonate (6.8 g, 31.2 mmol) dissolved in DCM (35 ml) was added and the reaction mixture was stirred vigorously at room temperature for 4 h. The reaction mixture was separated and the organic layer was washed with water (2 x 15 ml) and brine (2 x 15 ml), dried over sodium sulphate, filtered, evaporated and dried *in vacuo* to give *tert*-butyl 5-amino-3-[(3,5-dimethoxyphenyl)methoxy]pyrazole-1-carboxylate (8.70 g, 99%) as a cream solid.

^{1}H NMR (399.902 MHz, DMSO) δ 1.55 (s, 9H), 3.75 (s, 6H), 4.93 (s, 1H), 5.06 (s, 2H), 6.38 (s, 2H), 6.45 (t, J = 2.2 Hz, 1H), 6.60 (d, J = 2.3 Hz, 2H). MS: m/z = 350 (MH+)

Example 76

N-[5-[2-[5-(Dimethylaminomethyl)-2-furyl]ethyl]-1H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

A solution of potassium hydroxide (4.5M in water, 1.8ml, 8.10mmol, 8.10eq) was added to a stirred solution of 5-(2-{5-[(dimethylamino)methyl]-2-furyl}ethyl)-1H-pyrazol-3-amine (235mg, 1.0mmol, 1.0eq) in dichloromethane at room temperature. A solution of di-tert-butyl dicarbonate (230 mg, 1.05 mmol, 1.05eq) in dichloromethane (2.0ml) was then added and the reaction mixture stirred vigorously for 18 h. The reaction mixture was poured into a separating funnel and the layers were separated. The dichloromethane layer was washed with water (10ml) and saturated brine (10ml), dried over anhydrous sodium sulphate, filtered and the solvent removed *in vacuo* to afford tert-butyl 5-amino-3-(2-{5-[(dimethylamino)methyl]-2-furyl}ethyl)-1H-pyrazole-1-carboxylate as a golden oil, (320mg).

A portion of this material was used without further purification as follows:-

A solution of sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.7ml, 0.69mmol, 1.50eq) was added dropwise at room temperature to a stirred solution of tert-butyl 5-amino-3-(2-{5-[(dimethylamino)methyl]-2-furyl}ethyl)-1H-pyrazole-1-carboxylate (crude 154mg, 0.46mmol, 1.0eq) and methyl 4-(4-methylpiperazin-1-yl)benzoate (130mg, 0.55mmol, 1.20eq) in dry tetrahydrofuran (1.0 ml) under nitrogen. The mixture was allowed to stand at room temperature overnight and then the solvent was evaporated under reduced pressure to afford the crude product as a brown gum. This gum was dissolved in methanol (5ml) and the solution was applied to a SCX-2 column. The column was washed through with methanol containing 10% water. The column was then eluted with 2.0M anhydrous ammonia in methanol. Fractions containing the product were combined and evaporated to give a brown gum, 235mg. This material was further purified by silica column chromatography, eluting with a 3 – 10% gradient of methanol (containing ammonia at 2M) in dichloromethane. Pure product fractions were combined and evaporated to give a light brown gum, 32.9mg. This material was further purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to afford the title compound as a solid. (8mg, 4% yield); ^{1}H NMR (500.13 MHz, DMSO-d6) δ 2.17 (6H, d), 2.26 (3H, s), 2.48 (4H, t), 2.88 – 2.96 (4H, m), 3.30

(4H, t), 3.39 (2H, s), 6.03 (1H, d), 6.12 (1H, d), 6.95 (2H, d), 7.88 (2H, d), 9.95 (1H, broad s), 11.80 (1H, broad s). MS: m/z 437 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.34 μM.

5-(2-{5-[(dimethylamino)methyl]-2-furyl}ethyl)-1H-pyrazol-3-amine, used as starting material was prepared as follows:

Acetonitrile (0.258ml, 4.88mmol) was added to a slurry of sodium hydride (196mg dispersion in mineral oil, 4.88mmol) in anhydrous dioxan (15ml) and the mixture stirred at room temperature under an atmosphere of nitrogen for 5 mins. Ethyl 3-{5-[(dimethylamino)methyl]-2-furyl}propanoate (917mg, 4.07mmol) was then added and the reaction was refluxed for 18 h. The mixture was cooled to room temperature and ethanol (1.9ml) added followed by hydrazine hydrochloride (558mg, 8.14mmol). The mixture was refluxed for 1 h. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane containing 10% methanol (50mL) and the insoluble impurities were filtered off. The filtrate was evaporated to give the crude product as a golden oil, 1.07g. This material was purified by silica column chromatography, eluting with a 0 – 10% gradient of methanol (containing ammonia at 2M) in dichloromethane. Pure product fractions were combined and evaporated to give a clear oil. (520mg, 55% yield); ^{1}H NMR (399.9 MHz, DMSO-d6) δ2.16 (6H, s), 2.70 - 2.74 (2H, m), 2.81 - 2.85 (2H, m), 3.40 (2H , s), 5.20 (1H, s), 6.03 (1H, d), 6.15 (1H, d). MS: m/z 235 (MH+)

Ethyl 3-{5-[(dimethylamino)methyl]-2-furyl}propanoate, used as starting material was prepared as follows:

A mixture of ethyl 3-(2-furanyl)propionate (12.11g, 72.0mmol), dimethylammonium chloride (6.76g, 82.8mmol), 37% aqueous formaldehyde (6.43g, 79.2 mmol) in acetic acid (75ml) was stirred at room temperature until a solution formed. The solution was allowed to stand for 44 h. The mixture was evaporated to an oil. This was suspended in water and extracted with ethyl acetate (2 x 250ml). The aqueous layer (containing the product) was basified to pH11 with 4M sodium hydroxide solution and then extracted into ethyl acetate (2 x 250ml). These combined extracts were washed with brine, dried over magnesium sulphate and evaporated to give the crude product as a dark brown oil, 6.5g. This material was purified by silica column chromatography, eluting with a 0 – 10% gradient of methanol (containing ammonia at 2M) in

dichloromethane. Fractions containing the product were combined and evaporated to give a light brown oil (3.44g). This material was purified by silica column chromatography, eluting with a 0 – 5% gradient of methanol (containing ammonia at 2M) in dichloromethane. Fractions containing the product were combined and evaporated to give a light brown oil (1.36g, 8% yield).

1H NMR (399.9 MHz, CDCl3) δ 1.24 (3H, t), 2.29 (6H, s), 2.62 - 2.65 (2H, m), 2.95 (2H, t), 3.47 (2H, s), 4.11 - 4.15 (2H, m), 5.95 (1H, d), 6.11 (1H, d). MS: m/z 226 (MH+)

Example 77

N-[5-(2-Benzo[1,3]dioxol-5-ylethyl)-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

To a stirred solution of *tert*-butyl 5-amino-3-(2-benzo[1,3]dioxol-5-ylethyl)pyrazole-1-carboxylate (229mg, 0.69mmol, 1.0eq) in pyridine (5ml) at 5 °C was added 4-(4-methylpiperazin-1-yl)benzoyl chloride (181mg, 0.76mmol, 1.1 eq). The reaction mixture was stirred to 60 °C for 24 h. After this time, the mixture was concentrated and redissolved in DCM (10ml). Trifluoroacetic acid (464µl, 6.25mmol, 8.25eq) was added and the reaction mixture stirred for 2 h at 25 °C. The reaction mixture was then concentrated. The crude product was purified by reverse-phase prep. HPLC (basic) using a 30-50% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were combined and evaporated to afford the title compound as a white solid. (12mg, 4%); ^{1}H NMR (300.132 MHz, DMSO) δ 2.28 (s, 3H), 2.49 (t, 2H), 2.89 (s, 2H), 3.31 - 3.37 (m, 8H), 6.01 (s, 2H), 6.43 (s, 1H), 6.74 (d, 1H), 6.86 (d, 2H), 7.01 (d, 2H), 7.94 (d, 2H), 10.36 (s, 1H), 12.11 (s, 1H); MS: m/z 434 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.14 µM.

tert-butyl 5-amino-3-(2-benzo[1,3]dioxol-5-ylethyl)pyrazole-1-carboxylate, used as starting material was prepared as follows:

To a stirred solution of 5-(2-benzo[1,3]dioxol-5-ylethyl)-2H-pyrazol-3-amine in DCM (10ml) was added 4.5M aq. KOH solution (1.9ml, 8.66mmol, 8eq). A solution of BOC_2O (464 mg, 2.12mmol, 1.05eq) in DCM (2 mL) was then added and the reaction mixture stirred vigorously for 3 h. The reaction mixture was poured into a separating funnel and the layers separated. The organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4),

filtered and the solvent evaporated to afford the title compound as a white solid. (325mg, 91%); ^{1}H NMR (300.132 MHz, DMSO) δ 1.55 (s, 9H), 2.58 - 2.64 (m, 2H), 2.73 - 2.78 (m, 2H), 5.19 (s, 1H), 5.95 (s, 2H), 6.21 (s, 2H), 6.68 - 6.71 (m, 1H), 6.80 (d, 1H), 6.85 (d, 1H)

5-(2-benzo[1,3]dioxol-5-ylethyl)-2H-pyrazol-3-amine, used as starting material was prepared as follows:-

5-(2-Benzo[1,3]dioxol-5-ylethyl)-2H-pyrazol-3-amine used as starting material was prepared in a similar manner to 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine in example 11. Product was obtained as yellow oil. (3.04g, 44% yield).

1H NMR (300.132 MHz, DMSO): δ 2.63-2.79 (m, 4H), 4.40 (s, 2H), 5.18 (s, 1H), 5.95 (s, 2H), 6.66 (dd, 1H), 6.77-6.81 (m, 2H). MS: m/z 232 (MH+).

Example 78

N-[5-[2-(2,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Made in an analogous way to the compound in example 77, using *tert*-butyl 5-amino-3-[2-(2,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate (240mg, 0.69mmol, 1 eq) as starting material to afford the title compound as a white solid. (27mg, 9%);

^{1}H NMR (300.132 MHz, DMSO) δ 2.23 (s, 3H), 2.43 - 2.46 (m, 4H), 2.80 - 2.88 (m, 4H), 3.26 - 3.29 (m, 4H), 3.68 (s, 3H), 3.76 (s, 3H), 6.43 (s, 1H), 6.72 - 6.77 (m, 2H), 6.88 (d, 1H), 6.96 (d, 2H), 7.89 (d, 2H), 10.29 (s, 1H), 12.06 (s, 1H)

MS: m/z 450 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.47 μM.

tert-butyl 5-amino-3-[2-(2,5-dimethoxyphenyl)ethyl]pyrazole-1-carboxylate, used as starting material was made in an analogous way to *tert*-butyl 5-amino-3-(2-benzo[1,3]dioxol-5-ylethyl)pyrazole-1-carboxylate in Example 77, using 5-[2-(2,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (200mg, 0.87mmol, 1 eq) as starting material to afford the title compound as a white solid. (283mg, 94%).

1H NMR (300.132 MHz, DMSO) δ 1.60 (s, 9H), 2.61 - 2.67 (m, 2H), 2.79 - 2.84 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 5.25 (s, 1H), 6.26 (s, 2H), 6.75 - 6.79 (m, 1H), 6.84 (d, 1H), 6.92 (d, 1H)

5-[2-(2,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material, was prepared as follows:-

Sodium hydride (60%, 0.240g, 6mmol) was added to a stirred solution of methyl 3-(2,5-dimethoxyphenyl)propanoate (1.125g, 5mmol) in 1,4 dioxane (25 ml) in dry acetonitrile (0.314ml, 6mmol) under nitrogen. The mixture was stirred at r.t for 10 mins then heated at reflux under nitrogen for 18 h. After this time, the mixture was cooled to r.t. upon which a precipitate formed. Ethanol (2 ml) was added, followed by hydrazine monohydrochloride (0.686g, 10mmol). The mixture was heated to reflux for 4 h. In this time, the precipitate went into solution and a solid appeared. After filtration, the reaction mixture was concentrated *in vacuo* and partitioned between 2N HCl and ethyl acetate (25ml each). The aqueous layer was basified with ammonium hydroxide solution to pH 8, extracted with ethyl acetate and dried with MgSO4. This was filtered, and the solvents were evaporated *in vacuo* to give an orange oil (0.690g, 56 %).

4-(4-Methylpiperazin-1-yl)benzoyl chloride, used as starting material was prepared as per Example 61.

Example 79

N-[5-[2-(4-Methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

Made in an analogous way to the compound in example 77, using *tert*-butyl 5-amino-3-[2-(4-methoxy-2-methyl-phenyl)ethyl]pyrazole-1-carboxylate (229mg, 0.69mmol, 1 eq) as starting material to afford the title compound as a white solid. (15mg, 5%); ^{1}H NMR (300.132 MHz, DMSO) δ 2.26 (s, 3H), 2.72 - 2.83 (m, 5H), 2.88 (t, 4H), 3.41 (t, 4H), 3.69 (s, 3H), 5.70 (s, 1H), 6.41 (s, 1H), 6.65 - 6.73 (m, 2H), 6.99 (d, 2H), 7.06 (d, 1H), 7.91 (d, 2H) [*NB: With D4-Acetic added*]

MS: m/z434 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.2 μM.

tert-butyl 5-amino-3-[2-(4-methoxy-2-methyl-phenyl)ethyl]pyrazole-1-carboxylate, used as starting material was made in an analogous way to *tert*-butyl 5-amino-3-(2-benzo[1,3]dioxol-

5-ylethyl)pyrazole-1-carboxylate in Example 77, using 5-[2-(4-methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-amine (214mg, 0.87mmol, 1 eq) as starting material to afford the title compound as a white solid. (256mg, 89%).

1H NMR (300.132 MHz, DMSO) δ 1.60 (s, 9H), 2.30 (s, 3H), 2.58 - 2.64 (m, 2H), 2.76 - 2.81 (m, 2H), 3.75 (s, 3H), 5.26 (s, 1H), 6.26 (s, 2H), 6.70 - 6.74 (m, 1H), 6.77 (d, 1H), 7.13 (d, 1H)

5-[2-(4-methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as follows:-

5-[2-(4-methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-amine, used as starting material, was prepared in a method analogous to that used to synthesize 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine in example 11 using methyl 3-(4-methoxy-2-methyl-phenyl)propanoate as starting material to give 5-[2-(4-methoxy-2-methyl-phenyl)ethyl]-2H-pyrazol-3-amine as a red solid. MS: m/z 232 (MH+).

4-(4-Methylpiperazin-1-yl)benzoyl chloride, used as starting material was prepared as per example 61.

Example 80

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,5-dimethylpiperazin-1-yl)benzamide was prepared as for Example 94, but starting from methyl 4-(3,5-dimethylpiperazin-1-yl)benzoate (221 mg, 0.84 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (244mg, 0.7 mmol) and 1M NaHMDS (1.13 ml, 1.13mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 34-54% gradient of acetonitrile in water containing 1% 0.880 ammonia. The clean fractions were taken and evaporated to afford the title compound as a white solid (34 mg, 10%); ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.04 (6H, d), 2.22 (2H, t), 2.53 (2H, d), 2.82 (2H, t), 2.87 (4H, s), 3.71 (1H, s), 3.73 (7H, s), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 6.94 (2H, d), 7.89 (2H, d), 10.27 (1H, s), 12.07 (1H,s).

MS: m/z 464 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.011 μM.

2,6-Dimethylpiperazine(3.43 g, 30.00 mmol) was added to ethyl 4-fluorobenzoate (1.101 mL, 7.5 mmol), in DMSO (10 mL) warmed to 120°C under nitrogen. The resulting solution was stirred at 120 °C for 20 h. The reaction mixture was cooled and the solvent was evaporated. The crude product was purified by silica column chromatography, eluting with 10% methanol in dichloromethane containing 1% 0.880 ammonia. Pure fractions were evaporated to dryness to afford ethyl 4-(3,5-dimethylpiperazin-1-yl)benzoate (1.490 g, 76 %) as a colourless solid. 1H NMR (399.9 MHz, $CDCl_3$) δ 1.15 (6H, d), 1.37 (3H, t), 2.39 (1H, d), 2.42 (1H, d), 2.97 - 3.05 (2H, m), 3.65 - 3.69 (2H, m), 4.33 (2H, q), 6.84 - 6.87 (2H, m), 7.90 - 7.93 (2H, m) – NH not seen. MS: m/z = 264 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 81

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide was prepared as for Example 94, but starting from methyl 4-(3,4-dimethylpiperazin-1-yl)benzoate (221 mg, 0.84 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (244mg, 0.7 mmol) and 1M NaHMDS (1.13 ml, 1.13mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 38-58% gradient of acetonitrile in water containing 1% 0.880 ammonium hydroxide. The clean fractions were taken and evaporated to afford the title compound as a white solid (63 mg, 19%); ^{1}H NMR (500.13 MHz, DMSO-d_6) δ 1.12 (3H, d), 1.89 - 1.90 (3H, m), 2.32 (3H, s), 2.35 - 2.40 (1H, m), 2.64 - 2.68 (1H, m), 2.86-2.91 (1H, m), 2.89 (4H, t), 3.00 (1H, s), 3.64 - 3.68 (2H, m), 3.74 (6H, s), 6.32 (1H, s), 6.33 (1H, t), 6.42 (2H, d), 6.94 - 6.96 (2H, m), 7.86 - 7.88 (2H, m). MS: m/z 464 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.04 μM.

1,2-Dimethyl-piperazine (0.914 g, 8.00 mmol) and ethyl 4-fluorobenzoate (0.587 mL, 4 mmol) were dissolved in DMA (6 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 90 mins in the microwave reactor and cooled to room temperature. The reaction mixture was evaporated and the crude product was purified by silica column chromatography, eluting with 5 % MeOH in DCM (containing 0.1% 0.880 ammonia). Pure fractions were evaporated to dryness to afford ethyl 4-(3,4-dimethylpiperazin-1-yl)benzoate (0.380 g, 36.2 %) as a colourless waxy solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.15 (3H, d), 1.37 (3H, t), 2.20 - 2.25 (1H, m), 2.34 (3H, s), 2.37 - 2.41 (1H, m), 2.61 - 2.67 (1H, m), 2.87 - 2.92 (1H, m), 2.99 - 3.06 (1H, m), 3.58 - 3.62 (1H, m), 3.65 - 3.70 (1H, m), 4.33 (2H, q), 6.83 - 6.87 (2H, m), 7.90 - 7.94 (2H, m). MS: m/z = 263 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 82

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-iodo-benzamide

Trifluoroacetic acid (3.85 mL, 50.02 mmol) was added in one portion to tert-butyl 3-(3,5-dimethoxyphenethyl)-5-(4-iodobenzamido)-1H-pyrazole-1-carboxylate (288mg, 0.5 mmol) in DCM (10 mL) at room temperature. The resulting solution was stirred for 24 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (5 mL). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/Methanol and pure fractions were evaporated to dryness to afford a tan solid. The solid was triturated with DCM to give the title compound (58.0 mg, 24.3 %) as a white solid; ^{1}H NMR (399.9 MHz, DMSO-d6) δ 2.88 (4H, s), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.47 (1H, s), 7.77 (2H, d), 7.87 (2H, d), 10.73 (1H, s), 12.17 (1H, s).

MS m/z: 478 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.021 μM.

Tert-butyl 3-(3,5-dimethoxyphenethyl)-5-(4-iodobenzamido)-1H-pyrazole-1-carboxylate used as starting material was prepared as follows:

4-Iodobenzoyl chloride (1.332 g, 5.00 mmol) was added to *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (1.737 g, 5 mmol) and pyridine (0.445 mL, 5.50 mmol) in DCM (15 mL).The resulting suspension was stirred at 25°C for 24 h. The reaction mixture was evaporated to dryness and redissolved in EtOAc (25 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product.

The crude product was purified by silica column chromatography, eluting with a gradient of 5 - 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 3-(3,5-dimethoxyphenethyl)-5-(4-iodobenzamido)-1H-pyrazole-1-carboxylate (1.187 g, 41.1 %) as a white solid. 1H NMR (399.9 MHz, CDCl3) δ 1.70 (9H, s), 2.95 (4H, s), 3.78 (6H, s), 6.32 (1H, t), 6.42 (2H, d), 6.91 (1H, s), 7.64 - 7.67 (2H, m), 7.88 - 7.90 (2H, m), 11.13 (1H, s). MS m/z: 478 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 83

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-2-[(3-methyl-1,2-oxazol-5-yl)methylamino]benzamide

NaHMDS (1M solution in THF, 0.83ml, 0.828mmol, 2.5eq) was added dropwise to a solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (90mg, 0.364mmol, 1.1eq) and methyl 2-{[(3-methylisoxazol-5-yl)methyl]amino}-benzoate (115mg, 0.331mmol, 1eq), stirred in THF (4ml) under nitrogen. The solution was stirred at room temperature for 50 mins. The solution was quenched with satd. aq. NH_4Cl, diluted with water (5ml) and extracted with ethyl acetate (3 x 8ml). The crude product was purified by silica column chromatography, eluting with a gradient of 0-1.5% MeOH in DCM. Fractions containing product were evaporated and further purified by reverse phase prep. HPLC purification, eluting with a gradient of MeCN/H_2O + 0.1% TFA to afford the title compound as an off-white solid (16mg, 10% yield); ^{1}H NMR (399.902 MHz, DMSO) δ 2.20 (s, 3H), 2.88 (s, 4H), 3.73 (s, 6H), 4.57 (s, 2H), 6.21 (s, 1H), 6.33 (t, 1H), 6.41 (bs, 1H), 6.43 (d, 3H),

6.65 (t, 1H), 6.77 (d, 1H), 7.28 - 7.34 (m, 1H), 7.75 - 7.79 (m, 1H), 8.10 (bs, 1H), 10.50 (s, 1H). MS: m/z 462 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 1.0 μM.

Methyl 2-{[(3-methylisoxazol-5-yl)methyl]amino}-benzoate, used as starting material was prepared as follows:

1-(3-Methylisoxazol-5-yl)methanamine (155mg, 1.37mmol, 1.2eq), potassium phosphate (341mg, 1.60mmol, 1.4eq), S-Phos (95mg, 0.230mmol, 0.2eq) and Pd_2dba_3 (13mg, 0.06mmol, 0.05eq) were stirred in toluene (5ml) under nitrogen. Methyl 2-iodobenzoate (300mg, 1.14mmol, 1eq) was added and the mixture was stirred at room temperature for 3 days, then at 90°C for 6h. The reaction mixture was allowed to cool, poured into water (100ml) and extracted with ethyl acetate (3 x 60ml). The combined extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. The residual gummy oil was triturated with ether resulting in precipitation of a small amount of a yellow solid which was filtered off. The filtrate was evaporated and triturated again with methanol and a second precipitate was removed by filtration. The filtrate was evaporated, then purified by silica column chromatography, eluting with DCM. The product fractions were evaporated to afford methyl 2-{[(3-methylisoxazol-5-yl)methyl]amino}-benzoate as a yellow oily gum (128mg, 45% yield); ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.88 (s, 3H), 4.53 (d, 2H), 5.99 (s, 1H), 6.62 - 6.70 (m, 2H), 7.32 - 7.38 (m, 1H), 7.92 - 7.96 (m, 1H), 8.19 (t, 1H). MS: m/z 247 (MH+)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 84

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide

A solution of NaHMDS (1.500 ml, 1.50 mmol) in THF (1.0M) was added to a stirred solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (0.347 g,

1.0 mmol) and methyl 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxylate (0.284 g, 1.20 mmol) in THF (5.00 ml) cooled to 0°C under nitrogen.

The resulting solution was stirred at ambient temperature for 70 mins. The mixture was then partitioned between ethyl acetate and saturated aqueous ammonium chloride solution diluted with water (1:2). A solid was filtered off to give crude product as a white solid. This was purified by preparative LCMS using decreasingly polar mixtures of water (containing 0.1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.127 g, 28.1 %) as a white solid; ^{1}H NMR (500.13 MHz, DMSO-d_6, CD_3CO_2D) δ 2.69 (3H, s), 2.89 - 2.95 (4H, m), 3.07 - 3.08 (4H, m), 3.75 (6H, s), 3.92 - 3.97 (4H, m), 6.34 (1H, s), 6.42 (3H, s), 7.41 (1H, d), 8.00 (1H, d)

MS: m/z 452 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.39 μM.

Methyl 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxylate, used as starting material was prepared as follows:-

A suspension of 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide (221 mg, 1.00 mmol) in sodium hydroxide (2.0M aqueous) (10.000 mL, 20.00 mmol), was stirred at reflux for 3 h and then allowed to cool to room temperature. The reaction mixture was adjusted to pH7 by addition of 2M HCl (10mL) and saturated NaHCO3. The crude product was purified by ion exchange chromatography, using a SCX2 column. The desired product was eluted from the column using methanol and the fractions were evaporated to dryness to afford 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxylic acid as a white solid. This material was suspended in methanol (10.00 ml) at 0°C and treated with thionyl chloride (0.729 ml, 10.00 mmol), over a period of 5 mins. The resulting suspension was stirred at ambient temperature for 18 h. Sodium bicarbonate solution was added until basic and then the mixture was extracted with ethyl acetate (2 x 75mL). The solution was further extracted with 1-butanol (100mL). The organic extracts were combined and evaporated to dryness to give methyl 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxylate a white solid, 212mg.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.43 (4H, t), 3.74 (4H, t), 3.88 (3H, s), 7.30 (1H, d), 7.84 (1H, d)

MS: m/z 237 (MH+)

6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide, used as starting material was prepared as follows:

6-Chloropyridazine-3-carboxamide (0.315 g, 2 mmol) and 1-methylpiperazine (0.555 ml, 5.00 mmol) were suspended in 2-propanol (2.000 ml) and sealed into a microwave tube. The reaction was heated to 130 °C for 30 mins in the microwave reactor and cooled to ambient temperature. The resulting precipitate was collected by filtration, washed with 2-propanol (10 mL) and dried under vacuum to afford 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide (0.333 g, 75 %) as a white solid, which was used without further purification. A sample (100mg) of the crude product was purified by preparative LCMS using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-(4-methylpiperazin-1-yl)pyridazine-3-carboxamide (54mg) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.24 (3H, s), 2.44 (4H, t), 3.71 (4H, t), 7.34 (1H, d), 7.50 (1H, s), 7.84 (1H, d), 8.11 (1H, s)

MS: m/z 222 (MH+)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 85

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide

A solution of NaHMDS (2.100 ml, 2.10 mmol) in THF (1.0M) was added to a stirred solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (0.486 g, 1.4 mmol) and methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate (0.397 g, 1.68 mmol) in THF (7.00 ml, cooled to -20°C), over a period of 5 mins under nitrogen. The resulting solution was stirred at room temperature for 18 h. The mixture was heated to reflux for 90 min, then cooled to room temperature. More NaHMDS (2.100 ml, 2.10 mmol) was added and the mixture stirred for 70 mins. The mixture was allowed to stand for 96 h and then partitioned between ethyl acetate and 2.0M aqueous hydrochloric acid. The aqueous layer was separated and basified with 50% aqueous sodium hydroxide solution and then extracted with ethyl acetate (75 mL). The organic layer was washed with saturated brine (50

mL)and then dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by preparative LCMS using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (4.00 mg, 0.633 %) as a white solid; ^{1}H NMR (500.13 MHz, DMSO-d_6, CD_3CO_2D) δ 2.34 (3H, s), 2.53 (4H, t), 2.90 (4H, t), 3.74 (6H, s), 3.89 (4H, t), 6.33 (1H, t), 6.35 (1H, s), 6.42 (2H, d), 8.89 (2H, s)

MS: m/z 452 (MH+)

FGFR Kinase assay – Caliper, IC_{50} 0.118 μM.

FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0149 μM.

Methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate, used as starting material was prepared as follows:

Methyl 2-chloropyrimidine-5-carboxylate (0.863 g, 5.0mmol), N,N-diethylethanamine (0.697 ml, 5.00 mmol) and 1-methylpiperazine (0.565 ml, 5.09 mmol) were suspended in 2-propanol (10.00 ml) and sealed into a microwave tube. The reaction was heated to 100°C for 10 mins in the microwave reactor and cooled to room temperature. The precipitate was collected by filtration, washed with EtOH (5 mL) and dried under vacuum to afford methyl 2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxylate (0.405 g, 34.3 %) as a white solid, which was used without further purification.

MS: m/z 237 (MH+)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 86

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-methylpiperazine-1-carbonyl)benzamide

A solution of NaHMDS (1M in THF) (2.86 mL, 2.86 mmol) was added dropwise to a stirred solution of methyl 4-(4-methylpiperazine-1-carbonyl)benzoate (0.250 g, 0.95 mmol) and *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazole-1-carboxylate (0.397 g, 1.14 mmol) in THF (2 mL), over a period of 10 mins under nitrogen. The resulting solution was stirred at room temperature for 18 h. The reaction mixture was poured into saturated NH_4Cl

(25 mL), extracted with EtOAc (2 x 25 mL), washed with saturated brine and dried over $MgSO_4$, filtered and evaporated to afford the crude product (0.501 g) as a yellow gum. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% ammonium hydroxide) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.257 g, 56.5 %) as a yellow solid; ^{1}H NMR (399.9 MHz, DMSO-d6) δ 2.21 (3H, s), 2.25 - 2.40 (4H, m), 2.89 (4H, s), 3.16 - 3.20 (1H, d), 3.32 (4H, s), 3.72 (6H, d), 6.33 (1H, m), 6.42 - 6.44 (2H, d), 7.46 - 7.50 (2H, d), 8.02 - 8.06 (2H, d)

MS: m/z 478 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.096 μM.

Methyl 4-(4-methylpiperazine-1-carbonyl)benzoate , used as starting material was prepared as follows:

Oxalyl chloride (0.533 mL, 6.11 mmol) was added dropwise to a stirred suspension of 4-(methoxycarbonyl)benzoic acid (1 g, 5.55 mmol) in DCM (20 mL) under nitrogen. The resulting suspension was stirred at room temperature for 30 mins. DMF (0.05 mL) was added dropwise under nitrogen. The resulting suspension was stirred for 90 mins. A solution of 1-methylpiperazine (0.554 mL, 5.00 mmol) and pyridine (1.211 mL, 14.99 mmol) in DCM (15 mL) was added dropwise at 0°C, over a period of 60 mins under nitrogen. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was evaporated to dryness to afford the crude product (1.791 g) as a dark orange solid. The solid was redissolved in DCM and washed with $NaHCO_3$. The organic layer was evaporated to dryness to afford methyl 4-(4-methylpiperazine-1-carbonyl)benzoate (0.890 g, 61.1 %) as an orange gum, which solidified on standing. Used without further purification.

1H NMR (399.9 MHz, CDCl3) δ 2.78 (4H, s), 3.43 (4H, s), 7.42 - 7.45 (2H, m), 8.04 - 8.06 (2H, m)

MS: m/z 263 (MH+)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 87

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-propan-2-ylpiperazin-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-propan-2-ylpiperazin-1-yl)benzamide was prepared as for Example 94, but starting from methyl 4-(4-propan-2-yl-piperizin-1-yl)benzoate (263 mg, 0.84 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazole-1-carboxylate (244mg, 0.7 mmol) and 1M NaHMDS (1.13 ml, 1.13mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 38-58% gradient of acetonitrile in water containing 1% 0.880 ammonia. The clean fractions were taken and evaporated to afford the title compound as a white solid (18 mg, 5%); ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.02 (6H, d), 2.55 - 2.61 (4H, m), 2.65 - 2.76 (1H, m), 2.89 (2H, s), 3.21 – 3.28 (4H, s), 3.31 (2H, s), 3.72 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.45 (1H, s), 6.95 (2H, d), 7.90 (2H, d), 10.29 (1H, s), 12.07 (1H, s)
MS: m/z 478 (MH+).
Mean of n=5, FGFR Kinase assay – Caliper, IC_{50} 0.0004 μM.

Methyl 4-(4-propan-2-yl-piperizin-1-yl)benzoate used as starting material was prepared as follows:-

Tris(dibenzylideneacetone)dipalladium(0) (0.014g, 0.02 mmol) was added to a deoxygenated suspension of 1-isopropylpiperazine (0.151 g, 1.18 mmol), methyl 4-bromobenzoate (0.215 g, 1 mmol), potassium carbonate (0.193g, 1.4 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.012 g, 0.03 mmol) in DME (4 mL), and sealed into a microwave tube. The reaction was heated to 130°C for 10 mins in the microwave reactor and cooled to room temperature. The reaction mixture was evaporated to dryness, redissolved in EtOAc (25 mL) and washed sequentially with water (15 mL) and saturated brine (15 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by silica column chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(4-propan-2-yl-piperizin-1-yl)benzoate (0.170 g, 64.8 %) as a tan solid.
1H NMR (399.9 MHz, CDCl3) δ 1.09 (6H, d), 2.66 (4H, t), 2.73 (1H, q), 3.34 (4H, t), 3.86 (3H, s), 6.84 - 6.88 (2H, m), 7.89 - 7.93 (2H, m). MS: m/z 264 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 88

4-(4-Cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

4-(4-cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared as for Example 94, but starting from ethyl 4-(4-cyclopropylpiperazin-1-yl)benzoate (193 mg, 0.7 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (292mg, 0.84 mmol) and 1M NaHMDS (1.23 ml, 1.23mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (acidic) using a 16-36% gradient of acetonitrile in water containing 0.1% TFA. The clean fractions were neutralised and evaporated to afford the title compound as a white solid (40 mg, 12%); ^{1}H NMR (500.13 MHz, DMSO-d_6 + d_4 Acetic Acid) δ 0.46 (2H, d), 0.50 (2H, d), 1.79 – 1.84 (1H, m), 2.78 (4H, t), 2.90 (4H, s), 3.24-3.31 (4H, m), 3.75 (6H, s), 6.32 (1H, s), 6.33 (1H, t), 6.42 (2H, d), 6.94 – 6.96 (2H, m), 7.86 – 7.88 (2H, m).

FGFR Kinase assay – Caliper, IC_{50} 0.156 μM.

FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00077 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Ethyl 4-(4-cyclopropylpiperazin-1-yl)benzoate used as starting material was prepared as follows:-

Ethyl 4-fluorobenzoate (0.153 mL, 1.04 mmol) and 1-cyclopropylpiperazine (0.2637 g, 2.09 mmol) were taken up in DMA (2 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 90 mins in the microwave reactor and cooled to room temperature. The reaction mixture was evaporated to afford a brown gum, which solidified on standing. The crude product was purified by silica column chromatography, eluting with 10% MeOH(containing 0.1% aqueous ammonia) in DCM. Pure fractions were evaporated to dryness to afford the impure product as a yellow solid. The impure product was purified again by silica column chromatography, eluting with a gradient of 0 - 2.5% MeOH in DCM. Pure

fractions were evaporated to dryness to afford ethyl 4-(4-cyclopropylpiperazin-1-yl)benzoate (0.096 g, 33.6 %) as a beige solid.

1H NMR (399.9 MHz, CDCl3) δ 0.45 - 0.52 (5H, m), 1.36 (3H, t), 2.75 (4H, t), 3.29 (4H, t), 4.32 (2H, q), 6.84 - 6.88 (2H, m), 7.90 - 7.93 (2H, m)

m/z (ES+) (M+H)+ = 275

1-Cyclopropylpiperazine used as starting material was prepared as follows:-

A solution of tert-butyl 4-cyclopropylpiperazine-1-carboxylate (0.792 g, 3.50 mmol) in 4M HCl in 1,4-dioxane (4.37 mL, 17.50 mmol) was stirred at room temperature for 3 h under nitrogen. The reaction mixture was filtered and washed with ether to afford crude 1-cyclopropylpiperazine (0.659 g) as a white solid. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and pure fractions were evaporated to dryness to afford 1-cyclopropylpiperazine (0.264 g, 59.7 %) as a yellow oil.

1H NMR (399.9 MHz, DMSO-d6) δ 0.25 - 0.30 (2H, m), 0.35 - 0.40 (2H, m), 1.54 - 1.60 (1H, m), 2.43 (4H, t), 2.60 - 2.65 (4H, t), 3.30 (1H, s)

tert-Butyl 4-cyclopropylpiperazine-1-carboxylate used as starting material was prepared as follows:-

MeOH (0.3 mL), ((1-ethoxycyclopropyl)oxy)trimethylsilane (2 g, 11.47 mmol) and acetic acid (1.051 mL, 18.35 mmol) were added to a stirred solution of tert-butyl piperazine-1-carboxylate (1.068 g, 5.735 mmol) in THF (40 mL) under nitrogen. Sodium cyanoborohydride (0.541 g, 8.60 mmol) was added portionwise over a period of 10 mins. The resulting mixture was stirred at 60 °C for 24 h. The reaction mixture was evaporated to dryness and mixed with water (80 mL) and 1M HCl (25 mL). This solution was washed with EtOAc (2 x 50 mL), the aqueous layer was basified with K_2CO_3, and extracted with EtOAc (2 x 30 mL). The organic layers were combined, washed with saturated brine (30 mL), dried over MgSO4, filtered and evaporated to afford tert-butyl 4-cyclopropylpiperazine-1-carboxylate (0.792 g, 61.1 %) as a colourless oil which crystallised on standing.

1H NMR (399.9 MHz, DMSO-d6) δ 0.30 - 0.34 (2H, m), 0.40 - 0.44 (2H, m), 1.41 (9H, s), 1.60 - 1.65 (1H, m), 2.47 (4H, t), 3.26 (4H, t)

Example 89

4-(4-Cyclobutylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

4-(4-cyclobutylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared as for Example 94, but starting from ethyl 4-(4-cyclobutyllpiperazin-1-yl)benzoate (202 mg, 0.7 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (292mg, 0.84 mmol) and 1M NaHMDS (1.23 ml, 1.23mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 39-59% gradient of acetonitrile in water containing 1% 0.880 ammonia. . The clean fractions were combined and evaporated to afford the title compound (21 mg, 6%); ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.61-1.71 (2H, m), 1.81 - 1.86 (2H, m), 1.99 - 2.02 (2H, m), 2.38 (4H, t), 2.75 (1H, s), 2.85 - 2.87 (4H, m), 3.26 - 3.27 (4H, m), 3.72 (6H, d), 6.33 (1H, t), 6.42 - 6.43 (2H, m), 6.45 (1H, s), 6.95 (2H, d), 7.90 (2H, d), 10.29 (1H, s), 12.07 (1H, s). MS = m/z 490 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.009 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Ethyl 4-(4-cyclobutylpiperazin-1-yl)benzoate, used as starting material, was prepared as follows:

Ethyl 4-fluorobenzoate (0.225 mL, 1.53 mmol) and 1-cyclobutylpiperazine (0.430 g, 3.07 mmol) were taken up in DMA (3 mL) and sealed into a microwave tube. The reaction was heated to 150 °C for 90 mins in the microwave reactor and cooled to room temperature. The reaction was not complete, so it was reheated at 150°C for a further 1h. The reaction mixture was evaporated to dryness and the crude product purified by silica column chromatography, eluting with a gradient of 0 - 2.5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(4-cyclobutylpiperazin-1-yl)benzoate (0.050 g, 11.31 %) as a yellow solid. 1H NMR (399.9 MHz, CDCl3) δ 1.29 (3H, t), 1.65 - 1.70 (2H, m), 1.86 (2H, t), 2.00 (2H, q), 2.41 (4H, d), 2.68 - 2.75 (1H, m), 3.27 (4H, t), 4.25 (2H, q), 6.79 (2H, d), 7.85 (2H, d). MS= m/z = 289 (MH+).

1-Cyclobutylpiperazine, used as starting material, was prepared as follows: -

Trifluoroacetic acid (7.84 mL, 101.73 mmol) was added to a stirred solution of tert-butyl 4-cyclobutylpiperazine-1-carboxylate (2.445 g, 10.17 mmol) in DCM (25 mL) cooled to 0°C under nitrogen and stirred at 20 °C for 24 h. The reaction mixture was evaporated to dryness and diluted with DCM (30 mL). This was then washed with saturated NaHCO3 (2 x 10 mL) and the organic layers evaporated to dryness. Product was still present in the aqueous layer, so this was basified with 2M NaOH and extracted with DCM (3 x 10 mL) and EtOAc (1 x 10 mL). Organic fractions were combined and evaporated to dryness to afford 1-cyclobutylpiperazine (0.430 g, 30.1 %). 1H NMR (399.9 MHz, DMSO-d6) δ 1.60 - 1.67 (2H, m), 1.72 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.25 (4H, s), 2.57 - 2.60 (1H, d), 2.82 (4H, t)

tert-Butyl 4-cyclobutylpiperazine-1-carboxylate, used as starting material, was prepared as follows: -

Water (0.3 mL), cyclobutanone (2.000 g, 28.53 mmol) and acetic acid (3.48 mL, 60.86 mmol) were added to a stirred solution of tert-butyl piperazine-1-carboxylate (3.54 g, 19.02 mmol) in THF (40 mL) under nitrogen. Sodium cyanoborohydride (1.793 g, 28.53 mmol) was added portionwise over a period of 10 mins. The resulting mixture was stirred at 60 °C for 19 h. The reaction mixture was evaporated to dryness and mixed with water (80 mL) and 1M HCl (25 mL). The solution was washed with EtOAc (2 x 50 mL), basified with K_2CO_3 and extracted with EtOAc (2 x 30 mL). The organic layer was washed with saturated brine and dried over MgSO4, filtered and evaporated to afford pure tert-butyl 4-cyclobutylpiperazine-1-carboxylate (2.445 g, 53.5 %) as a colourless oil.

1H NMR (399.9 MHz, DMSO-d6) δ 1.40 (9H, s), 1.60 - 1.65 (2H, m), 1.75 - 1.80 (1H, m), 1.90 - 2.00 (2H, m), 2.17 (1H, t), 2.65 - 2.75 (1H, m), 3.30 (4H, d). MS = m/z 241 (MH+).

Example 90

4-(4-Acetylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]benzamide

4-(4-acetylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared as for Example 94, but starting from methyl 4-(4 - acetylpiperazin-1-yl)benzoate (221 mg, 0.84 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazole-1-carboxylate (244mg, 0.7 mmol) and 1M NaHMDS (1.13 ml, 1.13mmol) in THF (5ml). The

crude product was purified by reverse phase prep. HPLC (basic) using a 31-51% gradient of acetonitrile in water, containing 1% 0.880 ammonia. The clean fractions were taken and evaporated to afford the title compound as a white solid (3 mg, 1.0%); ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.06 (3H, s), 2.78 (4H, s), 3.28 (2H,s) 3.25 (2H, t), 3.49 – 3.56(4H, m), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.45 (1H, s), 6.99 (2H, d), 7.92 (2H, d), 10.32 (1H, s), 12.08 (1H, s).

MS: m/z 478 (MH+).

Mean of n=5, FGFR Kinase assay – Caliper, IC_{50} 0.056 μM.

A deoxygenated suspension of 1-acetylpiperazine (0.308 g, 2.40 mmol), methyl 4-bromobenzoate (0.430 g, 2 mmol), tri-potassium orthophosphate (0.594 g, 2.80 mmol), 2-dicyclohexylphosphino -2',6'-dimethoxy-1,1'-biphenyl (0.164 g, 0.40 mmol) and tris(dibenzylideneacetone)dipaladium(0) (0.092 g, 0.10 mmol) in toluene (10 mL) was stirred at 100°C, over a period of 24 h under nitrogen. The cooled reaction mixture was filtered and evaporated to give crude product. The crude product was purified by silica column chromatography, eluting with a gradient 0 - 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(4-acetylpiperazin-1-yl)benzoate (0.295 g, 56.2 %) as a yellow solid.

1H NMR (399.9 MHz, CDCl3) δ 2.07 (3H, s), 3.24 - 3.30 (4H, m), 3.56 (2H, t), 3.70 - 3.72 (2H, m), 3.80 (3H, s), 6.78 - 6.81 (2H, m), 7.85 - 7.89 (2H, m). MS: m/z 263 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 91

N-[5-[2-(3-Methoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(4-methylsulfonylpiperazin-1-yl)benzamide

A solution of formic acid (5 mL, 130.36 mmol) and N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(4-(methylsulfonyl)piperazin-1-yl)benzamide (255 mg, 0.47 mmol) was stirred at 85 °C for 2 h. The reaction mixture was cooled and evaporated to dryness. The crude product was purified by reverse phase prep. HPLC (basic) using a 36-46% gradient of acetonitrile in water, containing 1% 0.880 ammonia. The clean fractions were combined and

evaporated to afford the title compound (43.0 mg, 18.82 %) as a white solid; ^{1}H NMR (499.9 MHz, $DMSO_d6$ + CD_3CO_2D) δ 2.87 (3H, s), 2.88 –2.92 (4H, m), 3.28 – 3.32 (4H, m), 3.39 – 3.42 (4H, m), 3.73 (3H, s), 6.30 (1H, s), 6.71 – 6.74 (1H, m), 6.77 (1H, s0, 6.80 (2H, d), 6.94 – 6.98 (2H, m), 7.16 (1H, t), 7.85 – 7.89 (2H, m).

MS: m/z = 484 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.25 μM.

N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(4-(methylsulfonyl)piperazin-1-yl)benzamide used as starting material was prepared as follows:-

Methanesulphonyl chloride (0.042 mL, 0.55 mmol) was added at 0°C to a solution of N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(piperazin-1-yl)benzamide (0.231 g, 0.5 mmol) and N,N-diethylethanamine (0.077 mL, 0.55 mmol) in DCM (4 mL). The resulting solution was stirred at 20 °C for 1 h. The reaction mixture was diluted with saturated sodium hydrogen carbonate (10 ml) filtered and the solid washed with DCM (2 x 10 ml). The organic layers were combined and washed with water (20 ml) and saturated brine (20 ml). The organics were dried (MgSO4), filtered and evaporated to afford crude product. The crude product was purified by silica column chromatography, eluting with a gradient of 0 - 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(4-(methylsulfonyl)piperazin-1-yl)benzamide (0.255 g, 94 %) as a white solid. MS: m/z = 540 (MH+).

N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(piperazin-1-yl)benzamide was prepared as follows:-

A 2M solution of trimethylaluminium in toluene (6.25 mL, 12.50 mmol) was added dropwise to a stirred solution of and 1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-amine (1.367 g, 5.00 mmol) and ethyl 4-(piperazin-1-yl)benzoate (1.171 g, 5 mmol) in toluene (20 mL) at 4°C, over a period of 5 mins under nitrogen. The resulting solution was stirred at 20°C for 18 h. The reaction mixture was quenched with methanol (20 mL), filtered and evaporated to afford tan solid. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% MeOH in DCM and 0.1% ammonia. Pure fractions were evaporated to dryness to afford N-(1-tert-butyl-3-(3-methoxyphenethyl)-1H-pyrazol-5-yl)-4-(piperazin-1-yl)benzamide (0.520 g, 22.53 %) as a white solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.59 (9H, s), 2.81 - 2.91 (4H, m), 2.96 - 2.99 (4H, m), 3.23 (3H, t), 3.25 - 3.42 (1H, m), 3.72 (3H, s), 6.17 (1H, s), 6.64 - 6.68 (1H, m), 6.73 (1H, t), 6.78 (1H, d), 6.84 - 6.88 (2H, m), 7.12 (1H, t), 7.38 (1H, s), 7.67 - 7.71 (2H, m).

Piperazine (17.23 g, 200.00 mmol) was added to ethyl 4-fluorobenzoate (7.34 mL, 50 mmol), in DMSO (50 mL) warmed to 120°C under nitrogen. The resulting solution was stirred at 120 °C for 20 h. The reaction mixture was cooled and the solvent evaporated. The product was partitioned between saturated aq. sodium hydrogen carbonate solution (100 ml) and ethyl acetate (100ml). This was extracted with ethyl acetate (2 x 75 ml), washed with brine solution, dried over MgSO4, filtered and evaporated. The crude product was purified by silica column chromatography, eluting with 10% methanol in dichloromethane containing 0.1% 0.880 ammonia. Pure fractions were evaporated to dryness to afford the product as a solid.

The insoluble solid was slurried in DCM (500 ml) and stirred for 1 h. This solution was filtered and the organic solution dried over MgSO4, filtered and evaporated to give the bulk of the product as a solid. The solids were combined to give ethyl 4-(piperazin-1-yl)benzoate (9.53 g, 81 %). 1H NMR (399.9 MHz, $CDCl_3$) δ 1.28 - 1.32 (3H, m), 2.94 - 2.96 (4H, m), 3.20 - 3.22 (4H, m), 4.26 (2H, q), 6.77 - 6.81 (2H, m), 7.84 - 7.87 (2H, m). MS: m/z = 236 (MH+)

5-[2-(3-methoxyphenyl)ethyl]-2-tert-butyl-pyrazol-3-amine was prepared as outlined in Example 13.

Example 92

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(1-methyl-4-piperidyl)benzamide

A solution of NaHMDS (1M in THF) (5.91 mL, 5.91 mmol) was added dropwise to a stirred solution of methyl 4-(1-methylpiperidin-4-yl)benzoate (0.4594 g, 1.97 mmol) and *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazole-1-carboxylate (0.821 g, 2.36 mmol) in THF (4 mL), over a period of 10 mins under nitrogen. The resulting solution was stirred at room temperature for 18 h. The reaction mixture was poured into saturated NH_4Cl (25 mL), extracted with EtOAc (2 x 25 mL), washed with saturated brine and dried over $MgSO_4$, filtered and evaporated to afford the crude product (1.0719 g) as an orange gum. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water

(containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.142 g, 16.08 %) as a white solid;
^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.64 - 1.78 (4H, m), 1.97 - 2.01 (2H, m), 2.22 (3H, s), 2.53 - 2.58 (1H, m), 2.88 - 2.91 (6H, m), 3.73 (6H, s), 6.33 (1H, t), 6.42 - 6.44 (3H, m), 7.35 (2H, d), 7.93 (2H, d), 10.57 (1H, s), 12.08 (1H, s)
MS: m/z 449 (MH+)
Mean of n=1, FGFR Kinase assay – Caliper, IC_{50} 0.0079 μM.

Methyl 4-(1-methylpiperidin-4-yl)benzoate, used as starting material, was prepared as follows:-
Water (0.2 mL), paraformaldehyde (0.470 g, 15.64 mmol) and acetic acid (0.895 mL, 15.64 mmol) were added to a stirred suspension of 4-(4-(methoxycarbonyl)phenyl)piperidinium chloride (1 g, 3.91 mmol) in THF (20 mL) under nitrogen. Sodium cyanoborohydride (0.369 g, 5.87 mmol) was added portionwise over a period of 10 mins. The resulting mixture was stirred at 60 °C for 19 h. The reaction mixture was evaporated to dryness and mixed with water (20 mL) and 1M HCl (5 mL). The solution was washed with EtOAc (2 x 15 mL), basified with K_2CO_3 and extracted with EtOAc (2 x 15 mL). The organic layer was washed with saturated brine and dried over MgSO4, filtered and evaporated to afford pure methyl 4-(1-methylpiperidin-4-yl)benzoate (0.459 g, 50.4 %)as a colourless oil which crystallised on standing.
1H NMR (399.9 MHz, DMSO-d6) δ 1.63 - 1.72 (2H, m), 1.73 - 1.77 (2H, m), 1.96 - 2.03 (2H, m), 2.21 (3H, s), 2.87 - 2.90 (2H, m), 3.85 (3H, s), 4.30 - 4.31 (1H, m), 7.40 (2H, d), 7.88 - 7.91 (2H, m)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 93

4-(3,4,6,7,8,8a-Hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

4-(3,4,6,7,8,8a-Hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared as for Example 94, but

starting from methyl 4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)benzoate (193 mg, 0.7 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (292mg, 0.84 mmol) and 1M NaHMDS (1.23 ml, 1.23mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 33-53% gradient of acetonitrile in water, containing 1% 0.880 ammonia. The clean fractions were combined and evaporated to afford the title compound (34 mg, 10%); ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.37 - 1.41 (1H, m), 1.67 - 1.77 (2H, m), 1.84 - 1.88 (1H, m), 1.99 - 2.06 (1H, m), 2.09 (1H, t), 2.18 - 2.25 (1H, m), 2.80 - 2.84 (1H, m), 2.87 (4H, s), 3.01 - 3.06 (2H, m), 3.73 (6H, s), 3.80 - 3.83 (1H, m), 3.96 - 3.98 (1H, m), 6.33 (1H, t), 6.42 - 6.45 (3H, m), 6.97 (2H, d), 7.90 (2H, d), 10.28 (1H, s), 12.07 (1H, s)

MS = m/z 476 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.037 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Methyl 4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)benzoate, used as starting material was prepared as follows:-

Methyl 4-iodobenzoate (2.076 g, 7.92 mmol), cesium carbonate (5.16 g, 15.85 mmol), 2-acetylcyclohexanone (0.209 mL, 1.58 mmol) and copper(I) iodide (0.075 g, 0.40 mmol) were added to a stirred solution 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (1 g, 7.92 mmol) in DMF (20 mL) under nitrogen. The resulting suspension was stirred at 90 °C for 20 h. The reaction mixture was evaporated to dryness and redissolved in a mixture of methanol and water. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and pure fractions were evaporated to dryness to afford the desired compound (1.243 g, 60.2 %) as a brown gum.

1H NMR (399.9 MHz, DMSO-d6) δ 1.33 - 1.43 (1H, m), 1.57 - 1.79 (3H, m), 1.81 - 1.89 (1H, m), 1.99 - 2.03 (1H, m), 2.07 (1H, q), 2.16 - 2.23 (1H, m), 2.56 (1H, t), 2.83 - 2.95 (2H, m), 3.00 - 3.05 (2H, m), 3.06 - 3.09 (1H, m), 3.75 - 3.78 (3H, m), 3.86 (1H, t), 3.98 - 4.01 (1H, m), 6.98 - 7.02 (2H, m), 7.77 - 7.80 (2H, m).

MS = m/z 261 (MH+).

Example 94

4-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

A 1M solution of NaHMDS in THF (1.13 ml, 1.05 mmol) was added to a stirred solution of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (244mg, 0.7 mmol) and methyl 4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)benzoate (231 mg, 0.84 mmol) in THF (5ml) at 0°C under nitrogen, over 5 minutes. The reaction mixture was stirred for an additional 5 minutes at 0°C, then stirred at 20°C for 18 h. An additional amount of *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (80 mg, 0.23 mmol) was added with 1M NaHMDS in THF (1.13 ml, 1.13mmol). The reaction mixture was stirred for an additional 3 h. The reaction mixture was quenched with saturated ammonium chloride (20 ml) and extracted with ethyl acetate (3 x 20 ml). The extracts were washed with saturated brine solution (15 ml), dried (MgSO4) and evaporated to give crude product. The crude product was purified by reverse phase prep. HPLC (basic) using a 38-58% gradient of acetonitrile in water containing 1% 0.880 ammonium hydroxide. The clean fractions were taken and evaporated to afford the title compound as a white solid (32 mg, 9%); ^{1}H NMR (500.13 MHz, DMSO-d_6) δ 1.25 (1H, s), 1.62 (2H, t), 1.72 (1H, d), 1.93 - 1.95 (2H, m), 2.19 - 2.20 (1H, m), 2.44 (1H, s), 2.81 (3H, q), 2.87 (4H, s), 3.28 (1H, s), 3.69 (1H, s), 3.72 (6H, s), 3.77 (1H, d), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 6.96 (2H, d), 7.89 (2H, d), 10.29 (1H, s), 12.07 (1H, s). MS: m/z 490 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.081 μM.

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Methyl 4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)benzoate, used as starting material, was prepared as follows:-

A solution of 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine (5 g) in a mixture of methanol and water (1:1) was converted to the freebase by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH

and pure fractions were evaporated to dryness to afford the desired compound (1.5224 g, 10.86 mmol) as a yellow solid.

Methyl 4-iodobenzoate (2.84 g, 10.86 mmol), cesium carbonate (7.07 g, 21.71 mmol), 2-acetylcyclohexanone (0.286 mL, 2.17 mmol) and copper(I) iodide (0.103 g, 0.54 mmol) were added to a stirred solution of 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine (1.5224 g, 10.86 mmol) in DMF (30 mL) under nitrogen. The resulting suspension was stirred at 90 °C for 20 h. The reaction mixture was evaporated to dryness and dissolved in methanol. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and pure fractions were evaporated to dryness to afford a brown gum. This was purified again by silica column chromatography, eluting with 5% MeOH (containing 0.1% ammonium hydroxide) in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.503 g, 16.8 %) as an orange solid ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.29 - 1.33 (1H, m), 1.26 - 1.40 (1H, m), 1.62 (1H, d), 1.64 (1H, d), 1.65 - 1.68 (1H, m), 1.69 (1H, s), 1.80 - 1.82 (1H, m), 2.04 - 2.10 (2H, m), 2.32 - 2.39 (1H, m), 2.61 (1H, d), 2.89 (2H, d), 3.01 - 3.08 (1H, m), 3.58 - 3.63 (1H, m), 3.70 - 3.75 (1H, m), 3.86 (3H, s), 6.83 - 6.87 (2H, m), 7.89 - 7.93 (2H, m). MS m/z = 275 (MH+).

Example 95

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide

A solution of NaHMDS (1M in THF) (2.83 mL, 2.83 mmol) was added dropwise to a stirred solution of methyl 4-((4-methylpiperazin-1-yl)methyl)benzoate (0.351 g, 1.41 mmol) and *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazole-1-carboxylate (0.589 g, 1.70 mmol) in THF (3 mL), over a period of 10 mins under nitrogen. DMA (3 mL) was added. The resulting solution was stirred at room temperature for 60 h. A further aliquot of NaHMDS (1.415 mL, 1.415 mmol) was added dropwise and the solution was stirred at room temperature for a further 90 mins. The reaction mixture was poured into saturated NH_4Cl (25 mL), extracted with EtOAc (2 x 25 mL), washed with saturated brine and dried over $MgSO_4$, filtered and evaporated to afford the crude product (0.8776 g) as an orange gum. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were

evaporated to dryness to afford the title compound (0.034 g, 5.19 %) as a white solid; ^{1}H NMR (500.0 MHz, DMSO-d6) δ 2.18 (3H, s), 2.34 - 2.37 (2H, m), 3.54 (2H, s), 3.73 (3H, s), 6.32 - 6.33 (1H, t), 6.41 - 6.42 (2H, d), 7.38 - 7.39 (1H, d), 7.90 - 7.92 (1H, d), 10.02 (1H, s), 11.79 (1H, s)

MS: m/z 464 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper, IC_{50} 0.14 μM.

Methyl 4-((4-methylpiperazin-1-yl)methyl)benzoate, used as starting material was prepared as follows:

A solution of (trimethylsilyl)diazomethane ((0.611 mL, 3.84 mmol) 2.0M in diethyl ether) was added dropwise to a stirred suspension of 4-((4-methylpiperazin-1-yl)methyl)benzoic acid (0.75 g, 3.20 mmol) in toluene (21 mL) and methanol (7 mL) over a period of 10 mins under nitrogen. The resulting suspension was stirred at room temperature for 3 h. A further aliquot of (trimethylsilyl)diazomethane (1.222 mL, 7.68 mmol) was added dropwise and the solution was stirred at room temperature for a further 18 h. The reaction mixture was evaporated to dryness to afford the crude product (0.723 g) as a white solid. This was taken up in DCM and the insolubles were filtered off. The filtrate was evaporated to dryness to afford the crude product. This was taken up in DCM again and more insolubles were filtered off to afford methyl 4-((4-methylpiperazin-1-yl)methyl)benzoate (0.351 g, 44.2 %), which was used without purification.

1H NMR (399.9 MHz, CDCl3) δ 2.60 - 2.61 (3H, m), 2.77 (4H, t), 2.99 (4H, s), 3.58 (1H, s), 3.62 (1H, s), 3.85 (2H, d), 7.29 - 7.38 (2H, m), 7.92 - 7.80 (2H, m)

MS: m/z 249 (MH+)

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 96

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(3,4,5-trimethylpiperazin-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-1H-pyrazol-3-yl]-4-(3,4,5-trimethylpiperazin-1-yl)benzamide was prepared following the procedure as for Example 94, but starting from

ethyl 4-(3,4,5-trimethylpiperazin-1-yl)benzoate (310 mg, 0.86 mmol), *tert*-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate (225mg, 0.65mmol) and 1M NaHMDS (2.59 ml, 2.59mmol) in THF (5ml). The crude product was purified by reverse phase prep. HPLC (basic) using a 38-58% gradient of acetonitrile in water containing 1% 0.880 ammonia. The clean fractions were taken and evaporated to afford the title compound as a white solid (23mg, 5.6%);^{1}H NMR (399.99 MHz, $CDCl_3$) δ1.09 (6H, d), 2.17-2.28 (2H, m), 2.22 (3H, s), 2.56 (2H, t), 2.81 – 2.90 (4H, m), 3.48 (2H, d), 3.68 (6H, s), 6.22 (1H, t), 6.28 (2H, s), 6.56 (1H, s), 6.78 (2H, d), 7.68 (2H, d0, 8.86 (1H, s), 9.65 (1H, s). MS: m/z 464 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00054 μM.

Ethyl 4-(3,4,5-trimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:-

Titanium(IV) isopropoxide (0.598 mL, 2.00 mmol) was added to ethyl 4-(3,5-dimethylpiperazin-1-yl)benzoate (0.262 g, 1 mmol), and paraformaldehyde (0.120 g, 4.00 mmol) in ethanol (5 mL). The resulting solution was stirred at 60°C under nitrogen for 30 mins. This was cooled to 20°C and sodium borohydride (0.095 g, 2.5 mmol) was added in one portion. The solution was heated at 60°C for 24 h. The reaction mixture was quenched with 0.880 ammonia (0.5 mL), filtered, washed with diethyl ether (2 x 5 mL) and the organic extracts were evaporated. The crude product was purified by silica column chromatography, eluting with a gradient of 0 - 5% MeOH in DCM containing 0.1% ammonia. Fractions were evaporated to dryness to afford an oil. This was dissolved in acetonitrile (20ml), polymer supported isocyante resin (1mmol/g, 2g) was added and the suspension was stirred overnight. The resin was filtered off and the solution evaporated to dryness to give ethyl 4-(3,4,5-trimethylpiperazin-1-yl)benzoate (0.310 g, 112 %) as a white solid. MS: m/z 278 (MH+).

tert-butyl 5-amino-3-[2-(3,5-dimethoxyphenyl)ethyl]-1*H*-pyrazole-1-carboxylate, used as starting material was prepared as in Example 2.

Example 97

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)thiophene-2-carboxamide

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(3,4-dimethylpiperazin-1-yl)thiophene-2-carboxylate (0.268 g, 1 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (0.286 g, 1.00 mmol) in toluene (7.14 ml) at 80°C under nitrogen for 4 h and then at 70°C for 18 h.

Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow gum. The crude product was purified by preparative LCMS, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.036 g, 7.63 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6) δ 1.07 (3H, d), 2.26 - 3.12 (4H, m), 3.38 -3.47 (3H, m), 3.78 (6H, s), 5.09 (2H, s), 5.55 (1H, s), 6.17 (1H, d), 6.45 (1H, s), 6.61 (2H, d), 7.64 (1H, s).

MS: m/z 472 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00046 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Ethyl 5-(3,4-dimethylpiperazin-1-yl)thiophene-2-carboxylate, used as starting material was prepared as follows:

Palladium(II) acetate (0.112 g, 0.50 mmol) was added to a mixture of ethyl 5-bromothiophene-2-carboxylate (0.571 g, 5 mmol), 1,2-dimethyl-piperazine (1.175 g, 5 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.311 g, 0.50 mmol) and cesium carbonate (2.281 g, 7.00 mmol) in toluene (50.0 ml) at 20°C under nitrogen. The resulting suspension was stirred at 110°C for 23 h. The crude product was purified by ion exchange chromatography, using a SCX2 column. The crude material was dissolved in methanol and then applied to the column. The desired product was eluted from the column using 2M NH3

in methanol and pure fractions were evaporated to dryness to afford the crude product as a brown oil. This material was further purified by silica column chromatography, eluting with a gradient of 1 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 5-(3,4-dimethylpiperazin-1-yl)thiophene-2-carboxylate (0.640 g, 47.7 %) as a light brown solid.

1H NMR (399.9 MHz, CDCl3) δ 1.11 - 1.13 (3H, m), 1.33 (3H, t), 2.24 - 2.29 (1H, m), 2.33 (3H, s), 2.37 - 2.44 (1H, m), 2.73 (1H, d), 2.82 - 2.87 (1H, m), 3.08 - 3.14 (1H, m), 3.36 - 3.40 (1H, m), 3.43 - 3.48 (1H, m), 4.28 (2H, q), 6.01 (1H, d), 7.54 (1H, d)

MS: m/z 269 (MH+)

Example 98

4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide

A 2M solution of trimethylaluminium in toluene (0.853 mL, 1.71 mmol) was added dropwise to a stirred solution of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.170 g, 0.68 mmol) and methyl 4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)benzoate (0.187 g, 0.68 mmol) in toluene (10 mL), over a period of 5 mins under nitrogen. The resulting solution was stirred at room temperature for 18 h. The reaction was incomplete, so further trimethylaluminium (0.853 mL, 1.71 mmol) was added dropwise over a period of 5 mins and the solution was stirred at 60°C for 4 h. The reaction mixture was cooled and poured into acetone (50 mL), quenched with damp sodium sulphite, filtered and evaporated to dryness. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to the title compound (0.105 g, 31.3 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6) δ 1.21 - 1.26 (1H, m), 1.30 - 1.33 (1H, m), 1.53 - 1.57 (1H, m), 1.63 (1H, d), 1.65 (1H, d), 1.76 (1H, d), 1.98 (1H, d), 1.98 - 2.03 (1H, m), 2.22 - 2.27 (1H, m), 2.55 (1H, d), 2.79 (1H, t), 2.83 (2H, d), 3.68 - 3.70 (1H, m), 3.78 (7H, s), 5.10 (2H, s), 5.67 (1H, s), 6.46 (1H, t), 6.61 - 6.62 (2H, m), 6.97 (2H, d), 7.84 (2H, d), 10.20 (1H, s), 11.15 (1H, s). MS: m/z 492 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.003 μM.

Methyl 4-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)benzoate used as starting material was prepared as follows:

A solution of 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine dihydrochloride (5 g) in methanol (20 ml) and water (10 ml) was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine (1.5224 g, 10.86 mmol) as a yellow solid.

Methyl -4-iodobenzoate (2.84 g, 10.86 mmol), cesium carbonate (7.07 g, 21.71 mmol), 2-acetylcyclohexanone (0.286 mL, 2.17 mmol) and copper(I) iodide (0.103 g, 0.54 mmol) were added to a stirred solution of 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine (1.5224 g, 10.86 mmol) in DMF (30 mL) under nitrogen. The resulting suspension was stirred at 90 °C for 20 h. The reaction mixture was evaporated to dryness. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and fractions were evaporated to dryness to afford the crude product as an impure brown gum. The crude product was purified by silica column chromatography, eluting with 5% MeOH, 0.1% aqueous ammonia in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.681 g, 22.87 %) as an orange solid.

1H NMR (399.9 MHz, CDCl3) δ 1.29 - 1.33 (1H, m), 1.26 - 1.40 (1H, m), 1.62 (1H, d), 1.64 (1H, d), 1.65 - 1.68 (1H, m), 1.69 (1H, s), 1.80 - 1.82 (1H, m), 2.04 - 2.10 (2H, m), 2.32 - 2.39 (1H, m), 2.61 (1H, d), 2.89 (2H, d), 3.01 - 3.08 (1H, m), 3.58 - 3.63 (1H, m), 3.70 - 3.75 (1H, m), 3.86 (3H, s), 6.83 - 6.87 (2H, m), 7.89 - 7.93 (2H, m). MS: m/z 275 (MH+).

Example 99

4-(1-Cyclopropylpiperidin-4-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

Methyl 4-(1-cyclopropylpiperidin-4-yl)benzoate (0.259 g, 1 mmol), 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1.00 mmol) in toluene (10ml) was treated with a 2M solution of trimethylaluminium (1.250 ml, 2.50 mmol) in toluene,under nitrogen. The reaction mixture was heated at 60 °C for 18 h. The reaction mixture was cooled and the reaction quenched with methanol (40ml) and acidified with 2N HCl (1 ml). The crude reaction mixture was purified by ion exchange chromatography, using an SCX column. The

crude product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/methanol in DCM. Pure fractions were evaporated to dryness and the product crystallised from DCM/diethyl ether to give the title compound (0.170 g, 35.8 %) as.a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.31 - 0.33 (2H, m), 0.43 - 0.45 (2H, m), 1.58 - 1.66 (3H, m), 1.74 (1H, d), 1.77 (1H, s), 2.25 - 2.30 (2H, m), 2.55 (1H,d), 2.88 (4H, s), 3.05 (2H, d), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.47 (1H, s), 7.34 (2H, d), 7.92 (2H, d), 10.54 (1H, s), 12.13 (1H, s). MS: m/z 475 (MH+).

Mean of n=3, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00091 μM.

Methyl 4-(1-cyclopropylpiperidin-4-yl)benzoate used as starting material was prepared as follows:

Methyl 4-piperidin-4-ylbenzoate (1.279 g, 5 mmol) was dissolved in a mixture of THF (15 mL) and methanol (1 mL). [(1-Ethoxycyclopropyl)oxy]trimethylsilane (2.001 mL, 10.00 mmol) added followed by acetic acid (0.916 mL, 16.00 mmol). DCM (15.00 mL) was added to aid solubility. Solid sodium cyanoborohydride (0.471 g, 7.50 mmol) was added in portions over 5 mins. The reaction was stirred at 60 °C for 18 h. This was cooled, quenched with saturated ammonium chloride solution (5ml), diluted with methanol (20 ml) and partly purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford an oil. The crude product was purified by silica column chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.548 g, 42.3 %) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 0.42 - 0.50 (4H, m), 1.60 - 1.65 (2H, m), 1.70 - 1.75 (1H, m), 1.80 - 1.85 (2H, m), 2.25 - 2.32 (2H, m), 2.55 - 2.61 (1H, m), 3.15 - 3.18 (2H, m), 3.89 (3H, s), 7.27 - 7.30 (2H, m), 7.94 - 7.97 (2H, m). MS: m/z 260 (MH+).

Methyl 4-piperidin-4-ylbenzoate was prepared as follows:-

Methyl 4-(piperidin-4-yl)benzoate hydrochloride (5.0g, 17 mmol) was converted to the freebase by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness

to afford methyl 4-(piperidin-4-yl)benzoate (4.20g, 95%) as a white solid. MS: m/z 260 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 100

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide

A 2M solution of trimethylaluminium in toluene (1.875 mL, 3.75 mmol) was added dropwise to a stirred suspension of ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (0.394 g, 1.50 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.374 g, 1.5 mmol) in toluene (10 mL) at 20°C, over a period of 5 mins under nitrogen. The resulting solution was stirred at 60 °C for 5 h. The reaction mixture was cooled and the reaction quenched by diluting with acetone (100ml) and excess damp sodium sulphite added in portions. This was stirred for 60 mins. The resulting solid filtered off, washed with 10% methanol in DCM. The filtrate was evaporated to give crude product. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2M ammonia / MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (0.287 g, 41.1 %) as a white solid. 1H NMR (500.13 MHz, DMSO-d6) δ 1.08 (6H, d), 2.31 (2H, t), 3.70 - 3.73 (2H, m), 3.78 (6H, s), 5.10 (2H, s), 5.64 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 6.95 - 6.97 (2H, m), 7.83 - 7.85 (2H, m), 10.21 (1H, s), 11.09 (1H, s). MS: m/z 466 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0014 μM.

Ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows.

(2S,6R)-2,6-dimethylpiperazine (6.85 g, 60.00 mmol) was added to ethyl 4-fluorobenzoate (2.201 mL, 15 mmol), in DMSO (40 mL) warmed to 120°C under nitrogen. The resulting solution was stirred at 120 °C for 20 h. The reaction mixture was cooled and the solvent evaporated. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% methanol in dichloromethane containing 1% 880 ammonia. Pure fractions were evaporated to dryness to afford the desired compound (2.83 g, 71.9 %) as a

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brown oil. 1H NMR (399.9 MHz, CDCl3) δ 1.15 (6H, d), 1.37 (3H, t), 2.38 (1H, d), 2.41 (1H, d), 2.96 - 3.04 (2H, m), 3.65 - 3.69 (2H, m), 4.33 (2H, q), 6.84 - 6.87 (2H, m), 7.89 - 7.93 (2H, m). MS: m/z 263 (MH+).

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine was prepared as follows:
MP carbonate (2.74mmol/g) (12.00 g, 32.88 mmol) was added to 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (5 g, 17.50 mmol) in methanol (200 mL) and water (20 mL). The resulting suspension was stirred at room temperature for 18 h. The reaction mixture was filtered and MP carbonate was washed with 10% MeOH in DCM. This was evaporated to dryness to afford 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (2.94 g, 67.5 %) as an orange waxy solid. 1H NMR (399.9 MHz, DMSO-d6) δ 3.74 (6H, s), 4.76 (1H, s), 4.97 (2H, s), 6.42 (1H, t), 6.55 (2H, d).

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Example 101

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(3,4-dimethylpiperazin-1-yl)benzamide was prepared following the procedure for Example 100, but staring from ethyl 4-(3,4-dimethylpiperazin-1-yl)benzoate (0.394 g, 1.50 mmol), 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.374 g, 1.5 mmol) and 2M trimethylaluminium in toluene (1.875 mL, 3.75 mmol). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2M ammonia/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (0.301 g, 43.1 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6) δ 1.06 - 1.10 (3H, m), 2.22 - 2.30 (1H, m), 2.20 - 2.63 (4H, m), 2.61 - 2.65 (1H, m), 2.83 - 2.86 (1H, m), 2.96 - 3.02 (1H, m), 3.63 - 3.70 (2H, m), 3.78 (6H, s), 5.11 (2H, s), 5.66 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 6.96 - 6.98 (2H, m), 7.83 - 7.86 (2H, m), 10.15 (1H, s), 11.07 (1H, s). MS: m/z 466 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.021 μM.

Ethyl 4-(3,4-dimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:-

1,2-Dimethylpiperazine (2.284 g, 20.00 mmol) and ethyl 4-fluorobenzoate (1.467 mL, 10mmol) were dissolved in DMA (12 mL) and sealed in a microwave tube. The reaction was heated to 150 °C for 90 mins in the microwave reactor and cooled to room temperature. The reaction mixture was heated for a further 30 mins at 150°C and cooled to room temperature. The reaction mixture was evaporated and the crude product was purified by silica column chromatography, eluting with 5 % MeOH in DCM with 0.1% 0.880 ammonia. Pure fractions were evaporated to dryness to afford ethyl 4-(3,4-dimethylpiperazin-1-yl)benzoate (0.853 g, 32.5 %) as a colourless waxy solid.

1H NMR (399.9 MHz, CDCl3) δ 1.14 (3H, d), 1.37 (3H, t), 2.20 - 2.25 (1H, m), 2.33 (3H, s), 2.34 - 2.41 (1H, m), 2.62 (1H, t), 2.87 - 2.91 (1H, m), 2.99 - 3.05 (1H, m), 3.57 - 3.62 (1H, m), 3.65 - 3.70 (1H, m), 4.33 (2H, q), 6.83 - 6.87 (2H, m), 7.90 - 7.94 (2H, m). MS: m/z 263.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, used as starting material was prepared as in Example 100.

Example 102

***tert*-Butyl 4-[5-[[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]thiophen-2-yl]piperazine-1-carboxylate**

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of tert-butyl 4-(5-(methoxycarbonyl)thiophen-2-yl)piperazine-1-carboxylate (0.326 g, 1 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1.00 mmol) in toluene (7.14 ml) at 20°C under nitrogen. The reaction mixture was stirred at 20°C for 20 h. The temperature was increased to 60°C and the reaction mixture was stirred for 20 h and then allowed to cool. The reaction mixture was diluted with acetone (10 ml) and quenched with damp solid sodium sulphite. The mixture was stirred for 30 mins, and then a solution of 10% methanol in DCM (10mL) was added and the mixture stirred for a further 30 mins. The suspension was filtered and the solid washed with 10% methanol in DCM (20mL); the combined filtrates were evaporated to give a yellow foam. The crude product was purified by

silica column chromatography, eluting with a gradient of 1 to 10% 2M ammonia/methanol in DCM. Pure fractions were evaporated to dryness to afford the crude product. This was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford *tert*-butyl 4-[5-[[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]thiophen-2-yl]piperazine-1-carboxylate (0.272 g, 50.2 %) as a white dry film.
1H NMR (500.13 MHz, DMSO-d6) δ 1.46 (9H, s), 2.89 - 2.90 (6H, m), 3.22 (4H, t), 3.52 (4H, t), 3.75 (6H, s), 6.18 (1H, d), 6.27 (1H, s), 6.34 (1H, t), 6.42 - 6.42 (2H, m), 7.72 (1H, d), 9.81 (1H, s), 11.71 (1H, s); MS: m/z 542 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.028 μM.

tert-Butyl 4-(5-(methoxycarbonyl)thiophen-2-yl)piperazine-1-carboxylate, used as starting material was prepared as follows:-

2.0M (Trimethylsilyl)diazomethane solution in ether (0.525 ml, 1.05 mmol) was added dropwise to a stirred solution of 5-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]thiophene-2-carboxylic acid (0.312 g, 1mmol) in methanol (2.000 ml) and the mixture was stirred at ambient temperature for 20 h. More 2.0M (Trimethylsilyl)diazomethane solution in ether (0.500 ml, 1.00 mmol) was added and the mixture stirred for 2 h. The mixture was evaporated and the crude product was purified by silica column chromatography, eluting with a gradient of 1 to 3% EtOAc in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.141 g, 43.2 %) as a cream solid.
1H NMR (399.9 MHz, CDCl3) δ 1.48 (9H, s), 3.22 (4H, t), 3.58 (4H, t), 3.82 (3H, s), 6.06 (1H, d), 7.55 (1H, d). MS: m/z 327 (MH+)

5-[4-[(2-methylpropan-2-yl)oxycarbonyl]piperazin-1-yl]thiophene-2-carboxylic acid, used as starting material can be prepared by the method described in the literature (Stokes, Elaine Sophie Elizabeth; Waring, Michael James; Gibson, Keith Hopkinson. Preparation of amides as inhibitors of histone deacetylase. WO2003/092686).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 103

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(1-methylpiperidin-4-yl)benzamide

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(1-methylpiperidin-4-yl)benzamide was prepared following the procedure as for Example 159, but starting from methyl 4-(1-methylpiperidin-4-yl)benzoate (0.25 g, 1.07 mmol), 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.267 g, 1.07 mmol) and 2M trimethylaluminium in toluene (2.14 ml, 4.29 mmol). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 8% 2.5M NH3/MeOH in DCM. Pure fractions were evaporated to dryness, redissolved in DCM, triturated with ether and evaporated to dryness to afford the title compound (0.225 g, 46.5 %) as a white solid. 1H NMR (399.9 MHz, DMSO-d6) δ 1.69 (1H, d), 1.73 (2H, d), 1.77 (1H, s), 1.95 - 2.02 (2H, m), 2.21 (3H, s), 2.88 (2H, d), 3.76 (6H, s), 5.09 (2H, s), 5.62 (1H, s), 6.45 (1H, s), 6.60 (2H, s), 7.41 - 7.42 (2H, m), 7.89 - 7.91 (2H, m), 10.85 (1H, s), 11.58 (1H, s). MS: m/z 451 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00094 μM.

Methyl - 4-(1-methylpiperidin-4-yl)benzoate used as starting material was prepared as follows:

Water (0.4 mL), paraformaldehyde (0.742 g, 24.71 mmol) and acetic acid (1.415 mL, 24.71 mmol) were added to a stirred suspension of methyl 4-piperidin-1-ium-4-ylbenzoate chloride (1.58 g, 6.18 mmol) in THF (40 mL) under nitrogen. Sodium cyanoborohydride (0.582 g, 9.27 mmol) was added portion wise over a period of 10 mins. The resulting mixture was stirred at 60 °C for 18 h. The reaction mixture was evaporated to dryness and mixed with water (30 mL) and 1M HCl (10 mL). The solution was washed with ethyl acetate (2 x 25 mL), basified with solid potassium carbonate and extracted ethyl acetate (2 x 25 mL). The organic layer was washed with saturated brine and dried over MgSO4, filtered and evaporated to afford pure methyl 4-(1-methylpiperidin-4-yl)benzoate (0.784 g, 54.4 %) as a colourless oil which solidified on standing.

1H NMR (399.9 MHz, DMSO-d6) δ 1.62 - 1.71 (2H, m), 1.72 - 1.74 (2H, m), 1.95 - 2.02 (2H, m), 2.21 (3H, s), 2.54 - 2.59 (1H, m), 2.88 (2H, d), 3.85 (3H, s), 7.39 - 7.42 (2H, m), 7.88 - 7.91 (2H, m). MS: m/z 234 (MH+).

Example 104

4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide

4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide was prepared following the procedure as for Example 159, but starting from methyl 4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)benzoate (0.25 g, 0.96 mmol), 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.239 g, 0.96 mmol) and 2M trimethylaluminium in toluene (1.2 ml, 2.4 mmol). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.124 g, 27 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.37 - 1.44 (1H, m), 1.67 - 1.74 (2H, m), 1.83 - 1.89 (1H, m), 1.99 - 2.04 (1H, m), 2.08 (1H, q), 2.18 - 2.25 (1H, m), 2.82 - 2.89 (1H, m), 3.01 - 3.06 (2H, m), 3.75 (6H, s), 3.85 (1H, d), 3.99 - 4.02 (1H, m), 5.08 (2H, s), 5.57 (1H, s), 6.44 (1H, s), 6.59 - 6.60 (2H, m), 7.04 (2H, d), 7.85 (2H, d), 10.61 (1H, s), 11.49 (1H, s). MS: m/z 478 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0013 μM.

Methyl 4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)benzoate, used as starting material was prepared as follows:

Methyl 4-iodobenzoate (2.076 g, 7.92 mmol), cesium carbonate (5.16 g, 15.85 mmol), 2-acetylcyclohexanone (0.209 mL, 1.58 mmol) and copper(I) iodide (0.075 g, 0.40 mmol) were added to a stirred solution of 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (1 g, 7.92 mmol) in DMF (20 mL) under nitrogen. The resulting suspension was stirred at 90 °C for 20 h. The reaction mixture was evaporated to dryness and redissolved in a mixture of methanol and water. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and pure fractions were evaporated to dryness to afford methyl 4-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)benzoate (1.243 g, 60.2 %) as a brown gum.

1H NMR (399.9 MHz, DMSO-d6) δ 1.33 - 1.43 (1H, m), 1.57 - 1.79 (3H, m), 1.81 - 1.89 (1H, m), 1.99 - 2.03 (1H, m), 2.07 (1H, q), 2.16 - 2.23 (1H, m), 2.56 (1H, t), 2.83 - 2.95 (2H,

m), 3.00 - 3.05 (2H, m), 3.06 - 3.09 (1H, m), 3.75 - 3.78 (3H, m), 3.86 (1H, t), 3.98 - 4.01 (1H, m), 6.98 - 7.02 (2H, m), 7.77 - 7.80 (2H, m). MS: m/z 261(MH+).

Example 105

5-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

2,3,4,6,7,8,9,9a-Octahydro-1H-pyrido[1,2-a]pyrazine (477 mg, 3.40 mmol) was added in one portion to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (659 mg, 1.70 mmol) in anhydrous dimethylsulfoxide (1.70 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluant was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% formic acid) and MeCN as eluents. The sample was then put through a basic HPLC system to obtain the free base. Fractions containing the desired compound were evaporated to dryness to afford the title compound (395 mg, 47%) as a cream solid.

1H NMR (500.133 MHz, DMSO) δ 1.19 - 1.35 (3H, m), 1.51 - 1.60 (1H, m), 1.64 (1H, t), 1.73 - 1.79 (1H, m), 1.93 - 2.08 (2H, m), 2.17 - 2.25 (1H, m), 2.73 (1H, dd), 2.81 - 2.93 (6H, m), 3.13 (1H, td), 3.73 (6H, s), 4.28 - 4.33 (1H, m), 4.37 - 4.42 (1H, m), 6.32 (1H, t), 6.38 - 6.41 (3H, m), 8.26 (1H, d), 8.70 (1H, d), 9.59 (1H, br s), 11.82 (1H, br s). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.13 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide used as starting material was prepared as follows:-

Trimethylaluminium (2M in toluene, 9.64 ml, 19.28 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (1.91 g, 7.71 mmol) and methyl 5-chloropyrazine-2-carboxylate (1.33 g, 7.71 mmol) in anhydrous toluene (38.6 ml) at ambient temperature. The resulting solution was then stirred under nitrogen at ambient temperature for 18 h. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 3 h. The reaction mixture was quenched with methanol (10 mL) and HCl (2M aqueous solution). The mixture was diluted with EtOAc (100

mL) and water (250 mL) and then acidified with HCl (2N aqueous solution). The organic layer was removed and the aqueous further extracted with EtOAc (2 x 100 mL). The combined organics were washed with water (200 mL), brine (200 mL) dried over MgSO4 and concentrated under reduced pressure. Upon concentration a precipitate formed. The precipitate was collected by filtration, washed with MeOH (10 mL) and air dried to afford the desired compound (1.88 g, 63%) as a yellow solid, which was used without further purification.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.88 - 2.89 (4H, m), 3.73 (6H, s), 6.33 (1H, t), 6.43 (2H, d), 6.49 (1H, s), 8.93 (1H, s), 9.09 (1H, s), 10.44 (1H, s), 12.31 (1H, s). MS: m/z 388 (MH+).

Example 106

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)thiophene-2-carboxamide

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(4-methylpiperazin-1-yl)thiophene-2-carboxylate (0.254 g, 1 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1.00 mmol) in toluene (7.14 ml) at 20°C under nitrogen. The reaction mixture was stirred at ambient temperature for 16 h and then heated at 65°C for 24 h. Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow solid. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.154 g, 33.8 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 2.32 (3H, d), 2.58 (4H, t), 2.88 (4H, s), 3.26 (4H, t), 3.73 (3H, s), 3.74 (3H, s), 6.13 (1H, d), 6.25 (1H, s), 6.32 (1H, d), 6.40 (2H, d), 7.68 - 7.69 (1H, m); MS: m/z 456 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.001 μM.

Ethyl 5-(4-methylpiperazin-1-yl)thiophene-2-carboxylate, used as starting material was prepared as follows:

Palladium(II) acetate (0.225 g, 1.00 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (2.351 g, 10 mmol), 1-methylpiperazine (1.331 ml, 12.00 mmol), rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.623 g, 1.00 mmol)and cesium carbonate (4.56 g, 14.00 mmol) in toluene (100 ml) at 20°C under nitrogen. The resulting suspension was stirred at 110°C for 23 h. The mixture was filtered through celite and the filtrate was evaporated to dryness to give a brown oil. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford the crude product as a brown gum. This material was further purified by silica column chromatography, eluting with a gradient of 0 to 3% methanol in DCM. Pure fractions were evaporated to dryness to afford the desired compound (1.380 g, 54.3 %) as an orange oil.

1H NMR (399.9 MHz, CDCl3) δ 1.33 (3H, t), 2.34 (3H, s), 2.54 (4H, t), 3.28 (4H, t), 4.28 (2H, q), 6.02 (1H, d), 7.55 (1H, d); MS: m/z 255 (MH+)

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 107

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-methylpiperazin-1-yl)thiophene-2-carboxamide

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(4-methylpiperazin-1-yl)thiophene-2-carboxylate (0.254 g, 1 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (0.286 g, 1.00 mmol) in toluene (7.14 ml) at 20°C under nitrogen. The reaction mixture was stirred at room temperature for 18 h and then heated at 65°C for 6 h. Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow solid. The

crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.147 g, 32.1 %) as a white solid.
1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 2.29 (3H, s), 2.53 - 2.55 (4H, m), 3.25 - 3.28 (4H, m), 3.77 (6H, s), 5.09 (2H, s), 5.63 (1H, s), 6.16 (1H, d), 6.45 (1H, t), 6.60 (2H, d), 7.64 (1H, d); MS: m/z 458 (MH+)
Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0011 μM.

Ethyl 5-(4-methylpiperazin-1-yl)thiophene-2-carboxylate, used as starting material was prepared as outlines in Example 106.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Example 108

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3,3-dimethylpiperazin-1-yl)pyrazine-2-carboxamide

2,2-Dimethylpiperazine (343 mg, 3.00 mmol) was added in one portion to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (388 mg, 1 mmol) in anhydrous dimethylsulfoxide (1.00 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (217 mg, 47%) as a yellow solid.
1H NMR (399.9 MHz, DMSO-d6) δ 1.06 (6H, s), 2.04 (1H, s), 2.82 - 2.88 (6H, m), 3.51 (2H, s), 3.65 (2H, t), 3.72 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.32 (1H, s), 8.66 (1H, s), 9.71 (1H, s), 12.17 (1H, s). MS: m/z 466 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.002 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 109

5-(4-Cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (390 mg, 1.00 mmol) was added in one portion to 1-cyclopropylpiperazine, 2HCl (398 mg, 2.00 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.52 ml, 3.00 mmol) in anhydrous dimethylsulfoxide (1.00 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH_3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in DCM. Fractions containing desired product were evaporated to dryness to give a yellow solid. The solid was taken up in DCM and triturated with Et_2O to give a solid which was collected by filtration and dried under vacuum to give the title compound (130 mg, 27%) as a yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.38 - 0.40 (2H, m), 0.45 - 0.49 (2H, m), 1.66 - 1.70 (1H, m), 2.66 (4H, t), 3.71 (4H, t), 3.75 (6H, s), 5.08 (2H, s), 5.84 (1H, s), 6.45 (1H, s), 6.59 (2H, s), 8.33 (1H, s), 8.72 (1H, s), 10.80 (1H, s), 11.35 (1H, s). MS: m/z 480 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.003 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide used as starting material was prepared as follows:-

Trimethylaluminium (2M in toluene, 7.44 ml, 14.88 mmol) was added dropwise to a stirred suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (1.70 g, 5.95 mmol) and methyl 5-chloropyrazine-2-carboxylate (1.03 g, 5.95 mmol) in anhydrous toluene (29.8 ml) at ambient temperature. The resulting solution was then stirred under nitrogen at ambient temperature for 18 h. The reaction mixture was quenched with methanol (5 mL) and HCl (2M aqueous solution), diluted with water (200 mL) and extracted with EtOAc (3 x 150 mL). The organics were washed with water (200 mL), brine (200 mL) dried over MgSO4, filtered and concentrated. On evaporation a precipitate was formed which was collected by

filtration, washed with MeOH (20 mL) and air dried to afford the desired compound (1.65 g, 71%) as an orange solid, which was used without further purification.
1H NMR (500.13 MHz, DMSO-d6, 373K) δ 3.78 (6H, s), 5.12 (2H, s), 5.94 (1H, s), 6.46 (1H, s), 6.62 (2H, s), 8.87 (1H, s), 9.09 (1H, s), 10.99 (1H, s), 11.24 (1H, s). MS: m/z 390 (MH+)
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.060 μM.

Example 110

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]benzamide

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]benzamide was prepared following the procedure for Example 100, but starting from ethyl 4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)benzoate (0.276 g, 1.00 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.249 g, 1 mmol) and a 2M solution of trimethylaluminium in toluene (1.25 mL, 2.5 mmol). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.027 g, 5.63 %) as a white solid.
1HNMR (500.133 MHz, DMSO-d6 + CD3COOD) δ: 1.13 (6H, d), 2.31 (3H, s), 2.60 - 2.68 (2H, m), 3.19 (2H, s), 3.70 (1H, s), 3.65 (6H, s), 5.08 (2H, s), 5.68 (1H, s), 6.40 - 6.44 (1H, m), 6.58 (2H, s), 6.97 (2H, d), 7.82 (2H, d). MS: m/z 480 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00068 μM.

Ethyl 4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:-

Titanium (IV) isopropoxide (2.99 mL, 10.00 mmol) was added to ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (1.312 g, 5.00 mmol) and formaldehyde (0.601 g, 20.00 mmol) in ethanol (25 mL) warmed to 60°C over a period of 45 mins under nitrogen. The resulting solution was cooled to 20°C and sodium borohydride (0.473 g, 12.50 mmol) was added in one portion and the suspension stirred at 60 °C for 18 h. The reaction was quenched with ammonia (2 ml). The solid filtered off and washed with 10% MeOH in DCM (2 x 50 ml). The organic layer was evaporated to dryness and the crude product purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM containing 0.1%

ammonia. Fractions were evaporated to dryness to afford an oil. This was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the desired compound (0.320 g, 23.16 %) as a white crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.11 (6H, d), 1.29 (3H, t), 2.24 (3H, s), 2.25 - 2.30 (2H, m), 2.59 (1H, d), 2.62 (1H, d), 3.53 - 3.57 (2H, m), 4.26 (2H, q), 6.75 - 6.79 (2H, m), 7.82 - 7.86 (2H, m). MS: m/z 277 (MH+).

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, used as starting material was prepared as in Example 100.

Example 111

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(3,3-dimethylpiperazin-1-yl)benzamide

A 2M solution of trimethylaluminium in toluene (0.691 mL, 1.38 mmol) was added dropwise to a stirred solution of ethyl 4-(3,3-dimethylpiperazin-1-yl)benzoate (145 mg, 0.55 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (138 mg, 0.55 mmol) in toluene (5 mL) at 20°C, over a period of 5 mins under nitrogen. The resulting solution was stirred at 20 °C for 24 h. This was diluted with acetone (25 ml) and an excess of damp solid sodium sulphite was added. The mixture was stirred for 1 h and the solid filtered off. The solid was washed with 10% MeOH/DCM and the combined organics evaporated to dryness. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (27.0 mg, 10.49 %) as a colourless gum.

1HNMR (500.13 MHz, DMSO-d6 @ 373K) δ: 1.11 (6H, s), 2.85-2.91 (2H, m), 3.03 (2H, s), 3.18 - 3.22 (2H, m), 3.78 (6H, s), 5.09 (2H, s), 5.62 (1H, s), 6.44 (1H, t), 6.60 (2H, s), 6.92 (2H, d), 7.82 (2H, d), 10.19 (1H, s), 11.12 (1H, s). MS: m/z 466 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00076 μM.

Ethyl 4-(3,3-dimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:-

Ethyl 4-fluorobenzoate (0.151 mL, 1 mmol), 2,2-dimethylpiperazine (0.137 g, 1.20 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.349 mL, 2.00 mmol) were dissolved in DMA (2 mL) and sealed into a microwave tube. The reaction was heated to 200 °C for 4 h in the microwave reactor and cooled to room temperature. The crude mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 3.5M ammonia in methanol, fractions were evaporated to dryness to afford an oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 2M ammonia/MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(3,3-dimethylpiperazin-1-yl)benzoate (0.145 g, 55.3 %) as a white solid. 1H NMR (399.9 MHz, CDCl3) δ 1.15 (6H, d), 1.37 (3H, t), 2.38 (1H, d), 2.41 (1H, d), 2.96 - 3.04 (2H, m), 3.65 - 3.69 (2H, m), 4.33 (2H, q), 6.84 - 6.87 (2H, m), 7.89 - 7.93 (2H, m). MS: m/z 266 (MH+).

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, used as starting material was prepared as in Example 100.

Example 112

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrazine-2-carboxamide

(2S,6R)-2,6-Dimethylpiperazine (228 mg, 2.00 mmol) was added in one portion to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (388 mg, 1.00 mmol) in anhydrous dimethylsulfoxide (1.00 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (164 mg, 35%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.05 - 1.06 (6H, d), 2.43 - 2.50 (2H, m), 2.72 - 2.78 (2H, m), 2.88 (4H, s), 3.72 (6H, s), 4.39 (2H, d), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.34 (1H, d), 8.69 (1H, d), 9.73 (1H, s), 12.18 (1H, s), no NH observed. MS: m/z 466 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0017 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 113

5-(4-Cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (388 mg, 1.00 mmol) was added in one portion to 1-cyclopropylpiperazine, 2HCl (398 mg, 2.00 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.52 ml, 3.00 mmol) in anhydrous dimethylsulfoxide (1.00 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (45 mg, 9%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.39 (2H, t), 0.46 - 0.48 (2H, m), 1.67 - 1.70 (1H, m), 2.66 (4H, q), 2.88 (4H, s), 3.69 - 3.72 (4H, m), 3.72 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.35 (1H, d), 8.71 (1H, d), 9.76 (1H, s), 12.18 (1H, s). MS: m/z 478 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0023 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 114

5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

1,2,3,4,6,7,8,8a-Octahydropyrrolo[1,2-a]pyrazine (429 mg, 3.40 mmol) was added in one portion to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (659 mg, 1.70 mmol) in anhydrous dimethylsulfoxide (1.70 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion

exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% TFA) and MeCN as eluents. The material was then put through basic HPLC to obtain the free base. Fractions containing the desired compound were evaporated to dryness to afford the title compound (438 mg, 54%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.35 - 1.45 (1H, m), 1.63 - 1.80 (2H, m), 1.82 - 1.91 (1H, m), 1.93 - 2.01 (1H, m), 2.09 (1H, q), 2.16 - 2.20 (1H, m), 2.70 - 2.76 (1H, m), 2.88 (4H, s), 3.04 - 3.11 (3H, m), 3.72 (6H, s), 4.47 (1H, d), 4.63 (1H, d), 6.33 (1H, t), 6.42 (2H, d), 6.47 (1H, s), 8.36 (1H, d), 8.71 (1H, d), 9.76 (1H, s), 12.18 (1H, s). MS: m/z 478 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0016 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 115

5-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (585 mg, 1.50 mmol) was added in one portion to 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine, HCl (530 mg, 3.00 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (1.04 ml, 6.00 mmol) in anhydrous dimethylsulfoxide (1.50 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (302 mg, 41 %) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.21 - 1.29 (2H, m), 1.49 - 1.67 (1H, m), 1.60 - 1.64 (2H, m), 1.74 (1H, d), 1.90 (1H, t), 1.93 - 2.00 (1H, m), 2.10 - 2.17 (1H, m), 2.67 - 2.73 (1H, m), 2.82 (2H, d), 3.06 - 3.13 (1H, m), 3.75 (6H, s), 4.38 (1H, d), 4.46 (1H, d), 5.08 (2H, s),

5.84 (1H, s), 6.44 (1H, s), 6.59 (2H, d), 8.34 (1H, s), 8.71 (1H, s), 10.79 (1H, s), 11.35 (1H, s). MS: m/z 494 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0023 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as outlined in Example 109.

Example 116

4-(4-cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide

4-(4-Cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide was prepared following the procedure as outlined for Example 100, starting from ethyl 4-(4-cyclopropylpiperazin-1-yl)benzoate (0.329 g, 1.2 mmol), 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (0.343 g, 1.20 mmol) and 2M trimethylaluminium in toluene (1.500 mL, 3.00 mmol). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.022 g, 3.84 %) as a white solid. 1H NMR (500.13 MHz, DMSOd6) δ 0.34 - 0.40 (2H, m), 0.45 - 0.50 (2H, m), 1.67 - 1.75 (1H, m), 2.67 - 2.73 (4H, m), 3.24 - 3.32 (4H, m), 3.78 (6H, s), 5.08 (2H, s), 5.68 (1H, s), 6.42 - 6.46 (1H, m), 6.58 - 6.61 (2H, m), 6.95 (2H, d), 7.83 (2H, d), 10.30 (1H, s), 11.01 (1H, s). MS: m/z 478 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00093 μM.

Ethyl 4-(4-cyclopropylpiperazin-1-yl)benzoate used as starting material was prepared following the procedure as outlined for ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (Example 100), starting from ethyl 4-fluorobenzoate (0.880 mL, 6 mmol) and 1-cyclopropylpiperazine (1.666 g, 13.20 mmol) in DMSO (15 mL) The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 8% 2.5M ammonia/ MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (1.405 g, 85 %) as a beige solid.

1H NMR (399.9 MHz, CDCl3) δ 0.43 - 0.52 (4H, m), 1.34 - 1.39 (3H, m), 1.63 - 1.68 (1H, m), 2.75 (4H, t), 3.29 (4H, t), 4.32 (2H, q), 6.84 - 6.88 (2H, m), 7.90 - 7.97 (2H, m). MS: m/z 275 (MH+).

1-Cyclopropylpiperazine used as starting material was prepared as follows:

1-Cyclopropylpiperazine dihydrochloride (1.493 g, 7.5 mmol) was dissolved in water (5.00 mL) and methanol (5.00 mL) and converted to its freebase by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 3.5M ammonia in methanol and pure fractions were evaporated to dryness to afford 1-cyclopropylpiperazine (0.796 g, 84 %) as an oil.

1H NMR (399.9 MHz, CDCl3) δ 0.31 - 0.39 (4H, m), 1.51 - 1.56 (1H, m), 1.63 - 1.67 (1H, m), 2.51 (4H, s), 2.77 (4H, t).

1-Cyclopropylpiperazine dihydrochloride was prepared as follows:-

4.0M HCl in dioxane (42.7 mL, 170.78 mmol) was added to a stirred solution of tert-butyl 4-cyclopropylpiperazine-1-carboxylate (7.73 g, 34.16 mmol) in a mixture of methanol (50.0 mL) and ethyl acetate (200 mL). The resulting suspension was stirred at room temperature for 24 h under nitrogen. The white solid filtered off to give 1-cyclopropylpiperazine dihydrochloride (6.30 g, 93 %).

1H NMR (399.9 MHz, DMSO-d6) δ 0.73 - 0.86 (2H, m), 1.07 - 1.18 (2H, m), 2.85 - 2.99 (1H, m), 3.30 - 3.40 (4H, m), 3.52 - 3.65 (4H, m), 9.89 (2H, s), 11.99 (1H, s).

tert-Butyl 4-cyclopropylpiperazine-1-carboxylate was prepared as follows:-

A solution of tert-butyl piperazine-1-carboxylate (9.31 g, 50 mmol), [(1-ethoxycyclopropyl)oxy]trimethylsilane (20.11 mL, 100.00 mmol) and acetic acid(14.31 mL, 250.00 mmol) in tetrahydrofuran (100 mL), methanol (10 mL) was treated with sodium cyanoborohydride (4.71 g, 75.00 mmol) at 20°C. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was cooled, filtered and evaporated to dryness. 1N HCl (40 ml) and water (60 ml) were added and the solution extracted with ethyl acetate (3 x 50 ml). The aqueous layer was basified to pH 10 with solid potassium carbonate and extracted with ethyl acetate (4 x 50 ml). The organic extracts were washed with saturated sodium chloride solution

(50 ml) and dried over $MgSO_4$, filtered and evaporated to dryness to give tert-butyl 4-cyclopropylpiperazine-1-carboxylate (7.73 g, 68.3 %) as a white waxy solid.
^{1}H NMR (399.9 MHz, CDCl3) δ 0.33 - 0.40 (4H, m), 1.39 (9H, s), 1.52 - 1.55 (1H, m), 2.48 (4H, t), 3.31 (4H, t).

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Example 117

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methyl-4-oxidopiperazin-4-ium-1-yl)benzamide

3-Chloroperoxybenzoic acid (129 mg, 0.53 mmol) was added in one portion to N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide (225 mg, 0.50 mmol) in acetone (15 mL) at ambient temperature. The resulting solution was stirred at ambient temperature for 2 h. The reaction mixture was concentrated onto silica and the crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in DCM to 100% methanol. The residue was further purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford the title compound (183 mg, 79%) as a cream solid.
1H NMR (700.034 MHz, DMSO) δ 2.85 (4H, s), 2.94 (2H, d), 3.09 (3H, s), 3.44 (2H, td), 3.53 (2H, td), 3.65 (2H, d), 3.70 (6H, s), 6.31 (1H, t), 6.37 (1H, s), 6.40 (2H, d), 7.00 (2H, d), 7.90 (2H, d), 10.37 (1H, s), 12.00 (1H, s). MS: m/z 466 (MH+)
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0013 μM.

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide was prepared as outlined in Example 10.

Example 118

4-(4-Cyclobutylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide

4-(4-Cyclobutylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide was prepared following the procedure as outlined for Example 100, starting from 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.173 g, 0.69 mmol), ethyl 4-(4-cyclobutylpiperazin-1-yl)benzoate (0.2 g, 0.69 mmol) and a 2M solution of trimethylaluminium in toluene (1.387 mL, 2.77 mmol) in toluene (10 ml) at room temperature for 20 h. The reaction mixture was poured into acetone (20 mL), quenched with excess damp sodium sulphite, filtered and evaporated to afford a yellow solid. Acetonitrile (10 ml) was added and this was filtered to afford the title compound (0.079 g, 23.17 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.63 - 1.66 (1H, m), 1.67 - 1.70 (1H, m), 1.78 - 1.89 (2H, m), 1.97 - 2.03 (2H, m), 2.38 (4H, t), 2.75 (1H, t), 3.75 (6H, s), 5.08 (2H, s), 5.58 (1H, s), 6.45 (1H, s), 6.60 - 6.60 (2H, m), 7.01 (2H, d), 7.86 (2H, d), 10.61 (1H, s), 11.49 (1H, s). MS: m/z 492 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0011 μM.

Ethyl 4-(4-cyclobutylpiperazin-1-yl)benzoate used as starting material was prepared as follows:

Ethyl 4-fluorobenzoate (0.753 g, 4.48 mmol) was added to a solution of 1-cyclobutylpiperazine (0.571 g, 4.07 mmol) and potassium carbonate (0.563 g, 4.07 mmol) in DMSO (8 mL) under nitrogen. The resulting solution was stirred at 100 °C for 18 h and evaporated to dryness. The residue was triturated with diethyl ether, filtered, and evaporated and the crude product was purified by silica column chromatography, eluting with a gradient of 0 to 2.5% 2.5N MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(4-cyclobutylpiperazin-1-yl)benzoate (0.387 g, 32.9 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.28 - 1.32 (3H, t), 1.62 -1.70 (2H, m), 1.77 - 1.88 (2H, m), 1.95 - 2.04 (2H, m), 2.35 - 2.39 (4H, t), 2.70 - 2.78 (1H, m), 3.28 - 3.32 (4H, t), 4.22 - 4.27 (2H, m), 6.96 - 6.98 (2H, d), 7.66 - 7.80 (2H, d). MS: m/z 289 (MH+).

1-Cyclobutylpiperazine used as starting material was prepared as follows:

Water (0.15 mL), cyclobutanone (1 g, 14.27 mmol) and acetic acid (1.742 mL, 30.44 mmol) were added to a stirred solution of tert-butyl piperazine-1-carboxylate (1.772 g, 9.51 mmol) in THF (20 mL) under nitrogen. Sodium cyanoborohydride (0.897 g, 14.27 mmol) was added portion wise over a period of 10 mins. The resulting mixture was stirred at 60 °C for 20 h. The reaction mixture was evaporated to dryness and mixed with water (40 mL) and 1M HCl (15 mL). The solution was washed with EtOAc (2 x 25 mL), basified with solid K_2CO_3 and extracted with EtOAc (2 x 15 mL). The organic layer was washed with saturated brine and dried over MgSO4, filtered and evaporated to afford pure tert-butyl 4-cyclobutylpiperazine-1-carboxylate (1.155 g, 50.5 %) as a colourless oil.

1H NMR (399.9 MHz, DMSO-d6) δ 1.40 (9H, s), 1.62 - 1.65 (2H, m), 1.75 - 1.80 (2H, m), 1.92 - 1.98 (2H, m), 2.17 (4H, t), 2.68 (1H, t), 3.28 - 3.30 (4H, s).

A solution of tert-butyl 4-cyclobutylpiperazine-1-carboxylate (1.1553 g, 4.81 mmol) in ethyl acetate (10 mL) and methanol (10.00 mL) was treated with a 4M-solution hydrogen chloride in dioxane (1.669 mL, 48.07 mmol) was stirred at room temperature for 40 h under nitrogen. The reaction was incomplete so f 4M-solution hydrogen chloride in dioxane (10mL) was added and the solution was stirred at room temperature for a further 2 h. The reaction mixture was evaporated to dryness to afford a solid. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M NH3/MeOH and pure fractions were evaporated to dryness to afford 1-cyclobutylpiperazine (0.571 g, 85 %) as a yellow oil.

1H NMR (399.9 MHz, DMSO-d6) δ 1.64 (2H, s), 1.74 - 1.75 (2H, m), 1.92 (2H, s), 2.14 (4H, s), 2.63 - 2.66 (4H, m), 3.18 (1H, s).

Example 119

2-(1,3,4,6,7,8,9,9a-Octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 2.15 mL, 4.30 mmol) was added dropwise to a stirred suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (491 mg, 1.72 mmol) and methyl 2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate (475 mg, 1.72 mmol) in toluene (8.6 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h and then at 60 °C for 2 h. The reaction mixture was

cautiously quenched with methanol (20 mL) and treated with HCl (2N aqueous solution, until a freely stirred solution was obtained). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford crude product.The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (361 mg, 43%) as a solid.

1H NMR (500.13 MHz, DMSO-d6, 373K) δ 1.21 - 1.27 (1H, m), 1.28 - 1.35 (1H, m), 1.52 - 1.59 (1H, m), 1.59 - 1.64 (2H, m), 1.76 (1H, d), 1.85 - 1.91 (1H, m), 1.98 - 2.03 (1H, m), 2.10 - 2.15 (1H, m), 2.68 - 2.73 (1H, m), 2.80 - 2.84 (2H, m), 3.08 - 3.13 (1H, m), 3.78 (6H, s), 4.57 - 4.61 (1H, m), 4.67 - 4.71 (1H, m), 5.11 (2H, s), 5.70 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 8.86 (2H, s), 10.30 (1H, s), 11.30 (1H, s). MS: m/z 494 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0033 μM.

Methyl 2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate was prepared as outlined in Example 127.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Example 120

5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]thiophene-2-carboxamide

2M Trimethylaluminium (1.525 ml, 3.05 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)thiophene-2-carboxylate (0.342 g, 1.22 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.302 g, 1.22 mmol) in toluene (8.71 ml) at 20°C under nitrogen. The reaction mixture was stirred at ambient temperature for 18 h and then stirred and heated at 65°C for 20 h. Ethyl acetate (5mL) was added carefully to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated

brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow gum, 640mg. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the TFA salt of the product. This was dissolved in methanol and purified by ion exchange chromatography, using a SCX2 column. The desired product was eluted from the column using 2M NH3 in methanol and pure fractions were evaporated to dryness then triturated with acetonitrile to afford the title compound (0.174 g, 29.6 %) as a solid.

1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 1.41 - 1.43 (1H, m), 1.73 - 1.78 (2H, m), 1.87 - 1.91 (2H, m), 2.16 - 2.23 (2H, m), 2.34 - 2.38 (1H, m), 2.68 - 2.72 (1H, m), 2.89 (4H, s), 3.00 - 3.08 (3H, m), 3.50 - 3.53 (1H, m), 3.66 - 3.69 (1H, m), 3.74 (6H, d), 6.12 (1H, d), 6.25 (1H, s), 6.33 (1H, t), 6.41 (2H, d), 7.70 (1H, t); MS: m/z 482 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00098 μM.

Ethyl 5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)thiophene-2-carboxylate, used as starting material was prepared as follows:

Palladium(II) acetate (0.112 g, 0.50 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (1.175 g, 5 mmol), 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (0.631 g, 5.00 mmol), rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.311 g, 0.50 mmol) and cesium carbonate (2.281 g, 7.00 mmol) in toluene (50.0 ml) at 20°C under nitrogen. The resulting suspension was stirred at 110°C for 23 h. The mixture was filtered through celite washing through with ethyl acetate and the filtrate was evaporated to dryness to give a brown oil. The crude product was purified by ion exchange chromatography, using a SCX2 column. The crude material was dissolved in methanol and then applied to the column. The desired product was eluted from the column using 2M NH3 in methanol and pure fractions were evaporated to dryness to afford the crude product as a brown solid. This material was further purified by silica column chromatography, eluting with a gradient of 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.727 g, 51.9 %) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.33 (3H, t), 1.43 - 1.53 (1H, m), 1.63 (1H, s), 1.73 - 1.93 (3H, m), 2.10 - 2.22 (2H, m), 2.33 - 2.40 (1H, m), 2.74 (1H, t), 3.07 - 3.16 (3H, m), 3.51 - 3.55 (1H, m), 3.67 - 3.71 (1H, m), 4.28 (2H, q), 6.01 (1H, d), 7.55 (1H, d)

MS: m/z 281 (MH+)

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 121

5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]thiophene-2-carboxamide

2M Trimethylaluminium (1.525 ml, 3.05 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)thiophene-2-carboxylate (0.342 g, 1.22 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (0.304 g, 1.22 mmol) in toluene (8.71 ml) at 20°C under nitrogen. The reaction mixture was stirred at room temperature for 18 h and then heated at 65°C for 6 h.

Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow gum. The crude product was purified by preparative LCMS, using decreasingly polar mixtures of water (containing 1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the TFA salt of the product. This was dissolved in methanol and purified by ion exchange chromatography, using a SCX2 column. The desired product was eluted from the column using 2M NH3 in methanol and pure fractions were evaporated to dryness then triturated with ethanol to afford the title compound (0.266 g, 45.1 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 1.40 - 1.44 (1H, m), 1.72 - 1.80 (2H, m), 1.85 - 1.90 (2H, m), 2.17 - 2.22 (2H, m), 2.34 - 2.39 (1H, m), 2.73 (1H, t), 3.03 - 3.09 (3H, m), 3.52 - 3.54 (1H, m), 3.67 - 3.70 (1H, m), 3.77 (6H, s), 5.09 (2H, s), 5.62 (1H, s), 6.16 (1H, d), 6.45 (1H, t), 6.60 (2H, d), 7.64 (1H, d); MS: m/z 484 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00079 μM.

Ethyl 5-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)thiophene-2-carboxylate is prepared as outlined in Example 120.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, used as starting material was prepared as in Example 100.

Example 122

5-(3,4,6,7,8,8a-Hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (585 mg, 1.50 mmol) was added in one portion to 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (379 mg, 3.00 mmol) in anhydrous dimethylsulfoxide (1.50 ml) at 25°C. The resulting solution was stirred at 100 °C for 18 h. The residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford impure product as a yellow solid. The impure material was then repurified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford thetitle compound (269 mg, 37 %) as a yellow solid.

1H NMR (500.133 MHz, DMSO, 373K) δ 1.38 - 1.46 (1H, m), 1.67 - 1.82 (2H, m), 1.85 - 1.91 (1H, m), 2.04 - 2.10 (1H, m), 2.17 (1H, q), 2.22 - 2.29 (1H, m), 2.78 (1H, dd), 3.02 - 3.16 (3H, m), 3.76 (6H, s), 4.41 (1H, d), 4.57 (1H, d), 5.09 (2H, s), 5.85 (1H, s), 6.44 (1H, s), 6.59 (2H, d), 8.26 (1H, d), 8.71 (1H, s), 10.42 (1H, s), 11.13 (1H, s). MS: m/z 480 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0013 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 109.

Example 123

N-[5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)pyrazine-2-carboxamide

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (388 mg, 1.00 mmol) was added in one portion to 1,2-dimethyl-piperazine (228 mg, 2.00 mmol) in anhydrous dimethylsulfoxide (2.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (375 mg, 81%) as a yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.07 - 1.09 (3H, d), 2.06 - 2.20 (2H, m), 2.23 (3H, s), 2.76 - 2.86 (2H, m), 2.87 (4H, s), 3.13 - 3.19 (1H, m), 3.72 (6H, s), 4.27 - 4.30 (2H, m), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.35 (1H, d), 8.70 (1H, d), 9.75 (1H, s), 12.18 (1H, s). MS: m/z 466 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0022 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 124

N-[5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,4-dimethylpiperazin-1-yl)pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (390 mg, 1.00 mmol) was added in one portion to 1,2-dimethyl-piperazine (228 mg, 2.00 mmol) in anhydrous dimethylsulfoxide (2.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The residue was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (392 mg, 84%) as a yellow solid.

1H NMR (399.902 MHz, DMSO) δ 1.08 (3H, d), 2.06 - 2.12 (1H, m), 2.18 (1H, td), 2.23 (3H, s), 2.77 - 2.88 (2H, m), 3.14 - 3.21 (1H, m), 3.75 (6H, s), 4.32 (2H, t), 5.08 (2H, s), 5.84 (1H, s), 6.44 (1H, t), 6.59 (2H, d), 8.34 (1H, s), 8.71 (1H, s), 10.79 (1H, s), 11.35 (1H, s). MS: m/z 468 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0015 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as outlined in Example 109.

Example 125

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (271 mg, 0.70 mmol) was added in one portion to a 3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile (180 mg, 1.40 mmol) in anhydrous dimethylsulfoxide (1.40 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The reaction was incomplete and N-ethyl-N-propan-2-ylpropan-2-amine (0.24 ml, 1.40 mmol) was added and the solution was stirred at 60°C for a further 2 h. The reaction mixture was diluted with methanol (20 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (246 mg, 73%) as a yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.10 - 1.12 (6H, d), 2.15 - 2.21 (2H, m), 2.20 (3H, s), 2.75 (2H, t), 2.88 (4H, s), 3.72 (6H, s), 4.37 (2H, d), 6.33 (1H, s), 6.42 - 6.43 (2H, m), 6.46 (1H, s), 8.37 (1H, s), 8.70 (1H, s), 9.75 (1H, s), 12.18 (1H, s). MS: m/z 480 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0017μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile used as starting material was prepared as follows;-

Macroporous triethylammonium methylpolystyrene cyanoborohydride (2.31 mmol/g, 5.05 g, 11.67 mmol) was added to cis-3,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (1.00 g, 4.67 mmol), 37% aqueous formaldehyde (6.99 ml, 93.33 mmol) and acetic acid (0.53 ml, 9.33 mmol) in methanol (9.33 ml) at 25°C. The resulting suspension was stirred under nitrogen at ambient temperature for 24 h. The macroporous triethylammonium methylpolystyrene cyanoborohydride was removed by filtration, washing with methanol (50 mL). The filtrate was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness.

The residue was taken up in ethyl acetate (21.00 mL) and methanol (10.00 mL) and treated with hydrogen chloride (4M in 1,4-dioxane, 4.21 ml, 16.84 mmol) at 25°C under nitrogen. The resulting solution was stirred at ambient temperature for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford a 3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile (645 mg, quant.) as a colourless oil. This was used directly with no further purification.

Example 126

2-(4-cyclopropylpiperazin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.92 mL, 3.85 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (381 mg, 1.54 mmol) and methyl 2-(4-cyclopropylpiperazin-1-yl)pyrimidine-5-carboxylate (404 mg, 1.54 mmol) in toluene (7.7 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h and then heated at 60 °C for 2 h. The reaction mixture was quenched with methanol (20 mL) and treated with HCl (2N aqueous solution). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water

(containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (100 mg, 14%) as a solid.
1H NMR (399.9 MHz, DMSO-d6) δ 0.36 - 0.41 (2H, m), 0.45 - 0.47 (2H, m), 1.65 - 1.68 (1H, m), 2.61 (4H, t), 2.88 (4H, s), 3.72 (6H, s), 3.80 (4H, t), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.90 (2H, s), 10.60 (1H, s), 12.14 (1H, s). MS: m/z 478 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0036 μM.

Methyl 2-(4-cyclopropylpiperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows;-
A solution of methyl-2-chloropyrimidine-5-carboxylate (900 mg, 5.22 mmol) in dichloromethane (7.50 ml) was added to a stirred suspension of 1-cyclopropylpiperazine, 2HCl (1038 mg, 5.22 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (4.10 mL, 23.47 mmol) in dichloromethane (13 mL) at room temperature under nitrogen. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was poured onto ice (100 mL), extracted with dichloromethane (3 x 75 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford white solid. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford the desired compound (880 mg, 64%) as a white solid. This was used directly with no further purification.
1H NMR (399.9 MHz, DMSO-d6) δ 0.36 - 0.39 (2H, m), 0.45 - 0.47 (2H, m), 1.65 - 1.68 (1H, m), 2.61 (4H, t), 3.81 (3H, s), 3.81-3.84 (4H, t), 8.79 (2H, s). MS: m/z 263 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 127

2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.45 mL, 2.90 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (286 mg, 1.16 mmol) and methyl 2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate

(320 mg, 1.16 mmol) in toluene (5.8 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h and then at 60 °C for 2 h. The reaction mixture was quenched with methanol (20 mL) and treated with HCl (2N aqueous solution, until a freely stirred solution was obtained). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (238 mg, 42%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.14 - 1.32 (2H, m), 1.46 - 1.55 (1H, m), 1.61 (2H, d), 1.73 (1H, d), 1.80 - 1.83 (1H, m), 1.92 - 1.99 (1H, m), 2.03 - 2.10 (1H, m), 2.64 - 2.70 (1H, m), 2.79 (2H, d), 2.88 (4H, s), 3.02 - 3.09 (1H, m), 3.72 (6H, s), 4.55 - 4.59 (1H, m), 4.65 - 4.68 (1H, m), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.89 (2H, s), 10.59 (1H, s), 12.15 (1H, s). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0029 μM.

Methyl 2-(1,3,4,6,7,8,9,9a-octahydropyrido[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows;-

A solution of methyl 2-chloropyrimidine-5-carboxylate (900 mg, 5.22 mmol) in dichloromethane (7.50 ml) was added to a stirred suspension of 2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,2-a]pyrazine, HCl (1106 mg, 6.26 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (3.19 mL, 18.25 mmol) in dichloromethane (13.00 mL) at room temperature under nitrogen. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was poured onto ice (50 mL), extracted with DCM (3 x 50 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford yellow solid. The crude product was purified by crystallisation from IPA to afford the title compound (591 mg, 41%) as a white solid. The filtrate still contained some product and was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford a further sample of the title compound (402 mg, 28%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.14 - 1.30 (2H, m), 1.46 - 1.55 (1H, m), 1.61 (2H, d), 1.72 (1H, d), 1.81 (1H, t), 1.95 (1H, m), 2.06 (1H, m), 2.67 - 2.70 (1H, m), 2.80 (2H, d), 3.05 - 3.12 (1H, m), 3.81 (3H, s), 4.59 (1H, m), 4.68 (1H, d), 8.79 (2H, s). MS: m/z 277 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 128

2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 2.55 ml, 5.10 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (504 mg, 2.04 mmol) and methyl 2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate (535 mg, 2.04 mmol) in toluene (10.20 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 h and then at 60 °C for 2 h. The reaction mixture was quenched with methanol (20 mL) and treated with HCl (2N aqueous solution, until a freely stirred solution was obtained). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product.The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (288 mg, 30%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.36 - 1.40 (1H, m), 1.68 - 1.75 (2H, m), 1.83 - 1.90 (2H, m), 2.07 (2H, q), 2.67 - 2.72 (1H, m), 2.88 (4H, s), 3.01 - 3.08 (3H, m), 3.72 (6H, s), 4.71 - 4.75 (1H, m), 4.87 (1H, d), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.90 (2H, s), 10.59 (1H, s), 12.15 (1H, s). MS: m/z 478 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.003 μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows;-

A solution of methyl 2-chloropyrimidine-5-carboxylate (1.56 g, 9.04 mmol) in dichloromethane (7.50 ml) was added to a stirred suspension of 1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine (1.37 g, 10.85 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (3.95 ml, 22.60 mmol) in dichloromethane (22.60 ml) at room temperature under nitrogen. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was poured onto ice (100 mL), extracted with dichloromethane (3 x 100 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford a yellow solid. The aqueous layer was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford crude product. The combined crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the desired compound (1.36 g, 57%) as a yellow solid.

1H NMR (399.902 MHz, DMSO) δ 1.33 - 1.44 (1H, m), 1.63 - 1.78 (2H, m), 1.80 - 1.93 (2H, m), 2.04 - 2.11 (2H, m), 2.72 (1H, dd), 3.00 - 3.09 (3H, m), 3.81 (3H, s), 4.74 (1H, d), 4.88 (1H, d), 8.79 (2H, s). MS: m/z 263 (MH+).

Example 129

5-[(3R,5S)-4-(cyanomethyl)-3,5-dimethylpiperazin-1-yl]-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (271 mg, 0.70 mmol) was added in one portion to a 3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile (180 mg, 1.40 mmol) in anhydrous dimethylsulfoxide (1.40 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The reaction was incomplete and N-ethyl-N-propan-2-ylpropan-2-amine (0.24 ml, 1.40 mmol) was added and the solution was stirred at 60°C for a further 2 h. The reaction mixture was diluted with methanol (20 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM.

Pure fractions were evaporated to dryness to afford the title compound (77 mg, 22%) as a yellow solid.

1H NMR (399.9 MHz, CDCl3) δ 1.22 (6H, d), 2.71 - 2.79 (2H, m), 2.84 (1H, d), 2.87 (1H, d), 2.90 - 3.00 (4H, m), 3.77 (6H, s), 3.83 (2H, s), 4.32 - 4.35 (2H, m), 6.33 (1H, t), 6.36 (2H, d), 6.55 (1H, s), 8.01 (1H, d), 8.92 (1H, d), 9.73 (1H, s), One NH not observed. MS: m/z 505 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0035 μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 130

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (273 mg, 0.70 mmol) was added in one portion to a 3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile (180 mg, 1.40 mmol) in anhydrous dimethylsulfoxide (1.40 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The reaction was incomplete and N-ethyl-N-propan-2-ylpropan-2-amine (0.24 ml, 1.40 mmol) was added and the solution was stirred at 60°C for a further 2 h. The reaction mixture was diluted with methanol (20 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (248 mg, 74 %) as a yellow solid.

1H NMR (500.13 MHz, DMSO-d6, 373K) δ 1.13 - 1.14 (6H, m), 2.24 (3H, s), 2.25 - 2.31 (2H, m), 2.81 (1H, d), 2.83 (1H, d), 3.78 (6H, s), 4.30 - 4.33 (2H, m), 5.11 (2H, s), 5.90 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 8.27 (1H, d), 8.72 (1H, d), 10.3 (1H, s), 11.1 (1H, s). MS: m/z 482 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00059 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as outlined in Example 109.

Example 131

5-[(3R,5S)-4-(cyanomethyl)-3,5-dimethylpiperazin-1-yl]-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (273 mg, 0.70 mmol) was added in one portion to a 3:1 mixture of (2R,6S)-1,2,6-trimethylpiperazine and 2-[(2S,6R)-2,6-dimethylpiperazin-1-yl]acetonitrile (180 mg, 1.40 mmol) in anhydrous dimethylsulfoxide (1.40 ml) at 25°C. The resulting solution was stirred at ambient temperature for 2 h. The reaction was incomplete and N-ethyldiisopropylamine (0.24 ml, 1.40 mmol) was added and the solution was stirred at 60°C for a further 2 h. The reaction mixture was diluted with methanol (20 mL) and purified by ion exchange chromatography, using an SCX column. The desired product was' eluted from the column using 7M NH3/MeOH to afford impure material. The concentrated eluent was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (65 mg, 18%) as a yellow solid.
1H NMR (399.9 MHz, CDCl3) δ 1.22 (6H, t), 2.72 - 2.77 (2H, m), 2.86 (1H, d), 2.89 (1H, d), 3.80 (6H, s), 3.83 (2H, s), 4.33 - 4.37 (2H, m), 5.18 (2H, s), 5.50 (1H, s), 6.41 (1H, t), 6.61 (2H, d), 7.99 (1H, d), 8.88 (1H, d), 9.62 (1H, s), 10.7 (1H, s). MS: m/z 507 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0035 μM.

5-Chloro-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as outlined in Example 109.

Example 132

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.29 ml, 2.58 mmol) was added dropwise to a suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (295 mg, 1.03 mmol) and methyl 2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate (258 mg, 1.03 mmol) in toluene (5.16 ml) at 25°C. The resulting solution was stirred at 60 °C for 5 h. The

reaction mixture was poured into methanol (50 mL) and acidified with HCl (2M aqueous solution). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the title compound (298 mg, 62%) as a white crystalline solid.

1H NMR (500.133 MHz, DMSO, 373K) δ 1.05 (3H, d), 2.10 - 2.20 (2H, m), 2.24 (3H, s), 2.81 (1H, dt), 2.91 (1H, dd), 3.24 - 3.29 (1H, m), 3.76 (6H, s), 4.39 - 4.47 (2H, m), 5.09 (2H, s), 5.71 (1H, s), 6.44 (1H, t), 6.60 (2H, d), 8.84 (2H, s), 10.30 (1H, s), 11.28 (1H, s). MS: m/z 468 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0036 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Methyl 2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:-

A solution of methyl 2-chloropyrimidine-5-carboxylate (500 mg, 2.90 mmol) in dichloromethane (7.50 ml) was added to a stirred solution of 1,2-dimethylpiperazine (331 mg, 2.90 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (1.26 ml, 7.24 mmol) in dichloromethane (7.25 ml) at room temperature under nitrogen. The resulting solution was stirred at ambient temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the desired compound (713 mg, 98%) as a yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.04 - 1.06 (3H, m), 1.98 - 2.05 (1H, m), 2.06 - 2.13 (1H, m), 2.21 (3H, s), 2.78 - 2.84 (2H, m), 3.14 - 3.21 (1H, m), 3.81 (3H, s), 4.46 - 4.55 (2H, m), 8.78 (2H, s). MS: m/z 251 (MH+).

Example 133

2-(4-cyclopropylpiperazin-1-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 2.00 mL, 4.00 mmol) was added dropwise to a stirred suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (459 mg, 1.60 mmol) and methyl 2-(4-cyclopropylpiperazin-1-yl)pyrimidine-5-carboxylate (421 mg, 1.60 mmol) in toluene (8.0 mL) at 25°C.The resulting solution was stirred at ambient temperature for 18 h and then at 60 °C for 2 h. The reaction mixture was quenched with methanol (20 mL) and treated with HCl (2N aqueous solution, until a freely stirred solution was obtained). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (94 mg, 12%) as a solid.

1H NMR (500.13 MHz, DMSO-d6, 373K) δ 0.40 - 0.43 (2H, m), 0.44 - 0.49 (2H, m), 1.71 - 1.75 (1H, m), 2.65 (4H, t), 3.78 (6H, s), 3.84 (4H, t), 5.11 (2H, s), 5.71 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 8.86 (2H, s), 10.3 (1H, s), 11.3 (1H, s). MS: m/z 480 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0039 μM.

Methyl 2-(4-cyclopropylpiperazin-1-yl)pyrimidine-5-carboxylate was prepared as outlined in Example 126.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Example 134

2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 2.50 ml, 5.00 mmol) was added dropwise to a stirred suspension 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (572 mg, 2.00

mmol) and methyl 2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate (525 mg, 2.00 mmol) in toluene (10.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 h and then at 60 °C for 2 h. The reaction mixture was cautiously quenched with methanol (20 mL) and treated with HCl (2N aqueous solution, until a freely stirred solution was obtained). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product.The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (269 mg, 28%) as a solid.
1H NMR (500.13 MHz, DMSO-d6, 373K) δ 1.39 - 1.47 (1H, m), 1.69 - 1.75 (1H, m), 1.76 - 1.82 (1H, m), 1.84 - 1.90 (1H, m), 1.99 - 2.03 (1H, m), 2.13 - 2.21 (2H, m), 2.72 - 2.78 (1H, m), 3.04 - 3.13 (3H, m), 3.78 (6H, s), 4.70 - 4.75 (1H, m), 4.85 - 4.88 (1H, m), 5.11 (2H, s), 5.72 (1H, s), 6.46 (1H, t), 6.62 (2H, d), 8.87 (2H, s), 10.30 (1H, s), 11.30 (1H, s). MS: m/z 480 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0024 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Methyl 2-(3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c]pyrazin-2-yl)pyrimidine-5-carboxylate used as starting material was prepared as outlined in Example 128.

Example 135

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.31 ml, 2.62 mmol) was added dropwise to a suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (260 mg, 1.05 mmol) and methyl 2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate (263 mg, 1.05 mmol) in toluene (5.26 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was poured into methanol (50 mL) and acidified with HCl (2M aqueous solution, to obtain a clear freely stirring solution). The crude product was purified by ion exchange

chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in dichloromethane. Fractions containing product were evaporated to dryness to give material that was still impure. The residue was repurified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (175 mg, 36%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.05 - 1.07 (3H, m), 1.99 - 2.05 (1H, m), 2.07 - 2.13 (1H, m), 2.22 (3H, s), 2.76 - 2.84 (2H, m), 2.88 (4H, s), 3.12 - 3.19 (1H, m), 3.72 (6H, s), 4.46 - 4.55 (2H, m), 6.33 (1H, t), 6.42 (3H, m), 8.89 (2H, s), 10.60 (1H, s), 12.12 (1H, s). MS: m/z 466 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0026 μM.

5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(3,4-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as outlined in Example 132.

Example 136

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.04 ml, 2.08 mmol) was added dropwise to a suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (205 mg, 0.83 mmol) and methyl 2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxylate (220 mg, 0.83 mmol) in toluene (5.257 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was poured into methanol (50 mL) and acidified with HCl (2M aqueous solution, to obtain a clear freely stirring solution). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by preparative HPLC, using decreasingly polar mixtures of

water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (157 mg, 39%) as a white solid.
1H NMR (399.9 MHz, DMSO-d6) δ 1.09 - 1.10 (6H, m), 2.08 - 2.14 (2H, m), 2.20 (3H, s), 2.71 (1H, d), 2.74 (1H, d), 2.87 (4H, s), 3.72 (6H, s), 4.55 - 4.59 (2H, m), 6.33 (1H, t), 6.42 (3H, m), 8.89 (2H, s), 10.61 (1H, s), 12.15 (1H, s). MS: m/z 480 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0019 μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:-
Macroporous triethylammonium methylpolystyrene cyanoborohydride (2.31 mmol/g, 3.15 g, 7.29 mmol) was added to methyl 2-((3R,5S)-3,5-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate (730 mg, 2.92 mmol), formaldehyde (37% aqueous solution, 4.43 ml, 59.13 mmol) and acetic acid (0.334 ml, 5.83 mmol) in methanol (5.83 ml) at 25°C. The resulting suspension was stirred at ambient temperature for 5 h. The macroporous triethylammonium methylpolystyrene cyanoborohydride was removed by filtration, washing with methanol (50 mL). The filtrate was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by silica column chromatography, eluting with a gradient of 0 to 6% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the desired compound (474 mg, 62%) as a white oil which solidified on standing.
1H NMR (399.9 MHz, DMSO-d6) δ 1.09 (6H, d), 2.07 - 2.15 (2H, m), 2.19 (3H, s), 2.73 - 2.76 (2H, m), 3.81 (3H, s), 4.56 - 4.60 (2H, m), 8.79 (2H, s). MS: m/z 265 (MH+).

Methyl 2-((3R,5S)-3,5-dimethylpiperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:-
A solution of methyl 2-chloropyrimidine-5-carboxylate (535 mg, 3.10 mmol) in dichloromethane (7.50 ml) was added to a stirred solution of (2S,6R)-2,6-dimethylpiperazine (354 mg, 3.10 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (1.35 ml, 7.75 mmol) in

dichloromethane (7.24 ml) at room temperature under nitrogen. The resulting solution was stirred at ambient temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the desired compound (740 mg, 95%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.02 - 1.04 (6H, m), 2.33 (1H, s), 2.43 - 2.46 (2H, m), 2.64 - 2.69 (2H, m), 3.81 (3H, s), 4.62 - 4.66 (2H, m), 8.77 (2H, s). MS: m/z 251 (MH+).

Example 137

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[4-(1-hydroxypropan-2-yl)piperazin-1-yl]benzamide

2-(Piperazin-1-yl)propan-1-ol 2HCl (0.274 g, 1.26 mmol) was added to N-ethyl-N-propan-2-ylpropan-2-amine (0.330 mL, 1.89 mmol) in DMSO (5 mL). The reaction mixture was stirred at room temperature for 10 mins. N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluorobenzamide (0.233 g, 0.63 mmol) was added and the mixture heated at 110 °C for 18 h under nitrogen. Heating was continued for 12 additional days. The reaction was cooled and the crude mixture was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.048 g, 15.44 %) as a cream solid.

1H NMR (500.13 MHz-DMSO-d6 + CD3COOD @ 373K): 1.02 (3H, d), 2.70-2.81 (5H, m), 2.89 (4H, s), 3.28-3.34 (4H, m), 3.37-3.44 (1H, m), 3.50-3.55 (1H, m), 3.73 (6H, s), 6.27 - 6.32 (2H, m), 6.40 (2H, s0, 6.92 (2H, d), 7.82 - 7.88 (2H, m). MS: m/z (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00057 μM.

2-(Piperazin-1-yl)propan-1-ol. 2HCl used as starting material was prepared as follows:

A 1M solution of borane tetrahydrofuran complex (12.00 mL, 12.00 mmol) in THF, was added dropwise to a stirred suspension of 2-(1-tert-butoxycarbonylpiperazin-4-yl)propionic acid (2.58 g, 10 mmol) in tetrahydrofuran (50 mL) at 0°C, over a period of 10 mins under nitrogen. The resulting solution was stirred at 60 °C for 8 h. This was quenched with acetic acid/water (10ml, 1:2 mixture) and evaporated to dryness. The residuie was dissolved in ethyl acetate (50 ml), washed with saturated sodium bicarbonate (25 ml) and water, dried over MgSO4, filtered and evaporated to dryness to give tert-butyl 4-(1-hydroxypropan-2-yl)piperazine-1-carboxylate (0.810 g, 33.2 %)

1H NMR (399.9 MHz, CDCl3) δ 0.83 (3H, d), 1.39 (9H, s), 2.30 (2H, t), 2.51 - 2.57 (3H, m), 2.71 - 2.82 (1H, m), 3.34 - 3.40 (2H, m), 3.35 - 3.39 (4H, m).

A suspension of tert-butyl 4-(1-hydroxypropan-2-yl)piperazine-1-carboxylate (0.782 g, 3.2 mmol) in a mixture of ethyl acetate (10 ml) and methanol (10.00 mL), was treated drop-wise with 4.0M HCl in dioxane (12.00 ml, 48.00 mmol) at room temperature. The reaction mixture was stirred for 18 h. The reaction mixture was diluted with ether and the white solid filtered off, washed with ether and air dried to give 2-(piperazin-1-yl)propan-1-ol (0.525 g, 76 %), as its dihydrochloride salt.

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluorobenzamide used as starting material was prepared as follows:

A 2M solution of trimethylaluminium in toluene (3.00 mL, 3.00 mmol) was added drop-wise to a stirred solution of ethyl 4-fluorobenzoate (0.440 mL, 3.00 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.742 g, 3 mmol) in toluene (10 mL) at room temperature. The reaction was stirred at room temperature for 18 h. The reaction mixture was poured into acetone (50 mL) and treated with an excess of damp sodium sulphite. The reaction mixture was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford a yellow gum. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/ MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.245 g, 22.11 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.88 (4H, s), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.47 (1H, s), 7.32 (2H, t), 8.05 - 8.09 (2H, m), 10.69 (1H, s), 12.16 (1H, s). MS: m/z 370 (MH+).

Example 138

N-(3-(3,5-dimethoxybenzyloxy)-1H-pyrazol-5-yl)-2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.04 mL, 2.07 mmol) was added dropwise to a suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (237 mg, 0.83 mmol) and methyl 2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxylate (219 mg, 0.83 mmol) in toluene (4.2 mL) at 25°C. The resulting solution was stirred at 60 °C for 2 h. The reaction mixture was poured into methanol (50 mL) and acidified with HCl (2M aqueous solution). The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The impure material was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (158 mg, 40%) as a white solid.

1H NMR (500.133 MHz, DMSO, 373K) δ 1.10 (6H, d), 2.14 - 2.20 (2H, m), 2.22 (3H, s), 2.74 - 2.79 (2H, m), 3.76 (6H, s), 4.53 - 4.57 (2H, m), 5.08 (2H, s), 5.71 (1H, s), 6.44 (1H, t), 6.59 (2H, d), 8.84 (2H, s), 10.32 (1H, s), 11.31 (1H, s). MS: m/z 482 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0026 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Methyl 2-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)pyrimidine-5-carboxylate was prepared as outlined in Example 136.

Example 139

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(3,3-dimethylpiperazin-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluorobenzamide (0.1 g, 0.27 mmol) and 2,2-dimethylpiperazine (0.124 g, 1.04 mmol) were stirred at 60 °C for 20 mins. Potassium carbonate (0.033 ml, 0.54 mmol) and DMSO (1 ml) were added and the reaction stirred at 120 °C in a sealed tube for 16 days. The reaction mixture was cooled and evaporated. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (6.00 mg, 2.000 %) as a colourless gum.

1H NMR (399.9 MHz, CDCl3) δ 1.19 (6H, s), 2.92 - 2.95 (4H, m), 3.02 (4H, d), 3.04 (1H, s), 3.17 (2H, t), 3.75 (6H, s), 6.32 - 6.35 (3H, m), 6.84 (2H, d), 7.77 (2H, d), 8.73 (1H, s). MS: m/z 465 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00047 μM.

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-fluorobenzamide used as starting material was prepared as follows:-

A 2M solution of trimethylaluminium (3.54 ml, 7.08 mmol) in toluene was added dropwise to 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.7 g, 2.83 mmol) in toluene (35 ml). Methyl 4-fluorobenzoate (0.366 ml, 2.83 mmol) was then added and the resulting solution was stirred at room temperature for 18 h. An additional amount of methyl 4-fluorobenzoate (0.183 ml, 1.42 mmol) was added and the solution was stirred at room temperature for a further 20 h. The reaction mixture was poured into acetone (40 ml), and treated with an excess of damp sodium sulfite solution. The suspension was stirred for 2 h, filtered and the filtrate was purified by silica column chromatography, eluting with a gradient 2.5 to 5% 2.5N NH_3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound as a beige oil which solidified on standing (0.147 g, 14.06 %) to a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.88 (4H, s), 3.73 (6H, s), 6.33 (1H, t), 6.43 (2H, d), 6.47 (1H, s), 7.31 (2H, t), 8.05 - 8.09 (2H, m), 10.69 (1H, s), 12.16 (1H, s). MS: m/z 370 (MH+).

Example 140

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(3,3-dimethylpiperazin-1-yl)thiophene-2-carboxamide

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-(3,3-dimethylpiperazin-1-yl)thiophene-2-carboxylate (0.268 g, 1 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (0.286 g, 1.00 mmol) in toluene (7.14 ml) at 65°C under nitrogen. The reaction mixture was stirred and heated at 65°C for 4 h then 50°C for 18 h followed by 80°C for 5 h. Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow gum. The crude product was purified by preparative LCMS, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.073 g, 15.48 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 1.36 (6H, s), 3.24 (4H, s), 3.40 (2H, t), 3.74 (6H, s), 5.06 (2H, s), 5.64 (1H, s), 6.24 (1H, d), 6.41 (1H, s), 6.57 (2H, s), 7.62 - 7.63 (1H, m); MS: m/z 472 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00098 μM.

Ethyl 5-(3,3-dimethylpiperazin-1-yl)thiophene-2-carboxylate, used as starting material was prepared as follows:-

Palladium(II) acetate (0.112 g, 0.50 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (1.175 g, 5 mmol), 2,2-dimethyl-piperazine (0.571 g, 5.00 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.311 g, 0.50 mmol) and cesium carbonate (2.281 g, 7.00 mmol) in toluene (50.0 ml) at 20°C under nitrogen. The resulting suspension was stirred at 110°C for 23 h. The crude product was purified by ion exchange chromatography, using a SCX2 column. The crude material was dissolved in methanol and then applied to the column. The desired product was eluted from the column using 2M NH3 in methanol and pure fractions were evaporated to dryness to afford the crude product as a brown solid.

This material was further purified by silica column chromatography, eluting with a gradient of 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 5-(3,3-dimethylpiperazin-1-yl)thiophene-2-carboxylate (0.484 g, 36.1 %) as a brown gum.
1H NMR (399.9 MHz, CDCl3) δ 1.20 (6H, s), 1.33 (3H, t), 2.98 (2H, s), 3.05 (2H, d), 3.16 - 3.19 (2H, m), 4.28 (2H, q), 6.00 (1H, d), 7.54 (1H, d)
MS: m/z 269 (MH+)

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Example 141

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-ethylpiperazin-1-yl)thiophene-2-carboxamide

Trimethylaluminium (2M solution in toluene, 1.40 mL, 2.79 mmol) was added dropwise to a stirred suspension of 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (319 mg, 1.12 mmol) and ethyl 5-(4-ethylpiperazin-1-yl)thiophene-2-carboxylate (300 mg, 1.12 mmol) in toluene (5.60 mL) at 25°C. The resulting solution was then stirred at 60 °C under nitrogen for 5 h. The reaction mixture was cautiously quenched into methanol (100 mL), acidified with HCl (2M aqueous solution) and the mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure material. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Fractions were evaporated to dryness to afford impure N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-(4-ethylpiperazin-1-yl)thiophene-2-carboxamide as a cream solid. The residue was repurified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (72 mg, 14%) as a white solid.
1H NMR (500.133 MHz, DMSO, 373K) δ 1.04 (3H, t), 2.43 (2H, q), 2.53 - 2.54 (4H, m), 3.23 - 3.25 (4H, m), 3.76 (6H, s), 5.07 (2H, s), 5.60 (1H, s), 6.14 (1H, d), 6.44 (1H, t), 6.59 (2H, d), 7.63 (1H, d), 10.05 (1H, s), 11.09 (1H, s). MS: m/z 472 (MH+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00086 μM.

Ethyl 5-(4-ethylpiperazin-1-yl)thiophene-2-carboxylate used as starting material was prepared as follows:-

Tris(dibenzylideneacetone)dipalladium(0) (183 m,g, 0.20 mmol) followed by sodium tert-butoxide (538 mg, 5.60 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (1.034 g, 4.40 mmol), 1-ethylpiperazine (0.51 ml, 4.00 mmol) and (rac)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (249 mg, 0.40 mmol) in toluene (20.00 ml) at 25°C under nitrogen. The resulting suspension was stirred at 110 °C for 18 h. The cooled reaction mixture was diluted with methanol and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford crude product. The residue was purified by silica column chromatography, eluting with a gradient of 0 to 3% 7M NH3/MeOH in DCM. Fractions containing desired product were evaporated to dryness to give impure orange oil. The impure material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford ethyl 5-(4-ethylpiperazin-1-yl)thiophene-2-carboxylate (339 mg, 32%) as a yellow oil.

1H NMR (399.902 MHz, DMSO) δ 1.03 (3H, t), 1.25 (3H, t), 2.38 (2H, q), 2.49 (4H, m), 3.24 (4H, m), 4.19 (2H, q), 6.21 (1H, d), 7.51 (1H, d). MS: m/z 269 (MH+)

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl was prepared as outlined in Example 12.

Example 142

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methyl-1,4-diazepan-1-yl)thiophene-2-carboxamide

Ethyl 5-(4-methyl-1,4-diazepan-1-yl)thiophene-2-carboxylate (0.201 g, 0.75 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.185 g, 0.75 mmol) in toluene (10 mL) were stirred at 20°C and a 2M solution of trimethylaluminium in toluene (0.938 mL, 1.88 mmol) was added drop-wise. The reaction stirred under nitrogen at 60 °C for 18 h. The reaction mixture was cooled and quenched by pouring into methanol (50 ml), acidified with few drops of 2N hydrochloric acid. The crude product was purified by ion exchange

chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product.

The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.162 g, 46.0 %) as a tan solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.89 - 1.93 (2H, m), 2.28 (3H, s), 2.50 - 2.54 (2H, m), 2.63 (1H, d), 2.64 - 2.65 (1H, m), 2.85 (4H, s), 3.43 (2H, t), 3.50 (2H, t), 3.72 (6H, s), 5.86 (1H, d), 6.32 - 6.34 (2H, m), 6.41 (2H, d), 7.79 (1H, d), 10.15 (1H, s), 12.00 (1H, s). MS: m/z 470 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0021 μM.

Ethyl 5-(4-methyl-1,4-diazepan-1-yl)thiophene-2-carboxylate was prepared as follows: Palladium(II)acetate (0.135 g, 0.60 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (1.411 g, 6 mmol), 1-methyl-1,4-diazepane (0.822 g, 7.20 mmol), BINAP (0.374 g, 0.60 mmol) and cesium carbonate (2.74 g, 8.40 mmol) in dioxane (40 mL) warmed to 80°C for 18 h under nitrogen. The crude reaction mixture was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH. Fractions were evaporated to dryness to afford the crude product. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 3M ammonia/MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 5-(4-methyl-1,4-diazepan-1-yl)thiophene-2-carboxylate (0.204 g, 12.67 %) as a yellow gum.

1H NMR (399.9 MHz, CDCl3) δ: 1.34 (3H, t), 1.97 - 2.04 (2H, m), 2.38 (3H, s), 2.55 - 2.61 (2H, m), 2.67 (2H, m), 3.48 (2H, t), 3.54 - 3.57 (2H, m), 4.28 (4H, q), 5.79 (1H, d), 7.55 (1H, d). MS: m/z 269 (MH+).

Example 143

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-ethyl-3-methylpiperazin-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.65 ml, 3.31 mmol) was added dropwise to a stirred suspension of methyl 2-(4-ethyl-3-methylpiperazin-1-yl)pyrimidine-5-carboxylate (303 mg, 1.15 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (283 mg, 1.15 mmol) in toluene (5.73 ml) at room temperature. The resulting solution was stirred at 60°C

overnight. The reaction mixture was quenched into methanol (100 mL) and treated with HCl (2N aqueous solution, until the pH was 7 or lower). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product as a yellow dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (269 mg, 49%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 0.99 (3H, d), 1.03 (3H, d), 2.20-2.26 (1H, m), 2.35 - 2.43 (2H, m), 2.74 - 2.79 (1H, m), 2.83 (1H, m), 2.88 (4H, s), 3.02 - 3.07 (1H, m), 3.30 - 3.38 (1H, m), 3.72 (6H, s), 4.27 - 4.31 (2H, m), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.89 (2H, s), 10.58 (1H, s), 12.15 (1H, s). MS: m/z 480 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0027 μM.

Methyl 2-(4-ethyl-3-methylpiperazin-1-yl)pyrimidine-5-carboxylate, used as starting material, was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (300 mg, 1.74 mmol) in dichloromethane (4.30 ml) was added to a stirred solution of 1-ethyl-2-methylpiperazine (223 mg, 1.74 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.75 ml, 4.35 mmol) in dichloromethane (4.40 ml) at 25°C under nitrogen. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and diluted with MeOH (10 mL). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and was evaporated to dryness to afford impure product. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 3% 7M NH_3/MeOH in dichloromethane. Pure fractions were evaporated to dryness to afford the desired compound (382 mg, 83%) as a colourless oil.

1H NMR (399.9 MHz, DMSO-d_6) δ 0.98 (3H, t), 1.02 (3H, d), 2.20 - 2.27 (1H, m), 2.33 - 2.38 (1H, m), 2.40 - 2.45 (1H, m), 2.71 - 2.79 (1H, m), 2.81 - 2.85 (1H, m), 3.06 - 3.11 (1H, m), 3.35 - 3.42 (1H, m), 3.81 (3H, s), 4.28 - 4.35 (2H, m), 8.78 (2H, s). MS : m/z 265 (MH+)

Example 144

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-enylpiperidin-4-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-enylpiperidin-4-yl)benzamide was prepared following the procedure as outlined for Example 99, starting from methyl 4-(1-prop-2-enylpiperidin-4-yl)benzoate (0.259 g, 1.00 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1 mmol) and 2M trimethylaluminium (1.250 mL, 2.50 mmol) in toluene (10 ml). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/methanol in DCM. Pure fractions were evaporated to dryness and the product was crystallised from DCM/diethyl ether to give on filtration the title compound (0.182 g, 38.3 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.66 - 1.70 (2H, m), 1.73 - 1.79 (2H, m), 1.99 - 2.05 (2H, m), 2.55 (1H, d), 2.88 (4H, s), 2.95 (1H, s), 2.99 (3H, d), 3.73 (6H, s), 5.12 - 5.18 (1H, m), 5.22 (1H, t), 5.83 - 5.89 (1H, m), 6.33 (1H, t), 6.43 (2H, d), 6.47 (1H, s), 7.35 (2H, d), 7.93 (2H, d), 10.55 (1H, s), 12.13 (1H, s). MS: m/z 475 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.000041 μM.

Methyl 4-(1-prop-2-enylpiperidin-4-yl)benzoate used as starting material was prepared as follows:

3-Bromoprop-1-ene (0.433 mL, 5.00 mmol) was added dropwise over 5 mins under nitrogen to a stirred solution of methyl 4-piperidin-4-ylbenzoate (1.096 g, 5 mmol) and N-ethyl-N-isopropylpropan-2-amine (2.066 mL, 12.50 mmol) in DCM (10 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature. This was evaporated to dryness and partially purified on a SCX column, eluting with 3.5N ammonia in methanol. Fractions containing product were combined and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (1.004 g, 77 %) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.78 - 1.86 (4H, m), 2.02 - 2.08 (2H, m), 2.53 - 2.57 (1H, m), 3.03 - 3.05 (3H, m), 3.07 (1H, t), 3.90 (3H, s), 5.14 - 5.23 (2H, m), 5.85 - 5.97 (1H, m), 7.28 - 7.31 (2H, m), 7.95 - 7.98 (2H, m). MS: m/z 260 (MH+).

Methyl 4-piperidin-4-ylbenzoate was prepared as outlined in Example 99.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 145

4-(1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

4-(1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared following the procedure as outlined for Example 99, starting starting from ethyl 4-(1,4-diazepan-1-yl)benzoate (0.497 g, 2 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.495 g, 2.00 mmol) and 2M trimethylaluminium (2.50 mL, 5.0 mmol) in toluene (10 ml). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 2.5 M ammonia MeOH in DCM. Fractions containing the product were evaporated to dryness and further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.024 g, 2.67 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6 + d4HOAc) δ 2.07 (2H, t), 2.90 (4H, s), 3.10 (2H, t), 3.24 (2H, t), 3.62 (2H, t), 3.74 - 3.76 (8H, m), 6.33 (2H, t), 6.42 (2H, d), 6.81 - 6.83 (2H, m), 7.88 - 7.89 (2H, m). MS: m/z 450 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0007 μM.

Ethyl 4-(1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows: Ethyl 4-fluorobenzoate (11.01 mL, 75mmol) and 1,4-diazepane (30.0 g, 300.00 mmol) in DMSO (150 mL) warmed to 100°C under nitrogen. The resulting solution was stirred at 100 °C for 24 h. The reaction mixture was cooled and evaporated to dryness. The reaction mixture was quenched with 2M NaOH (150 mL), extracted with EtOAc (3 x 75 mL), the organic layer was washed with saturated brine (100 ml), dried over MgSO4, filtered and evaporated to afford ethyl 4-(1,4-diazepan-1-yl)benzoate (17.43 g, 94 %) as a colourless oil.

1H NMR (399.9 MHz, CDCl3) δ 1.27 - 1.31 (3H, m), 1.71 (1H, s), 1.79 - 1.85 (2H, m), 2.74 (1H, d), 2.74 (1H, d), 2.95 (1H, d), 2.96 (1H, d), 3.51 (2H, t), 3.56 (2H, t), 4.21 - 4.27 (2H, m), 6.56 - 6.60 (2H, m), 7.80 - 7.83 (2H, m). MS: m/z 249 (MH+).

5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 146

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-ynylpiperidin-4-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-prop-2-ynylpiperidin-4-yl)benzamide was prepared following the procedure as outlined for Example 99, starting from methyl 4-(1-prop-2-ynylpiperidin-4-yl)benzoate (0.257 g, 1.00 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1 mmol) in dry toluene (10 mL) with 2M trimethylaluminium (1.250 mL, 2.50 mmol). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/methanol in DCM. Pure fractions were evaporated to dryness and the product crystallised from DCM/diethyl ether to give the title compound (0.245 g, 51.8 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6 + d4HOAc) δ 1.64 - 1.73 (2H, m), 1.79 (2H, d), 2.24 - 2.29 (2H, m), 2.49 - 2.54 (1H, m), 2.88 (4H, s), 2.90 (1H, s), 2.93 (1H, s), 3.15 (1H, t), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 7.36 (2H, d), 7.93 (2H, d), 10.57 (1H, s), 11.95 (4H, s). MS: m/z 473 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0011 μM.

Methyl 4-(1-prop-2-ynylpiperidin-4-yl)benzoate used as starting material was prepared following the procedure as for methyl 4-(1-prop-2-enylpiperidin-4-yl)benzoate (Example 144), but starting from 3-bromoprop-1-yne (0.356 mL, 4.00 mmol) (80% solution in toluene), methyl 4-piperidin-4-ylbenzoate (0.877 g, 4 mmol) and N-ethyl-N-isopropylpropan-2-amine (1.653 mL, 10.00 mmol) in DCM (5 mL). The crude product was purified by silica column chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.748 g, 72.7 %) as a white solid. 1H NMR (399.9 MHz, CDCl3) δ 1.81 - 1.90 (4H, m), 2.27 (1H, t), 2.32 - 2.38 (2H, m), 2.54 - 2.59 (1H, m), 3.00 - 3.04 (2H, m), 3.36 (2H, d), 3.90 (3H, s), 7.27 - 7.30 (2H, m), 7.95 - 7.98 (2H, m). MS: m/z 258 (MH+).

Methyl 4-piperidin-4-ylbenzoate was prepared as outlined in Example 144.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 147

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-5-[(3S,5R)-3,5-dimethylpiperazin-1-yl]thiophene-2-carboxamide

2M Trimethylaluminium (1.250 ml, 2.50 mmol) in toluene, was added dropwise to a stirred solution of ethyl 5-((3R,5S)-3,5-dimethylpiperazin-1-yl)thiophene-2-carboxylate (0.268 g, 1 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride (0.286 g, 1.00 mmol) in toluene (7.14 ml) at room temperature and then the mixture was heated at 80°C under nitrogen for 4 h and then at 70°C for 18 h. Ethyl acetate (5mL) was added to the reaction mixture followed by a solution of potassium sodium tartrate (5mL, 20% aqueous). More ethyl acetate (50mL) and water (25mL) was added and the mixture was filtered through celite. The filtrate was transferred to a separating funnel and the aqueous layer removed. The ethyl acetate layer was washed with saturated brine and then dried over magnesium sulphate. After filtration the solvent was evaporated to give the crude product as a yellow gum. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.154 g, 32.7 %) as a white solid.

1H NMR (500.13 MHz, DMSO-d6, CD3CO2D) δ 1.23 (6H, d), 2.79 (2H, t), 3.26 - 3.34 (2H, m), 3.63 - 3.66 (2H, m), 3.76 (6H, s), 5.08 (2H, s), 5.63 (1H, s), 6.25 (1H, d), 6.43 (1H, t), 6.59 (2H, d), 7.66 (1H, d), 11.08 (1H, s)

MS: m/z 472 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0018 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Ethyl 5-((3R,5S)-3,5-dimethylpiperazin-1-yl)thiophene-2-carboxylate, used as starting material was prepared as follows:-

Palladium(II) acetate (0.225 g, 1.00 mmol) was added to ethyl 5-bromothiophene-2-carboxylate (2.351 g, 10 mmol), (2S,6R)-2,6-dimethylpiperazine (1.142 g, 10.00 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.623 g, 1.00 mmol) and cesium carbonate (4.56 g, 14.00 mmol) in dioxane (100 ml) at 20°C under nitrogen. The resulting suspension was stirred at 105°C for 23 h. The mixture was evaporated to dryness to give a brown oil. This crude product was purified by ion exchange chromatography, using a SCX2 column. The crude material was dissolved in methanol and then applied to the column. The desired product was eluted from the column using 2M NH3 in methanol and pure fractions were evaporated to dryness to afford the crude product as a brown solid.

This material was further purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 5-((3S,5R)-3,5-dimethylpiperazin-1-yl)thiophene-2-carboxylate (1.600 g, 59.6 %) as a white solid.
1H NMR (399.9 MHz, CDCl3) δ 1.12 - 1.14 (6H, m), 1.33 (3H, t), 2.46 -2.56 (2H, m), 2.98 - 3.07 (2H, m), 3.42 - 3.46 (2H, m), 4.28 (2H, q), 6.00 (1H, d), 7.55 (1H, d)
MS: m/z 269 (MH+)

Example 148

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[1-(2-methoxyethyl)piperidin-4-yl]benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[1-(2-methoxyethyl)piperidin-4-yl]benzamide was prepared following the procedure as outlined for Example 99, starting from methyl 4-(1-(2-methoxyethyl)piperidin-4-yl)benzoate (0.428 g, 1.25 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.309 g, 1.25 mmol) and 2M trimethylaluminium (1.56 mL, 3.13 mmol) in toluene (10 ml). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/methanol in DCM. Pure fractions were evaporated to dryness and the product was crystallised from DCM/diethyl ether to afford the title compound (0.215 g, 34.9 %) as an off white solid.
1H NMR (399.9 MHz, CDCl3) δ 1.76 - 1.91(4H, m), 2.10 - 2.17 (2H, m), 2.54 - 2.58 (1H, m), 2.63 (2H, t), 2.92 - 2.96 (4H, m), 3.10 (2H, d), 3.37 (3H, s), 3.56 (2H, t), 3.76 (6H, s), 6.33 - 6.35 (3H, m), 6.68 (1H, s), 7.32 (2H, d), 7.80 (2H, d), 8.65 (1H, s), 9.28 (1H, s). MS: m/z 493 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00087 μM.

Methyl 4-(1-(2-methoxyethyl)piperidin-4-yl)benzoate used as starting material was prepared as follows:

A solution of methyl 4-(piperidin-4-yl)benzoate, HCl (1.279 g, 5 mmol), N-ethyl-N-propan-2-ylpropan-2-amine (3.49 mL, 20.00 mmol) and 1-bromo-2-methoxyethane (0.470 mL, 5.00 mmol) in dichloromethane (10 mL) was heated at 40°C or 18 h. A few drops of DMF were added to aid solubility. The reaction mixture was cooled, diluted with DCM (30 ml) and washed with water (2 x 30 ml) and saturated sodium chloride solution (30 ml). This was dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(1-(2-methoxyethyl)piperidin-4-yl)benzoate (0.723 g, 52.1 %) as a colourless oil.

1H NMR (399.9 MHz, CDCl3) δ 1.75 (1H, t), 1.81 - 1.90 (3H, m), 2.09 - 2.15 (2H, m), 2.55 (1H, q), 2.60 - 2.63 (2H, m), 3.08 - 3.11 (2H, m), 3.37 (3H, s), 3.53 - 3.56 (2H, m), 3.89 - 3.90 (3H, m), 7.27 - 7.31 (2H, m), 7.95 - 7.98 (2H, m). MS: m/z 278 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 149

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[(3S)-3-propan-2-ylpiperazin-1-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.23 mL, 2.46 mmol) was added dropwise to a stirred suspension of (S)-methyl 2-(3-propan-2-ylpiperazin-1-yl)pyrimidine-5-carboxylate (260 mg, 0.98 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (243 mg, 0.98 mmol) in toluene (8.38 mL) at room temperature. The reaction was then stirred at 60°C for 18 h under a nitrogen atmosphere. The reaction mixture was quenched into methanol (100 mL) and treated with HCl (2N aqueous solution, until the pH was 7 or lower). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions

containing the desired compound were evaporated to dryness to afford the title compound (292 mg, 62 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 0.95 - 0.97 (6H, d), 1.63 (1H, m), 2.26 - 2.31 (1H, m), 2.57 - 2.64 (1H, m), 2.68 (1H, d), 2.88 (4H, s), 2.89 - 2.97 (1H, m) 2.98 - 3.02 (1H, m), 3.72 (6H, s), 4.57 (1H, d), 4.66 (1H, d), 6.33 (1H, t), 6.41 - 6.44 (3H, m), 8.88 (2H, s), 10.56 (1H, s), 12.14 (1H, s). MS: m/z 480 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0044 μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

(S)-methyl 2-(3-propan-2-ylpiperazin-1-yl)pyrimidine-5-carboxylate, used as starting material was prepared as follows:

A solution of (2S)-2-propan-2-ylpiperazine (223 mg, 1.74 mmol) in dichloromethane (4.40 mL) was added to a stirred solution of methyl 2-chloropyrimidine-5-carboxylate (300 mg, 1.74 mmol) in dichloromethane (4.30 mL) at 25°C. N-Ethyl-N-propan-2-ylpropan-2-amine (0.752 mL, 4.35 mmol) was added. The resulting solution was stirred at room temperature for 18 h under a nitrogen atmosphere. The reaction mixture was concentrated and diluted with methanol. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford the desired compound (456.1 mg, 99%) as a yellow oil. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d_6) δ 0.94 - 0.96 (6H, m), 1.58 - 1.66 (1H, m), 2.25 - 2.30 (1H, m), 2.56 - 2.63 (1H, m), 2.68 - 2.74 (1H, m), 2.95 - 3.02 (2H, m), 3.81 (3H, s), 4.56 - 4.60 (1H, m), 4.64 - 4.68 (1H, m), 8.78 (2H, s). MS: m/z 265 (MH+)

(2S)-2-propan-2-ylpiperazine, used as starting material was prepared as follows:

A solution of *tert*-butyl (2S)-2-propan-2-ylpiperazine-1-carboxylate (2 g, 8.76 mmol) in a mixture of ethyl acetate (20 mL) and methanol (20.00 mL) was stirred at room temperature with 4M HCl in dioxane (30 mL) for 40 h under nitrogen.The reaction mixture was evaporated to dryness. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 3.5M

NH3/MeOH and pure fractions were evaporated to dryness to afford (2S)-2-propan-2-ylpiperazine (1.052 g, 94 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.83 - 0.87 (6H, m), 1.39 - 1.47 (1H, m), 2.15 - 2.22 (2H, m), 2.41 - 2.47 (1H, m), 2.53 - 2.59 (1H, m), 2.67 (1H, d), 2.75 - 2.80 (2H, m) – 2 protons not seen.

Example 150

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.23 mL, 2.46 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (243 mg, 0.98 mmol) and methyl 2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxylate (246 mg, 0.98 mmol) in toluene (5.00 mL) at 25°C. The resulting solution was stirred at 60 °C for 24 h. The reaction mixture was added to methanol (100 mL), then treated with HCl (2N aqueous solution, until pH was 7 or lower). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 0.1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (204 mg, 45 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.88 - 2.91 (7H, m), 3.44 (2H, t), 3.72 (6H, s), 4.08 (2H, t), 4.33 (2H, s), 6.33 (1H, t), 6.40 -6.47 (3H, m), 8.95 (2H, s), 10.66 (1H, s), 12.16 (1H, s).

MS: m/z 466 (MH+)

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.012 μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxylate, used as starting material was prepared as follows:

A solution of 1-methylpiperazin-2-one (198 mg, 1.74 mmol) in dichloromethane (4.00 mL) was added to a stirred solution of methyl 2-chloropyrimidine-5-carboxylate (300 mg, 1.74

mmol) in dichloromethane (4.70 mL) at 25°C. The resulting solution was stirred at room temperature for 4 h under nitrogen. The reaction mixture was concentrated and dissolved in ethyl acetate (25ml) and NaOH (50ml, 1M aqueous solution). The organic layer was washed with ethyl acetate (25ml). The organic layers were combined and washed with brine (50ml), dried using MgSO4, filtered and evaporated to dryness to afford methyl 2-(4-methyl-3-oxopiperazin-1-yl)pyrimidine-5-carboxylate (246 mg, 57 %) as a cream solid.
1H NMR (399.9 MHz, DMSO-d_6) δ 2.91 (3H, s), 3.44 (2H, t), 3.83 (3H, s), 4.09 (2H, t), 4.35 (2H, s), 8.86 (2H, s). MS: m/z 501 (2MH+)

Example 151

4-(1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridin-6-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide

4-(1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridin-6-yl)-N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]benzamide was prepared following the procedure as for Example 115, but starting from methyl 4-(1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridin-6-yl)benzoate (0.221 g, 0.85 mmol) and 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine HCl (0.243 g, 0.85 mmol) and 2M trimethylaluminium in toluene (1.06 ml, 2.13 mmol). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.124 g, 30.5 %) as a white solid.
1H NMR (399.9 MHz, DMSO-d_6) δ 1.36 - 1.45 (1H, m), 1.50-1.60 (1H, m), 1.63 - 1.75 (2H, m), 2.12 (1H, s), 2.27 -2.38 (1H, m), 2.83 (1H, d), 3.16 (1H, d), 3.26 - 3.36 (2H, m), 3.37 - 3.45 (2H, m), 3.85 (6H, s), 5.08 (2H, s), 5.54 (1H, s), 6.44 (1H, s), 6.52 (2H, d), 6.57 (2H, s), 7.82 (2H, d), 10.46 (1H, s0, 11.45 (1H, s). 1 proton not seen. MS: m/z 478 (MH+).
Mean of n=3, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0013μM.

Methyl 4-(1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridin-6-yl)benzoate used as starting material was prepared as follows:

2,3,4,4a,5,6,7,7a-Octahydro-1H-pyrrolo[3,4-b]pyridine. 2HCl (0.813 g, 5 mmol) was dissolved in water (10ml) and placed on a SCX2 column (50g). This was washed through with methanol and released the freebase from the column with 7N ammonia in methanol. The

freebase and methyl 4-fluorobenzoate (0.291 mL, 2.25 mmol) were dissolved in DMSO (10 mL) and heated at 120 °C for 12 h. The crude reaction mixture was partly purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 3M ammonia/MeOH in DCM. Pure fractions were evaporated to dryness to afford the desired compound (0.230 g, 17.67 %) as a white solid.

1HNMR (700.03MHz, CDCl3)δ: 1.48 - 1.53 (1H, m), 1.57 - 1.68 (2H, m), 1.74 - 1.83 (1H, m), 2.34 - 2.40 (1H, m), 2.66 - 2.70 (1H, m), 2.97 - 3.02 (1H, m), 3.23 - 3.27(1H, m), 3.83 - 3.87 (1H, m), 3.46 - 3.50 (3H, m), 3.85 (3H, s), 6.49 (2H, d), 7.89 (2H, d). MS: m/z 261 (MH+).

Example 152

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(1-methylpiperidin-4-yl)pyrazine-2-carboxamide

Trimethylaluminium (2 M in toluene, 1.73 ml, 3.46 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (247 mg, 1.00 mmol) and methyl 5-(1-methylpiperidin-4-yl)pyrazine-2-carboxylate (235 mg, 1.00 mmol) in anhydrous toluene (5.00 ml) at room temperature. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was quenched into methanol (100 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH. At this point a white solid precipitated from the eluent. The precipitate was collected by suction filtration and dried under vacuum to afford the product (90 mg, 20%) as a cream solid. The filtrate was concentrated and a second sample of product was obtained by crystallisation from methanol to afford the title compound (93 mg, 21%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.80 - 1.89 (4H, m), 1.98 - 2.04 (2H, m), 2.22 (3H, s), 2.83 - 2.90 (7H, m), 3.73 (6H, s), 6.33 (1H, t), 6.43 (2H, d), 6.50 (1H, d), 8.73 (1H, d), 9.18 (1H, d), 10.27 (1H, s), 12.27 (1H, s). MS: m/z 451 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0013μM.

Methyl 5-(1-methylpiperidin-4-yl)pyrazine-2-carboxylate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (530 mg, 2.50 mmol) was added to methyl 5-(piperidin-4-yl)pyrazine-2-carboxylate (221 mg, 1.00 mmol), formaldehyde (37% aqueous solution, 1.50 ml, 20.00 mmol) and acetic acid (0.11 ml, 2.00 mmol) in methanol (5.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was quenched with water (5 mL) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 5-(1-methylpiperidin-4-yl)pyrazine-2-carboxylate (239 mg, 100%) as a yellow waxy solid. This was used directly with no further purification.

1H NMR (399.9 MHz, CDCl3) δ 1.92 - 1.99 (4H, m), 2.07 - 2.13 (2H, m), 2.34 (3H, s), 2.79 - 2.87 (1H, m), 2.99 - 3.03 (2H, m), 4.03 (3H, s), 8.61 (1H, d), 9.21 (1H, d). MS: m/z 236 (MH+).

Methyl 5-(piperidin-4-yl)pyrazine-2-carboxylate used as starting material was prepared as follows:

Hydrogen chloride (4M in 1,4-dioxane, 0.37 ml, 1.48 mmol) was added to methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]piperidin-4-yl]pyrazine-2-carboxylate (120 mg, 0.37 mmol) in MeOH (3.70 ml). The resulting solution was stirred at ambient temperature for 24 h. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 5-(piperidin-4-yl)pyrazine-2-carboxylate (83 mg, 100%) as a pale yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, CDCl3) δ 1.76 - 1.86 (2H, m), 1.92 - 1.97 (2H, m), 2.80 (2H, d), 2.97 - 3.05 (1H, m), 3.23 - 3.27 (2H, m), 4.04 (3H, s), 8.61 (1H, d), 9.22 (1H, d), NH not observed. MS: m/z 222 (MH+).

Methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]piperidin-4-yl]pyrazine-2-carboxylate used as starting material was prepared as follows:

Palladium, 10% on carbon (21 mg, 0.20 mmol) and methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrazine-2-carboxylate (183 mg, 0.57 mmol) in

ethanol (5.73 mL) was stirred under an atmosphere of hydrogen at ambient temperature and atmospheric pressure for 6 h. The reaction mixture was filtered through celite and concentrated under reduced pressure to give a yellow oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]piperidin-4-yl]pyrazine-2-carboxylate (126 mg, 68%) as a yellow oil.
1H NMR (DMSO, 399.99 MHz) δ1.43 (9H, s), 1.58 - 1.68 (2H, m), 1.89 (2H, d), 2.88 (2H, s), 3.07 - 3.14 (1H, m), 3.92 (3H, s), 4.07 - 4.11 (2H, m), 8.78 (1H, d), 9.13 (1H, d). MS: m/z 322 (MH+).

Methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrazine-2-carboxylate used as starting material was prepared as follows:
Saturated aqueous sodium hydrogen carbonate solution (5.00 ml) was added to methyl 5-chloropyrazine-2-carboxylate (173 mg, 1.00 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (371 mg, 1.20 mmol), palladium(II) acetate (11 mg, 0.05 mmol) and triphenylphosphine (52 mg, 0.20 mmol) in 1,2-dimethoxyethane (5.00 ml) at 25°C under nitrogen. The resulting mixture was stirred at 80 °C for 4 h. The reaction mixture was diluted with water (50mL) and washed with EtOAc (50 mL). The aqueous layer was adjusted to pH 1 using HCl (2M aqueous solution) and extracted with EtOAc (2 x 50 mL). The combined organics were dried over MgSO4 and concentrated under reduced pressure to afford 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrazine-2-carboxylic acid (305 mg, 100%) as a yellow solid. This was used directly in the next reaction, with no further purification.
1H NMR (DMSO, 399.9MHz) δ1.45 (9H, s), 2.64 (2H, d), 3.58 (2H, t), 4.13 (2H, d), 7.02 (1H, s), 9.01 (1H, d), 9.12 (1H, d), 13.40 (1H, br s). MS: m/z 306 (MH+).

Example 153

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyrazine-2-carboxamide

Trimethylaluminium (2M in toluene, 1.74 ml, 3.48 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (343 mg, 1.39 mmol) and methyl 5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyrazine-2-carboxylate (324 mg, 1.39

mmol) in anhydrous toluene (6.94 ml) at ambient temperature. The resulting solution was then stirred at 60 °C for 18 h. The reaction mixture was quenched into methanol (100 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (152 mg, 24%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.33 (3H, s), 2.63 - 2.64 (4H, m), 2.86 - 2.89 (4H, m), 3.16 (2H, s), 3.73 (6H, s), 6.33 (1H, s), 6.43 - 6.43 (2H, m), 6.50 (1H, s), 7.04 (1H, s), 8.96 (1H, s), 9.17 (1H, s), 10.26 (1H, s), 12.28 (1H, s). MS: m/z 449 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00082μM.

Methyl 5-(1-methyl-3,6-dihydro-2H-pyridin-4-yl)pyrazine-2-carboxylate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (749 mg, 3.53 mmol) was added to methyl 5-(1,2,3,6-tetrahydropyridin-4-yl)pyrazine-2-carboxylate (310 mg, 1.41 mmol), formaldehyde (37% aqueous solution, 2.10 ml, 28.30 mmol) and acetic acid (0.16 ml, 2.83 mmol) in methanol (7.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was quenched with saturated aqueous NaHCO3 solution (5 mL), diluted with methanol (10 mL) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford the desired compound (324 mg, 98%) as a tan waxy solid. This was used directly with no further purification.

1H NMR (399.9 MHz, CDCl3) δ 2.44 (3H, s), 2.69 - 2.75 (4H, m), 3.23 - 3.25 (2H, m), 4.03 (3H, s), 6.89 - 6.91 (1H, m), 8.79 (1H, d), 9.20 (1H, d). MS: m/z 234 (MH+).

Methyl 5-(1,2,3,6-tetrahydropyridin-4-yl)pyrazine-2-carboxylate used as starting material was prepared as follows:

Hydrogen chloride (4M in 1,4-dioxane, 1.57 ml, 6.29 mmol) was added to methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrazine-2-carboxylate (502 mg, 1.57 mmol) in methanol (15.70 ml) at room temperature The resulting solution was

stirred at ambient temperature for 18 h. The reaction mixture was diluted with water (20 mL) and the crude product purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford the desired compound (316 mg, 92 %) as a yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 2.47 - 2.54 (2H, m, partially obscured by solvent peak), 2.94 (2H, t), 3.49 (2H, q), 3.92 (3H, s), 7.09 - 7.11 (1H, m), 9.00 (1H, d), 9.12 (1H, d), NH not observed. MS: m/z 261 (M+MeCN+H+).

Methyl 5-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrazine-2-carboxylate used as starting material was prepared as outlined in Example 152.

Example 154

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide was prepared following the procedure as for Example 155, but starting with ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (0.525 g, 2 mmol), 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.495 g, 2.00 mmol) and 2M trimethylaluminium (2.5ml, 5.0 mmol in toluene). The crude mixture was chromatographed on a SCX column, eluting with 7N ammonia in methanol. Fractions containing product were combined and evaporated to give an oil. The oil was suspended in dichloromethane (20 ml) and product slowly crystallised out. This was filtered to give the title compound (0.465 g, 50.2 %).

1H NMR (399.9 MHz, DMSO-d6) δ 1.04 - 1.05 (6H, m), 1.92 (2H, s), 2.20 - 2.25 (2H, m), 2.80 - 2.82 (1H, m), 2.81 - 2.84 (1H, m), 2.87 (4H, s), 3.71 - 3.74 (2H, m), 3.73 (6H, s), 6.33 (1H, t), 6.40 (1H, s), 6.42 (2H, d), 6.95 (2H, d), 7.89 (2H, d), 10.30 (1H, s). MS: m/z 464 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00075μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 155

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-[(3R,5S)-3,4,5-trimethylpiperazin-1-yl]benzamide

A 2M solution of trimethylaluminium (2.500 mL, 5.00 mmol) in toluene, was added dropwise to a stirred suspension of ethyl 4-((3R, 5S)-3,4,5-trimethylpiperazin-1-yl)benzoate (0.643 g, 2 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.495 g, 2.00 mmol) in toluene (10 mL) at room temperature. The solution was then heated at 60 °C for 18 h. The reaction mixture was cooled and quenched with methanol (15 ml) and 2N hydrochloric acid (5ml). The crude reaction mixture was purified by ion exchange chromatography on a SCX column, eluting with 7N ammonia in methanol. The appropriate fractions were evaporated to give an oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 2.5N ammonia / MeOH in DCM. Pure fractions were evaporated to dryness to afford, on crystallisation from DCM/diethyl ether, the title compound (0.322 g, 33.7 %) as a cream solid.

1HNMR (500.13MHz, DMSOd + CD3COOD @ 373K) δ: 1.16 (6H, d), 2.34 (3H, s), 2.48 - 2.55 (2H, m), 2.66 (2H, t), 2.88 (4H, s), 3.69 - 3.75 (2H, m), 3.73 (3H, s), 6.28 - 6.92 (2H, m), 6.47 - 6.49 (2H, m), 6.92 (2H, d), 7.85 (2H, d). MS: m/z 478 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00045μM.

Ethyl 4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (5.30 g, 25.00 mmol) was added to ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (2.62 g, 10 mmol), and acetic acid (1.145 mL, 20.00 mmol) in methanol (15 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was quenched with saturated NaHCO3 (15 mL) to pH7 and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford an oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-((3R,5S)-3,4,5-trimethylpiperazin-1-yl)benzoate (1.960 g, 70.9 %) as a yellow oil. MS: m/z 277 (MH+).

Ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate used as starting material was prepared as follows:

(2S,6R)-2,6-dimethylpiperazine (6.85 g, 60.00 mmol) was added to ethyl- 4-fluorobenzoate (2.20 mL, 15 mmol), in DMSO (40 mL) and warmed to 120°C under nitrogen. The resulting solution was stirred at 120 °C for 20 h. The reaction mixture was cooled and the solvent evaporated. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% methanol in dichloromethane containing 1% 0.880 ammonia. Pure fractions were evaporated to dryness to afford ethyl 4-((3R,5S)-3,5-dimethylpiperazin-1-yl)benzoate (2.83 g, 71.9 %) as a brown oil, which solidified on standing.

1H NMR (399.9 MHz, CDCl3) δ 1.15 (6H, d), 1.37 (3H, t), 2.38 (1H, d), 2.41 (1H, d), 2.96 - 3.04 (2H, m), 3.65 - 3.69 (2H, m), 4.33 (2H, q), 6.84 - 6.87 (2H, m), 7.89 - 7.93 (2H, m). MS: m/z 263 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 156

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide was prepared following the procedure as for Example 115, but starting from of methyl 4-(4-methyl-1,4-diazepan-1-yl)benzoate (0.372 g, 1.5 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.371 g, 1.5 mmol) and 2M trimethylaluminium in toluene (1.875 ml, 3.75 mmol). The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% 2.5M ammonia/ MeOH in DCM. Pure fractions were evaporated to dryness and the residual oil crystallised from DCM/diethyl ether to afford the title compound (0.142 g, 20.42 %) as a white solid. 1HNMR (500.13MHz, DMSOd6 + CD3COOD @ 373K) δ: 2.08 - 2.15 (2H, m), 2.69 (3H, s), 2.88 (4H, s), 3.11 (2H, t), 3.19 - 3.24 (2H, m), 3.56 (2H, t), 3.72 (3H, s), 3.74 (2H, t), 6.30 (1H, d), 3.32 (1H,s), 6.49 (2H, s), 6.79 (2H, d), 7.86 (2H, d). MS: m/z 464 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00081μM.

Methyl 4-(4-methyl-1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows:

1-Methyl-1,4-diazepane (15.07 g, 132.00 mmol) was added to methyl 4-fluorobenzoate (7.76 mL, 60 mmol) in DMA (150 mL). The resulting solution was stirred at 100 °C for 40 h. The reaction mixture was evaporated and quenched with 2M sodium hydroxide (50 ml). This was extracted with DCM (3 x 50 ml). The combined organic extracts were washed with saturated brine (50 ml), dried over MgSO4, filtered and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(4-methyl-1,4-diazepan-1-yl)benzoate (3.59 g, 24.10 %) as a tan waxy solid.

1H NMR (399.9 MHz, CDCl3) δ 1.95 (2H, q), 2.31 (3H, s), 2.48 (2H, d), 2.63 - 2.65 (2H, m), 3.47 (2H, t), 3.54 - 3.56 (2H, m), 3.78 (3H, s), 6.56 - 6.59 (2H, m), 7.79 - 7.83 (2H, m).

Example 157

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3-dimethylaminopyrrolidin-1-yl)pyrazine-2-carboxamide

N,N-dimethylpyrrolidin-3-amine (114 mg, 1.00 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (136 mg, 0.35 mmol) in anhydrous dimethylsulfoxide (1.75 ml) at 25°C. The resulting solution was stirred at room temperature for 20 mins. The reaction mixture was diluted with methanol (5.00 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product as a brown oil. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (130 mg, 80%) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.86 (1H, t), 2.16 - 2.21 (1H, m) 2.23 (6H, s), 2.83 - 2.85 (1H, m), 2.88 (4H, s), 3.25 - 3.29 (1H, m), 3.45 - 3.54 (1H, m), 3.72 (6H, s), 3.73 - 3.79 (1H, m), 3.81 - 3.86 (1H, m), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.01 (1H, d), 8.71 (1H, d), 9.73 (1H, s), 12.17 (1H, s). MS: m/z 466 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0024μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 158

5-(3-diethylaminopyrrolidin-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

N,N-diethylpyrrolidin-3-amine (142 mg, 1.00 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (136 mg, 0.35 mmol) in anhydrous dimethylsulfoxide (1.75 ml) at 25°C. The resulting solution was stirred at room temperature for 50 mins. The reaction mixture was diluted with methanol (5.00 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product as a brown dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (141 mg, 82%) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 0.99 (6H, t), 1.80 - 1.90 (1H, m), 2.17 - 2.23 (1H, m), 2.56 - 2.68 (4H, m), 2.88 (4H, s), 3.20 - 3.26 (1H, m), 3.34 - 3.41 (1H, m), 3.43 - 3.50 (1H, m), 3.72 (6H, s), 3.73 - 3.78 (1H, m) 3.82 - 3.87 (1H, m), 6.33 (1H, t), 6.42 (2H, d), 6.46 (1H, s), 8.01 (1H, d), 8.71 (1H, d), 9.73 (1H, s), 12.17 (1H, s). MS: m/z 494 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0029μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 159

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(1-ethylpiperidin-4-yl)benzamide

A 2M solution of trimethylaluminium in toluene (0.413 mL, 0.83 mmol), was added drop-wise to a suspension of methyl 4-(1-ethylpiperidin-4-yl)benzoate (0.082 g, 0.33 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.082 g, 0.33 mmol) in toluene (2 mL)

at room temperature. The solution was then heated at 60 °C for 18 h. The reaction mixture was cooled, quenched with methanol (2 ml) and 2N hydrochloric acid (1 ml). The reaction mixture was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and 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. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.058 g, 38.0 %) as a white solid.

1H NMR (500.13 MHz, DH4OAcDMSO-d6) δ 1.21 (3H, t), 1.26 (2H, s), 1.84-1.93 (1H, m), 1.95 - 2.04 (2H, m), 2.77 (2H, t), 2.89 (4H, s), 2.94 (2H, q), 3.34 - 3.40 (2H, m), 3.72 (6H, s), 6.30 (1H, d), 6.35 (1H, d), 6.41 (2H, d), 7.34 (2H, d), 7.89 (2H, d). MS: m/z 463 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00097μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 4-(1-ethylpiperidin-4-yl)benzoate used as starting material was prepared as follows:
Sodium triacetoxyborohydride (0.397 g, 1.88 mmol) was added portion-wise to acetaldehyde (0.168 mL, 3.00 mmol), methyl 4-(piperidin-4-yl)benzoate, HCl (0.192 g, 0.75 mmol) and sodium acetate (0.062 g, 0.75 mmol) in methanol (5 mL) at room temperature. The resulting solution was stirred at room temperature for 18 h. The reaction mixture was quenched with saturated $NaHCO_3$ (3 mL) to pH7 and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford an oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford methyl 4-(1-ethylpiperidin-4-yl)benzoate (0.082 g, 44.2 %) as a colourless oil. MS: m/z 248 (MH+).

Example 160

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-[3-(methoxymethyl)piperazin-1-yl]pyrimidine-5-carboxamide

Trimethylaluminium (2M in toluene, 1.596 mL, 3.19 mmol) was added dropwise to a solution of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (314 mg, 1.27 mmol) and methyl 2-(3-(methoxymethyl)piperazin-1-yl)pyrimidine-5-carboxylate (338 mg, 1.27 mmol) in toluene (6.35 mL) at 25°C. The resulting mixture was stirred at 60 °C for 18 h under nitrogen. The reaction mixture was added to methanol (100 mL) and treated with HCl (2N aqueous solution, until pH was 7 or lower). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford the crude product as a yellow dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (348 mg, 57 %) as a white solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 2.72 - 2.77 (2H, m), 2.82 - 2.92 (5H, m), 2.97 - 3.04 (2H, m), 3.24 - 3.28 (1H, m), 3.30 (3H, s), 3.35 - 3.38 (1H, m), 3.69 (6H, s), 4.61 (2H, d), 6.25 - 6.28 (3H, m), 6.61 (1H, s), 8.73 (1H, s), 8.76 (2H, s), 9.6 (1H, s). MS: m/z 482 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0043μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(3-(methoxymethyl)piperazin-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (300 mg, 1.74 mmol) in DCM (4.70 mL) was added to a stirred solution of 2-(methoxymethyl)piperazine (226 mg, 1.74 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.752 mL, 4.35 mmol) in DCM (4.00 mL) at 25°C under nitrogen. The resulting solution was stirred at room temperature for 6 h. The reaction mixture was concentrated and diluted with MeOH. The resulting mixture was filtered. The filtrate was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford methyl 2-(3-(methoxymethyl)piperazin-1-yl)pyrimidine-5-

carboxylate (346 mg, 75 %) as a yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, $CDCl_3$) δ 2.72 - 2.79 (2H, m), 2.84 - 2.90 (1H, m), 2.99 - 3.07 (2H, m), 3.25 - 3.30 (1H, m), 3.31 (3H, s), 3.38 - 3.42 (1H, m), 3.80 (3H, s), 4.61 - 4.68 (2H, m), 8.76 (2H, s). MS: m/z 267 (MH+)

2-(Methoxymethyl)piperazine used as starting material was prepared as follows:

1,4-Dibenzyl-2-(methoxymethyl)piperazine (1.578 g, 5.08 mmol) and palladium (10% on carbon, 0.163 g, 1.53 mmol) in ethanol (50.8 ml) were stirred under an atmosphere of hydrogen at room temperature for 3 days. The reaction mixture was filtered through celite, washing with ethanol. The resulting mixture was evaporated to dryness to afford crude product. The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford 2-(methoxymethyl)piperazine (0.559 g, 84 %) as a yellow oil. This was used directly without further purification.

1H NMR (399.9 MHz, $CDCl_3$) δ 2.37 - 2.43 (1H, m), 2.65 - 2.76 (2H, m), 2.78 - 2.86 (3H, m), 2.89 - 2.92 (1H, m), 3.14 - 3.18 (1H, m), 3.24 - 3.27 (1H, m), 3.27 (3H, s).

1,4-Dibenzyl-2-(methoxymethyl)piperazine used as starting material was prepared as follows:

Sodium hydride (0.857 g, 21.42 mmol) was added portionwise to stirred Et_2O (23.0 ml) at 25°C under nitrogen. A solution of (1,4-dibenzylpiperazin-2-yl)methanol (1.411 g, 4.76 mmol) in DMF (8.0 ml) was added portionwise under nitrogen. The resulting suspension was stirred at room temperature for 1 h. A solution of methyl iodide (0.454 ml, 7.28 mmol) in Et_2O (7.0 ml) was added dropwise to the reaction mixture at 10°C, under nitrogen. The resulting mixture was stirred at room temperature for 21 h. The reaction mixture was quenched with water (35 mL and extracted with Et_2O (3 x 50 mL). The organic layers were combined and washed with water (50 mL), dried over MgSO4, filtered and evaporated to afford 1,4-dibenzyl-2-(methoxymethyl)piperazine (1.580 g, 107 %) as a yellow oil. This was used directly without further purification.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.10 - 2.23 (3H, m), 2.44 - 2.48 (1H, m), 2.57 - 2.63 (3H, m), 3.21 (3H, s), 3.35 - 3.39 (1H, m), 3.44 (2H, d), 3.60 - 3.63 (1H, m), 3.95 - 3.99 (1H, m), 7.20 - 7.34 (10H, m). 1H obscured by water peak. MS: m/z 311 (MH+)

Example 161

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(3-methylaminopyrrolidin-1-yl)pyrazine-2-carboxamide

Hydrogen chloride (4M in dioxane, 0.57 mL, 2.26 mmol) was added to tert-butyl N-[1-[5-[[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyrazin-2-yl]pyrrolidin-3-yl]-N-methylcarbamate (312 mg, 0.57 mmol) in methanol (2.80 mL) at 25°C. The resulting solution was stirred at room temperature for 48 h. The reaction was incomplete and further hydrogen chloride (4M in dioxane, 0.28 mL, 1.12 mmol) was added and the solution was stirred at room temperature for a further 16 h. The reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (101 mg, 39 %) as a white solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.85 - 1.93 (1H, m), 2.14 - 2.22 (1H, m), 2.43 (3H, s), 2.84 - 2.92 (4H, m), 3.39 - 3.42 (2H, m), 3.51 - 3.57 (1H, m), 3.63 - 3.68 (2H, m), 3.70 (6H, s), 6.25 - 6.26 (1H, m), 6.30 (2H, d), 6.43 (1H, s), 7.69 (1H, d), 8.85 (1H, d), 9.65 (1H, s). MS: m/z 452 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.003μM.

tert-butyl N-[1-[5-[[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]carbamoyl]pyrazin-2-yl]pyrrolidin-3-yl]-N-methylcarbamate used as starting material was prepared as follows:

A solution of *tert*-butyl N-methyl-N-pyrrolidin-3-ylcarbamate (200 mg, 1.00 mmol) in dioxane (0.75 ml) was added to a stirred solution of 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (136 mg, 0.35 mmol) in dioxane (0.75 ml) and NMP (0.25 ml) at 25°C. The resulting solution was stirred at room temperature for 24 h. The reaction was incomplete so N-ethyl-N-propan-2-ylpropan-2-amine (0.06 ml, 0.35 mmol) was added and the solution was stirred at room temperature for a further 17 h. The reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from

the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product (312 mg, 162 %) as a yellow oil. This was used directly with no further purification. MS: m/z 552 (MH+)

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 162

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(1-methylpiperidin-4-yl)pyrimidine-5-carboxamide

Trimethylaluminium (2 M in toluene, 1.168 ml, 2.34 mmol) was added dropwise to a suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (231 mg, 0.93 mmol) and methyl 2-(1-methylpiperidin-4-yl)pyrimidine-5-carboxylate (220 mg, 0.93 mmol) in anhydrous toluene (4.671 ml) at 25 °C. The resulting solution was stirred at 60 °C for 2 h. The reaction mixture was poured into methanol (100 mL), acidified with 2M HCl and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (166 mg, 39%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.80 - 1.88 (2H, m), 1.94 (2H, d), 1.98 - 2.03 (2H, m), 2.21 (3H, s), 2.80 - 2.85 (3H, m), 2.89 (4H, s), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.49 (1H, s), 9.20 (2H, s), 11.04 (1H, s), 12.24 (1H, s). MS: m/z 451 (MH+).

Mean of n=4, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.036μM.

Methyl 2-(1-methylpiperidin-4-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (532 mg, 2.51 mmol) was added to methyl 2-(piperidin-4-yl)pyrimidine-5-carboxylate (222 mg, 1.00 mmol), formaldehyde (37% aqueous solution, 1.50 ml, 20.07 mmol) and acetic acid (0.115 ml, 2.01 mmol) in methanol (4.994 ml) at 25°C. The resulting solution was stirred at ambient temperature for 3 days. The reaction mixture was diluted with methanol (20 mL) and the crude product was purified by ion exchange

chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(1-methylpiperidin-4-yl)pyrimidine-5-carboxylate (223 mg, 94%) as a cream waxy solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.77 - 1.88 (2H, m), 1.95 (2H, d), 2.00 - 2.07 (2H, m), 2.22 (3H, s), 2.83 - 2.90 (3H, m), 3.91 (3H, s), 9.19 (2H, s). MS: m/z 236 (MH+).

Methyl 2-piperidin-4-ylpyrimidine-5-carboxylate used as starting material was prepared as follows:

Hydrogen chloride (4M in 1,4-dioxane, 3.04 ml, 12.15 mmol) was added to a stirred suspension of methyl 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrimidine-5-carboxylate (976 mg, 3.04 mmol) in methanol (15.20 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 hours. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(piperidin-4-yl)pyrimidine-5-carboxylate (600 mg, 89%) as a yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.63 - 1.73 (2H, m), 1.86 - 1.89 (2H, m), 2.58 - 2.65 (2H, m), 2.96 - 3.07 (3H, m), 3.91 (3H, s), 9.19 (2H, s), NH not observed. MS: m/z 222 (MH+).

Methyl 2-[1-[(2-methylpropan-2-yl)oxycarbonyl]piperidin-4-yl]pyrimidine-5-carboxylate used as starting material was prepared as follows:

Methyl 2-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-5-carboxylate (960 mg, 3.01 mmol) and palladium, 10% on carbon (96 mg, 0.09 mmol) in ethanol (10 ml) and ethyl acetate (40.0 ml) were stirred under an atmosphere of hydrogen at atmospheric pressure and ambient temperature for 18 h. The reaction mixture was filtered through celite, washing with methanol, ethyl acetate and dichloromethane and concentrated under reduced pressure to give methyl 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)pyrimidine-5-carboxylate (966 mg, 100%) as a yellow oil, which crystallised on standing. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.42 (9H, s), 1.61 - 1.70 (2H, m), 1.97 (2H, d), 2.91 (2H,

s), 3.10 - 3.16 (1H, m), 3.91 (3H, s), 4.03 (2H, d), 9.20 (2H, s). MS: 322 m/z (MH+).

Methyl 2-[1-[(2-methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrimidine-5-carboxylate used as starting material was prepared as follows:

(Trimethylsilyl)diazomethane, 2M in hexanes (4.19 ml, 8.38 mmol) was added dropwise to 2-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-5-carboxylic acid (1.28 g, 4.19 mmol) in toluene (12 ml) and methanol (3.00 ml) at 25°C over a period of 2 mins under nitrogen. The resulting solution was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with the dropwise addition of acetic acid until bubbling ceased, then the reaction mixture was diluted with EtOAc (100 mL) and water (100 mL). The organic layer was removed and the aqueous further extracted with EtOAc (2 x 50 mL). The combined organics were washed with sodium hydrogen carbonate solution (100 mL), water (100 mL), brine (100 mL) and dried over MgSO4, filtered and evaporated to afford methyl 2-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-5-carboxylate (1.182 g, 88%) as a yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.44 (9H, s), 2.63 - 2.66 (2H, m), 3.56 (2H, t), 3.92 (3H, s), 4.16 (2H, d), 7.38 (1H, s), 9.21 (2H, s). MS: m/z 320 (MH+).

2-[1-[(2-Methylpropan-2-yl)oxycarbonyl]-3,6-dihydro-2H-pyridin-4-yl]pyrimidine-5-carboxylic acid used as starting material was prepared as follows:

Saturated aqueous sodium hydrogen carbonate solution (25.00 ml) was added to methyl 2-chloropyrimidine-5-carboxylate (0.863 g, 5 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.855 g, 6.00 mmol), palladium(II) acetate (0.056 g, 0.25 mmol) and triphenylphosphine (0.262 g, 1.00 mmol) in 1,2-dimethoxyethane (25.00 ml) at 25°C under nitrogen. The resulting mixture was stirred at 80 °C for 4 h.The cooled reaction mixture was taken up in water (50 mL), washed with EtOAc (50 mL) and then the aqueous layer was acidified to pH1 with 2N HCl. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organics washed with brine, dried over MgSO4 and concentrated under reduced pressure to afford 2-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyrimidine-5-carboxylic acid (1.280 g, 84%) as a yellow solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.44 (9H, s), 2.65 (2H, q), 3.56 (2H, t), 4.15 (2H, m), 7.36 (1H, s), 9.18 (2H, s), 13.6 (1H, s). MS: m/z 304 (M-H).

5-[2-(3,5-Dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 163

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-methyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide

1-methyl-1,4-diazepane (0.20 ml, 1.60 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (310 mg, 0.80 mmol) in DMSO (4.00 ml) at 25°C. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product as an orange dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (296 mg, 79 %) as a white solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.95 - 2.01 (2H, m), 2.32 (3H, s), 2.53 (2H, t), 2.66 (2H, t), 2.84 - 2.92 (4H, m), 3.65 - 3.75 (2H, m), 3.70 (6H, s), 3.81 - 3.86 (2H, m), 6.26 (1H, t), 6.29 (2H, d), 6.45 (1H, s), 7.82 (1H, d), 8.83 (1H, d), 9.65 (1H, s). One NH peak not observed. MS: m/z 466 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0018μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 164

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-prop-2-enyl-1,4-diazepan-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-prop-2-enyl-1,4-diazepan-1-yl)benzamide was prepared using the same procedure as for Example 159, but starting from ethyl 4-(4-allyl-1,4-diazepan-1-yl)benzoate (0.288 g, 1 mmol, 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1 mmol) and a 2M solution of trimethylaluminium (1.250 mL, 2.50 mmol) in toluene. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford a gum, which solidified on trituration with DCM/Ether to afford the title compound (0.071 g, 14.50 %).

1H NMR (399.9 MHz, $CDCl_3$) δ 1.87 - 1.93 (2H, m), 2.53 (2H, t), 2.68 (2H, t), 2.86 - 2.91 (4H, m), 3.07 (2H, d), 3.43 (2H, t), 3.48 (1H, t), 3.50 (1H, d), 3.71 (6H, s), 5.11 - 5.13 (1H, m), 5.12 - 5.17 (1H, m), 5.79 - 5.86 (1H, m), 6.28 (1H, t), 6.33 (2H, d), 6.59 (2H, d), 7.75 (2H, d), 9.26 (1H, s). MS: m/z 490 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00078μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Ethyl 4-(4-allyl-1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows: 3-Bromoprop-1-ene (0.433 mL, 5.00 mmol) was added to a stirred solution of ethyl 4-(1,4-diazepan-1-yl)benzoate (1.242 g, 5 mmol) and DIPEA (2.183 mL, 12.50 mmol) in dichloromethane (20 mL). The reaction mixture was stirred under nitrogen at room temperature for 24 h. This was diluted with dichloromethane (20 mL), washed with water (2 x 25 ml) and saturated sodium chloride solution (20 ml), dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 2.5M ammonia/MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(4-allyl-1,4-diazepan-1-yl)benzoate (0.700 g, 48.5 %) as a yellow oil.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.36 (3H, t), 1.94 - 2.00 (2H, m), 2.57 - 2.60 (2H, m), 2.75 (1H, d), 2.77 - 2.77 (1H, m), 3.10 - 3.12 (2H, m), 3.54 - 3.64 (4H, m), 4.31 (2H, q), 5.11 - 5.15 (1H, m), 5.11 - 5.19 (1H, m), 5.78 - 5.91 (1H, m), 6.62 - 6.66 (2H, m), 7.87 - 7.90 (2H, m). MS: m/z 289 (MH+).

Ethyl 4-(1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows:
Ethyl 4-fluorobenzoate (11.01 mL, 75mmol) and 1,4-diazepane (30.0 g, 300.00 mmol) in DMSO (150 mL) warmed to 100°C under nitrogen. The resulting solution was stirred at 100 °C for 24 h. The reaction mixture was cooled and evaporated to dryness. The reaction mixture was quenched with 2M NaOH (150 mL), extracted with EtOAc (3 x 75 mL), the organic layer was washed with saturated brine (100 ml), dried over MgSO4, filtered and evaporated to afford ethyl 4-(1,4-diazepan-1-yl)benzoate (17.43 g, 94 %) as a colourless oil.
1H NMR (399.9 MHz, CDCl3) δ 1.27 - 1.31 (3H, m), 1.71 (1H, s), 1.79 - 1.85 (2H, m), 2.74 (1H, d), 2.74 (1H, d), 2.95 (1H, d), 2.96 (1H, d), 3.51 (2H, t), 3.56 (2H, t), 4.21 - 4.27 (2H, m), 6.56 - 6.60 (2H, m), 7.80 - 7.83 (2H, m). MS: m/z 249 (MH+).

Example 165

4-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide

4-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]benzamide was prepared using the same procedure as for Example 159, but starting from ethyl 4-(4-cyclopropyl-1,4-diazepan-1-yl)benzoate (0.288 g, 1 mmol, 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.247 g, 1 mmol) and a 2M solution of trimethylaluminium (1.250 mL, 2.50 mmol) in toluene. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford a gum which solidified on trituration with DCM/Ether to afford the title compound (0.165 g, 33.7 %).

1H NMR (500.13 MHz, DMSOd6 + CD3COOD @ 373K) δ 0.32-0.36 (2H, m), 0.41-0.47 (2H, m), 1.84 – 1.90 (2H, m), 2.93-2.98 (1H, m), 2.76 (2H, t), 2.87 (4H, s), 2.93 (2H, t), 3.50 –3.58 (4H, m), 3.72 (6H, s), 6.29 (1H, s), 6.30-6.32 (1H, m), 6.39 (2H, d), 6.72 (2H, d), 7.81 (2H, d). MS: m/z 490 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.000064μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Ethyl 4-(4-cyclopropyl-1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows:

A solution of ethyl 4-(1,4-diazepan-1-yl)benzoate (0.621 g, 2.5 mmol), (1-ethoxycyclopropoxy)trimethylsilane (2.51 mL, 12.50 mmol) and acetic acid (0.286 mL, 5.00 mmol) in tetrahydrofuran (50 mL), methanol (5 mL) was treated with sodium cyanoborohydride (0.393 g, 6.25 mmol) at 20°C. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was cooled, filtered and evaporated to dryness. 1N HCl (40 ml) and water (60 ml) were added and the solution extracted with ethyl acetate (3 x 50 ml). The aqueous layer was basified to pH 10 with solid potassium carbonate and extracted with ethyl acetate (4 x 50 ml). The organic extracts washed with saturated NaCl (50 ml) and dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(4-cyclopropyl-1,4-diazepan-1-yl)benzoate (0.849 g, 118 %) as a colourless oil.

1H NMR (399.9 MHz, $CDCl_3$) δ 0.33 (1H, t), 0.34 - 0.35 (1H, m), 0.36 - 0.41 (1H, m), 0.37 - 0.40 (1H, m), 1.29 (3H, t), 1.74 - 1.79 (1H, m), 1.84 - 1.90 (2H, m), 2.69 (2H, t), 2.86 (2H, t), 3.47 (2H, t), 3.49 (2H, t), 4.24 (2H, q), 6.58 (1H, d), 6.60 (1H, s), 7.81 - 7.84 (2H, m). MS: m/z 289 (MH+) (ESI+).

Example 166

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-propan-2-yl-1,4-diazepan-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-propan-2-yl-1,4-diazepan-1-yl)benzamide was prepared using the same procedure as for Example 159, but starting from ethyl 4-(4-isopropyl-1,4-diazepan-1-yl)benzoate (0.212 g, 0.73 mmol), 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.181 g, 0.73 mmol) and a 2M solution of trimethylaluminium (0.913 ml, 1.83 mmol) in toluene. The crude product was purified by

preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford a gum which solidified on trituration with DCM/Ether to afford the title compound (0.154 g, 42.9 %) as a cream solid.

1H NMR (500.13 MHz, DMSOd6 + CD3COOD @ 373K) δ 1.00 (6H, s), 1.85-1.90 (2H, m), 2.64 (2H, t) 2.80-2.85 (2H, m), 2.88 (4H, s), 2.94-3.01 (1H, m), 3.53-3.59 (4H, m), 3.72 (6H, s), 6.29 (1H, s), 6.30-6.32 (1H, m), 6.40 (2H, d), 6.73 (2H, d), 7.81 (2H, d). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0007μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Ethyl 4-(4-isopropyl-1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows:

A solution of ethyl 4-fluorobenzoate (0.293 mL, 2 mmol) and 1-isopropyl-1,4-diazepane (0.539 mL, 4.00 mmol) in dimethylsulfoxide (10 mL), was heated at 120 °C for 18 h. The reaction mixture was diluted with water (75 ml) and extracted with ethyl acetate (3 x 25 ml). The extracts were washed with saturated sodium chloride solution (50 ml), dried over MgSO4, filtered and evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 4-(4-isopropyl-1,4-diazepan-1-yl)benzoate (0.212 g, 36.5 %) as a yellow oil.

1H NMR (399.9 MHz, CDCl3) δ 0.92 (6H, d), 1.28 (3H, t), 1.80 - 1.86 (2H, m), 2.46 (2H, t), 2.69 (2H, t), 2.81 - 2.89 (1H, m), 3.51 (4H, t), 4.24 (2H, q), 6.58 (2H, d), 7.81 (2H, d). MS: m/z 291 (MH+) (ESI+).

Example 167

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-propan-2-yl-1,4-diazepan-1-yl)pyrazine-2-carboxamide

1-isopropyl-1,4-diazepane (228 mg, 1.60 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (310 mg, 0.80 mmol) in

DMSO (4.00 ml) at 25°C. The resulting solution was stirred at room temperature for 2 hours. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 2 h. The reaction was still incomplete so the reaction mixture was stirred for a further 18 h at room temperature. The reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product as an orange dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (167 mg, 42%) as a pale yellow solid.
1H NMR (399.9 MHz, $CDCl_3$) δ 0.93 (6H, d), 1.83 - 1.89 (2H, m), 2.54 (2H, t), 2.72 (2H, t), 2.82 - 2.92 (5H, m), 3.70 (6H, s), 3.73 - 3.76 (4H, m), 6.26 (1H, d), 6.29 (2H, d), 6.43 (1H, s), 7.81 (1H, d), 8.82 (1H, d), 9.64 (1H, s). One NH signal not observed. MS: m/z 494 (MH+).
Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00063μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 168

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-propan-2-yl-1,4-diazepan-1-yl)thiophene-2-carboxamide

Trimethylaluminium (0.751 ml, 1.50 mmol) was added dropwise to a stirred suspension of 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (148 mg, 0.60 mmol) and ethyl 5-(4-propan-2-yl-1,4-diazepan-1-yl)thiophene-2-carboxylate (178 mg, 0.60 mmol) in toluene (3.002 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was added to methanol (50 mL) and treated with HCL (2M aqueous solution, to pH7 or below) and purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure material. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (123 mg, 41%) as a yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.95 - 0.96 (6H, m), 1.79 - 1.85 (2H, m), 2.54 - 2.56 (2H, m), 2.72 (2H, m), 2.85 (4H, s), 2.88 (1H,m), 3.42 - 3.48 (4H, m), 3.72 (6H, s), 5.86 (1H, d), 6.33 (1H, s), 6.34 (1H, s), 6.41 (2H, d), 7.78 (1H, d), 10.14 (1H, s), 12.00 (1H, s). MS: m/z 498 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0015μM.

Ethyl 5-(4-propan-2-yl-1,4-diazepan-1-yl)thiophene-2-carboxylate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (396 mg, 1.87 mmol) was added portionwise to ethyl 5-(1,4-diazepan-1-yl)thiophene-2-carboxylate (190 mg, 0.75 mmol) and acetic acid (0.086 ml, 1.49 mmol) in acetone (1.917 ml) at room temperature. The resulting solution was stirred at ambient temperature for 18 h under nitrogen. The reaction mixture was concentrated and diluted with water (200 mL) and basified with 2M NaOH. The aqueous was extracted with diethyl ether (3 x 100 mL) and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford desired product ethyl 5-(4-isopropyl-1,4-diazepan-1-yl)thiophene-2-carboxylate (181 mg, 82%). This was used directly with no further purification.

1H NMR (399.9 MHz, $CDCl_3$) δ 0.99 - 1.01 (6H, m), 1.33 (3H, t), 1.89 - 1.95 (2H, m), 2.59 - 2.62 (2H, m), 2.75 - 2.77 (2H, m), 2.88 - 2.95 (1H, m), 3.48 - 3.52 (4H, m), 4.27 (2H, q), 5.77 - 5.78 (1H, d), 7.54 (1H, d). MS: m/z 297 (MH+).

Ethyl 5-(1,4-diazepan-1-yl)thiophene-2-carboxylate used as starting material was prepared as follows:

Palladium(II) acetate (52.1 mg, 0.23 mmol) followed by sodium tert-butoxide (624 mg, 6.49 mmol) was added to a stirred solution of ethyl 5-bromothiophene-2-carboxylate (1090 mg, 4.64 mmol), homopiperazine (511 mg, 5.10 mmol) and (rac)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (289 mg, 0.46 mmol) in toluene (20 mL) at 25°C under nitrogen. The resulting suspension was stirred at 110 °C for 3 h. The cooled reaction mixture was diluted with MeOH and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions containing the desired product were evaporated to dryness to afford impure product as a brown oil. The crude product was purified by silica column chromatography, eluting with a

gradient of 0 to 5% 7N NH3/MeOH in DCM and then 0 to 3% NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford ethyl 5-(4-ethylpiperazin-1-yl)thiophene-2-carboxylate (195 mg, 17%) as a yellow oil.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, t), 1.89 - 1.95 (2H, m), 2.88 (2H, t), 3.03 - 3.06 (2H, m), 3.49 - 3.54 (2H, m), 3.57 (2H, t), 4.27 (2H, q), 5.80 (1H, d), 7.54 (1H, d) NH not observed. MS: m/z 255 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 169

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-ethyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide

1-ethyl-1,4-diazepane (205 mg, 1.60 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (310 mg, 0.80 mmol) in DMSO (4.00 ml) at 25°C. The resulting solution was stirred at room temperature for 2 h. The reaction was incomplete so the temperature was increased to 60°C and the reaction mixture was stirred for a further 15 mins. The reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product as an orange dry film. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (228 mg, 59 %) as a white solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.00 (3H, t), 1.91 - 1.97 (2H, m), 2.50 (2H, q), 2.56 (2H, t), 2.72 (2H, t), 2.84 - 2.91 (4H, m), 3.69 (6H, s), 3.67 - 3.71 (2H, m), 3.79 - 3.82 (2H, m), 6.25 (1H, t), 6.29 (2H, d), 6.45 (1H, s), 7.81 (1H, d), 8.83 (1H, d), 9.68 (1H, s). MS: m/z 480 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0027μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 170

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-ethyl-1,4-diazepan-1-yl)benzamide

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-ethyl-1,4-diazepan-1-yl)benzamide was prepared using the same procedure as for Example 159, but starting from ethyl 4-(4-ethyl-1,4-diazepan-1-yl)benzoate (0.502 g, 1.4 mmol), 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (0.346 g, 1.40 mmol) and A 2M solution of trimethylaluminium (1.750 mL, 3.50 mmol) in toluene. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford a gum which solidified on trituration with DCM/Ether to afford the title compound (0.171 g, 25.6 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.00 (3H, t), 1.89 (2H, d), 2.53 (2H, d), 2.73 (4H, s), 2.87 (4H, s), 3.49 - 3.54 (2H, m), 3.54 - 3.58 (2H, m), 3.73 (6H, s), 6.33 (1H, t), 6.42 (3H, d), 6.73 (2H, d), 7.87 (2H, d), 10.17 (1H, s), 12.04 (1H, s). MS: m/z 478 (MH+) (ESI+).
Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00071μM.

Ethyl 4-(4-ethyl-1,4-diazepan-1-yl)benzoate used as starting material was prepared as follows:

A solution of ethyl 4-(1,4-diazepan-1-yl)benzoate (0.621 g, 2.5 mmol), acetaldehyde (0.701 mL, 12.50 mmol) and acetic acid (0.286 mL, 5.00 mmol) in tetrahydrofuran (30 mL), methanol (3 mL) was treated with sodium cyanoborohydride (0.393 g, 6.25 mmol) at 20°C. The resulting solution was stirred at 60 °C for 18 h. The reaction mixture was cooled and extra amount of acetaldehyde (2.146 mL, 38 mmol) and sodium triacetoxyborohydride (1.060 g, 5.00 mmol) were added. The reaction was stirred at room temperature for 18 h. The reaction mixture was filtered and evaporated to dryness. The residue was dissolved in 2N HCl (5 ml) and methanol (20 ml). The solution of crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using

7M NH3/MeOH and pure fractions were evaporated to dryness to afford ethyl 4-(4-ethyl-1,4-diazepan-1-yl)benzoate (0.526 g, 76 %)

1H NMR (399.9 MHz, $CDCl_3$) δ 1.07 (3H, t), 1.36 (3H, t), 1.90 - 2.05 (2H, m), 2.52 - 2.61 (2H, m), 2.70 - 2.77 (2H, m), 3.54 (2H, t), 3.57 (2H, t), 4.29 - 4.34 (2H, m), 6.63 - 6.67 (2H, m), 7.86 - 7.90 (2H, m). MS: m/z 277 (MH+).

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Example 171

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-ethyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (1.25 ml, 2.50 mmol) was added dropwise to a stirred suspension of methyl 2-(4-ethyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (265 mg, 1.00 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (248 mg, 1.00 mmol) in toluene (5.01 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was quenched into methanol (50 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing desired product still contained an impurity, so they were concentrated to dryness and purified by crystallisation from MeCN to afford the title compound (104 mg, 22%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.99 (3H, t), 1.82 - 1.87 (2H, m), 2.48 (2H, q, partially obscured by DMSO peak), 2.52 - 2.57 (2H, m, partially obscured by DMSO peak), 2.71 (2H, m), 2.87 (4H, s), 3.72 (6H, s), 3.82 (2H, t), 3.87 (2H, t), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.88 (2H, s), 10.56 (1H, s), 12.13 (1H, s). MS: m/z 480 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0092μM.

Methyl 2-(4-ethyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (200 mg, 1.16 mmol) in dichloromethane (4.00 mL) was added to a stirred solution of 1-ethyl-1,4-diazepane (149 mg, 1.16 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.902 mL, 5.22 mmol) in dichloromethane (4.00 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(4-ethyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (268 mg, 87%) as a cream oil which crystallised on standing. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 0.98 (3H, t), 1.81 - 1.87 (2H, m), 2.45- 2.50 (2H, m), 2.55 (2H, m), 2.70 - 2.72 (2H, m), 3.81 (3H, s), 3.82 (2H, q), 3.86 - 3.89 (2H, m), 8.79 (2H, s). MS: m/z 265 (MH+).

1-Ethyl-1,4-diazepane used as starting material was prepared as follows:

Lithium aluminum hydride (38.2 ml, 38.19 mmol) was added to 1-(1,4-diazepan-1-yl)ethanone (1.697 g, 11.93 mmol) in THF (59.7 ml) at 0°C under nitrogen. The resulting solution was stirred at ambient temperature for 1 h and then at 60°C for 1 h. The cooled reaction mixture was poured onto ice (500 mL), acidified with HCl (2M aqueous solution) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford 1-ethyl-1,4-diazepane (0.610 g, 40%) as a yellow liquid. This was used directly with no further purification.

1H NMR (399.9 MHz, CDCl3) δ 1.07 (3H, t), 1.74 - 1.80 (2H, m), 2.58 (2H, q), 2.64 - 2.70 (4H, m), 2.89 - 2.95 (4H, m).

Example 172

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-5-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrazine-2-carboxamide

1-Prop-2-enyl-1,4-diazepane (224 mg, 1.60 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (310 mg, 0.80 mmol) in DMSO (4.00 ml) at 25°C. The resulting solution was stirred at room temperature for 3 h. The

reaction mixture was diluted with MeOH (5 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product as an orange oil. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (271 mg, 69 %) as a yellow solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.91 - 1.97 (2H, m), 2.57 (2H, t), 2.72 (2H, t), 2.84 - 2.91 (4H, m), 3.06 (2H, d), 3.70 (6H, s), 3.74 - 3.83 (4H, m), 5.07 - 5.13 (2H, m), 5.73 - 5.83 (1H, m), 6.25 (1H, t), 6.29 (2H, d), 6.43 (1H, s), 7.82 (1H, d), 8.83 (1H, d), 9.64 (1H, s). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0034μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 173

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-propan-2-yl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (1.19 ml, 2.38 mmol) was added dropwise to a stirred suspension of methyl 2-(4-propan-2-yl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (265 mg, 0.95 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (235 mg, 0.95 mmol) in toluene (4.76 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was quenched into methanol (50 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product.The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (81 mg, 17%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.94 - 0.95 (6H, m), 1.78 (2H, m), 2.51 - 2.54 (2H, m, partially obscured by DMSO peak), 2.67 - 2.74 (3H, m), 2.87 (4H, s), 3.73 (6H, s), 3.82 (4H,

t), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.88 (2H, s), 10.55 (1H, s), 12.13 (1H, s). MS: m/z 494 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.018μM.

Methyl 2-(4-propan-2-yl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (209 mg, 1.21 mmol) in dichloromethane (4.00 ml) was added to a stirred solution of 1-propan-2-yl-1,4-diazepane (172 mg, 1.21 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.523 ml, 3.02 mmol) in dichloromethane (4.00 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(4-propan-2-yl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (267 mg, 79 %) as a cream oil which crystallised on standing. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 0.92 - 0.94 (6H, m), 1.74 - 1.80 (2H, m), 2.71 (2H, t), 2.82 - 2.89 (1H, m), 3.81 (3H, s), 3.80 - 3.85 (4H, m), 8.78 - 8.78 (2H, m), 1 x (2H, m) obscured by DMSO peak. MS: m/z 279 (MH+).

1-Propan-2-yl-1,4-diazepane used as starting material was prepared as follows:

Benzyl 4-propan-2-yl-1,4-diazepane-1-carboxylate (3.00 g, 10.85 mmol) and palladium, 10% on carbon (0.289 g, 2.71 mmol) in ethanol (54.3 ml) were stirred under an atmosphere of hydrogen at atmospheric pressure and ambient temperature for 18 h. The reaction mixture was filtered through celite, washing with ethanol, methanol and dichloromethane and the filtrate concentrated under reduced pressure to afford 1-propan-2-yl-1,4-diazepane (1.54 g, 100%) as a yellow liquid. This was used directly with no further purification.

1H NMR (399.9 MHz, CDCl3) δ 1.00 - 1.02 (6H, m), 1.69 - 1.74 (2H, m), 1.94 (1H, br s), 2.63 - 2.68 (4H, m), 2.87 - 2.94 (5H, m).

Benzyl 4-propan-2-yl-1,4-diazepane-1-carboxylate used as starting material was prepared as follows:

Sodium triacetoxyborohydride (5.79 g, 27.32 mmol) was added portionwise to benzyl 1,4-diazepane-1-carboxylate (2.56 g, 10.93 mmol) and acetic acid (1.251 mL, 21.85 mmol) in acetone (5.00 mL) at room temperature. The resulting solution was stirred at ambient temperature for 18 h under nitrogen. The reaction mixture was concentrated and diluted with water (200 mL) and basified with 2M NaOH. The aqueous was extracted with diethyl ether (3 x 100 mL) and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford the desired product (3.00 g, 99%). This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 0.92 - 0.95 (6H, m), 1.63 - 1.69 (2H, m), 2.60 (2H, t), 2.80 - 2.88 (1H, m), 3.38 - 3.45 (4H, m), 5.09 (2H, s), 7.29 - 7.40 (5H, m), one (2H, m) obscured by solvent peak. MS: m/z 277 (MH+).

Example 174

5-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide

1-Cyclopropyl-1,4-diazepane, 2HCl (205 mg, 0.96 mmol) was added to 5-chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide (310 mg, 0.80 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.48 ml, 2.80 mmol) in DMSO (4.00 ml) at 25°C. The resulting solution was stirred at room temperature for 24 h. The reaction was incomplete so the temperature was increased to 80°C and the reaction mixture was stirred for a further 3 h. The reaction mixture was diluted with MeOH (5ml). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford crude product as a brown oil. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (277 mg, 70%) as a yellow solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 0.32 - 0.37 (2H, m), 0.38 - 0.43 (2H, m), 1.75 - 1.80 (1H, m), 1.86 - 1.92 (2H, m), 2.74 (2H, t), 2.83 - 2.92 (6H, m), 3.70 (6H, s), 3.70 - 3.77 (4H, m), 6.26 (1H, t), 6.29 (2H, d), 6.42 (1H, s), 7.82 (1H, d), 8.83 (1H, d), 9.64 (1H, s). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0037μM.

5-Chloro-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrazine-2-carboxamide was prepared as shown in Example 105.

Example 175

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (1.35 ml, 2.70 mmol) was added dropwise to a stirred suspension of methyl 2-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (300 mg, 1.09 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (268 mg, 1.09 mmol) in toluene (5.43 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was quenched into methanol (50 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (220 mg, 41%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.82 - 1.88 (2H, m), 2.53 - 2.57 (2H, m, partially obscured by DMSO peak), 2.71 (2H, t), 2.88 (4H, s), 3.08 (2H, d), 3.73 (6H, s), 3.83 (2H, t), 3.86 - 3.88 (2H, m), 5.10 - 5.13 (1H, m), 5.17 (1H, d), 5.77 - 5.87 (1H, m), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.89 (2H, s), 10.56 (1H, s), 12.13 (1H, s). MS: m/z 492 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.007μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(4-prop-2-enyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (200 mg, 1.16 mmol) in dichloromethane (4.00 mL) was added to a stirred solution of 1-prop-2-enyl-1,4-diazepane (163 mg, 1.16 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.501 mL, 2.90 mmol) in

dichloromethane (4.00 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was evaporated to dryness and redissolved in MeCN (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford the desired compound (304 mg, 95%) as a cream oil which crystallised on standing. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.81 - 1.87 (2H, m), 2.55 (2H, m), 2.70 - 2.72 (2H, m), 3.06 - 3.09 (2H, m), 3.81 (3H, s), 3.80 - 3.89 (4H, m), 5.09 - 5.13 (1H, m), 5.13 - 5.19 (1H, m), 5.76 - 5.86 (1H, m), 8.79 (2H, d). MS: m/z 277 (MH+).

1-Prop-2-enyl-1,4-diazepane used as starting material was prepared as follows:

To a solution of tert-butyl 1-homopiperazinecarboxylate (9.73 mL, 50 mmol) in dichloromethane (250 mL) was added PS-TBD resin (40g, 100mmol) and 3-bromoprop-1-ene (4.33 mL, 50 mmol) dropwise at 25°C. The mixture was stirred for 2h. The PS-TBD was filtered off and the filtrate evaporated to dryness, redissolved in MeOH/EtOAc (1:9) and then filtered through a short silica column. The filtrate obtained was evaporated to dryness, treated with TFA (20 ml) and then stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (50 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford 1-prop-2-enyl-1,4-diazepane (4.07 g, 58.0 %) as a pale yellow oil.

1H NMR (399.902 MHz, CDCl3) δ 1.70 (m, 2H), 1.98 (s, 1H), 2.59 (m, 4H), 2.85 (m, 4H), 3.06 (m, 2H), 5.07 (m, 2H), 5.81 (m, 1H)

Example 176

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-2-(4-methyl-1,4-diazepan-1-yl)pyrimidine-5-carboxamide

Trimethylaluminium (1.35 ml, 2.70 mmol) was added dropwise to a stirred suspension of methyl 2-(4-methyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (270 mg, 1.08 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (267 mg, 1.08 mmol) in toluene (5.39 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was quenched into methanol (50 mL) and treated with HCl (2M aqueous solution, to pH7 or

lower) and purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing pure desired compound were evaporated to dryness to afford the title compound (136 mg, 27%) as a cream solid. The fractions containing impure product were concentrated and purified by crystallisation from MeCN to afford the title compound (56.0 mg, 11%) as a beige solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.86 - 1.92 (2H, m), 2.27 (3H, s), 2.64 (2H, t), 2.88 (4H, s), 3.73 (6H, s), 3.81 (2H, t), 3.89 (2H, t), 6.33 (1H, t), 6.41 - 6.45 (3H, m), 8.89 (2H, s), 10.57 (1H, s), 12.13 (1H, s). 2H obscured by DMSO peak. MS: m/z 466 (MH+).

Mean of n=1, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0058μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(4-methyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (200 mg, 1.16 mmol) in dichloromethane (4.00 mL) was added to a stirred solution of 1-methyl-1,4-diazepane (0.144 mL, 1.16 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.902 mL, 5.22 mmol) in dichloromethane (4.00 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (20 mL) and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(4-methyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (274 mg, 94%) as a white solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 1.86 - 1.89 (2H, m), 2.26 (3H, s), 2.49 - 2.54 (2H, m, partially obscured by DMSO peak), 2.62 - 2.64 (2H, m), 3.81 (3H, s), 3.80 - 3.84 (2H, m), 3.89 - 3.91 (2H, m), 8.79 (2H, d). MS: m/z 251 (MH+)

Example 177

2-(4-cyclopropyl-1,4-diazepan-1-yl)-N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]pyrimidine-5-carboxamide

Trimethylaluminium (1.402 ml, 2.80 mmol) was added dropwise to a stirred suspension of methyl 2-(4-cyclopropyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (310 mg, 1.12 mmol) and 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (277 mg, 1.12 mmol) in toluene (5.61 ml) at 25°C. The resulting solution was stirred at 60 °C for 18 h. The cooled reaction mixture was quenched into methanol (50 mL) and treated with HCl (2M aqueous solution, to pH7 or lower) and purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford impure product. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (8.00 mg, 1%) as a cream solid. Some impure fractions were combined and concentrated to dryness and purified by crystallisation from MeCN to afford the title compound (51 mg, 9%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 0.31 (2H, m), 0.41 - 0.44 (2H, m), 1.84 - 1.89 (3H, m), 2.71 (2H, t), 2.88 (4H, s), 3.73 (6H, s), 3.81 - 3.87 (4H, m), 6.33 (1H, t), 6.42 (2H, d), 6.44 (1H, s), 8.89 (2H, s), 10.55 (1H, s), 12.14 (1H, s), 2H obscured by DMSO peak. MS: m/z 492 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0073μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 2-(4-cyclopropyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate used as starting material was prepared as follows:

A solution of methyl 2-chloropyrimidine-5-carboxylate (200 mg, 1.16 mmol) in dichloromethane (4.00 mL) was added to a stirred solution of 1-cyclopropyl-1,4-diazepane (247 mg, 1.16 mmol) and N-ethyl-N-propan-2-ylpropan-2-amine (0.902 mL, 5.22 mmol) in dichloromethane (4.00 mL) at 25°C. The resulting solution was stirred at ambient temperature for 18 h. The reaction mixture was evaporated to dryness and redissolved in MeOH (20 mL)

and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and evaporated to dryness to afford methyl 2-(4-cyclopropyl-1,4-diazepan-1-yl)pyrimidine-5-carboxylate (312 mg, 97%) as a cream solid. This was used directly with no further purification.

1H NMR (399.9 MHz, DMSO-d6) δ 0.28 - 0.31 (2H, m), 0.40 - 0.45 (2H, m), 1.80 - 1.84 (2H, m), 1.85 - 1.89 (1H, m), 2.71 (2H,m), 2.85 - 2.88 (2H, m), 3.81 (3H, s), 3.82 - 3.88 (4H, m), 8.79 (2H, s). MS: m/z 277 (MH+)

Example 178

N-[5-[2-[3-(methylcarbamoyl)phenyl]ethyl]-2H-pyrazol-3-yl]-4-(4-methylpiperazin-1-yl)benzamide

A 2M solution of trimethylaluminium (0.936 mL, 1.87 mmol) in toluene, was added drop-wise to a stirred suspension of 3-(2-(5-amino-1H-pyrazol-3-yl)ethyl)-N-methylbenzamide (0.183 g, 0.75 mmol) and methyl 4-(4-methylpiperazin-1-yl)benzoate (0.176 g, 0.75 mmol) in toluene (5 mL) at room temperature. The solution was then stirred at 60 °C for 18 h. The reaction mixture was cooled, poured into methanol (5 ml) and acidified with 2N HCl (15ml). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford an oil. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the title compound (0.109 g, 32.6 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.88 (3H, s), 2.23 (3H, s), 2.45 (4H, t), 2.87 - 3.02 (4H, m), 3.40 (4H, t), 6.39 (1H, s), 6.97 (2H, d), 7.37 (1H, s), 7.38 (2H, t), 7.65 - 7.67 (1H, m), 7.75 (1H, s), 7.90 (2H, d), 8.36 (1H, d), 10.36 (1H, s). MS: m/z 447 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0011μM.

3-(2-(5-Amino-1H-pyrazol-3-yl)ethyl)-N-methylbenzamide used as starting material was prepared as follows:

1.8M LDA in THF (30.0 mL, 54.00 mmol) was added to tetrahydrofuran (60 mL) and cooled to -78 °C. Acetonitrile (2.82 mL, 54.00 mmol) was added drop-wise over 15 mins. A solution of methyl 3-(3-(methylcarbamoyl)phenyl)propanoate (2.99 g, 13.5 mmol) in tetrahydrofuran

(10 ml) was added. The resulting mixture stirred at -78 °C for 10 mins. The reaction mixture was warmed to 5°C and stirred for 30 mins, hydrazine hydrochloride (3.70 g, 54.00 mmol) and ethanol (60.0 mL) were added and the reaction mixture heated at 80°C for 18 h. The reaction mixture was cooled and evaporated to dryness. The residue was dissolved in methanol (50 ml) and the crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH fractions were evaporated to dryness to afford an oil. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 3-(2-(5-amino-1H-pyrazol-3-yl)ethyl)-N-methylbenzamide (0.450 g, 13.64 %) as a yellow oil.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.73 - 2.79 (4H, m), 2.89 (1H, d), 3.18 (3H, d), 4.09 (1H, d), 5.19 (1H, s), 7.35 (1H, s), 7.35 - 7.37 (1H, m), 7.63 - 7.66 (1H, m), 7.72 (1H, s), 8.38 (1H, d) – 1 proton not seen. MS: m/z 245 (MH+).

Methyl 3-(3-(methylcarbamoyl)phenyl)propanoate used as starting material was prepared as follows:

A solution of (E)-methyl 3-[3-(methylcarbamoyl)phenyl]prop-2-enoate (3.77 g, 17.20 mmol) and 10% palladium on carbon (0.458 g, 0.43 mmol) in a mixture of ethanol (100 mL) and DMF (10.00 mL) was stirred at room temperature for 18 h under a balloon of hydrogen. The reaction mixture was filtered through celite and evaporated to dryness to afford methyl 3-(3-(methylcarbamoyl)phenyl)propanoate (3.05 g, 80 %) as a white solid. MS: m/z 222 (MH+).

(E)-methyl 3-[3-(methylcarbamoyl)phenyl]prop-2-enoate used as starting material was prepared as follows:

A solution of 3-formyl-N-methylbenzamide (2.9 g, 17.77 mmol) and methyl 2-triphenylphosphoranylideneacetate (8.91 g, 26.66 mmol) in dichloromethane (85 mL), was stirred at room temperature for 18 h. The reaction mixture was evaporated to dryness. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford impure product. Re-purified by silica column chromatography, eluting with a gradient of 50 to 100% EtOAc in hexanes. Pure fractions were evaporated to dryness to afford (E)-methyl 3-[3-(methylcarbamoyl)phenyl]prop-2-enoate (3.77 g, 97 %).

1H NMR (399.9 MHz, $CDCl_3$) δ 3.02 - 3.03 (3H, m), 3.81 (3H, s), 6.34 (1H, s), 6.51 (1H, s), 7.42 - 7.48 (2H, m), 7.61 - 7.66 (1H, m), 7.67 (1H, d), 7.74 - 7.76 (1H, m), 7.93 (1H, t).

3-Formyl-N-methylbenzamide used as starting material was prepared as follows:

A 2M solution of methylamine in THF (44mL, 5eq, 87.5mmol) was added to methyl 3-formylbenzoate (2.875g, 1eq, 17.5mmol) in dry THF (65ml). The reaction mixture was cooled to –50°C under nitrogen and a 2M solution of trimethylaluminium in toluene (22ml, 2.5eq, 43.75mmol) was added slowly over 15 mins. The reaction mixture was allowed to warm slowly to room temperature and stirred for 18 h. The reaction mixture was quenched with a 20% w/v solution of potassium sodium tartrate in water (50ml). This was extracted with ethyl acetate (2x100ml) and washed with water (50ml), saturated sodium chloride solution (50ml), dried over $MgSO_4$ and evaporated under reduced pressure to give a gum. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 2.5% methanol in DCM. Pure fractions were combined and evaporated to afford 3-formyl-N-methylbenzamide (1.6502g, 58%) as an off-white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.78 - 2.85 (3H, m), 7.70 - 7.75 (1H, t), 8.05 - 8.08 (1H, m), 8.04 - 8.09 (1H, m), 8.37 - 8.39 (1H, d), 8.63 - 8.70 (1H, s), 10.08 (1H, s). MS: m/z 164 (MH+).

Example 179

N-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-4-(4-ethylpiperazin-1-yl)benzamide

Trimethylaluminium (2M in toluene, 1.51 mL, 3.02 mmol) was added dropwise to 5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine, HCl (345 mg, 1.21 mmol) and methyl 4-(4-ethylpiperazin-1-yl)benzoate (300 mg, 1.21 mmol) in toluene (6.0 mL) at 25°C. The resulting solution was stirred at 60 °C for 19 h under nitrogen. The reaction was incomplete and further trimethylaluminium (0.50 mL, 3.02 mmol) was added and the solution was stirred at 60 °C for a further 4 h. The reaction mixture was added to methanol (100ml) and treated with HCl (2N aqueous solution, until pH was 7 or lower). The crude product was purified by ion exchange chromatography, using a SCX column. Some product crystallised out of the pure fractions and was collected by vacuum filtration to give the title compound (95 mg, 17%) as a white solid. The filtrate was evaporated to dryness to give a further sample of the title compound (115 mg,

20 %) as a white solid. Impure fractions containing the desired product were repurified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to afford a third sample of the title compound (27 mg, 5 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.05 (3H, t), 2.38 (2H, q), 3.75 (6H, s), 5.08 (2H, s), 5.67 (1H, s), 6.45 (1H, t), 6.60 (2H, d), 7.01 (2H, d), 7.86 (2H, d). At approximately δ 2.5, 4H peak obscured by DMSO. At approximately δ 3.3, 4H peak obscured by H_2O. MS: m/z 466 (MH+)

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.00068 μM.

5-[(3,5-Dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine hydrochloride, used as starting material was prepared as in Example 12.

Methyl 4-(4-ethylpiperazin-1-yl)benzoate, used as starting material, was prepared as follows:

1-Ethylpiperazine (3.68 mL, 29.0 mmol) was added to methyl 4-fluorobenzoate (1.50 mL, 11.6 mmol) in dimethylsulfoxide (29.0 mL) at 25°C. The resulting solution was stirred at 120 °C for 18 h. The reaction mixture was concentrated and diluted with EtOAc (50 mL) and water (20 mL). NaOH (2N aqueous solution, 20 mL) was added and the layers were separated and washed with EtOAc (40 mL). The organic layers were combined and washed with water (40 mL) and saturated brine (40 mL). The organic layer was dried over magnesium sulphate, filtered and evaporated to afford the desired product (1.960 g, 68%). This was used without further purification.

1H NMR (399.9 MHz, $CDCl_3$) δ 1.06 (3H, t), 2.40 (2H, q), 2.52 (4H, t), 3.29 (4H, t), 3.79 (3H, s), 6.78 - 6.81 (2H, m), 7.83 - 7.86 (2H, m). MS: m/z 249 (MH+)

Example 180

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-4-(4-ethylpiperazin-1-yl)benzamide

Trimethylaluminium (2M in toluene, 1.51 mL, 3.02 mmol) was added dropwise to 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (299 mg, 1.21 mmol) and methyl 4-(4-ethylpiperazin-1-yl)benzoate (300 mg, 1.21 mmol) in toluene (6.0 mL) at 25°C. The resulting suspension was stirred at 60 °C for 24 h under nitrogen. The reaction mixture was added to methanol (100 mL) and was treated with HCl (2N aqueous solution, until the pH was 7 or

lower). The crude product was purified by ion exchange chromatography, using a SCX column. The desired product was eluted from the column using 7M NH3/MeOH and fractions were evaporated to dryness to afford impure product. The crude product was purified by silica column chromatography, eluting with a gradient of 0 to 5% 7M NH3/MeOH in DCM. Pure fractions were evaporated to dryness to afford the title compound (288 mg, 51 %) as a cream solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.05 (3H, t), 2.38 (2H, q), 2.50 (4H, peak obscured by DMSO), 2.87 (4H, s), 3.26 - 3.29 (4H, m), 3.73 (6H, s), 6.33 (1H, t), 6.42 (2H, d), 6.45 (1H, s), 6.96 (2H, d), 7.90 (2H, d), 10.29 (1H, s), 12.07 (1H, s). MS: m/z 464 (MH+).

Mean of n=2, FGFR Kinase assay – Caliper Echo Dosing, IC_{50} 0.0017μM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as indicated in Example 2.

Methyl 4-(4-ethylpiperazin-1-yl)benzoate, used as starting material, was prepared as outlined in Example 179.

Enzyme Assays

FGFR Kinase assay - Caliper

To determine inhibition of FGFR activity, kinase assays were conducted using Caliper technology.

Kinase activity assays were performed in Greiner 384-well low volume plates, with a total reaction volume of 12ul per well. Final concentration of FGFR1 active kinase in each reaction well was 7.2nM. The substrate for each assay was a custom peptide with fluorescent tag (13 amino acids in length, KKSRGDYMTMQIG with the fluorescene tag on the first K).

Compounds were serially diluted in 5% (v/v) DMSO, before being added to assay plates. The Enzyme (at 7.2nM [final]) and Substrate (at 3.6uM [final]) were added separately to the compound plates, in reaction buffer [comprising: 50mM MOPS (Sigma, Catalogue No. M1254) – pH 6.5, 0.004% Triton (Sigma, Catalogue No. X-100), 2.4mM DTT, 12mM $MgCl_2$, 408uM ATP] resulting in a final DMSO concentration in the reaction mix of 0.8%.

Assay plates were incubated at room temperature for 1.5h, before the reaction was stopped with the addition of buffer [comprising: 100mM HEPES – pH7.5, 0.033% Brij-35

(Sigma Catalogue No. B4184), 0.22% Caliper Coating Reagent #3 (Caliper Life Sciences Catalogue No. 760050), 88mM EDTA, 5% DMSO]. Stopped assay plates were then read using the Caliper LabChip® LC3000 (which uses microfludics to measure a shift in mobility between fluorescent labelled peptide and the FGFR1 kinase - phosphorylated form of this peptide).

In the assay, compounds were tested at a range of concentrations. The mean data values for each concentration, along with untreated control wells and 100% inhibition control wells were used to derive a plot of inhibition against concentration. From this data, the IC50 value or a percentage inhibition value at fixed concentration may be determined.

Percentage inhibition at 1uM, as expressed herein, is a calculated value based on the curve fit that was generated experimentally. From the fitted curve plot, the effect of compound at a concentration of 1uM was calculated as a percentage inhibition. The IC_{50} is the concentration of compound, which inhibits FGFR1 kinase activity by 50% in the context of this assay.

Results of FGFR Inhibition Tests for Examples

Example	Activity class
3	A
4	A
5	A
6	A
7	A
8	A
9	A
13	B
14	B
15	A
16	B
17	B
18	B
19	B

20 A

Activity: A less than 0.3μM

B greater than 0.3μM and less than 1μM

C greater than 1μM and less than 30μM

Eg. Example 14 is 612nM.

FGFR Kinase assay – Caliper Echo Dosing

To determine inhibition of FGFR activity, kinase assays were conducted using Caliper technology.

Kinase activity assays were performed in Greiner 384-well low volume plates, with a total reaction volume of 12ul per well. Final concentration of FGFR1 active kinase in each reaction well was 7.2nM. The substrate for each assay was a custom peptide with fluorescent tag (13 amino acids in length, KKSRGDYMTMQIG with the fluorescene tag on the first K).

Compounds were dispensed directly in to assay plates using a Labcyte Echo 550 acoustic droplet ejection unit. Each well received 120nl of DMSO containing compound such that the final concentration of compound in the assay prior to the addition of the stop solution ranged between 30uM and 30pM. In addition to compounds each plate carried maximum and minimum control wells, the max wells contained 120nl of DMSO and the min wells contained 120nl of 10mM staurosporine (LC Laboratories, MA 01801, USA Catalogue No. S-9300). The Enzyme (at 7.2nM [final]) and Substrate (at 3.6uM [final]) were added separately to the compound plates, in reaction buffer [comprising: 50mM MOPS (Sigma, Catalogue No. M1254) – pH 6.5, 0.004% Triton (Sigma, Catalogue No. X-100), 2.4mM DTT, 12mM $MgCl_2$, 408uM ATP] resulting in a final DMSO concentration in the reaction mix of 1%.

Assay plates were incubated at room temperature for 1.5h, before the reaction was stopped with the addition of buffer [comprising: 100mM HEPES – pH7.5, 0.033% Brij-35 (Sigma Catalogue No. B4184), 0.22% Caliper Coating Reagent #3 (Caliper Life Sciences Catalogue No. 760050), 88mM EDTA, 5% DMSO]. Stopped assay plates were then read using the Caliper LabChip® LC3000 (which uses microfludics to measure a shift in mobility between fluorescent labelled peptide and the FGFR1 kinase - phosphorylated form of this peptide).

In the assay, compounds were tested at a range of concentrations. The mean data values for each concentration, along with untreated control wells and 100% inhibition control wells were used to derive a plot of inhibition against concentration. From this data, the IC50 value or a percentage inhibition value at fixed concentration may be determined.

Percentage inhibition at 1uM, as expressed herein, is a calculated value based on the curve fit that was generated experimentally. From the fitted curve plot, the effect of compound at a concentration of 1uM was calculated as a percentage inhibition. The IC_{50} is the concentration of compound, which inhibits FGFR1 kinase activity by 50% in the context of this assay. This value is calculated using a standard curve fitting software package Origin™. Where compounds have been tested on more than one occasion the IC_{50} value is sited as a geometric mean.

FGFR Kinase assay - Elisa

To determine inhibition of FGFR activity, kinase assays were conducted using ELISA (Enzyme-Linked Immunosorbent Assay) technology.

Kinase activity assays were performed in 384-well polypropylene plates (Matrix, Catalogue No. 4311. Matrix are part of Thermo Fisher Scientific, 22 Friars Drive, Hudson, New Hampshire 03051, USA) with a total volume of 40µl in each well. Each well was coated with 2µg of polyEAY substrate (Sigma, Catalogue No. P3899) at 4°C overnight. The plates were then washed once with 100µl PBS and once with 100µl 50mM HEPES (pH 7.4) prior to the addition of the kinase assay reagents. Reactions contained His_6-tagged FGFR kinase domain (FGFR kinase domain (amino acids 458-765, C488A, C584S) N-terminally fused to a His_6-tag and TEV cleavage site encoded by the following sequence; [MHHHHHHEFKGSTSLYKKAGSSENLYFQGA]. The final alanine denotes the start of the FGFR protein sequence. The resultant protein was expressed and purified based on Mohammadi et al, Cell Vol 86, 577-587 (1996). Each kinase reaction contained 0.1ng His_6-tagged FGFR kinase domain, 50mM HEPES (pH 7.4), 0.1mM Na_3VO_4, 0.1mM DTT, 0.05% (v/v) Triton X100, 20mM $MgCl_2$, 160µM ATP. Various concentrations of test compounds were each added in 5% (v/v) DMSO to yield a final assay DMSO concentration of 1.25% (v/v). The kinase reactions were incubated at room temperature for 45 minutes and stopped by washing the plate three times with 100µl PBS plus 0.05% Tween. 40µl of a one in 10000 dilution of 4G10-HRP antibody (Upstate Biotechnology, UBI 16-105. Upstate are part of

Millipore Corporation, 290 Concord Road, Billerca MA 01821 USA) made up in 0.5% (w/v) BSA/ PBS was then added to each well and the plates incubated at room temperature for one hour. Following this, the plates were then washed repeatedly with 100µl PBS plus 0.05% Tween to remove all traces of the antibody solution. 40µl of 50µg/ml 3,3′,5,5′-Tetramethylbenzidine (Sigma, Catalogue No. T2885), 0.05M phosphate-citrate buffer, containing 0.03% sodium perborate was added to each well and the plates incubated at room temperature for twelve minutes. The colour reaction was stopped by the addition of 20µl 2M H_2SO_4 and the plates read at 450nm on a Spectrafluor Plus (Tecan Trading AG, Switzerland). In the assay, compounds were tested at a range of concentrations. The mean data values for each concentration, along with untreated control wells and 100% inhibition control wells were used to derive a plot of inhibition against concentration. From this data, the IC50 value or a percentage inhibition value at fixed concentration may be determined.

Percentage inhibition at 1uM, as expressed herein, is a calculated value based on the curve fit that was generated experimentally. From the fitted curve plot, the effect of compound at a concentration of 1uM was calculated as a percentage inhibition. The IC_{50} value is the concentration of test compound that inhibits 50% of FGFR kinase activity.

Results of FGFR Inhibition Tests for Examples

Example	Activity class
1	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	B

14	**B**
15	**A**
16	**B**
17	**B**
18	**B**
19	**A**
20	**A**

Activity: A less than 0.3μM

B greater than 0.3μM and less than 1μM

C greater than 1μM and less than 30μM

Eg Example 14 is 732nM

Cell Assays

Cell pErk - Growth factor stimulated Erk phosphorylation

These and other assays were used to evaluate the ability of a test compound to inhibit growth factor stimulated cellular signalling in mammalian cell lines. This was achieved by measuring the amount of receptor tyrosine kinase regulated Erk phosphorylation within a cell following compound treatment.

NIH 3T3 (ECACC, 93061524) cells were routinely passaged in DMEM (Gibco BRL, 41966) plus 10% foetal calf serum (FCS), 1% L-glutamine (Gibco BRL, 25030) to a confluence not greater than 80%. To undertake the assay, NIH 3T3's were seeded at $1x10^4$ cells/ well in DMEM plus 10% foetal calf serum, 1% L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5% CO_2) in a humidified incubator. Once the cells had fully adhered (typically following 4-5 hours incubation) the media was removed from each well and the cells gently washed with 100μl warm serum free media. 90μl of serum free DMEM plus 1% L-glutamine was then added to each well and the plates were returned to a humidified 37°C (+5% CO_2) incubator. The following day, the plates were dosed with 10μl compound (diluted from 10 mM stock in DMSO using serum free DMEM) and the plates were returned to a humidified 37°C (+5% CO_2) incubator for one hour. NIH 3T3 cells were then stimulated with a final concentration of 3 ng/ml bFGF (Sigma, F0291) for 20 minutes at

37°C. Following stimulation the cells were fixed by adding formaldehyde (4% v/v final concentration) and incubating at room temperature for 20 minutes. The fixative solution was then removed and the wells were washed twice with 100µl phosphate buffered saline (PBS/A) before permeabilising the cells by the addition of 50µl/ well 0.1% triton/ PBS/A for 10 minutes at room temperature. The permeabilisation solution was then removed and the cells washed twice more with 100µl/ well PBS/A before the addition of 50µl/ well anti-phospho p44/42 antibody (Cell Signalling Technology, 9106), diluted 1/500 with PBS/A plus 10% FCS. The anti-phospho p44/42 antibody recognises Erk phosphorylated at threonine 202 and tyrosine 204. Following incubation at room temperature for 2 hours, the antibody solution was removed and the wells were washed twice with 100µl/ well PBS/A. 50µl/ well 1/250 goat anti-mouse alexa fluor 488 secondary antibody (Molecular Probes, A11001) and 1/10000 Hoescht (Molecular Probes, H-3570) diluted with PBS/A plus 10% FCS was added and the plate incubated in the dark at room temperature for one hour. Finally, the plates were washed three times with 100µl/ well PBS/A, leaving the final wash in the wells before sealing the plates. The plates were read at 350nm and 488nm using an Arrayscan (Cellomics). The mean average intensity fluorescence values for each test compound concentration, untreated control wells and 100% inhibition control wells were used to determine the test compounds IC_{50} value. IC_{50} value is the concentration of test compound that inhibits 50% of Erk phosphorylation.

Results of FGFR Inhibition Tests for Examples

Example	Activity class
1	B
2	A
7	C
8	A
9	B
10	A
11	A
18	B

Activity: A less than 0.3μM

B greater than 0.3μM and less than 1μM

C greater than 1μM and less than 30μM

Eg Example 18 is 877nM.

Cell FGFR1 - Cell based inhibition of transiently expressed FGFR1 IIIc phosphorylation (measured using phospho-specific primary and fluorescent secondary antibodies).

This assay is designed to detect inhibitors of transiently expressed FGFR1 phosphorylation by antibody staining of fixed cells detected using ArrayScan technology. (For a description of ArrayScan technology see http://www.cellomics.com/content/menu/Arrayscan/)

Cos-1 cells were routinely passaged in DMEM (Gibco BRL, 41966) plus 3% foetal calf serum (FCS), 1% L-glutamine (Gibco BRL, 25030) to a confluence of 80%. To undertake the assay, Cos-1 cells were harvested at 90-95% confluence for cell transfection. For each 96-well plate, 24ul Lipofectamine 2000 (Invitrogen, Catalogue No. 11668-019) was added to 809ul OptiMEM (Invitrogen, Catalogue No. 11058-021) and incubated at room temperature for 5 minutes. For each 96 well plate, 20ug 3' FLAG tagged FGFR1/ pcDNA3.1 (In-house clone 15, MSD 4793) was diluted with OptiMEM to a total volume of 833ul. Equal volumes of DNA and Lipofectamine 2000 were combined (DNA: Lipid = 1:1.2 ratio) and incubated at room temperature for 20 minutes. The "FLAG-tag" was a purification/detection tag which comprises the amino sequence: N-DYKDDDDK-C. The "FLAG-tag" was cloned at the N-terminus of FGFR1. The clone was full-length, wild-type FGFR1 IIIc isoform.

The harvested Cos-1 cells are counted using a coulter counter and diluted further with 1% FCS/DMEM to 2.5 x 10^5 cells/ml. For each 96-well, 8.33ml cells were required. The complexed transfection solution was added to the cell solution and the cells were seeded at 2.5x10^5 cells/ well in DMEM plus 1% foetal calf serum, 1% L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5% CO_2) in a humidified incubator overnight (24hrs). The following day, the plates were dosed with 25 μl compound (diluted from 10 mM stock in DMSO using serum free DMEM) and the plates were returned to a humidified 37°C (+5% CO_2) incubator for one hour. Media was removed from the wells using vacuum aspiration; cells were fixed by adding 50μl of 100% methanol to each well and incubated at room

temperature for 20 minutes. The fixative solution was then removed and the wells were washed once with 200µl phosphate buffered saline (PBS/A) before permeabilising the cells by the addition of 50ul/ well 0.1% triton/ PBS/A for 20 minutes at room temperature. The permeabilisation solution was then removed and the cells washed once more with 200ul / well PBS/A before the addition of 40µl 1/1000 primary antibody solution (Cell Signalling Technologies #CS3476; mouse anti-phospho FGFR1 diluted in PBS/A with 10% FCS + 0.1% Tween20) to each well.

Following incubation at room temperature for 1 hour, the antibody solution was removed and the wells were washed once with 200ul / well PBS/A. Then 40µl 1/500 secondary antibody (A11005; goat anti-mouse 594) solution and 1/10000 Hoechst (diluted together in PBS/A with 10% FCS + 0.1% Tween 20) were added and the plate incubated in the dark at room temperature for one hour. Finally, the plates were washed once with 200µl / well PBS/A, leaving the final wash in the wells before sealing the plates. The plates were read on an Arrayscan (Cellomics). The Channel 2 (594nm) values obtained from undosed (max) and reference compound (min) wells within a plate are used to set boundaries for 0% and 100% compound inhibition. Compound data was normalized against these values to determine the dilution range of a test compound that gives 50% inhibition of phosphorylated FGFR1.

Cell FGFR1 (ECHO) - Cell based inhibition of transiently expressed FGFR1 IIIc phosphorylation via use of ECHO technology (measured using phospho-specific primary and fluorescent secondary antibodies).

This assay is designed to detect inhibitors of transiently expressed FGFR1 phosphorylation by antibody staining of fixed cells detected using ArrayScan technology.

Cos-1 cells were routinely passaged in DMEM (Gibco BRL, 41966) plus 3% foetal calf serum (FCS), 1% L-glutamine (Gibco BRL, 25030) to a confluence of 80%. To undertake the assay, Cos-1 cells were harvested at 90-95% confluence for cell transfection. For each 96-well plate, 24µl Lipofectamine 2000 was added to 809ul OptiMEM and incubated at room temperature for 5 minutes. For each 96 well plate, 20ug 3' FLAG tagged FGFR1/ pcDNA3.1 (In-house clone15, MSD 4793) was diluted with OptiMEM to a total volume of 833µl. Equal

volumes of DNA and Lipofectamine 2000 were combined (DNA: Lipid = 1:1.2 ratio) and incubated at room temperature for 20 minutes.

The harvested Cos-1 cells are counted using a coulter counter and diluted further with 1% FCS/DMEM to 2.5 x 10^5 cells/ml. For each 96-well, 8.33ml cells were required. The complexed transfection solution was added to the cell solution and the cells were seeded at $2.5x10^5$ cells/ well in DMEM plus 1% foetal calf serum, 1% L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5% CO_2) in a humidified incubator overnight (24hrs).

The following day, compounds from dry weight samples were dissolved in 100% DMSO to give 10mM concentration. 40µl of the compound was dispensed into the wells of each quadrant across the 384 Labcyte plate (Labcyte Catalogue No. P-05525) (inclusive of a positive control (100% DMSO), a negative control (10µM) and a reference compound (250nM)). The 384 Labcyte plate was then transferred to the Hydra to dilute the compounds 1:100 into the remaining wells of the quadrant. 70µl of media was aspirated from the assay plate using the Quadra before the plate was transferred onto the ECHO 550. The 384 Labcyte compound plate was also transferred onto the ECHO 550. Compound transfer to the assay plate on the ECHO 550 was at concentration ranges 1) 10 µM, 2) 3 µM, 3) 1µM, 4) 0.3µM, 5) 0.1µM, 6) 0.01.

The plates were gently tapped to mix compound in with the cell media and left to incubate at 37^0C with 5% CO_2 for 1 hour.

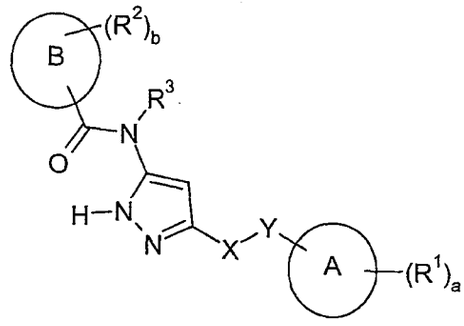
Media was removed from the wells using vacuum aspiration; cells were fixed by adding 50µl of 100% methanol to each well and incubated at room temperature for 20 minutes. The fixative solution was then removed and the wells were washed once with 200µl phosphate buffered saline (PBS/A) before permeabilising the cells by the addition of 50ul/ well 0.1% triton/ PBS/A for 20 minutes at room temperature. The permeabilisation solution was then removed and the cells washed once more with 200µl / well PBS/A before the addition of 40µl 1/1000 primary antibody solution (Cell Signalling Technologies #CS3476; mouse anti-phospho FGFR1 diluted in PBS/A with 10% FCS + 0.1% Tween20) to each well.

Following incubation at room temperature for 1 hour, the antibody solution was removed and the wells were washed once with 200ul / well PBS/A. Then 40µl 1/500 secondary antibody (A11005; goat anti-mouse 594) solution and 1/10000 Hoechst (diluted together in PBS/A with

10% FCS + 0.1% Tween 20) were added and the plate incubated in the dark at room temperature for one hour. Finally, the plates were washed once with 200µl / well PBS/A, leaving the final wash in the wells before sealing the plates. The plates were read on an Arrayscan (Cellomics). The Channel 2 (594nm) values obtained from undosed (max) and reference compound (min) wells within a plate are used to set boundaries for 0% and 100% compound inhibition. Compound data was normalized against these values to determine the dilution range of a test compound that gives 50% inhibition of phosphorylated FGFR1.

CLAIMS

1. A compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof

wherein

ring **A** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

ring **B** represents a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur;

R^1 each independently represents

a halogen,

a hydroxyl group,

a cyano group,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^4R^5$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_{3-5}cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^6R^7$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_3alkenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -NR^8R^9 (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a phenyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{10}R^{11}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 6-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, -$NR^{12}R^{13}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, -$NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a –$NR^{16}R^{17}$ group,

a –$OCOR^{18}$ group,

a –CO_2R^{19} group,

a –$CONR^{20}R^{21}$ group,

a $-NR^{22}COR^{23}$ group,

a $-NR^{24}CO_2R^{25}$ group.

a $-OSO_2R^{26}$ group,

or two adjacent R^1 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{27}R^{28}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

R^2 each independently represents

a hydroxyl group,

a halogen,

a cyano group,

a $-CO_2R^{29}$ group,

a $-CONR^{30}R^{31}$ group,

a $-NR^{32}COR^{33}$ group,

a $-NR^{34}CO_2R^{35}$ group,

a $-NR^{36}R^{37}$ group,

a $-SO_2R^{38}$ group,

a $-SO_2NR^{39}R^{40}$ group,

a $-NR^{41}SO_2R^{42}$ group,

a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{43}R^{44}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, cyano, hydroxyl trifluoromethyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, C_3-C_6cycloalkyl, amino ($-NH_2$), mono- and di-

C_1-C_3alkylamino, cyano, hydroxyl, trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), cyano, halogen and hydroxyl,

a C_3-C_6cycloalkyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{48}R^{49}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{50}R^{51}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_2-C_6alkenyl group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{52}R^{53}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl, and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, $-NR^{54}R^{55}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl,

C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a 4- to 7-membered heterocyclyl group optionally fused to a 4- to 7-membered carbocyclyl or heterocyclyl group and optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, cyano, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, oxo, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

a C_1-C_6alkoxy group optionally substituted by one or more substituents selected from C_1-C_6alkoxy, C_3-C_6cycloalkyl, -$NR^{62}R^{63}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylthio, -$NR^{64}R^{65}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or two adjacent R^2 groups together with the atoms to which they are attached form a 4- to 7-membered carbocyclyl or heterocyclyl ring

optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{66}R^{67}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

$\mathbf{R^3}$ represents hydrogen,

a C_1-C_3alkyl group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, C_1-C_3alkylthio, $-NR^{68}R^{69}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl;

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

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

$\mathbf{R^4}$ and $\mathbf{R^5}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^6}$ and $\mathbf{R^7}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^8}$ and $\mathbf{R^9}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{10}}$ and $\mathbf{R^{11}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

$\mathbf{R^{12}}$ and $\mathbf{R^{13}}$ each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{14} and R^{15} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{16} and R^{17} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{16} and R^{17} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{18} represents C_1-C_4alkyl, or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{19} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{20} and R^{21} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{22} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{23} represents C_1-C_4alkyl or C_3-C_6cycloalkyl(each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{24} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{25} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{26} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{27} and R^{28} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{27} and R^{28} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{29} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{30} and R^{31} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{30} and R^{31} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{32} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{33} represents hydrogen, C_1-C_4alkyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur (each of which may be optionally substituted by one or more

substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{34} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{35} represents hydrogen, C_1-C_4alkyl, C_2-C_4alkenyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{36} and R^{37} each independently represent hydrogen, C_1-C_4alkyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl or a 5- or 6-membered aromatic group optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, or R^{36} and R^{37} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl and 4- to 7-membered carbocyclyl or heterocycly group which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl, trifluoromethyl);

R^{38} represents C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{39} and R^{40} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{39} and R^{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{41} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{42} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, C_1-C_3alkylthio, amino (-NH_2), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl);

R^{43} and R^{44} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{43} and R^{44} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{45} and R^{46} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{45} and R^{46} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{47} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{48} and R^{49} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{48} and R^{49} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{50} and R^{51} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{50} and R^{51} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{52} and R^{53} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{52} and R^{53} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{54} and R^{55} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{54} and R^{55} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{56} and R^{57} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{56} and R^{57} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{58} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{59} and R^{60} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{59} and R^{60} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{61} represents C_1-C_4alkyl or C_3-C_6cycloalkyl;

R^{62} and R^{63} each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{62} and R^{63} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{64} and R^{65} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{64} and R^{65} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{66} and R^{67} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{66} and R^{67} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{68} and R^{69} each independently represent hydrogen, C_1-C_6alkyl or C_3-C_6cycloalkyl, or R^{68} and R^{69} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and where

when **Y** represents CH_2, **X** represents CH_2, O, NR^{70} or $S(O)_X$ wherein R^{70} represents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **x** is 0, 1 or 2; or

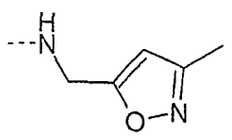
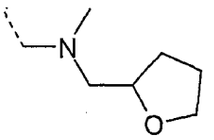
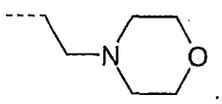
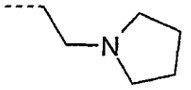
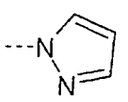
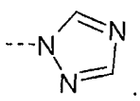
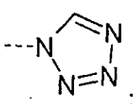
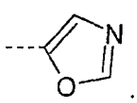
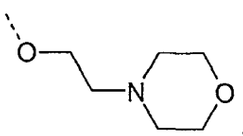
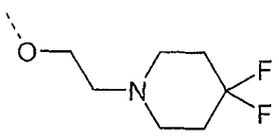
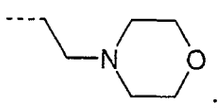
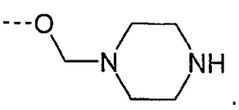
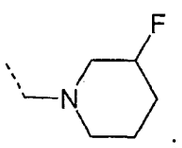
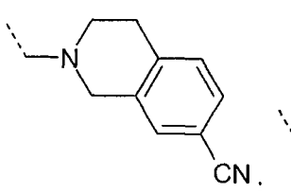
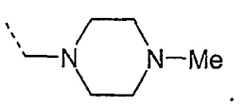
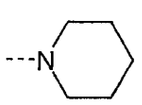
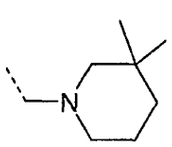
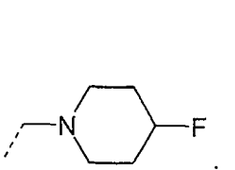
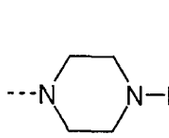
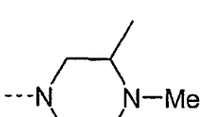
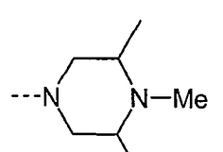
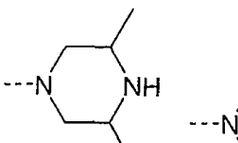
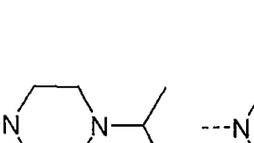
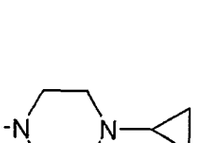
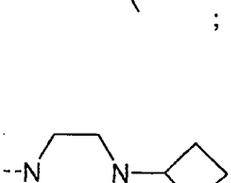
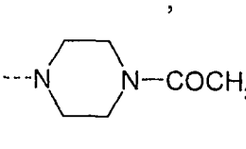
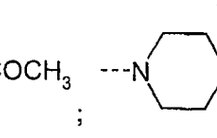
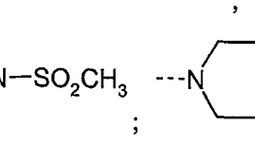
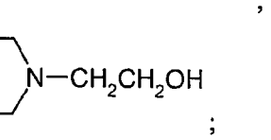
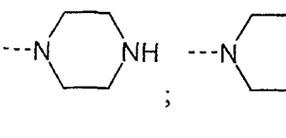
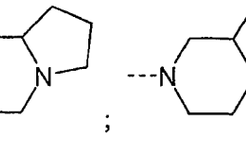
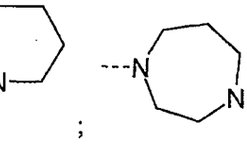
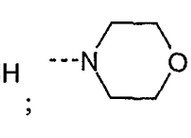
when **X** represents CH_2, **Y** represents CH_2, O, NR^{71} or $S(O)_y$ wherein R^{71} respresents hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl and **y** is 0, 1 or 2.

2. A compound of formula **(I),** or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein R^3 is hydrogen.

3. A compound of formula **(I),** or a pharmaceutically acceptable salt thereof, according to Claim 1 or 2 wherein X represents CH_2 or O; and Y represents CH_2.

4. A compound of formula **(I),** or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 3 wherein each R^2 independently represents a –Cl; -F; -I; -OH; -CN; $-CH_3$; $-CH_2OH$; $-CH_2N(CH_3)_2$; $-CH_2CH(CH_3)NH_2$; $-OCH_3$; $-OCH_2CH_2OH$; $-OCH_2CH_2OCH_2CH_3$; $-SO_2CH_3$; $-N(CH_3)_2$; -NHPh; $-NHCH_2C{\equiv}CH$; $-NHCH_2CH_3$;

-$NHCH_2CH_2N(CH_3)_2$; -$NHCO_2CH_2CH{=}CH_2$; -$NHCOCH_3$; -NHCOH; -NHCOPh; -$CONH_2$; -$NHSO_2Me$; -$SO_2N(CH_3)_2$; -CO_2H; -CO_2CH_3; -$CO_2CH_2CH_3$;


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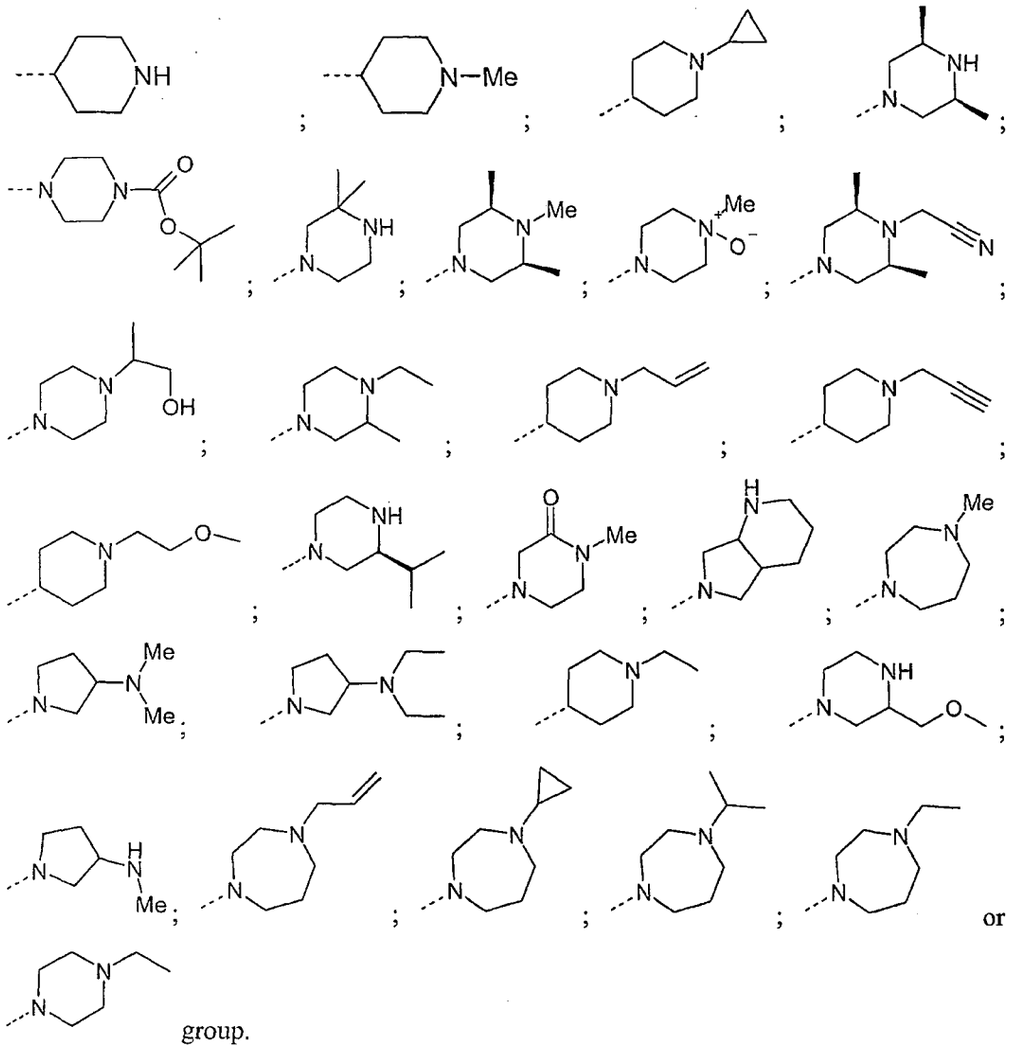
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group.

5. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 4 wherein each R^1 independently represents a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkyamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or a $-CONR^{20}R^{21}$ group.

6. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 5 wherein ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring.

7. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 6 wherein ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring.

8. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring;

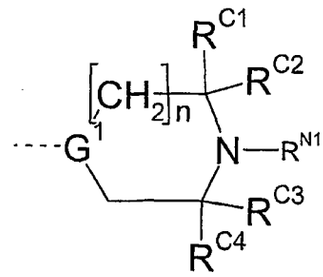
ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, thienyl or thiazolyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from cyano, halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, -$NR^{59}R^{60}$, -SO_2R^{61} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino

($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected fromC_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

9. A compound of formula **(I),** or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

ring A represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

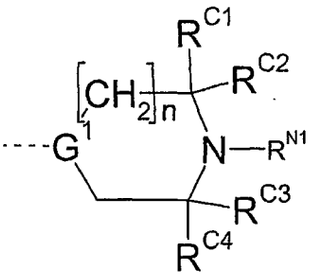
ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be

optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

10. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

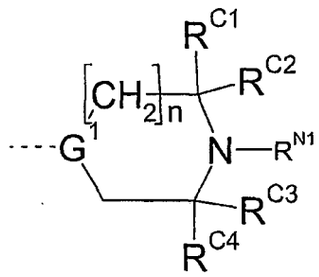
ring A represents furyl, phenyl or pyridyl ring;

ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

11. A compound of formula (I), or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

ring A represents phenyl ring;

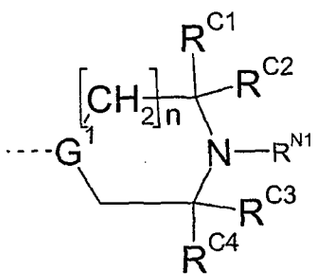
ring B represents phenyl, pyrazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group optionally substituted by one or more substituents selected from C_1-C_3alkoxy, C_3-cycloalkyl, $-NR^{14}R^{15}$, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_3alkyl, C_1-C_3alkoxy, amino ($-NH_2$), mono- and di-C_1-C_3alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl, or

a $-CONR^{20}R^{21}$ group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen, halogen and hydroxyl, or

R^{C1} and R^{C2} and/or R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 6-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, or

R^{C1} and R^{C3} together with the atoms to which they are attached and the nitrogen atom to which the R^{N1} group is attached form a 5- to 7-membered carbocyclic or heterocyclic ring optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl, and

R^{N1} is selected from selected from C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), hydrogen and a 4- to 7-membered heterocyclyl group optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen and hydroxyl,

or R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring optionally substituted by one or more substituents selected from C_1-C_3alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_1-C_3alkoxy, C_3-C_5cycloalkyl, C_1-C_3alkylthio, $-NR^{56}R^{57}$, SO_2R^{58} (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy,

C_1-C_2alkylthio, amino (-NH_2), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl), halogen, hydroxyl;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

b is 1.

12. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

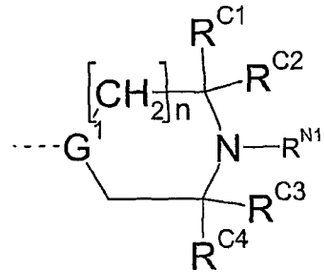
ring A represents phenyl ring;

ring B represents furyl, phenyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl or thienyl ring;

each R^1 independently represents

a C_1-C_3alkoxy group;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a 3- to 5-membered carbocyclic ring,

and

R^{N1} is selected from selected from C_1-C_2alkyl, C_2-C_3alkenyl, C_2-C_3alkynyl, C_3-C_5cycloalkyl, (each of which may be optionally substituted by one or more substituents selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, C_1-C_2alkylthio, amino ($-NH_2$), mono- and di-C_1-C_2alkylamino, hydroxyl and trifluoromethyl) and hydrogen, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl ring;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2;

a is 0, 1 or 2; and

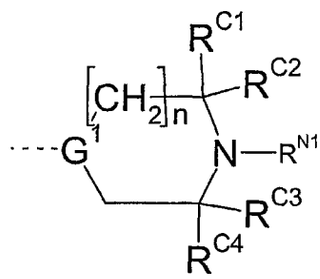
b is 1.

13. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

$A(R^1)_a$ represents 3,5-dimethoxyphenyl;

ring B represents phenyl, pyrazinyl, pyrimidinyl or thienyl ring;

R^2 represents



wherein

G^1 is C or N,

n is 1 or 2,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring,

and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl, propenyl, propynyl, propyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring;

R^3 represents hydrogen;

X represents CH_2 or O;

Y represents CH_2; and

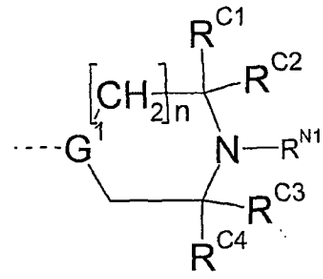
b is 1.

14. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to Claim 1 wherein:

$A(R^1)_a$ represents 3,5-dimethoxyphenyl;

ring B represents phenyl, pyrazinyl, pyrimidinyl or thienyl ring;

R^2 represents



wherein

G^1 is C or N,

n is 1,

R^{C1}, R^{C2}, R^{C3} and R^{C4} are each independently selected from hydrogen, methyl, ethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl, 2,2,2-trifluoroethyl, or

R^{C3} and R^{C4} together with the atom to which they are attached form a cyclopropyl ring,

and

R^{N1} is selected from selected from hydrogen, methyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl, propenyl, propynyl, i-propyl, $-CH(CH_3)CH_2OH$, cyclopropyl, cyclobutyl, cyclopentyl, or

R^{N1} and R^{C4} together with the atoms to which they are attached form a 5- or 6-membered heterocyclyl ring;

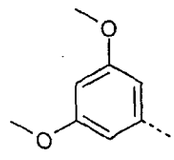
R^3 represents hydrogen;

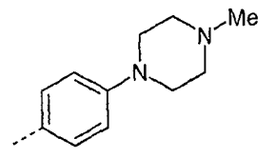
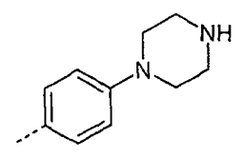
X represents CH_2 or O;

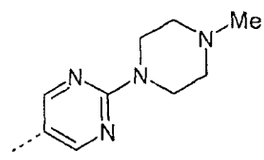
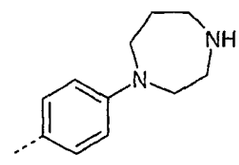
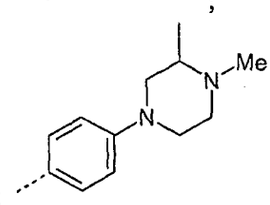
Y represents CH_2; and

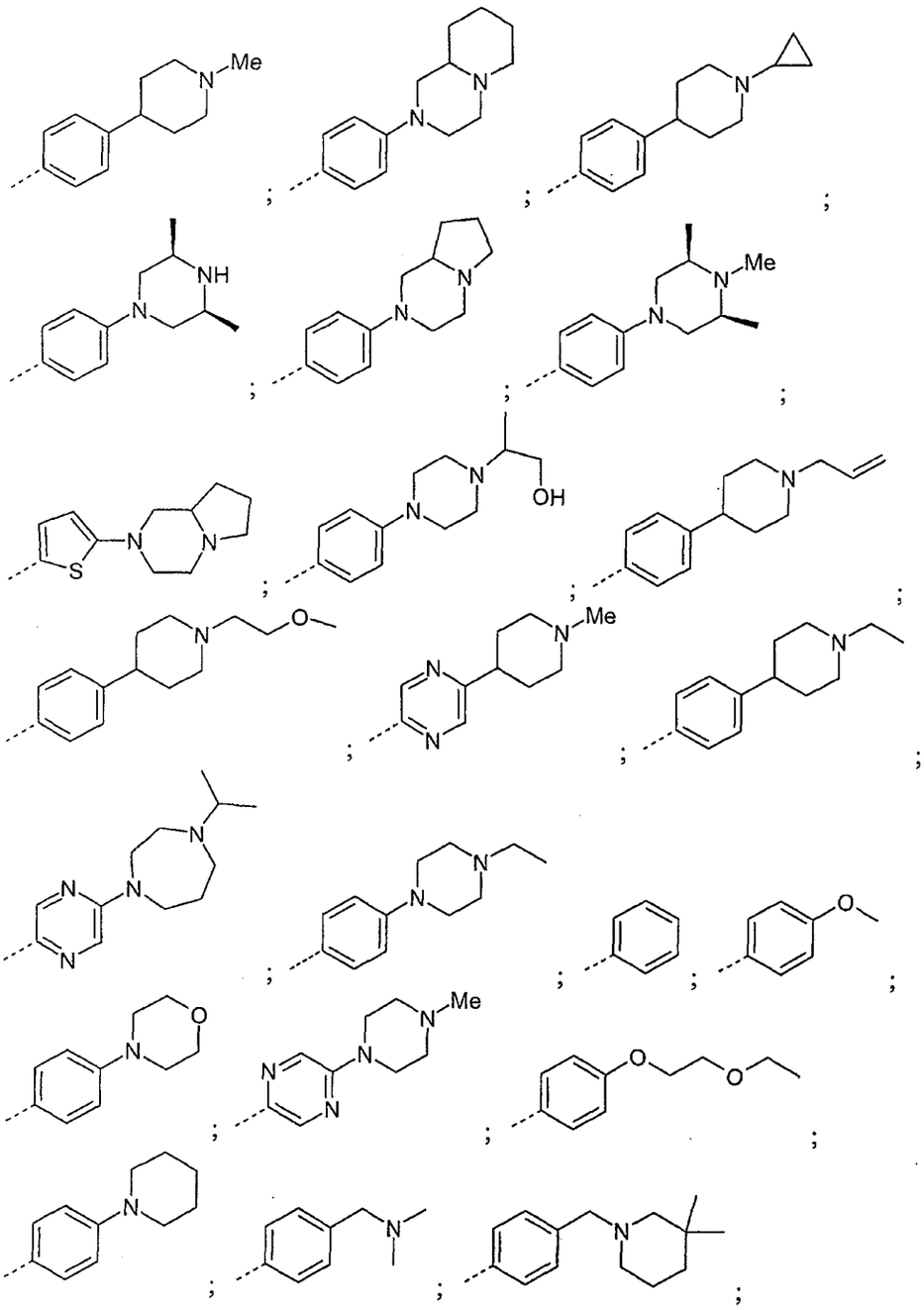
b is 1.

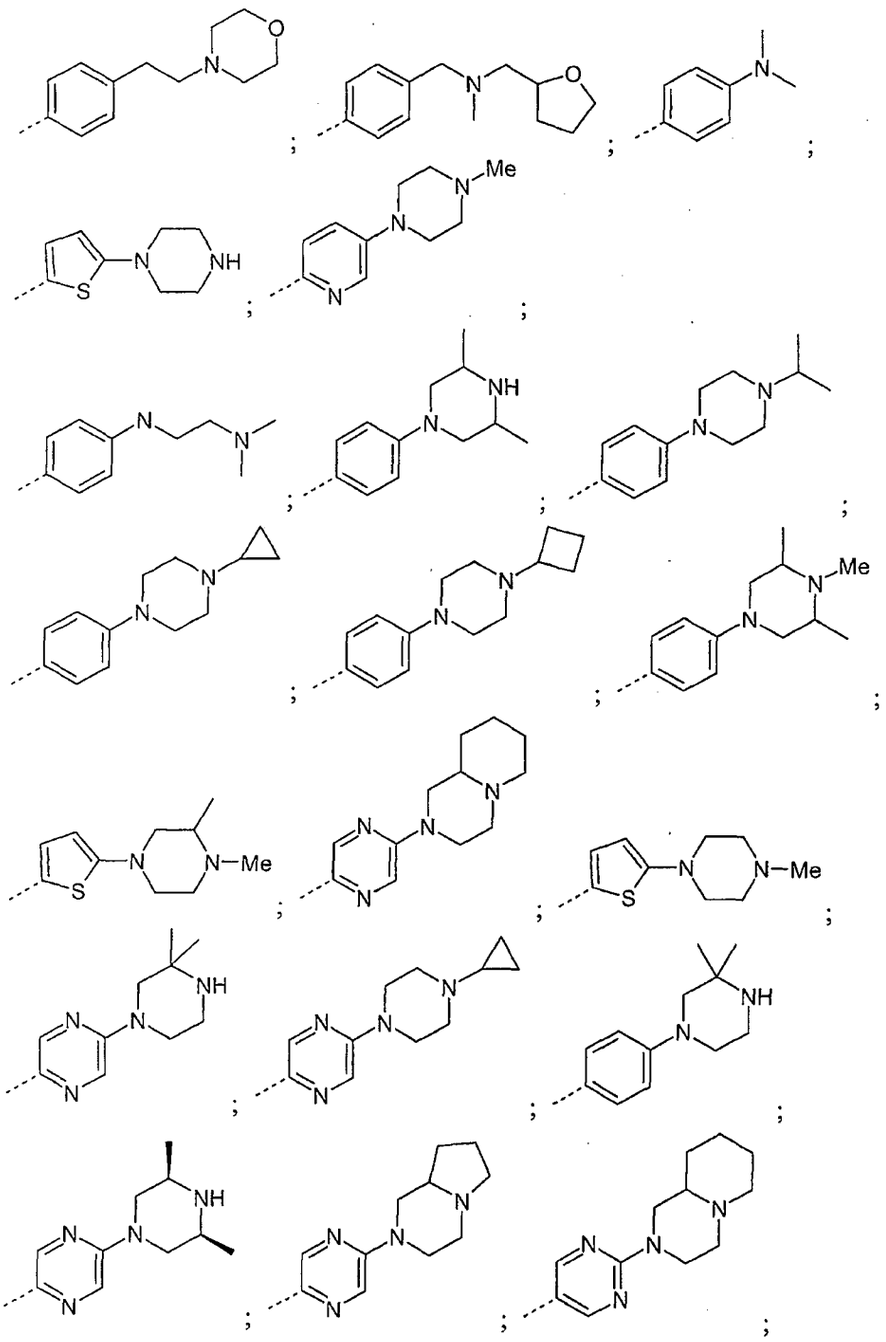
15. A compound of formula **(I),** or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 3 wherein:

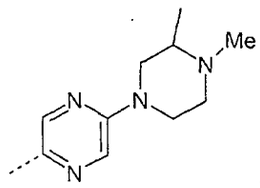
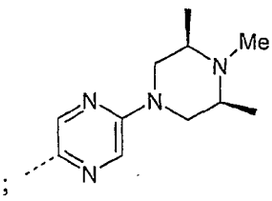
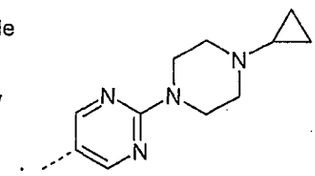
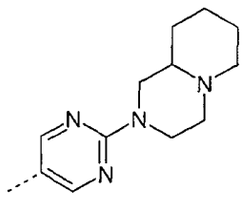
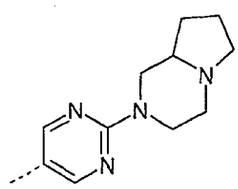
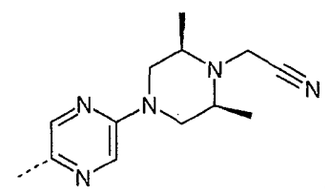
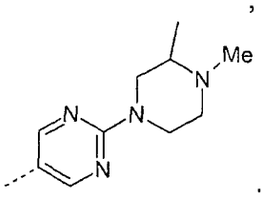
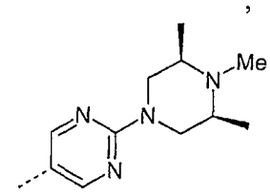
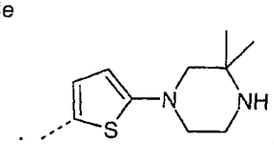
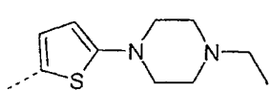
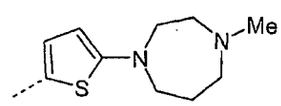
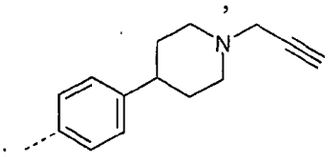
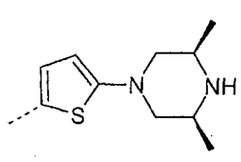
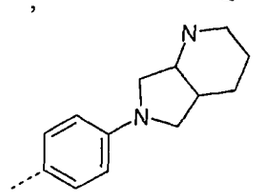
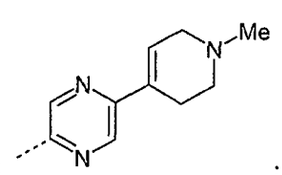
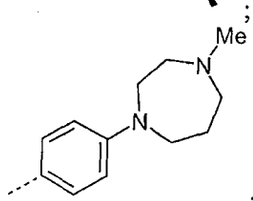
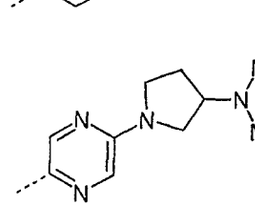
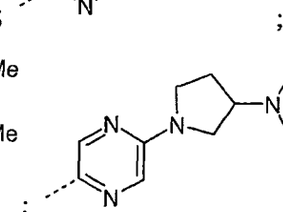
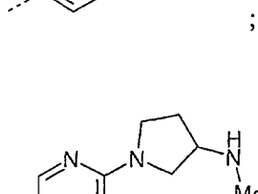
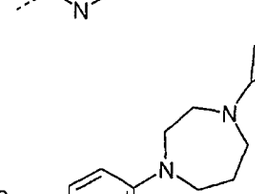
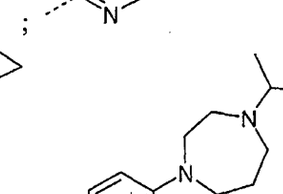
-A-$(R^1)_a$ represents a  group; and

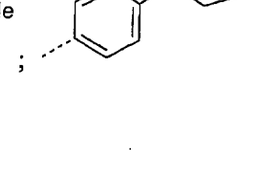
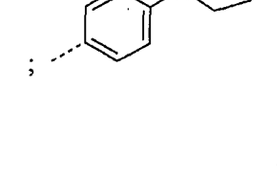
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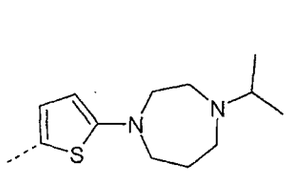
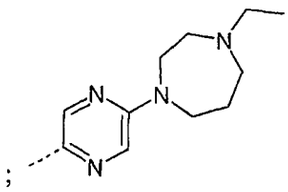
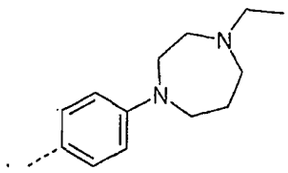
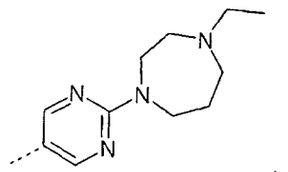
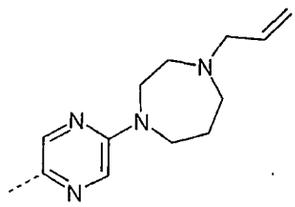
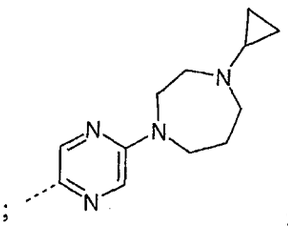
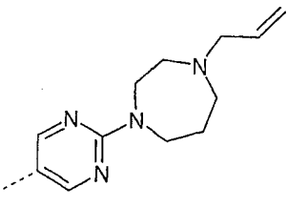
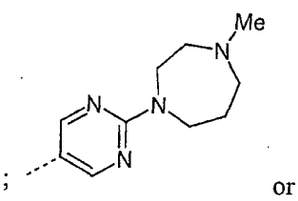
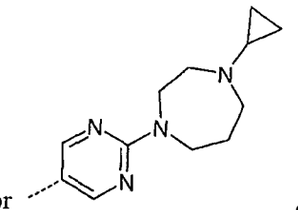
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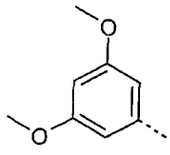


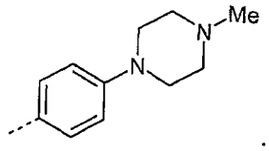
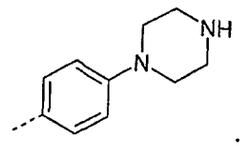
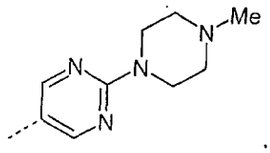
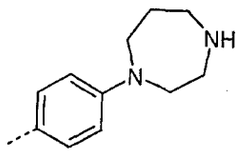
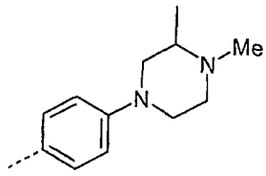






















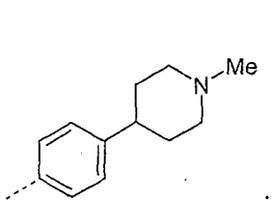



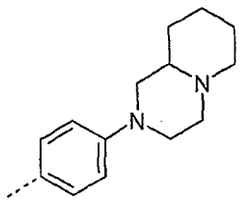

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or

group.

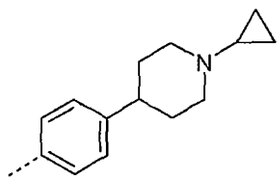
16. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 3 wherein:

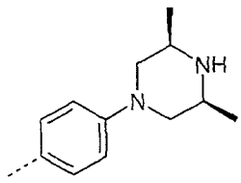
-A-$(R^1)_a$ represents a  group; and

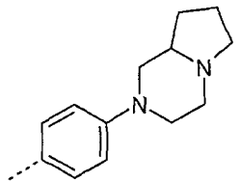
-B-$(R^2)_b$ represents a 
;

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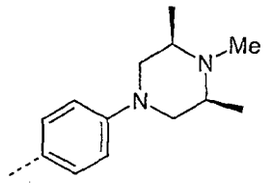


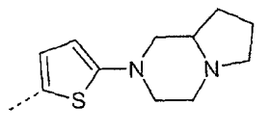
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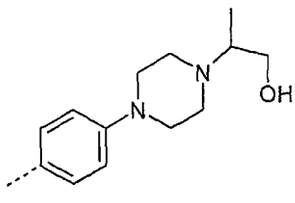
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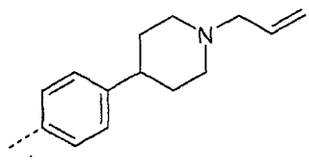
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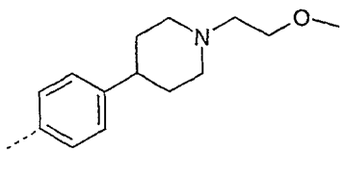
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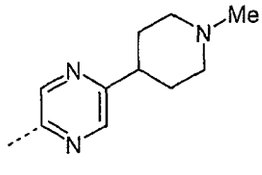
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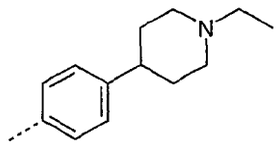
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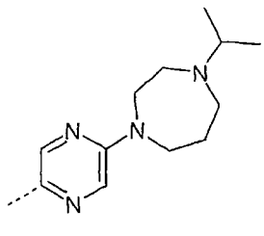
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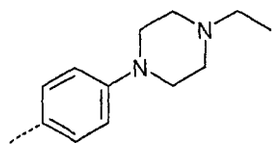
;


;


;


;


;


or


group.

17. A compound of formula **(I)**, or a pharmaceutically-acceptable salt thereof, according to any one of Claims 1 to 16 for use in therapy.

18. A compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16 for use in a method of treatment of the human or animal body by therapy.

19. The use of a compound of formula **(I)**, or a pharmaceutically acceptable salt, according to any one of Claims 1 to 16 in the manufacture of a medicament for use in therapy.

20. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16.

21. A compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16 for use as a medicament.

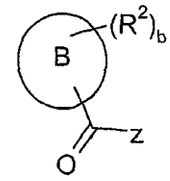
22. The use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16 in the manufacture of a medicament for use in the production of a FGFR inhibitory effect in a warm-blooded animal.

23. The use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16 in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal.

24. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25. A process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1 to 16, with a pharmaceutically acceptable adjuvant, diluent or carrier.

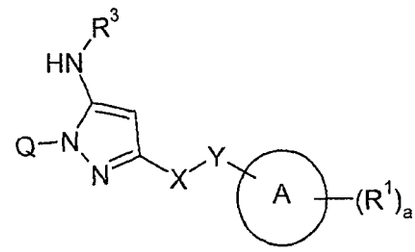
26. A process for the preparation of a compound of formula **(I)** according to Claim 1, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula **(II)**



(II)

wherein Z represents a leaving group, and B, R^2 and b are as defined in Claim 1 for a compound formula **(I)**,

with a compound of formula **(III)**



(III)

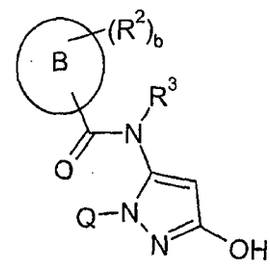
wherein Q is hydrogen or a protecting group, and A, R^1, R^3, X, Y and a are as defined in Claim 1 for a compound of formula **(I)**

to give a compound of formula **(I)**,

and optionally carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

27. A process for the preparation of a compound of formula **(I)** according to Claim 1, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of formula **(IV)**

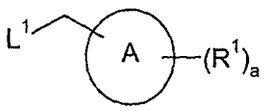


(IV)

wherein Q is hydrogen or a protecting group; and

B, R^2, R^3 and b are as defined in Claim 1 for a compound of formula **(I)**,

with a compound of formula **(V)**



(V)

wherein L^1 represents OH or a leaving group; and A, R^1 and a are as defined in Claim 1 for a compound of formula **(I)**

to give a compound of formual **(I)**

and optionally carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

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

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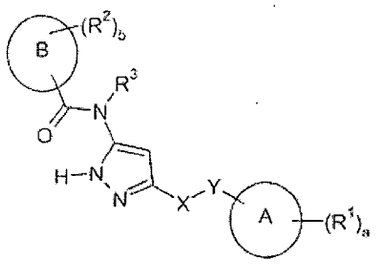
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(54) Title: ACYLAMINOPYRAZOLES AS FGFR INHIBITORS

(54) Título: ACILAMINOPIRAZOLES COMO INHIBIDORES DE FGFR



(I)

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

(57) Resumen: Se proporciona un compuesto de fórmula (I): o una sal farmacéuticamente aceptable del mismo. También se proporcionan procedimientos para la fabricación de un compuesto de fórmula 1, y el uso de un compuesto de fórmula 1 como un medicamento y en el tratamiento de cáncer.

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ACILAMINOPIRAZOLES COMO INHIBIDORES DE FGFR

La presente invención se refiere a derivados de pirazol, a un procedimiento para su preparación, a composiciones farmacéuticas que los contienen, a un procedimiento para preparar las composiciones farmacéuticas, y a su uso en terapia.

Las proteína cinasas son una clase de proteínas (enzimas) que regulan una variedad de funciones celulares. Esto se logra mediante la fosforilación de aminoácidos específicos sobre sustratos proteínicos, dando como resultado la alteracón conformacional de la proteína sustrato. El cambio conformacional modula la actividad del sustrato, o su capacidad para interactuar con otras parejas de unión. La actividad enzimática de la proteína cinasa se refiere a la velocidad a la que la cinasa añade grupos fosfato a un sustrato. Se puede medir, por ejemplo, determinando la cantidad de un sustrato que se convierte en un producto en función del tiempo. La fosforilación de un sustrato se produce en el sitio activo de una proteína cinasa.

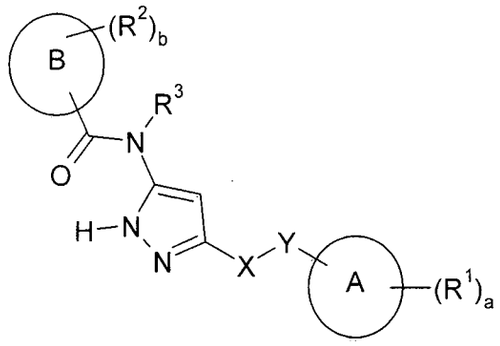
Las tirosina cinasas son un subconjunto de proteína cinasas que catalizan la transferencia del fosfato terminal de trifosfato de adenosina (ATP) a restos de tirosina sobre sustratos proteínicos. Estas cinasas desempeñan una parte importante en la propagación de la transducción de la señal del factor de crecimiento que conduce a la proliferación, diferenciación y migración celular.

El factor de crecimiento de fibroblastos (FGF) se ha reconocido como un mediador importante de muchos procesos fisiológicos, tales como la morfogénesis durante el desarrollo y angiogénesis. Actualmente hay alrededor de 25 miembros conocidos de la familia de FGF. La familia de receptores del factor de crecimiento de fibroblastos (FGFR) consiste en cuatro miembros, cada uno compuesto de un dominio de unión a ligando extracelular, un único dominio transmembránico y un dominio de tirosina cinasa proteínico citoplásmico intracelular. Al estimularlos con FGF, los FGFR se dimerizan y se transfosforilan, lo que da como resultado la activación del receptor. La activación de los receptores es suficiente para el reclutamiento y activación de parejas de señalización en dirección 3' específicas que participan en la regulación de diversos procesos, tales como el crecimiento celular, el metabolismo celular y la supervivencia celular (repasad en Eswarakumar, V.P. et. al., Cytokine & Growth Factor Reviews 2005, 16, p139-149). En consecuencia, el FGF y los FGFR tienen el potencial de iniciar y/o promover la tumorigénesis.

Ahora hay pruebas considerables que relacionan directamente la señalización de FGF con el cáncer humano. Se ha dado a conocer la gran expresión de diversos FGF en un

intervalo amplio de tipos de tumores, tales como de vejiga, de células renales y de próstata (entre otros). El FGF también se ha descrito como un factor angiogénico poderoso. También se ha dado a conocer la expresión de los FGFR en células endoteliales. Se han asociado mutaciones activantes de diversos FGFR con el cáncer de vejiga y el mieloma múltiple (entre otros), mientras que también se ha documentado la expresión de los receptores en el cáncer de próstata y de vejiga entre otros (revisado en Grose, R. et. al., Cytokine & Growth Factor Reviews 2005, 16, p179-186 y Kwabi-Addo, B. et. al., Endocrine-Related Cancer 2004, 11, p709-724). Por estas razones, el sistema de señalización de FGF es una diana terapéutica atractiva, particularmente puesto que las terapias dirigidas contra lo FGFR y/o la señalación de FGF pueden afectar tanto directamente a las células tumorales como a la angiogénesis del tumor.

Según la presente invención, se proporciona un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente aceptable del mismo

en la que

el anillo **A** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

el anillo **B** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

cada $\mathbf{R^1}$ representa independientemente

un halógeno,

un grupo hidroxilo,

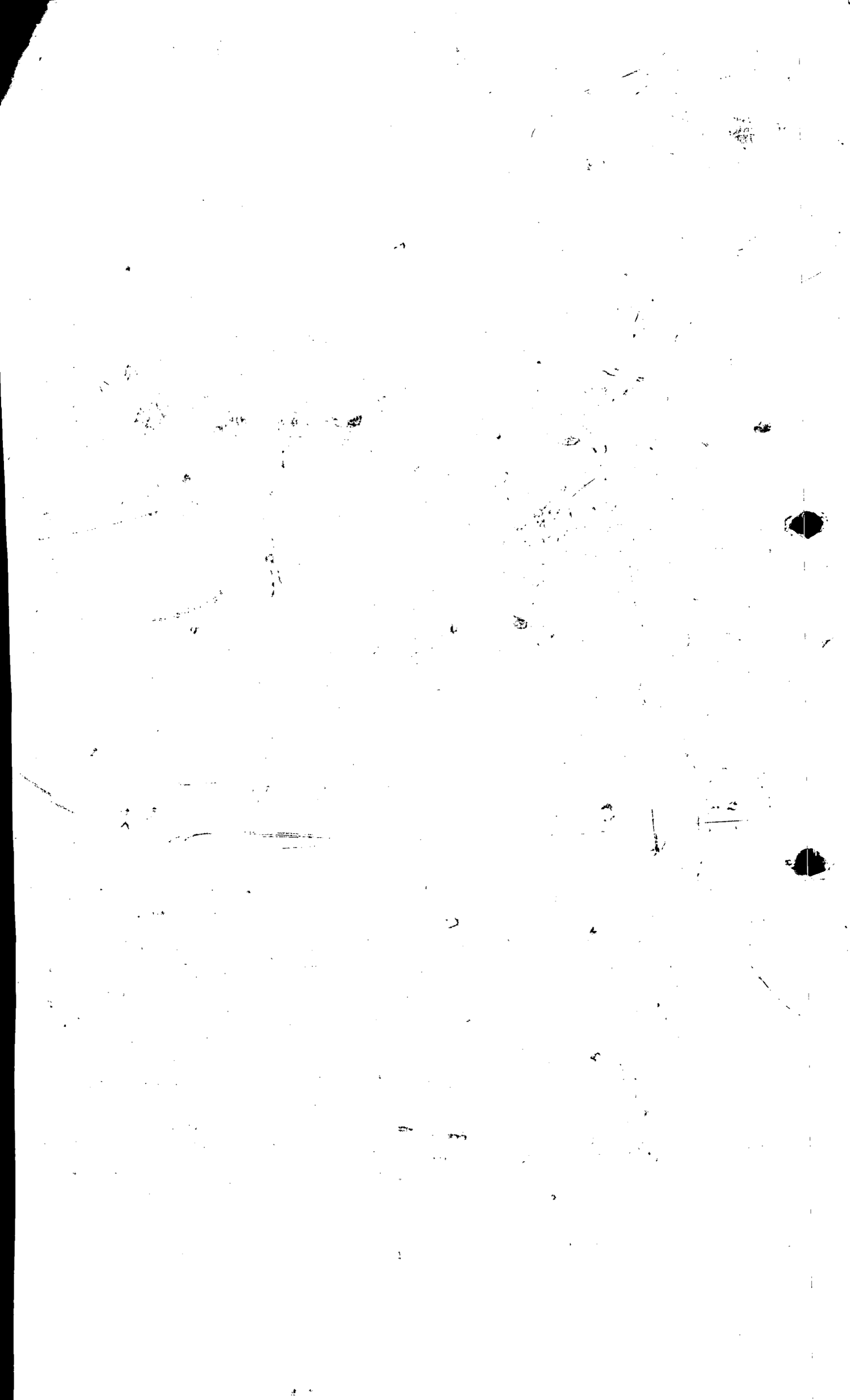
un grupo ciano,

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un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_{3-5} opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^6R^7$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^8R^9$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{10}R^{11}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{12}R^{13}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-

tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo $-NR^{16}R^{17}$,

un grupo $-OCOR^{18}$,

un grupo $-CO_2R^{19}$,

un grupo $-CONR^{20}R^{21}$,

un grupo $-NR^{22}COR^{23}$,

un grupo $-NR^{24}CO_2R^{25}$.

un grupo $-OSO_2R^{26}$,

o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada $\mathbf{R^2}$ representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo $-CO_2R^{29}$,

un grupo $-CONR^{30}R^{31}$,

un grupo $-NR^{32}COR^{33}$,

un grupo $-NR^{34}CO_2R^{35}$,

un grupo $-NR^{36}R^{37}$,

un grupo $-SO_2R^{38}$,

un grupo $-SO_2NR^{39}R^{40}$,

un grupo $-NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo,

un grupo cicloalquilo C_3-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{48}R^{49}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclico de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{50}R^{51}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más

sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{52}R^{53}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{54}R^{55}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros, y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o dos grupos R^2 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{66}R^{67}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{68}R^{69}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

a es 0, 1, 2, 3 ó 4;

b es 0, 1, 2, 3 ó 4;

R^4 y R^5 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^4 y R^5, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6;

R^6 y R^7 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^6 y R^7, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^8 y R^9 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^8 y R^9, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{10} y R^{11} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{10} y R^{11}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{12} y R^{13} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{12} y R^{13}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{14} y R^{15} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{14} y R^{15}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{16} y R^{17} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{16} y R^{17}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{18} representa alquilo C_1-C_4, o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{19} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{20} y R^{21} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{20} y R^{21}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{22} representa hidrógeno, alquil C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{23} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{24} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{25} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{26} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{27} y R^{28} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{27} y R^{28}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{29} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes

seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{30}}$ y $\mathbf{R^{31}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{30} y R^{31}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{32}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{33}}$ representa hidrógeno, alquilo C_1-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{34}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{35}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{36}}$ y $\mathbf{R^{37}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, o R^{36} y R^{37}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo y un grupo carbociclilo o heterociclilo de 4 a 7 miembros que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo);

$\mathbf{R^{38}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{39}}$ y $\mathbf{R^{40}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{39} y R^{40}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{41}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{42}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{43}}$ y $\mathbf{R^{44}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{43} y R^{44}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{45}}$ y $\mathbf{R^{46}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{45} y R^{46}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{47}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{48} y R^{49} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{48} y R^{49}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{50} y R^{51} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{50} y R^{51}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{52} y R^{53} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{52} y R^{53}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{54} y R^{55} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{54} y R^{55}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{56} y R^{57} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{56} y R^{57}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{58} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{59} y R^{60} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{59} y R^{60}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{61} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{62} y R^{63} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{62} y R^{63}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{64} y R^{65} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{64} y R^{65}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

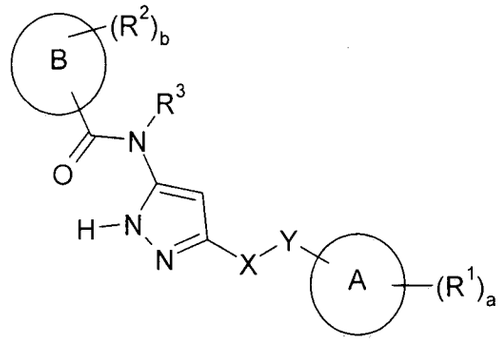
R^{66} y R^{67} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{66} y R^{67}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{68} y R^{69} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{68} y R^{69}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros; y en la que

cuando **Y** representa CH_2, **X** representa CH_2, O, NR^{70} o $S(O)_x$, en el que R^{70} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, y **x** es 0, 1 ó 2; o

cuando **X** representa CH_2, **Y** representa CH_2, O, NR^{71} o $S(O)_y$, en el que R^{71} respresenta hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, e **y** es 0, 1 ó 2.

Según la presente invención, se proporciona un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente aceptable del mismo

en la que

el anillo **A** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

el anillo **B** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

cada $\mathbf{R^1}$ representa independientemente

un halógeno,

un grupo hidroxilo,

un grupo ciano,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_{3-5} opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^6R^7$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^8R^9$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{10}R^{11}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{12}R^{13}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi

C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo –$NR^{16}R^{17}$,

un grupo –$OCOR^{18}$,

un grupo –CO_2R^{19},

un grupo –$CONR^{20}R^{21}$,

un grupo –$NR^{22}COR^{23}$,

un grupo –$NR^{24}CO_2R^{25}$,

un grupo –OSO_2R^{26},

o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, -$NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada $\mathbf{R^2}$ representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo -CO_2R^{29},

un grupo –$CONR^{30}R^{31}$,

un grupo –$NR^{32}COR^{33}$,

un grupo –$NR^{34}CO_2R^{35}$,

un grupo –$NR^{36}R^{37}$,

un grupo -SO_2R^{38},

un grupo -$SO_2NR^{39}R^{40}$,

un grupo –$NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente

sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo,

un grupo C_3-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{48}R^{49}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{50}R^{51}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-lamino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{52}R^{53}$, (cada uno de los cuales puede estar opcionalmente

sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{54}R^{55}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{59}R^{60}$, -SO_2R^{61} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, -$NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7

miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o dos grupos R^2 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{66}R^{67}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{68}R^{69}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

a es 0, 1, 2, 3 ó 4;

b es 0, 1, 2, 3 ó 4;

R^4 y **R^5** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^4 y R^5, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^6 y **R^7** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^6 y R^7, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^8 y R^9 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^8 y R^9, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{10} y R^{11} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{10} y R^{11}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{12} y R^{13} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{12} y R^{13}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{14} y R^{15} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{14} y R^{15}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{16} y R^{17} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{16} y R^{17}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{18} representa alquilo C_1-C_4, o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{19} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{20} y R^{21} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{20} y R^{21}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{22} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{23} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{24} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{25} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{26} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{27} y R^{28} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{27} y R^{28}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{29} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{30} y R^{31} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{30} y R^{31}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{32}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{33}}$ representa hidrógeno, alquilo C_1-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{34}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{35}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{36}}$ y $\mathbf{R^{37}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4, cicloalquilo C_3-C_6 o a un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, o R^{36} y R^{37}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo y un grupo carbociclilo o heterociclilo de 4 a 7 miembros que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo);

R^{38} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{39} y R^{40} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{39} y R^{40}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{41} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{42} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{43} y R^{44} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{43} y R^{44}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{45} y R^{46} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{45} y R^{46}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{47} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{48} y R^{49} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{48} y R^{49}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{50} y R^{51} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{50} y R^{51}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{52} y R^{53} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{52} y R^{53}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{54} y R^{55} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{54} y R^{55}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{56} y R^{57} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{56} y R^{57}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{58} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{59} y R^{60} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{59} y R^{60}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{61} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{62} y R^{63} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{62} y R^{63}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{64} y R^{65} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{64} y R^{65}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{66} y R^{67} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{66} y R^{67}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{68} y R^{69} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{68} y R^{69}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros; y en la que

cuando **Y** representa CH_2, **X** representa CH_2, O, NR^{70} o $S(O)_X$, en el que R^{70} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, y **x** es 0, 1 ó 2; o

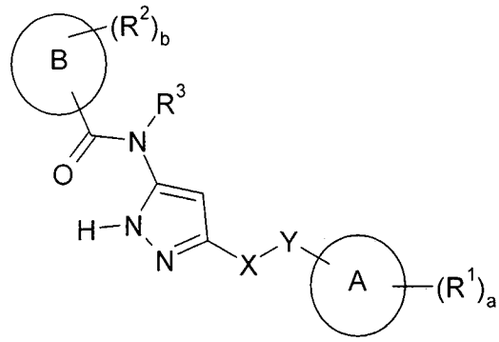
cuando **X** representa CH_2, **Y** representa CH_2, O, NR^{71} o $S(O)_y$, en el que R^{71} respresenta hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, e **y** es 0, 1 ó 2; y

con la condición de que el compuesto no sea

4-benzamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,

6-anilino-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
N-[5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-il]carbamato de prop-2-enilo,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-6-pirazol-1-il-piridin-3-carboxamida, o 6-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-3-carboxilato de metilo.

Según un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente aceptable del mismo

en la que

el anillo **A** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

el anillo **B** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

cada $\mathbf{R^1}$ representa independientemente

un halógeno,

un grupo hidroxilo,

un grupo ciano,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y

di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_{3-5} opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^6R^7$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^8R^9$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3 alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{10}R^{11}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{12}R^{13}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi

C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo –$NR^{16}R^{17}$,

un grupo –$OCOR^{18}$,

un grupo –CO_2R^{19},

un grupo –$CONR^{20}R^{21}$,

un grupo –$NR^{22}COR^{23}$,

un grupo –$NR^{24}CO_2R^{25}$,

un grupo –OSO_2R^{26},

o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, -$NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada **R^2** representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo –CO_2R^{29},

un grupo –$CONR^{30}R^{31}$,

un grupo –$NR^{32}COR^{33}$,

un grupo –$NR^{34}CO_2R^{35}$,

un grupo –$NR^{36}R^{37}$,

un grupo –SO_2R^{38},

un grupo –$SO_2NR^{39}R^{40}$,

un grupo –$NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente

sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo,

un grupo cicloalquilo C_3-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{48}R^{49}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{50}R^{51}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{52}R^{53}$, (cada uno de los cuales puede estar opcionalmente

sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{54}R^{55}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{59}R^{60}$, -SO_2R^{61} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, -$NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes

seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o dos grupos R^2 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, -$NR^{66}R^{67}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, -$NR^{68}R^{69}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

a es 0, 1, 2, 3 ó 4;

b es 0, 1, 2, 3 ó 4;

R^4 y **R^5** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^4 y R^5, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^6 y **R^7** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^6 y R^7, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^8 y R^9 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^8 y R^9, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{10} y R^{11} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{10} y R^{11}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{12} y R^{13} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{12} y R^{13}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{14} y R^{15} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{14} y R^{15}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{16} y R^{17} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{16} y R^{17}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{18} representa alquilo C_1-C_4, o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{19} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{20} y R^{21} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{20} y R^{21}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{22} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{23} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{24} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{25} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{26} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{27} y R^{28} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{27} y R^{28}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{29} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{30} y R^{31} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{30} y R^{31}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{32}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{33}}$ representa hidrógeno, alquilo C_1-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{34}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{35}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{36}}$ y $\mathbf{R^{37}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, o R^{36} y R^{37}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo y un grupo carbociclilo o heterociclilo de 4 a 7 miembros que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo);

R^{38} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{39} y R^{40} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{39} y R^{40}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{41} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{42} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{43} y R^{44} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{43} y R^{44}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{45} y R^{46} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{45} y R^{46}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{47} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{48} y R^{49} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{48} y R^{49}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{50} y R^{51} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{50} y R^{51}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{52}}$ y $\mathbf{R^{53}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{52} y R^{53}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{54}}$ y $\mathbf{R^{55}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{54} y R^{55}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{56}}$ y $\mathbf{R^{57}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{56} y R^{57}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{58}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

$\mathbf{R^{59}}$ y $\mathbf{R^{60}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{59} y R^{60}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{61}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

$\mathbf{R^{62}}$ y $\mathbf{R^{63}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{62} y R^{63}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{64}}$ y $\mathbf{R^{65}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{64} y R^{65}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

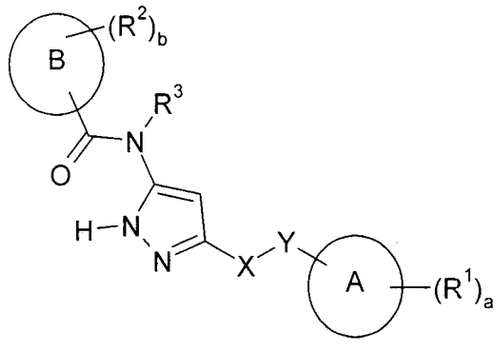
$\mathbf{R^{66}}$ y $\mathbf{R^{67}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{66} y R^{67}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{68}}$ y $\mathbf{R^{69}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{68} y R^{69}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros; y en la que

cuando **Y** representa CH_2, **X** representa CH_2, O, NR^{70} o $S(O)_X$, en el que R^{70} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, y **x** es 0, 1 ó 2; o

cuando **X** representa CH_2, **Y** representa CH_2, O, NR^{71} o $S(O)_y$, en el que R^{71} respresentas hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, e **y** es 0, 1 ó 2.

Según un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente aceptable del mismo

en la que

el anillo **A** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

el anillo **B** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

cada $\mathbf{R^1}$ representa uno independientemente

un halógeno,

un grupo hidroxilo,

un grupo ciano,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_{3-5} opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^6R^7$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$),

mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^8R^9$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{10}R^{11}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{12}R^{13}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo $-NR^{16}R^{17}$,

un grupo $-OCOR^{18}$,

un grupo $-CO_2R^{19}$,

un grupo $-CONR^{20}R^{21}$,

un grupo $-NR^{22}COR^{23}$,

un grupo $-NR^{24}CO_2R^{25}$,

un grupo $-OSO_2R^{26}$,

o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada $\mathbf{R^2}$ representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo $-CO_2R^{29}$,

un grupo $-CONR^{30}R^{31}$,

un grupo $-NR^{32}COR^{33}$,

un grupo $-NR^{34}CO_2R^{35}$,

un grupo $-NR^{36}R^{37}$,

un grupo $-SO_2R^{38}$,

un grupo $-SO_2NR^{39}R^{40}$,

un grupo $-NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo

C_3-C_6, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{45}R^{46}$, -CO_2R^{47} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_3-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{48}R^{49}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{50}R^{51}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{52}R^{53}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{54}R^{55}$ (cada uno de los

cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o dos grupos R^2 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{66}R^{67}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{68}R^{69}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

a es 0, 1, 2, 3 ó 4;

b es 0, 1, 2, 3 ó 4;

R^4 y R^5 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^4 y R^5, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^6 y R^7 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^6 y R^7, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^8 y R^9 representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^8 y R^9, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{10} y R^{11} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{10} y R^{11}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{12} y R^{13} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{12} y R^{13}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{14} y R^{15} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{14} y R^{15}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{16} y R^{17} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{16} y R^{17}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{18} representa alquilo C_1-C_4, o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{19} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{20} y R^{21} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{20} y R^{21}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{22} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{23} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{24}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{25}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{26}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{27}}$ y $\mathbf{R^{28}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{27} y R^{28}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

$\mathbf{R^{29}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{30}}$ y $\mathbf{R^{31}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{30} y R^{31}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{32}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{33} representa hidrógeno, alquilo C_1-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{34} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{35} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{36} y R^{37} representan cada uno independientemente hidrógeno, alquilo C_1-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, o R^{36} y R^{37}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo y un grupo arilo de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre);

R^{38} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{39} y R^{40} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{39} y R^{40}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{41} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{42} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{43} y R^{44} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{43} y R^{44}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{45} y R^{46} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{45} y R^{46}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{47} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{48} y R^{49} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{48} y R^{49}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{50} y R^{51} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{50} y R^{51}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{52} y R^{53} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{52} y R^{53}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{54} y R^{55} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{54} y R^{55}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{56} y R^{57} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{56} y R^{57}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{58} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{59} y R^{60} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{59} y R^{60}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{61} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{62} y R^{63} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{62} y R^{63}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{64} y R^{65} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{64} y R^{65}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{66} y R^{67} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{66} y R^{67}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros;

R^{68} y R^{69} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{68} y R^{69}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclo saturado de 4 a 6 miembros; y en la que

cuando **Y** representa CH_2, **X** representa CH_2, O, NR^{70} o $S(O)_X$, en el que R^{70} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, y **x** es 0, 1 ó 2; o

cuando **X** representa CH_2, **Y** representa CH_2, O, NR^{71} o $S(O)_y$, en el que R^{71} respresenta hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, e **y** es 0, 1 ó 2.

En el contexto de la presente memoria descriptiva, excepto que se indique de otro modo, el término "alquilo" incluye grupos alquilo tanto de cadena lineal como ramificada, pero las referencias a grupos individuales, tal como "*n*-propilo", son específicas para la versión lineal solamente, y las referencias a versiones de cadena ramificada individuales, por ejemplo "*i*-propilo", son específicas para la versión ramificada solamente. Se aplica una convención similar a otros radicales.

Por ejemplo, ejemplos de "alquilo C_1-C_6" y "alquilo C_1-C_4" incluyen metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, *i*-butilo y *t*-butilo. Ejemplos de "alcoxi C_1-C_6" y "alcoxi C_1-C_3" incluyen metoxi, etoxi, *n*-propoxi e *i*-propoxi. Ejemplos de "alquenilo C_2-C_6" incluyen vinilo, alilo y 1-propenilo. Ejemplos de "cicloalquilo C_3-C_6" incluyen ciclopropilo, ciclopentilo y ciclohexilo. Ejemplos de "mono- y di-alquil C_1-C_6-amino" incluyen metilamino,

dimetilamino, etilamino, dietilamino y etilmetilamino. Ejemplos de "alquil C_1-C_6-tio" incluyen metiltio, etiltio y propiltio.

Ejemplos de halógeno incluyen flúor, cloro, bromo y yodo.

Un "grupo carbociclilo de 4 a 7 miembros", excepto que se establezca de otro modo, incluye anillos monocíclicos, saturados y completa o parcialmente insaturados, que tienen 4, 5, 6 ó 7 átomos de carbono. Un "grupo carbociclilo de 4 a 7 miembros" incluye los grupos tales como cicloalquilo C_4-C_7, cicloalquenilo C_4-C_7 y arilo C_6.

Un "grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre" o "grupo arilo de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre" es un anillo monocíclico aromático, completamente insaturado, que contiene 5 ó 6 átomos, de los cuales al menos uno es un heteroátomo seleccionado de nitrógeno, oxígeno y azufre, que puede estar, excepto que se especifique de otro modo, enlazado por carbono o nitrógeno. De forma adecuada, un "anillo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre" es un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo y triazolilo.

Un "grupo heterociclilo de 4 a 7 miembros", excepto que se establezca de otro modo, incluye anillos monocíclicos, saturados y completa o parcialmente insaturados, que tienen 4, 5, 6 ó 7 átomos, de los cuales al menos uno es un heteroátomo seleccionado de nitrógeno, oxígeno y azufre, y que puede estar, excepto que se especifique de otro modo, enlazado por carbono o nitrógeno. Un "grupo heterociclilo de 4 a 7 miembros" adecuado, que puede comprender al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre incluye azetidina, *gamma*-butirolactona, diazepina, dioxolano, dioxano, dihidro-oxazina, dihidrotiofeno, ditiolano, furano, hexahidroazepina, imidazol, imidazolina, imidazolidina, isotiazol, isoxazol, morfolina, oxadiazol, oxazina, oxazol, oxetano, piperidina, piperazina, *alpha*-pirano, *gamma*-pirano, pirazina, pirazolidina, pirazol, pirazolina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolina, tetrahidrofurano, tetrahidrofuranona, tetrahidropirano, tetrazina, tetrazol, tiadiazol, tiazol, tiolano, tiomorfolina, S,S-dióxido de tiomorfolina, tiofeno y triazina.

Cuando R^4 y R^5, o R^6 y R^7, o R^8 y R^9, o R^{10} y R^{11}, o R^{12} y R^{13}, o R^{14} y R^{15}, o R^{27} y R^{28}, o R^{43} y R^{44}, o R^{45} y R^{46}, o R^{48} y R^{49}, o R^{50} y R^{51}, o R^{52} y R^{53}, o R^{54} y R^{55}, o R^{56} y R^{57}, o R^{59} y R^{60}, o R^{62} y R^{63}, o R^{64} y R^{65}, o R^{66} y R^{67}, o R^{68} y R^{69} representan un heterociclo saturado de 4 a 6 miembros, se debe entender que, cuando sólo está presente un heteroátomo, éste es el átomo de nitrógeno al que están unidos R^4 y R^5, o R^6 y R^7, o R^8 y R^9, o R^{10} y R^{11}, o R^{12} y R^{13}, o R^{14} y R^{15}, o R^{27} y R^{28}, o R^{43} y R^{44}, o R^{45} y R^{46}, o R^{48} y R^{49}, o R^{50} y R^{51}, o R^{52} y R^{53}, o R^{54} y R^{55}, o R^{56} y R^{57}, o R^{59} y R^{60}, o R^{62} y R^{63}, o R^{64} y R^{65}, o R^{66} y R^{67}, o R^{68} y R^{69}. El "heterociclo saturado de 4 a 6 miembros", excepto que se establezca de otro modo, incluye anillos monocíclicos saturados que contienen 4, 5 ó 6 átomos en los que al menos un átomo es nitrógeno y los otros átomos se seleccionan de carbono, nitrógeno, oxígeno y azufre. Un "heterociclo saturado de 4 a 6 miembros" adecuado incluye pirrolidina, pirazolidina, imidazolidina, piperidina, piperazina, morfolina, tiomorfolina y S,S-dióxido de tiomorfolina.

Un "grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros", excepto que se establezca de otro modo, incluye anillos monocíclicos o bicíclicos, saturados y completa o parcialmente insaturados, conteniendo cada anillo 4, 5, 6 ó 7 átomos, y al menos un átomo anular de un anillo es un heteroátomo seleccionado de nitrógeno, oxígeno y azufre, y que puede estar, excepto que se especifique de otro modo, enlazado por carbono o nitrógeno. Un "grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros" adecuado, que puede comprender al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, incluye azetidina, benzofurano, bencimidazol, benzotiofeno, *gamma*-butirolactona, diazepina, dioxolano, dioxano, dihidro-oxazina, dihidrotiofeno, ditiolano, furano, hexahidroazepina, imidazol, imidazolina, imidazolidina, indazol, indol, isotiazol, isoxazol, morfolina, oxadiazol, oxazina, oxazol, oxetano, piperidina, piperazina, *alpha*-pirano, *gamma*-pirano, pirazina, pirazolidina, pirazol, pirazolina, piridazina, piridina, pirimidina, pirrol, pirrolidina, pirrolina, quinazolina, quinolina, tetrahidrofurano, tetrahidrofuranona, tetrahidropirano, tetrahidroquinolina, tetrazina, tetrazol, tiadiazol, tiazol, tiolano, tiomorfolina, S,S-dióxido de tiomorfolina, tiofeno y triazina.

Para evitar dudas, cuando se indica que los sustituyentes pueden tener sustituyentes adicionales, por ejemplo en las definiciones de expresiones tales como "un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, -NR^4R^5 (cada uno de los cuales puede estar opcionalmente

sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo)", se entiende que los átomos, tales como átomos de carbono que pueden ser capaces de llevar opcionalmente sustituyentes por sustitución de radicales hidrógeno, en los grupos alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio y -NR^4R^5 (independientemente de cualesquiera sustituyentes adicionales definidos en las definiciones de R^4 o R^5) pueden estar sustituidos con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo. Por ejemplo, R^4 o R^5 también puede estar sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo.

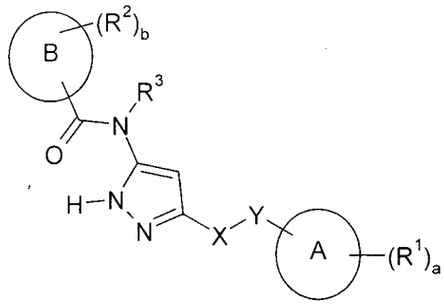
Una sal farmacéuticamente aceptable adecuada de un compuesto de la invención es, por ejemplo, una sal de adición de ácidos de un compuesto de la invención que es suficientemente básica, por ejemplo, una sal de adición de ácidos con, por ejemplo, un ácido inorgánico u orgánico, por ejemplo ácido clorhídrico, bromhídrico, sulfúrico, fosfórico, trifluoroacético, cítrico o maleico. Además, una sal farmacéuticamente aceptable adecuada de un compuesto de la invención que sea suficientemente ácida es una sal de metal alcalino, por ejemplo una sal sódica o potásica, una sal de metal alcalino-térreo, por ejemplo una sal de calcio o de magnesio, una sal de amonio o una sal con una base orgánica que produce un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Un éster hidrolizable *in vivo* de un compuesto de la fórmula **(I)** que contiene un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo del ser humano o del animal para producir el ácido o alcohol progenitor. Los ésteres adecuados farmacéuticamente aceptables para carboxi incluyen ésteres alcoxi C_{1-6} metílicos, por ejemplo metoximetilo, ésteres alcanoil C_{1-6}-oximetílicos, por ejemplo pivaloiloximetilo, ésteres ftalidílicos, ésteres cicloalcoxi C_{3-8}-carboniloxi-alquílicos C_{1-6}, por ejemplo 1-ciclohexilcarboniloxietilo, ésteres 1,3-dioxolen-2-onilmetílicos, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo, y ésteres alcoxi C_{1-6}-carboniloxietílicos, por ejemplo 1-metoxi-carboniloxietilo, y se pueden formar en cualquier grupo carboxi en los compuestos de esta invención.

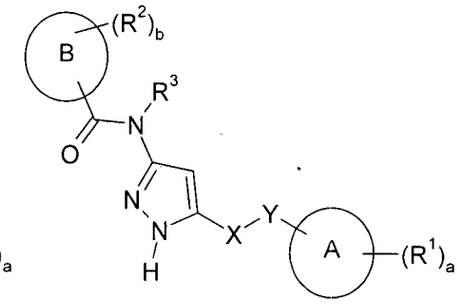
Un éster hidrolizable *in vivo* de un compuesto de la fórmula **(I)** que contiene un grupo hidroxi incluye ésteres inorgánicos tales como ésteres de fosfato y éteres α-aciloxialquílicos, y compuestos relacionados que, como resultado de la hidrólisis *in vivo* del éster, se rompen para dar el grupo hidroxi progenitor. Los ejemplos de éteres α-aciloxialquílicos incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos formadores de ésteres hidrolizables *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo, y benzoilo y fenilacetilo sustituidos, alcoxicarbonilo (para dar ésteres de carbonato de alquilo), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para dar carbamatos), dialquilaminoacetilo y carboxiacetilo. Los ejemplos de sustituyentes en el benzoilo incluyen morfolino y piperazino enlazados a partir de un átomo de nitrógeno anular vía un grupo metilénico a la posición 3 ó 4 del anillo benzoílico.

Algunos compuestos de la fórmula **(I)** pueden tener centros quirales y/o centros isómeros geométricos (isómeros E y Z), y se entenderá que la invención engloba todos los citados isómeros ópticos, diastereoisómeros e isómeros geométricos que posean actividad inhibidora de FGFR.

La invención se refiere a cualquiera y a todas las formas tautómeras de los compuestos de la fórmula **(I)** que posean actividad inhibidora de FGFR. Por ejemplo, el compuesto de fórmula (IA) es un tautómero del compuesto de fórmula (I).



(I)



(IA)

También se entenderá que ciertos compuestos de la fórmula **(I)** pueden existir en formas solvatadas así como no solvatadas, tales como, por ejemplo, formas hidratadas. Se entenderá que la invención engloba todas las citadas formas solvatadas que posean actividad inhibidora de FGFR.

Los valores particulares de grupos variables son los siguientes. Tales valores se pueden usar, cuando sea apropiado, con cualquiera de las definiciones, reivindicaciones o

realizaciones definidas aquí anteriormente o aquí en lo siguiente.

En otra realización de la invención, A representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo.

En otra realización de la invención, A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo.

En otra realización de la invención, A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo.

En otra realización de la invención, A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, o pirimidinilo.

En otro aspecto de la invención, A representa un anillo furilo, fenilo, piridilo o pirimidinilo.

En otro aspecto de la invención, A representa un anillo furilo, fenilo o piridilo.

En otro aspecto de la invención, A representa un anillo furilo o fenilo.

En otro aspecto de la invención, A representa un anillo fenilo.

En otra realización de la invención, B representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo.

En otra realización de la invención, B representa un anillo furilo, isotiazolilo, isoxazolilo, oxadiazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo o tienilo.

En otra realización de la invención, B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo.

En otra realización de la invención, B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo.

En otra realización de la invención, B representa un anillo fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo o pirimidinilo.

En otra realización de la invención, B representa un anillo fenilo, pirazinilo, piridilo, tienilo o pirimidinilo.

En otro aspecto de la invención, B representa un anillo piridilo, pirimidinilo o fenilo.

En otra realización de la invención, B representa un anillo fenilo, pirazinilo, tienilo o pirimidinilo.

En otro aspecto de la invención, B representa un anillo fenilo.

En una realización de la invención, cada R^1 representa independientemente un halógeno; un grupo hidroxilo; un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo $-CONR^{20}R^{21}$.

En otra realización de la invención, cada R^1 representa independientemente un halógeno; un grupo hidroxilo; un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; un grupo $-CONR^{20}R^{21}$; o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otra realización de la invención, cada R^1 representa independientemente un halógeno; un grupo hidroxilo; un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$ (cada uno de los

cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo –$CONR^{20}R^{21}$.

En otra realización de la invención, cada R^1 representa independientemente un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, -$NR^{14}R^{15}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otra realización de la invención, cada R^1 representa independientemente un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de metoxi, -$N(Me)_2$ e hidroxilo.

En otro aspecto adicional de la invención, cada R^1 representa independientemente un grupo -$CONR^{20}R^{21}$.

En otro aspecto adicional de la invención, cada R^1 representa independientemente un grupo metoxi; -OCH_2CH_2OMe; -CH_2NMe_2 o dos grupos R^1 adyacentes forman juntos un puente -OCH_2O-.

En otro aspecto adicional de la invención, cada R^1 representa independientemente un grupo hidroxilo; -$CONH_2$; –CONHMe; -$CONMe_2$ o un grupo metoxi.

En otro aspecto adicional de la invención, cada R^1 representa independientemente -CONHMe o un grupo metoxi.

En otro aspecto adicional de la invención, R^1 representa –CONHMe.

En otro aspecto adicional de la invención, R^1 representa metoxi.

En otra realización de la invención, cada R^2 representa independientemente un grupo -$NR^{36}R^{37}$; un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un

grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otra realización de la invención, cada R^2 representa independientemente un grupo $-NR^{36}R^{37}$; un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$),

mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otro aspecto de la invención, cada R^2 representa independientemente un grupo hidroxilo; un halógeno; un grupo ciano; un grupo $-CO_2R^{29}$; un grupo $-CONR^{30}R^{31}$; un grupo

$-NR^{32}COR^{33}$; un grupo $-NR^{34}CO_2R^{35}$; un grupo $-NR^{36}R^{37}$; un grupo $-SO_2R^{38}$; un grupo $-SO_2NR^{39}R^{40}$; un grupo $-NR^{41}SO_2R^{42}$; un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo; un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo

heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otro aspecto de la invención, cada R^2 representa independientemente un grupo hidroxilo; un halógeno; un grupo ciano; un grupo $-CO_2R^{29}$; un grupo $-CONR^{30}R^{31}$; un grupo $-NR^{32}COR^{33}$; un grupo $-NR^{34}CO_2R^{35}$; un grupo $-NR^{36}R^{37}$; un grupo $-SO_2R^{38}$; un grupo $-SO_2NR^{39}R^{40}$; un grupo $-NR^{41}SO_2R^{42}$; un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo; un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más

sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

En otro aspecto de la invención, cada R^2 representa independientemente un grupo $-NR^{36}R^{37}$; un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de $-NR^{43}R^{44}$ (que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y morfolino, piperidina o piperazina opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), y morfolino, piperidina o piperazina opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo; o morfolina, piperidina o piperazina opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno

o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

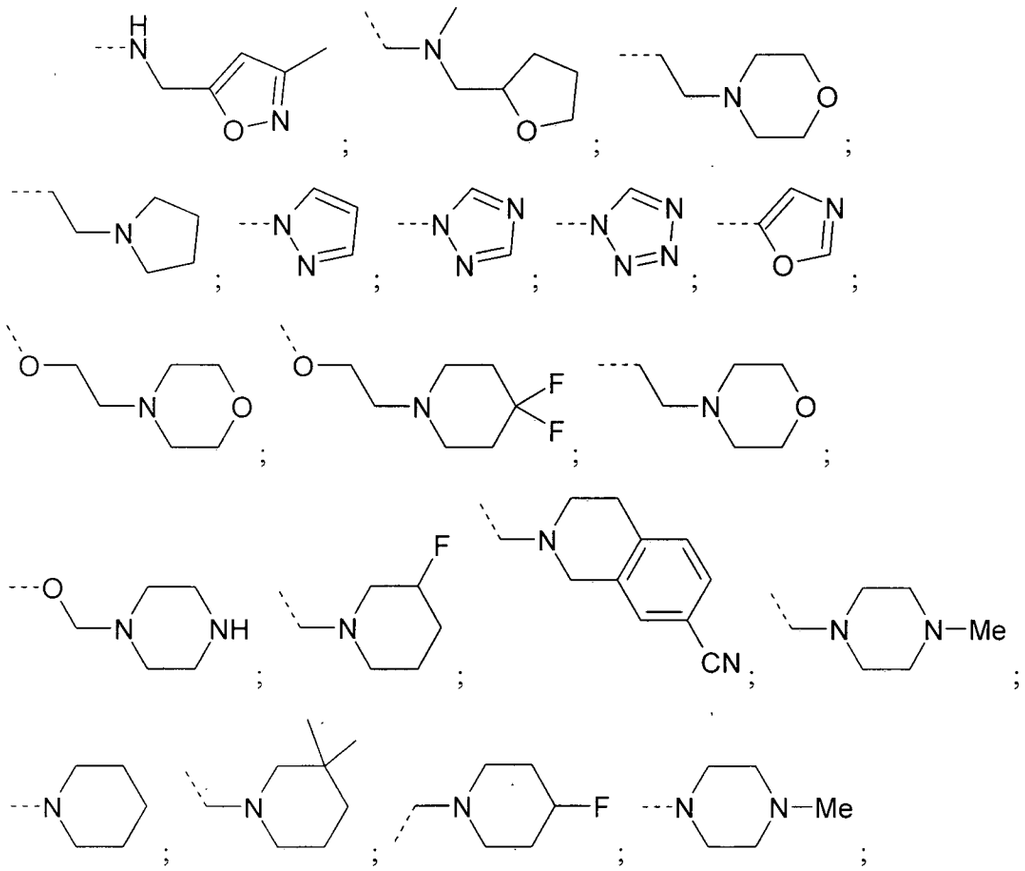
En otro aspecto de la invención, cada R^2 representa independientemente un grupo metilo o metoxi opcionalmente sustituido con un grupo morfolina, piperidina o piperazina cada uno opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo.

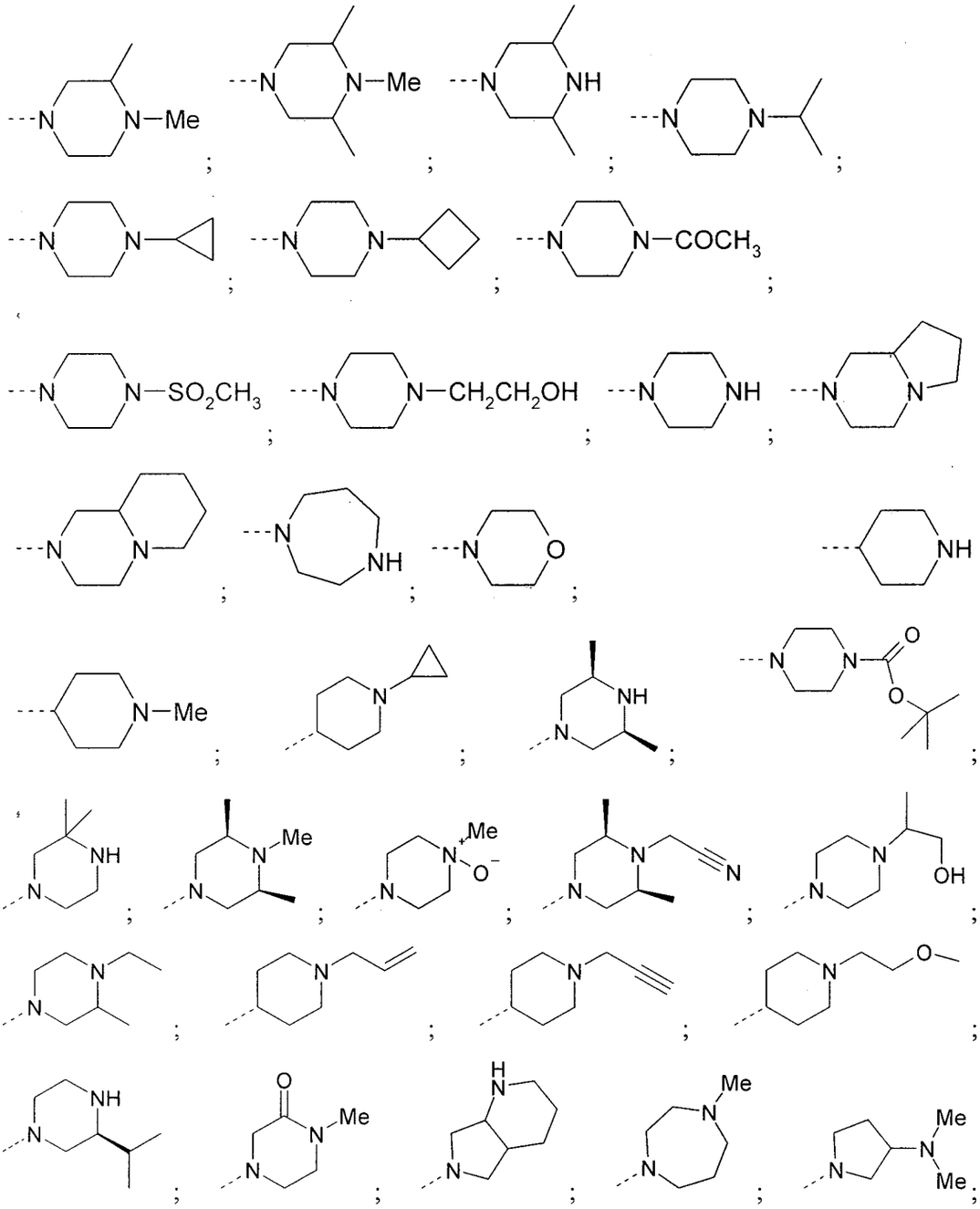
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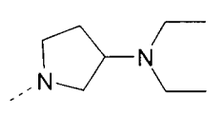
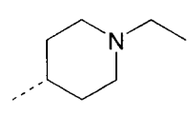
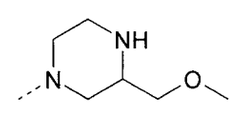
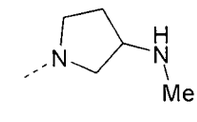
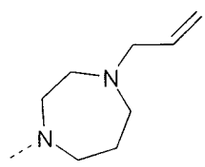
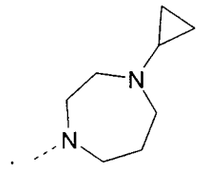
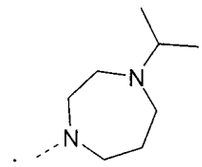
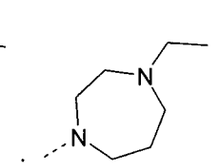
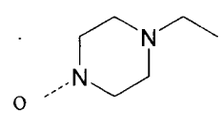
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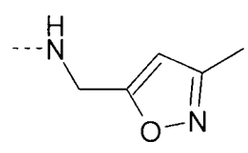
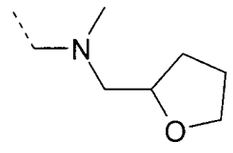
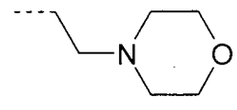
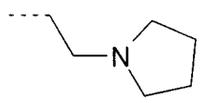
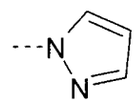
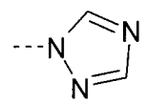
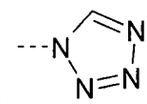
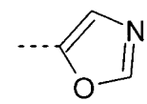
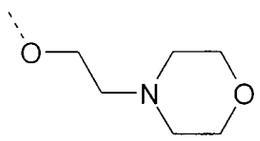
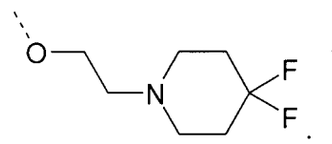
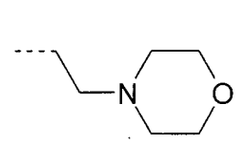
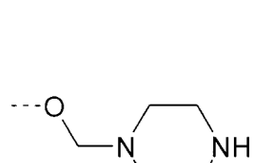
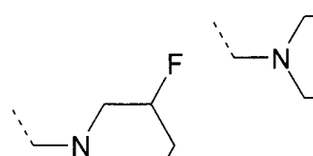
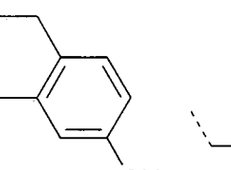
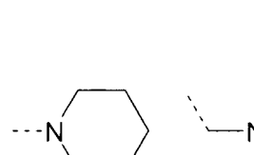
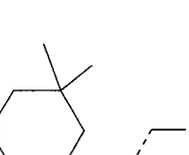
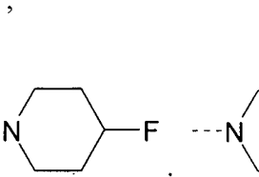
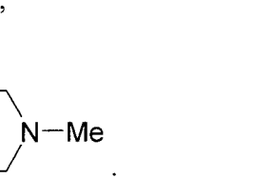
En otro aspecto de la invención, cada R^2 representa independientemente un grupo –Cl; -F; -I; -OH; -CN; $-CH_3$; $-CH_2OH$; $-CH_2N(CH_3)_2$; $-CH_2CH(CH_3)NH_2$; $-OCH_3$; $-OCH_2CH_2OH$; $-OCH_2CH_2OCH_2CH_3$; $-SO_2CH_3$; $-N(CH_3)_2$; -NHPh; $-NHCH_2C{\equiv}CH$; $-NHCH_2CH_3$; $-NHCH_2CH_2N(CH_3)_2$; $-NHCO_2CH_2CH{=}CH_2$; $-NHCOCH_3$; -NHCOH; -NHCOPh; $-CONH_2$; $-NHSO_2Me$; $-SO_2N(CH_3)_2$; $-CO_2H$; $-CO_2CH_3$; $-CO_2CH_2CH_3$;






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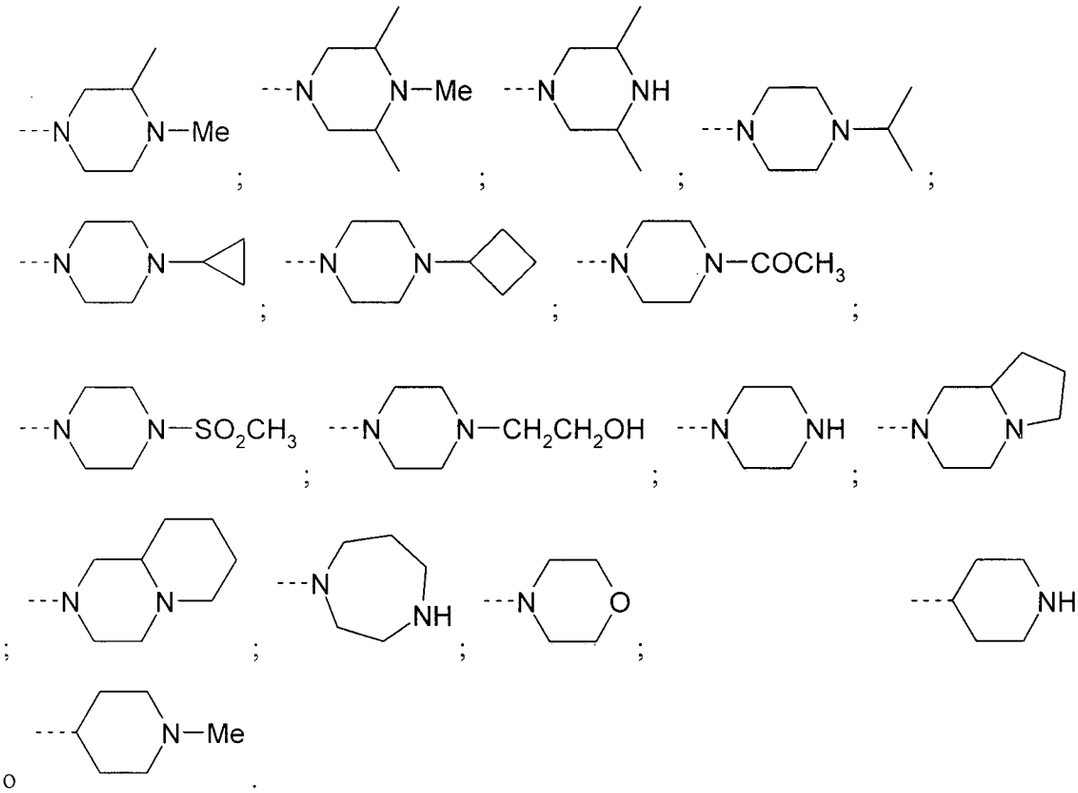

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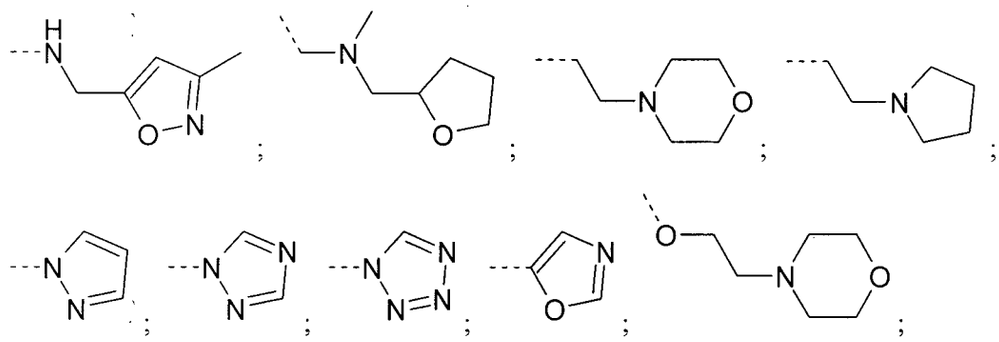
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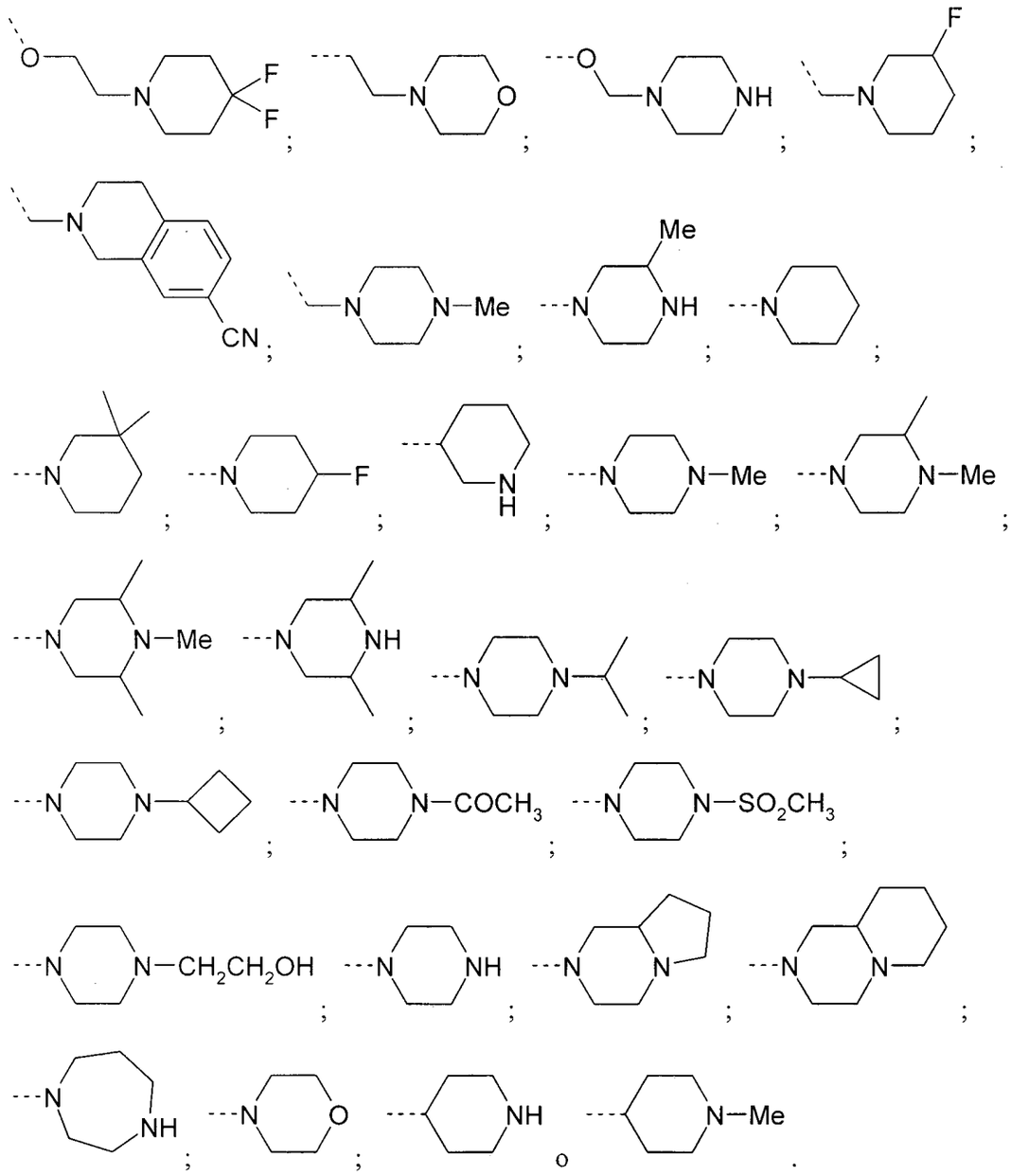
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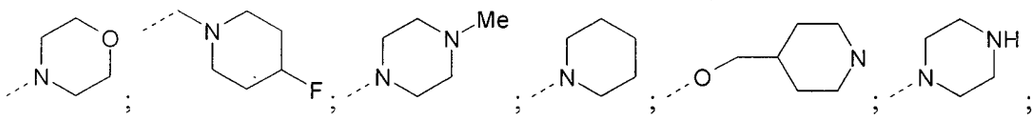


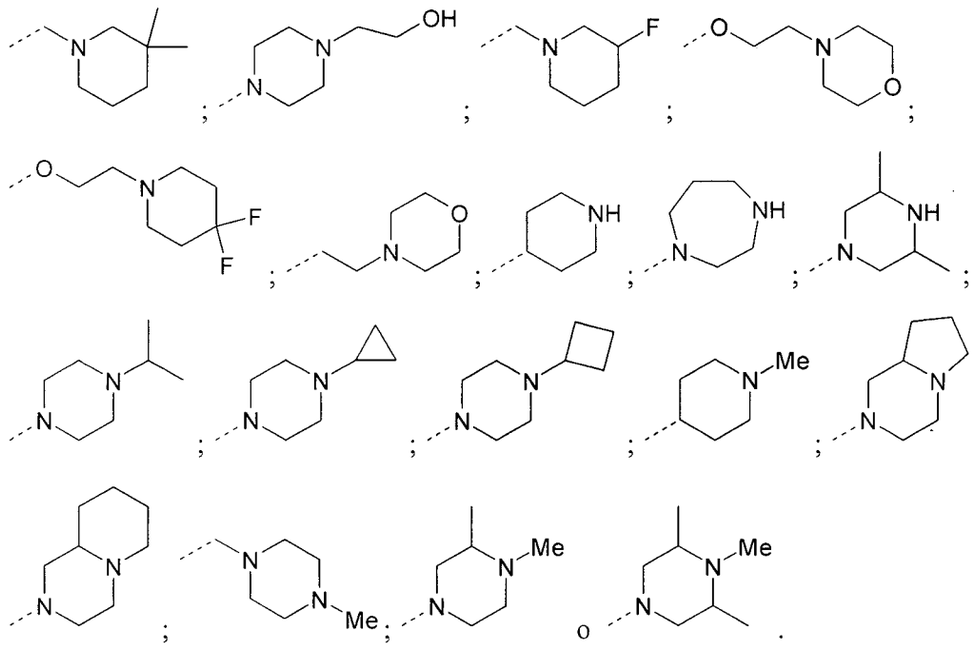
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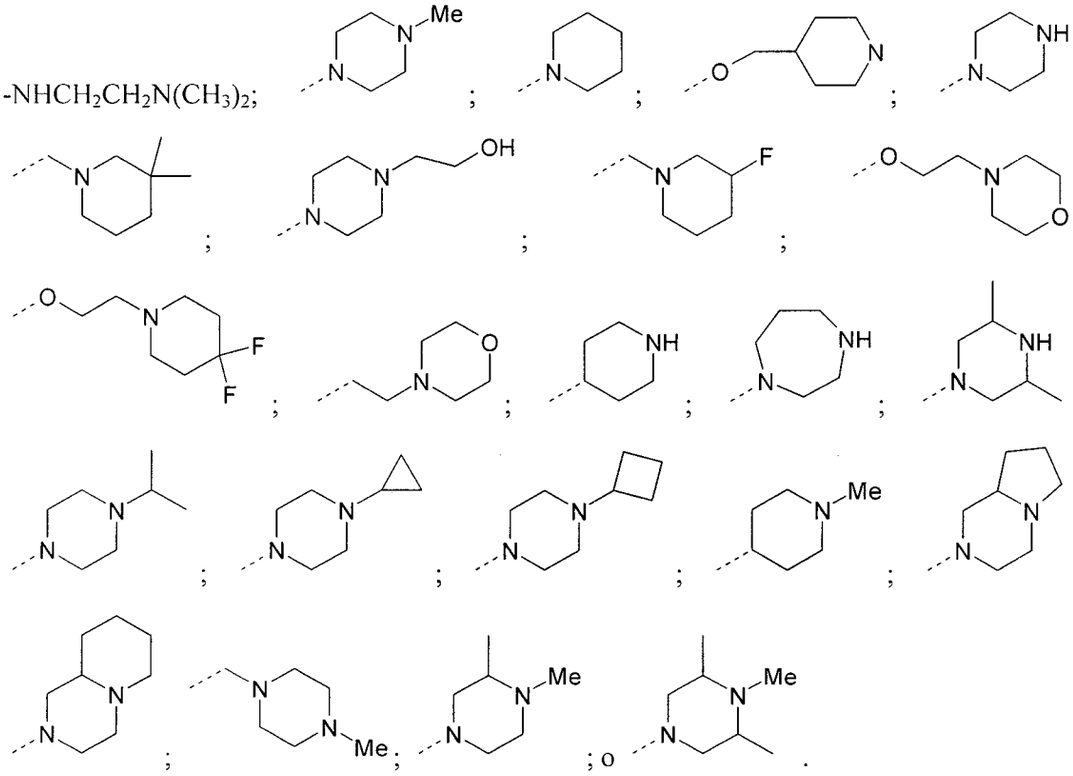


En otro aspecto de la invención, cada R^2 representa independientemente un grupo -OMe; $-OCH_2CH_2OCH_2CH_3$; $-OCH_2CH_2OH$; $-CH_2N(CH_3)_2$; $-NHCH_2CH_2N(CH_3)_2$;

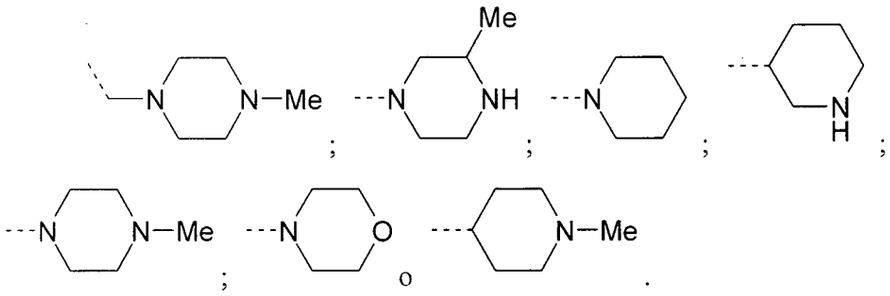




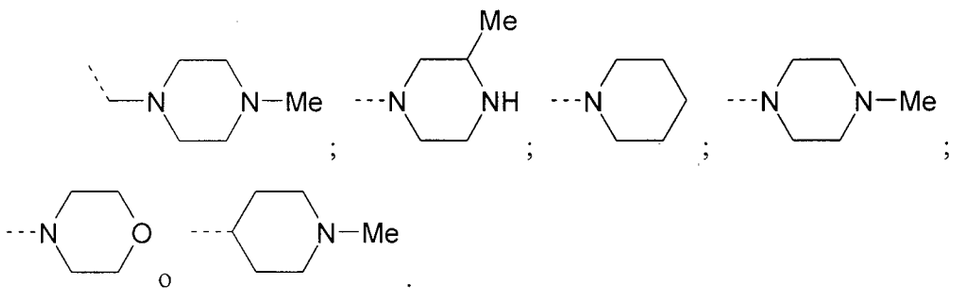
En otro aspecto de la invención, cada R^2 representa independientemente un grupo $-NHCH_2CH_2N(CH_3)_2$;



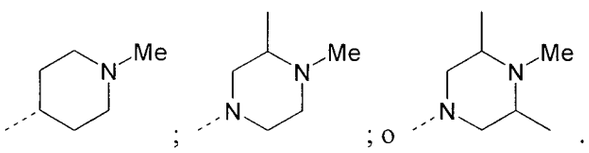
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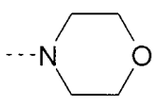
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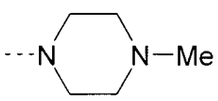
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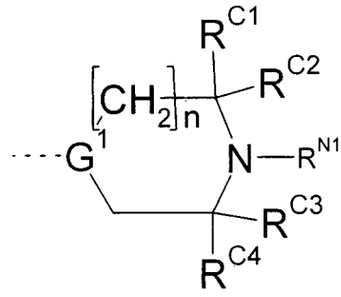
En otro aspecto de la invención, R^2 representa un grupo



En otro aspecto de la invención, R^2 representa un grupo



En otro aspecto de la invención, R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3 alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

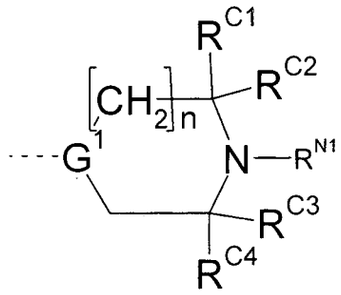
R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de ciano, halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, -$NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo.

En otro aspecto de la invención, R^2 representa independientemente



en la que

G^1 es C o N,

n es 1 ó 2,

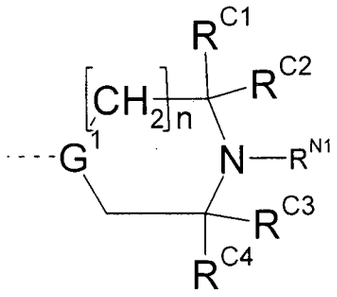
R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico de 3 a 5 miembros, y

R^{N1} se selecciona de alquilo C_1-C_2, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo) e hidrógeno, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros.

En otro aspecto de la invención, R^2 representa independientemente



en la que

G^1 es C o N,

n es 1 ó 2,

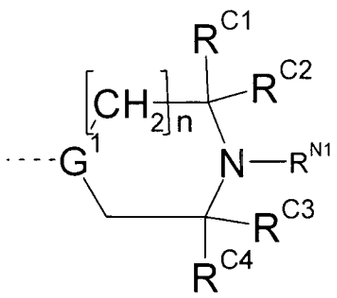
R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo, y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo propenilo, propinilo, propilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros.

En otro aspecto de la invención, R^2 representa independientemente



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo, y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo propenilo, propinilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros.

En otro aspecto de la invención, R^3 representa hidrógeno.

En otra realización de la invención, X representa CH_2 o O.

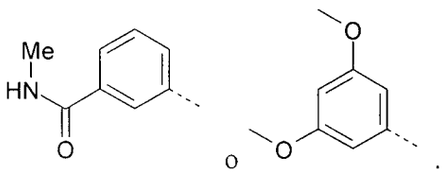
En otra realización de la invención, Y representa CH_2.

En otra realización de la invención, a es 0, 1 ó 2.

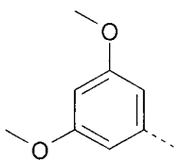
En otra realización de la invención, b es 0, 1 ó 2.

En otro aspecto de la invención, b es 1.

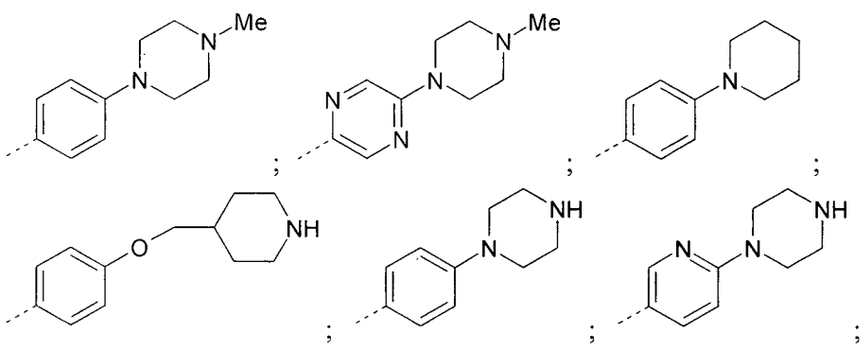
En otro aspecto de la invención, $-A-(R^1)_a$ representa un grupo

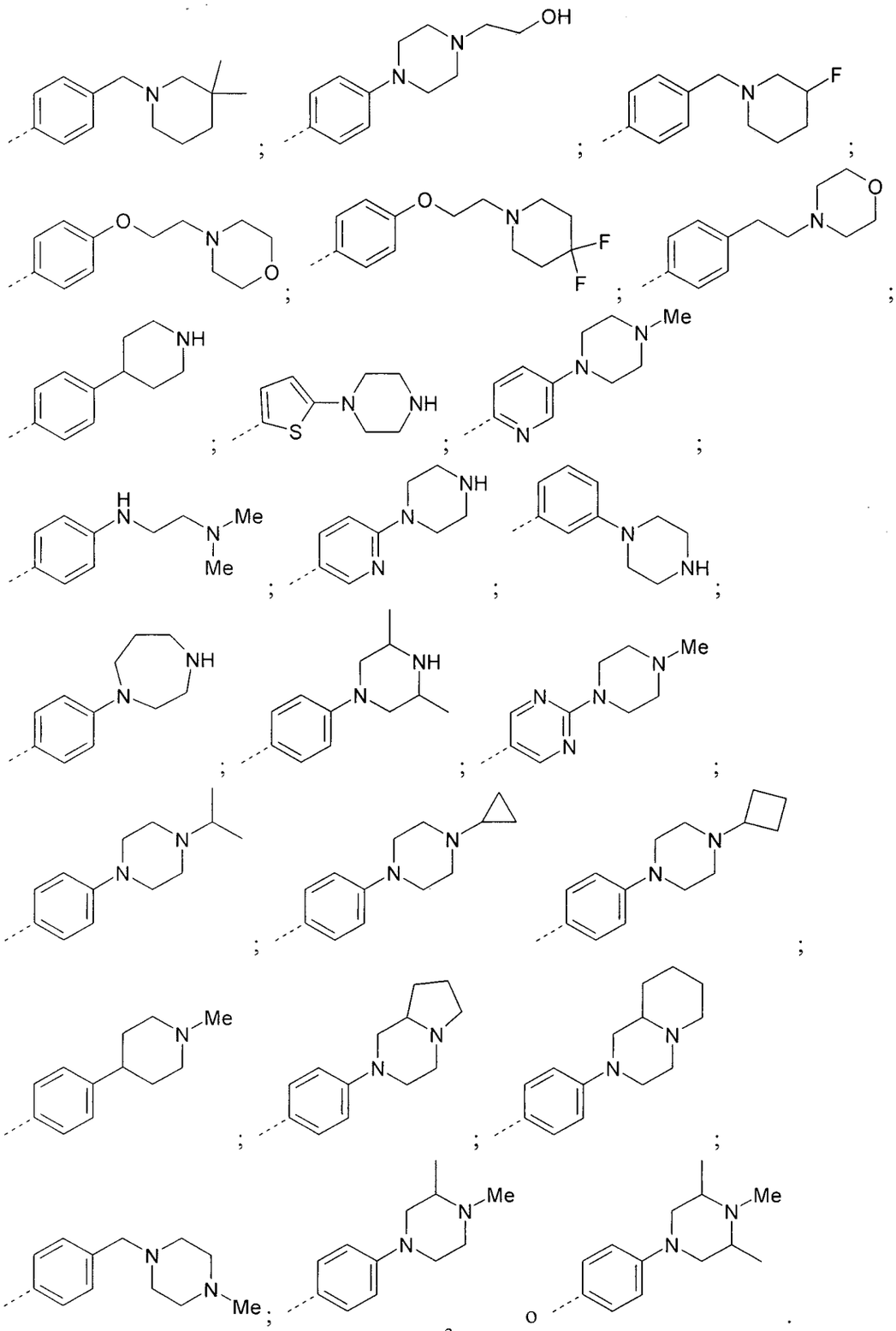


En otro aspecto de la invención, $-A-(R^1)_a$ representa un grupo

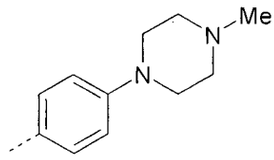
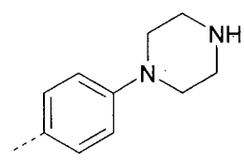
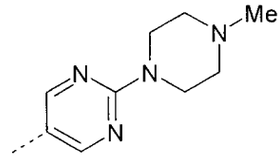
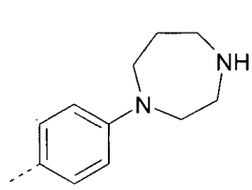
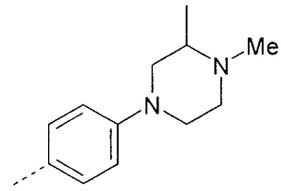
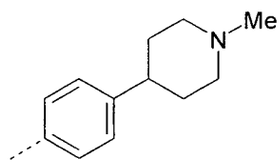
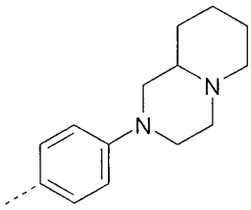
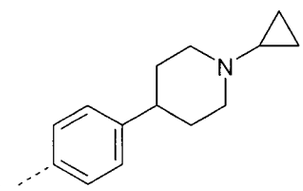
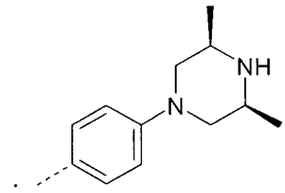
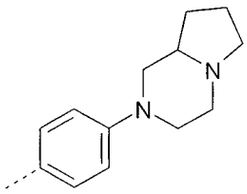
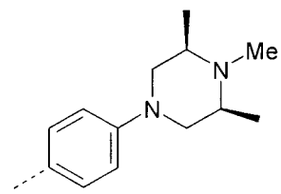
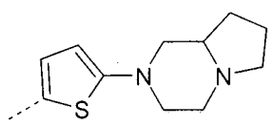
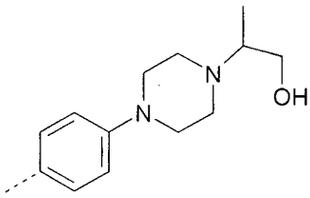
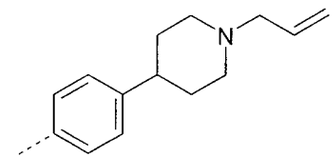
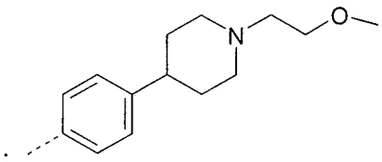
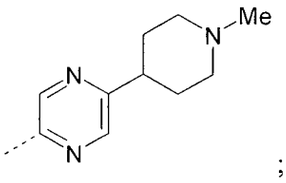
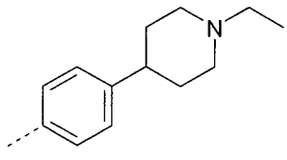
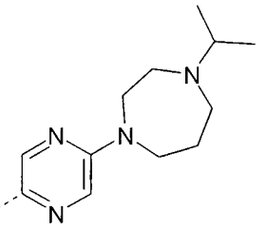
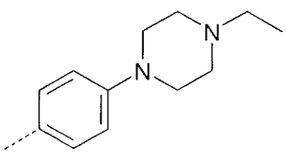
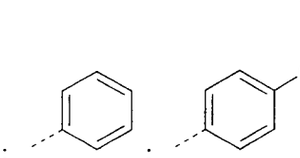
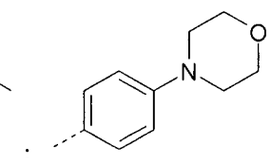


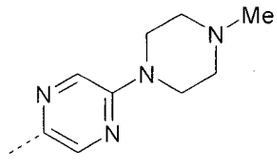
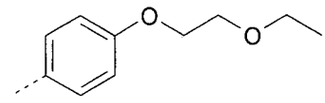
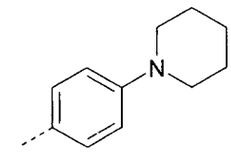
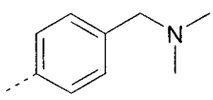
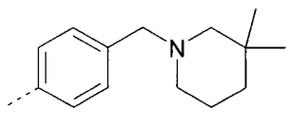
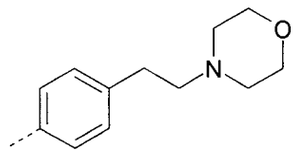
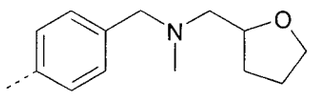
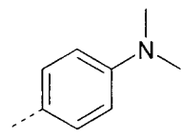
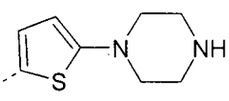
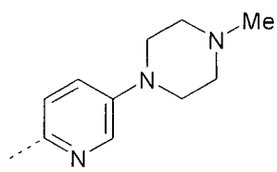
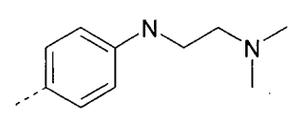
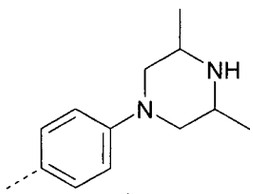
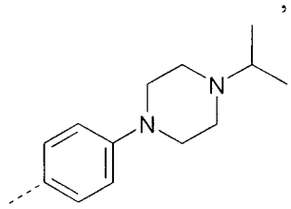
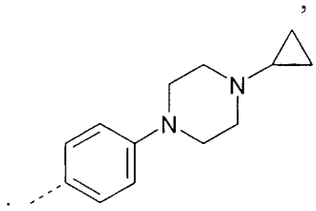
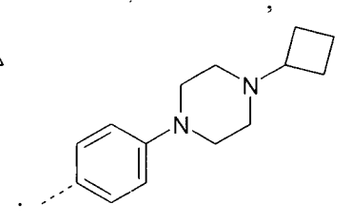
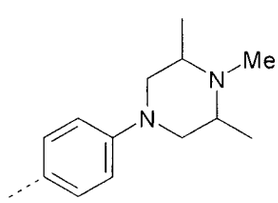
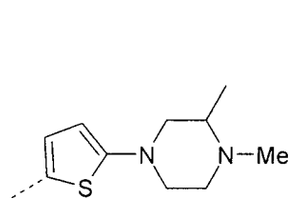
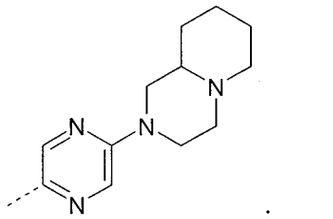
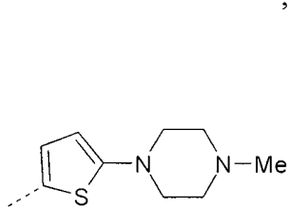
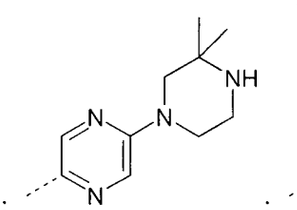
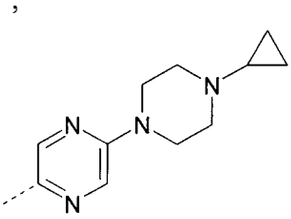
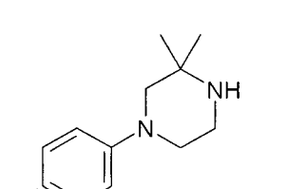
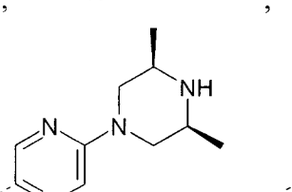
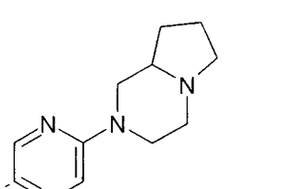
En otro aspecto de la invención, $-B-(R^2)_b$ representa un grupo



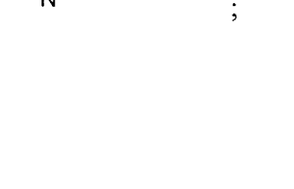


En otro aspecto de la invención, -B-$(R^2)_b$ representa un grupo


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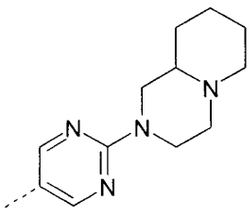
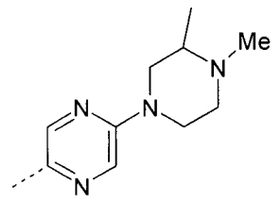
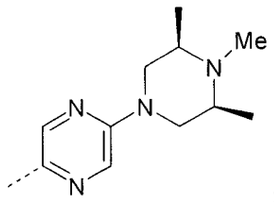
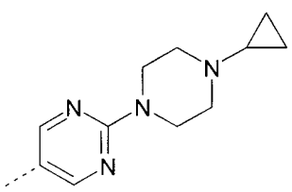
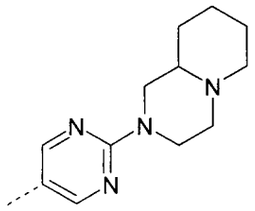
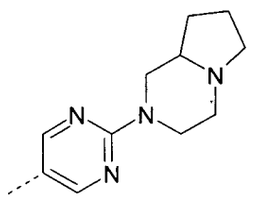
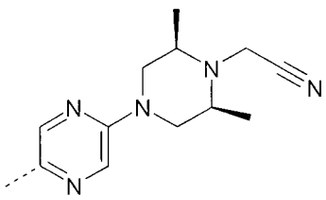
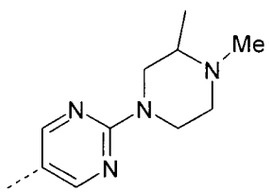
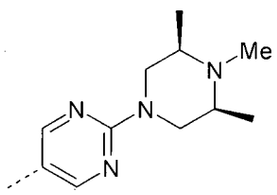
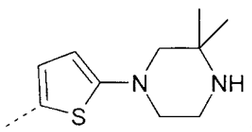
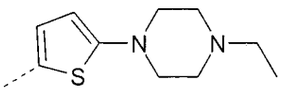
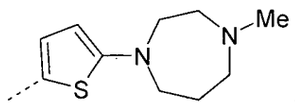
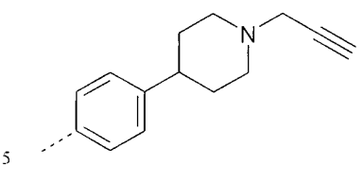
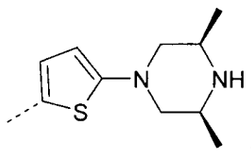
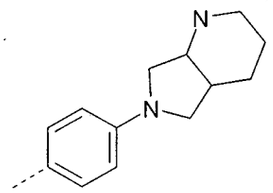
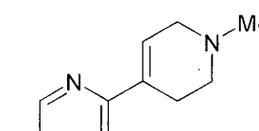
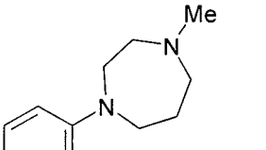
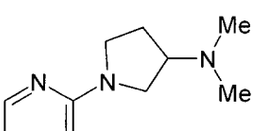
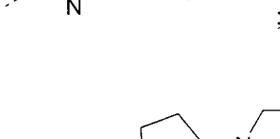
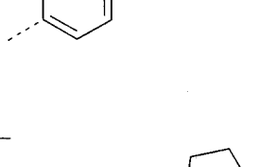
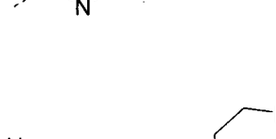
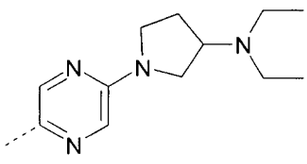
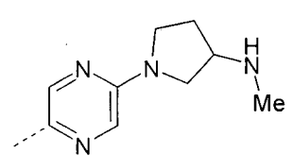
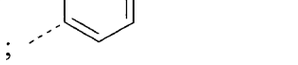
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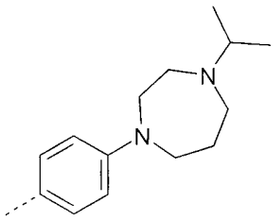
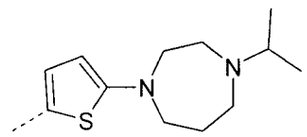
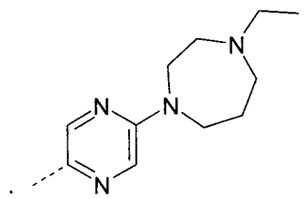
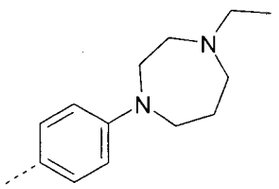
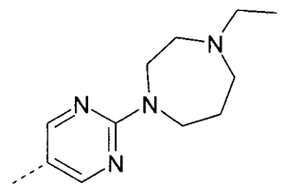
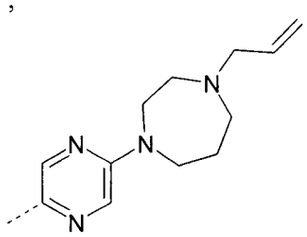
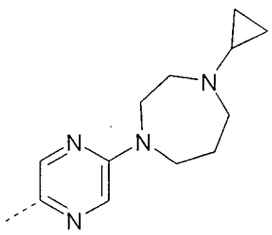
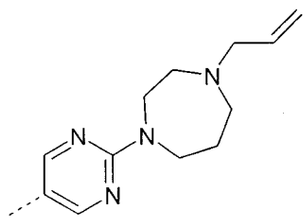
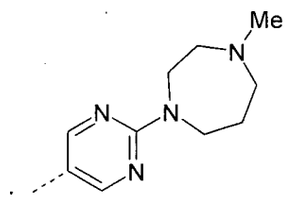
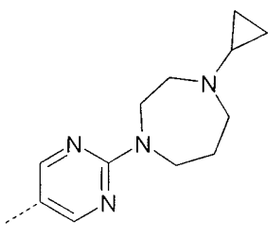
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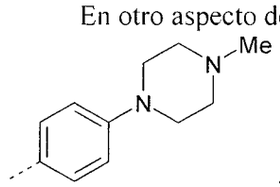
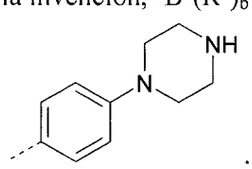
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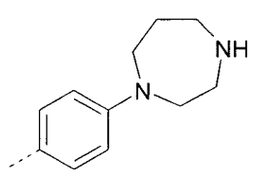
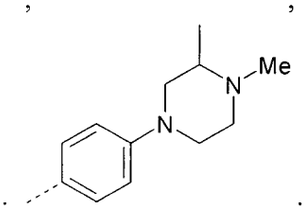
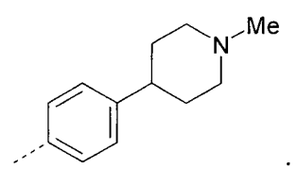
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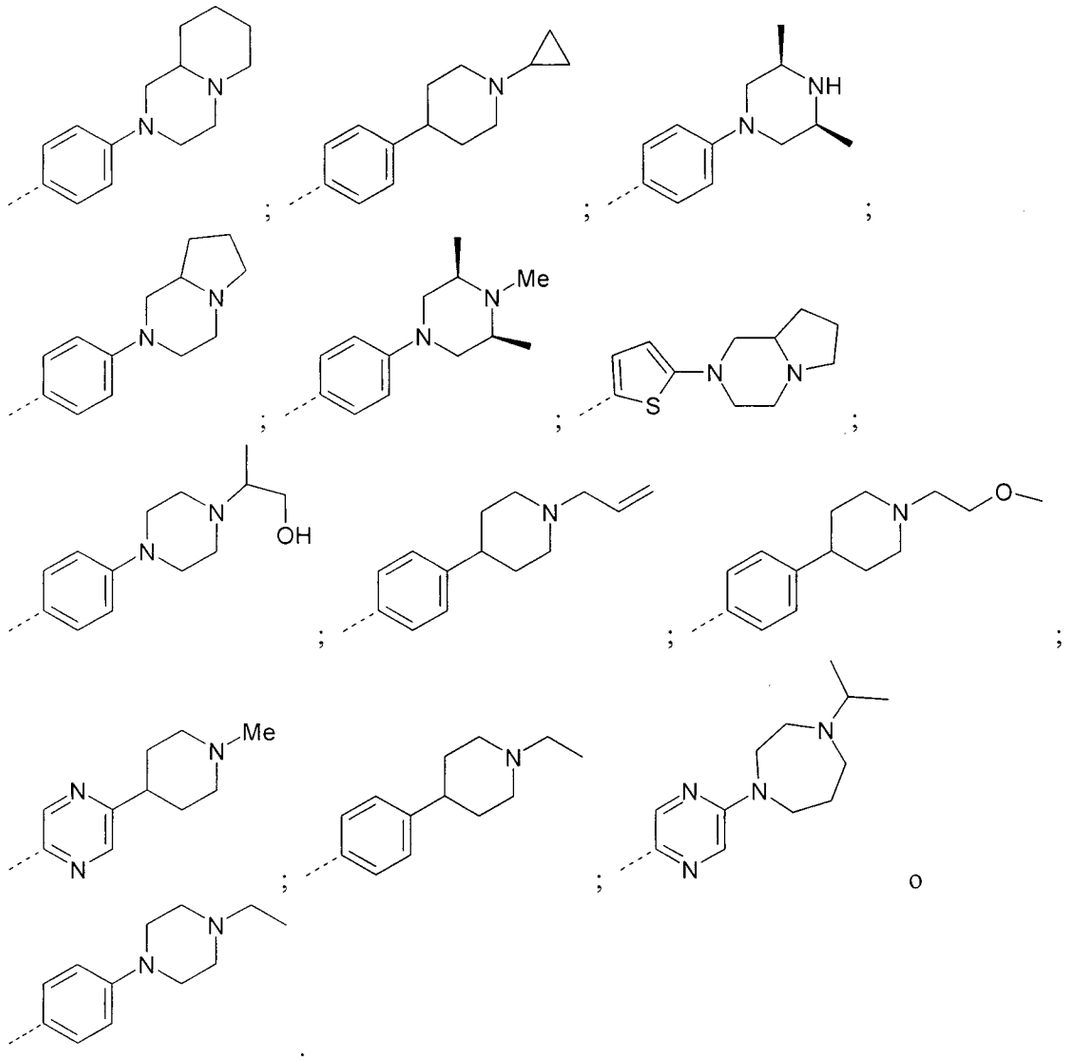

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En otro aspecto de la invención, -B-$(R^2)_b$ representa un grupo


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En una realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo;

el anillo B representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo,

piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo;

cada R^1 representa independientemente

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

cada R^2 representa independientemente

un grupo $-NR^{36}R^{37}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo

de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y

di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

En una realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolil;

el anillo B representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo;

cada R^1 representa independientemente

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

cada R^2 representa independientemente

un grupo $-NR^{36}R^{37}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

En una realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo;

el anillo B representa un anillo furilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, fenilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidinilo, pirrolilo, tetrazolilo, tiadiazolilo, tiazolilo, tienilo, triazinilo o triazolilo;

cada R^1 representa independientemente

un halógeno,

un grupo hidroxilo,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo $-CONR^{20}R^{21}$, o

dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada R^2 representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo $-CO_2R^{29}$,

un grupo $-CONR^{30}R^{31}$,

un grupo $-NR^{32}COR^{33}$,

un grupo $-NR^{34}CO_2R^{35}$,

un grupo $-NR^{36}R^{37}$,

un grupo $-SO_2R^{38}$,

un grupo $-SO_2NR^{39}R^{40}$,

un grupo $-NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo

trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de

halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, -$NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, -$NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo –$CONR^{20}R^{21}$;

cada R^2 representa independientemente

un grupo -$NR^{36}R^{37}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de $-NR^{43}R^{44}$ (que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), y una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo

C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, -$NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo –$CONR^{20}R^{21}$;

cada R^2 representa independientemente

un grupo -$NR^{36}R^{37}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de -$NR^{43}R^{44}$ (que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino (-NH_2), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más

sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo trifluorometilo), y una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o una morfolina, piperidina o piperazina opcionalmente sustituida con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

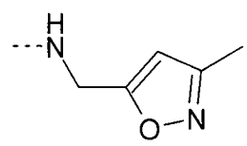
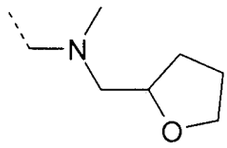
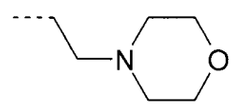
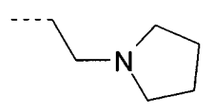
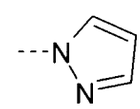
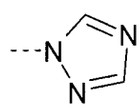
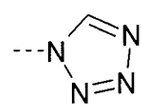
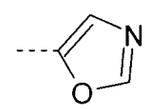
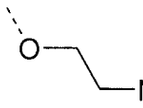
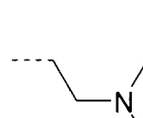
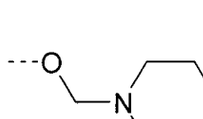
el anillo A representa un anillo furilo, fenilo o piridilo;

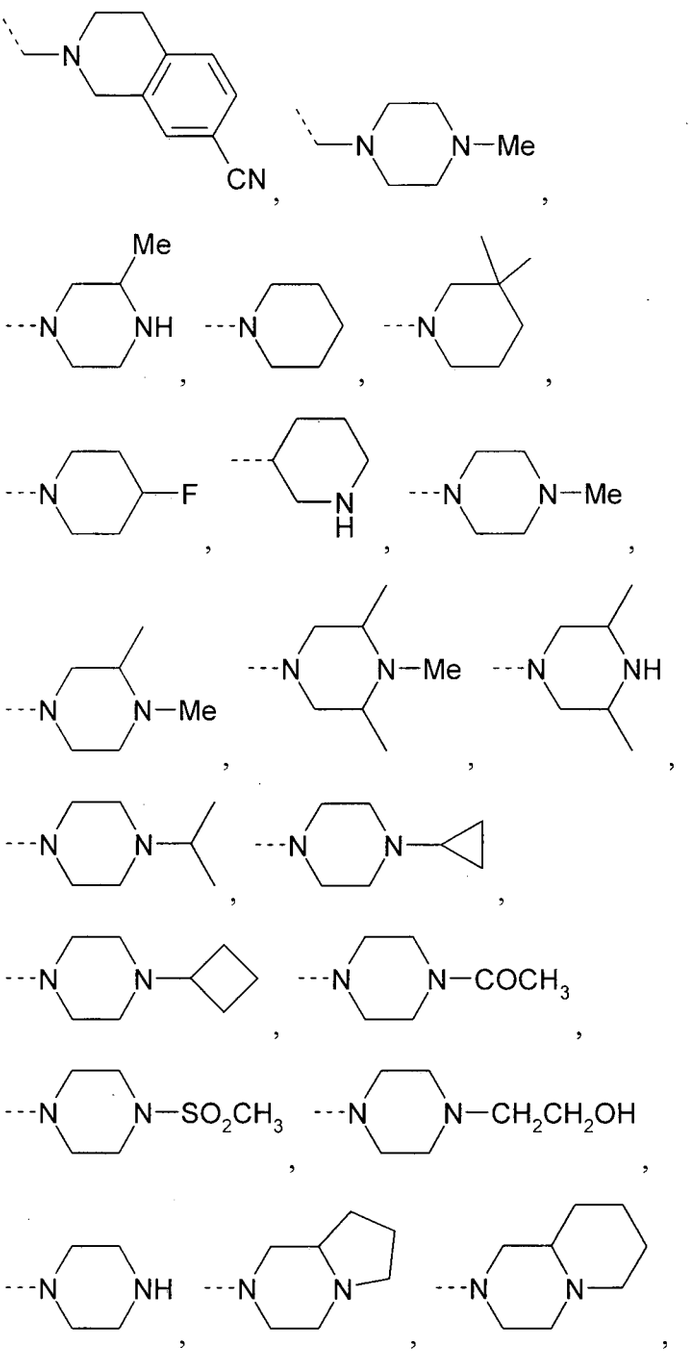
el anillo B representa un anillo fenilo, pirazinilo, piridilo, pirimidinilo o tienilo;

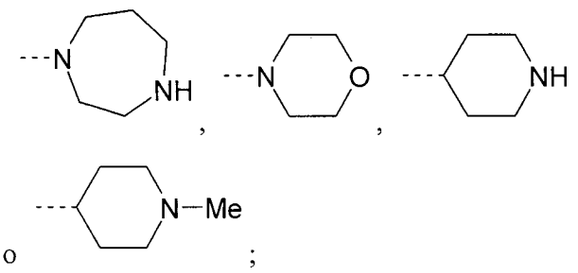
cada R^1 representa independientemente

un grupo metoxi, $-OCH_2CH_2Ome$, $-CH_2NMe_2$, o dos grupos R^1 adyacentes forman juntos un puente $-OCH_2O-$;

cada R^2 representa independientemente

un grupo –Cl, -F, -I, -OH, -CN, $-CH_3$, $-CH_2OH$, $-CH_2N(CH_3)_2$, $-CH_2CH(CH_3)NH_2$, $-OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2OCH_2CH_3$, $-SO_2CH_3$, $-N(CH_3)_2$, -NHPh, $-NHCH_2C{\equiv}CH$, $-NHCH_2CH_3$, $-NHCH_2CH_2N(CH_3)_2$, $-NHCO_2CH_2CH{=}CH_2$, $-NHCOCH_3$, -NHCOH, -NHCOPh, $-CONH_2$, $-NHSO_2Me$, $-SO_2N(CH_3)_2$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 


N
CN
N
N—Me
Me
NH
F
N—Me
N—Me
N—Me
NH
N
N
N
N
N—COCH3
N—SO2CH3
N—CH2CH2OH
NH



R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 0, 1 ó 2.

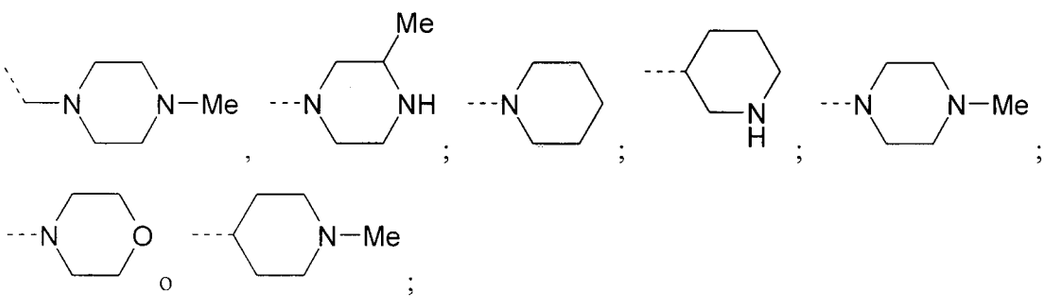
En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

el anillo A representa un anillo furilo, fenilo, piridilo o pirimidinilo;

el anillo B representa un anillo fenilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente –CONHMe o un grupo metoxi;

R^2 representa un grupo



X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

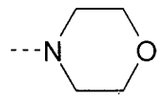
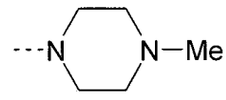
b es 1.

En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

el anillo A representa un anillo furilo, fenilo, piridilo o pirimidinilo;

el anillo B representa un anillo fenilo, piridilo o pirimidinilo;

R^1 representa metoxi;

R^2 representa un grupo  o  ;

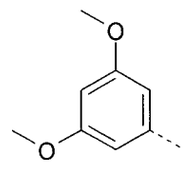
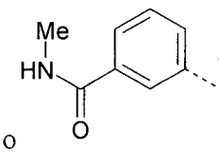
X representa CH_2 o O;

a es 0, 1 ó 2; y

b es 1,

o una sal farmacéuticamente aceptable del mismo.

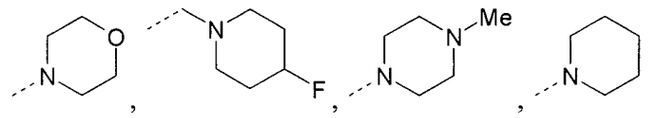
En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

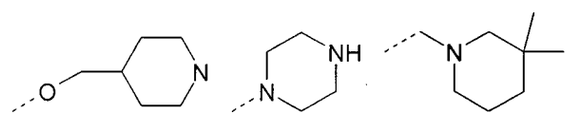
-A-$(R^1)_a$ representa un grupo  o  ;

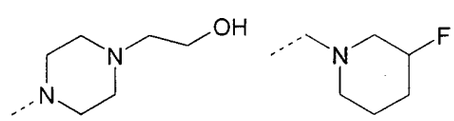
el anillo B representa un anillo fenilo, pirazinilo, piridilo, pirimidinilo o tienilo;

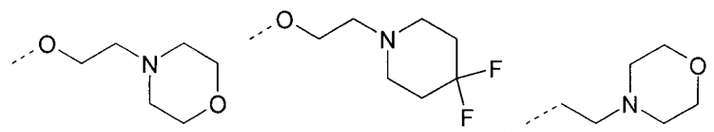
cada R^2 representa independientemente

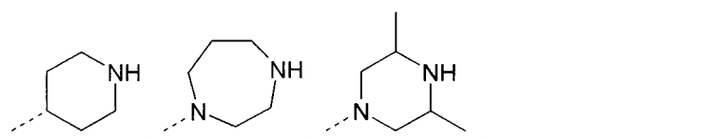
un grupo –OMe, $-OCH_2CH_2OCH_2CH_3$, $-OCH_2CH_2OH$, $-CH_2N(CH_3)_2$, $-NHCH_2CH_2N(CH_3)_2$,

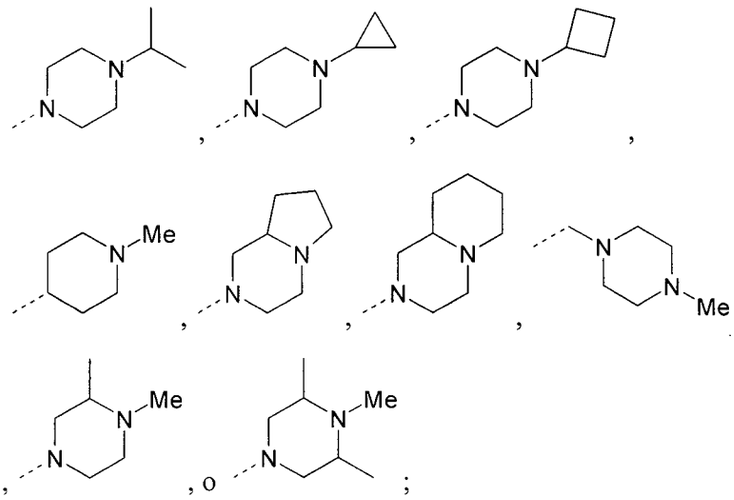












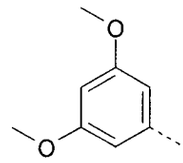
R^3 representa hidrógeno;

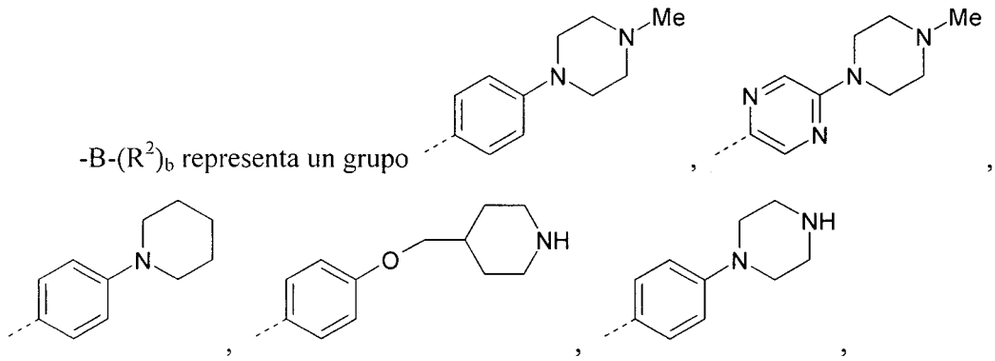
X representa CH_2 o O;

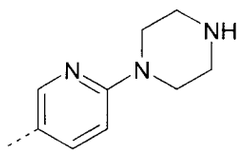
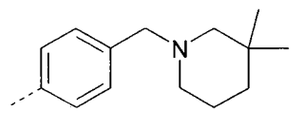
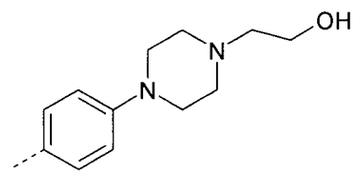
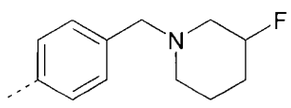
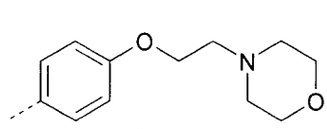
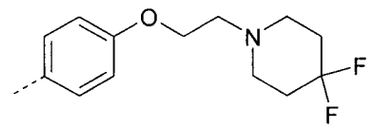
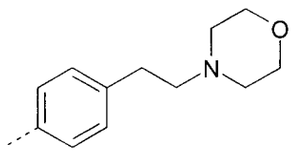
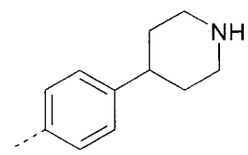
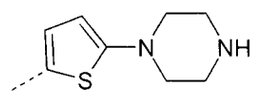
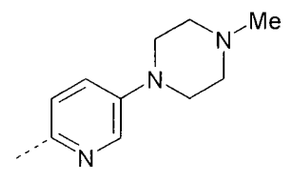
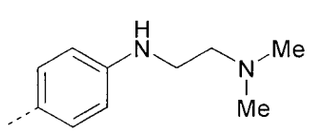
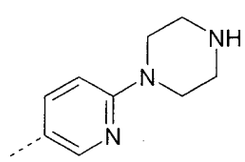
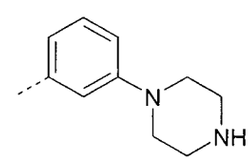
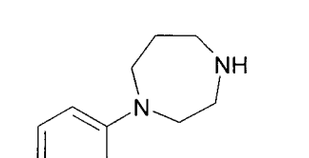
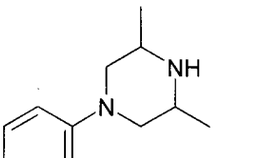
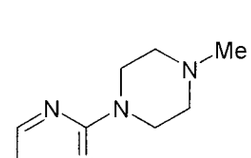
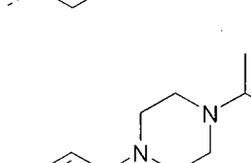
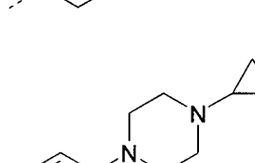
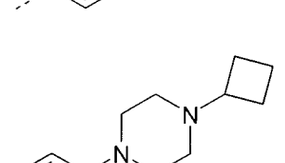
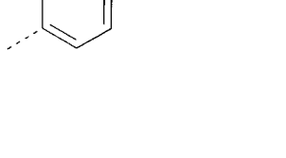
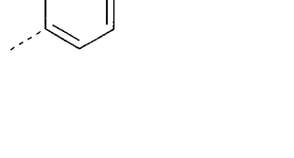
Y representa CH_2;

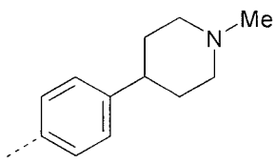
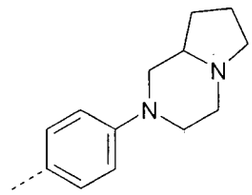
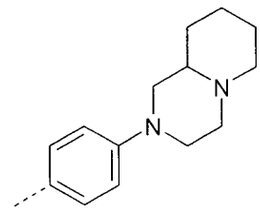
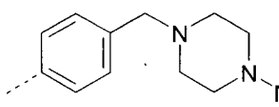
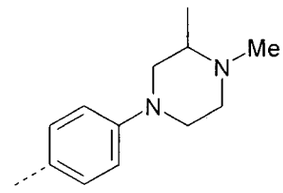
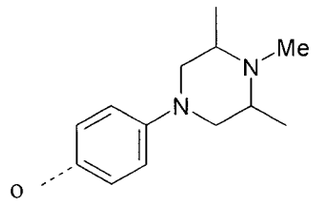
b es 1.

En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

-A-$(R^1)_a$ representa un grupo  ;

-B-$(R^2)_b$ representa un grupo 

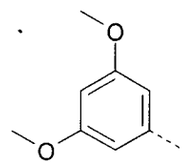






















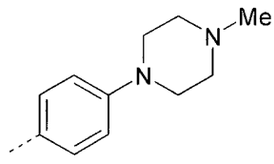
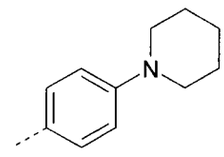
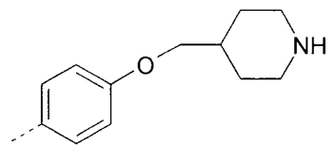
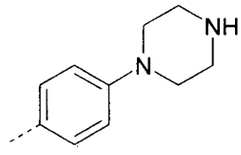
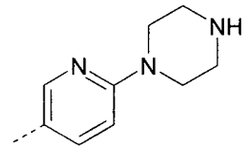
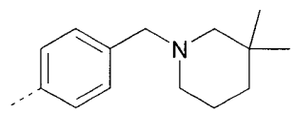
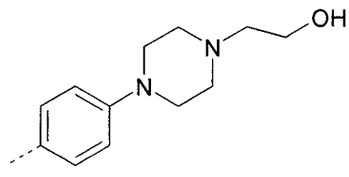
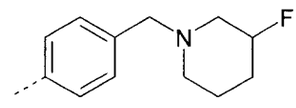








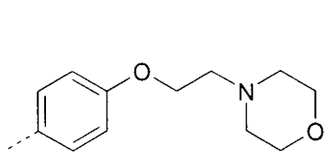
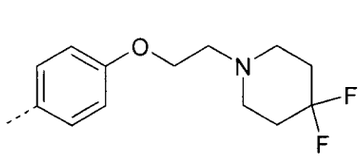
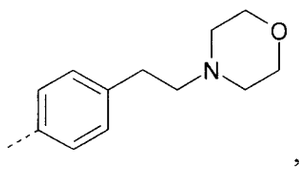
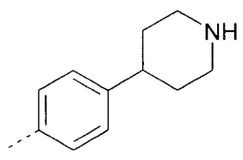
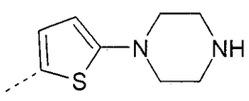
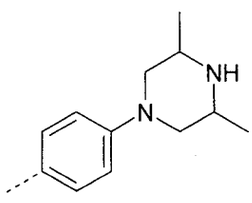
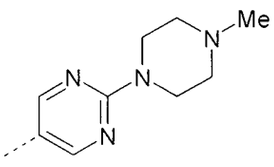
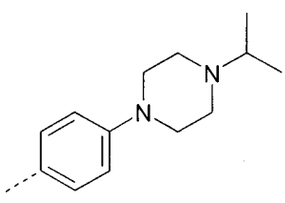
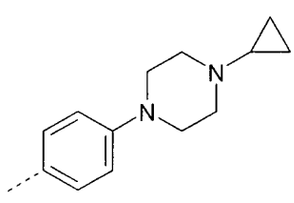
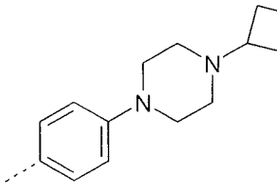
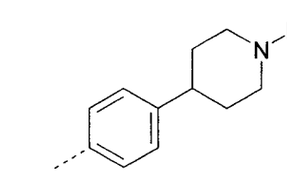
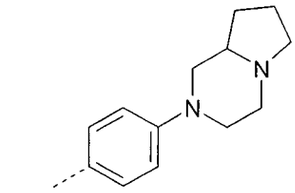
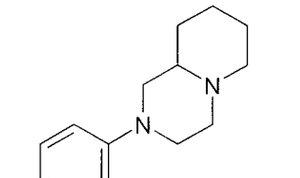
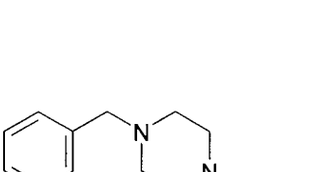
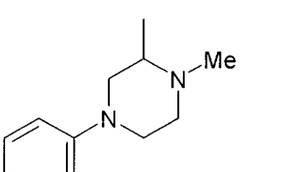
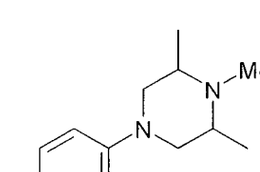
X representa CH_2 o O,

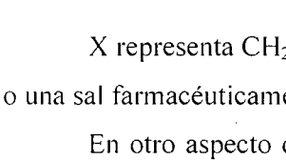
o una sal farmacéuticamente aceptable del mismo.

En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

-A-$(R^1)_a$ representa un grupo  ;

-B-$(R^2)_b$ representa un grupo 








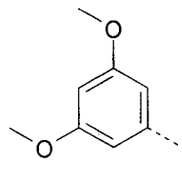


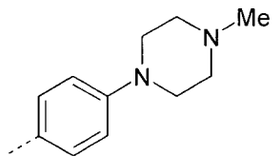
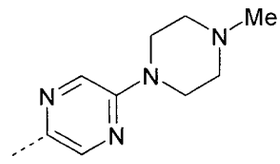
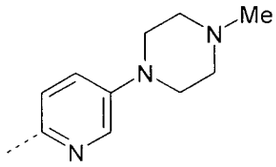
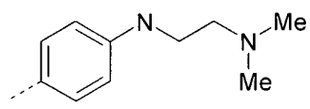
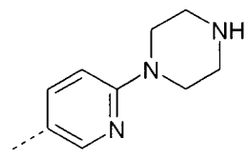
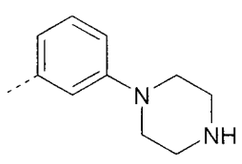
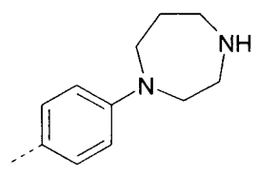
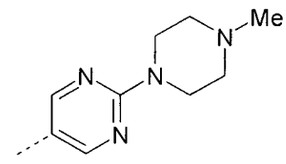
; y

X representa CH_2,

o una sal farmacéuticamente aceptable del mismo.

En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

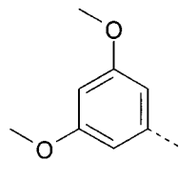
-A-$(R^1)_a$ representa un grupo  ;

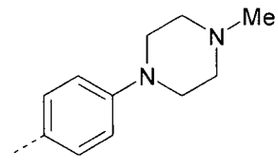
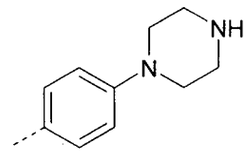
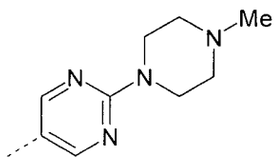
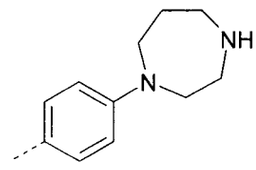
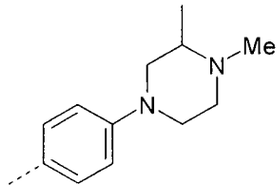
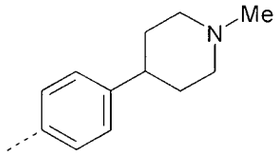
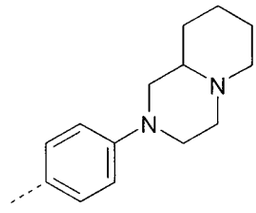
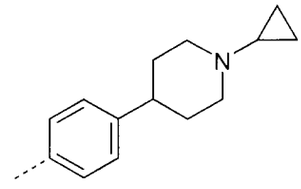
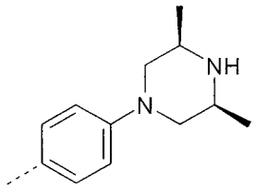
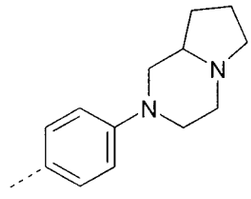
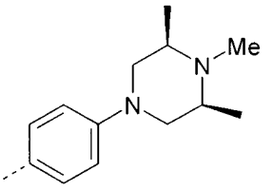
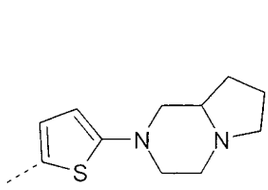
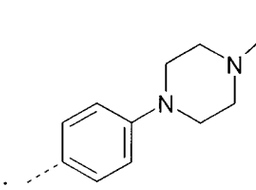
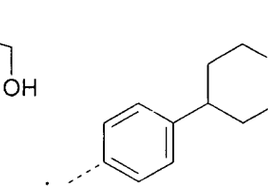
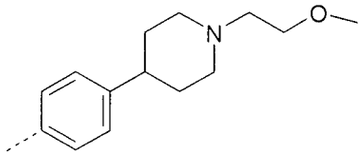
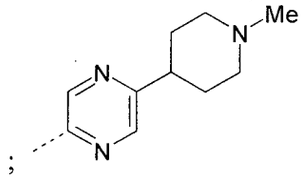
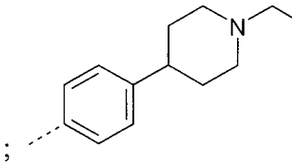
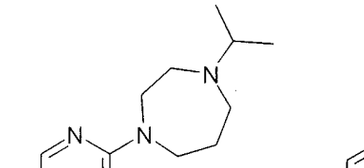
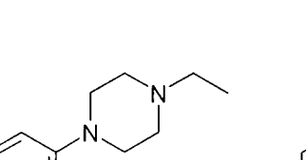
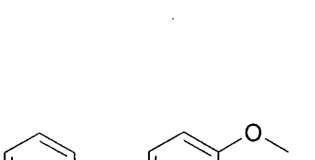
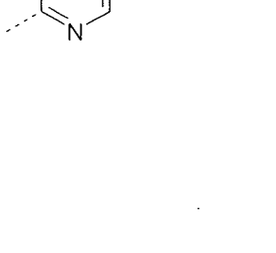
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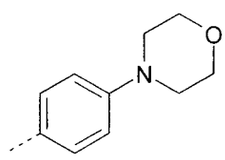
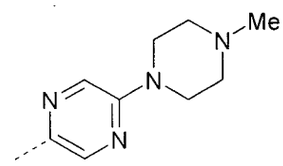
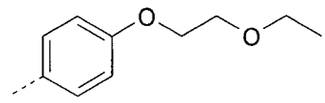
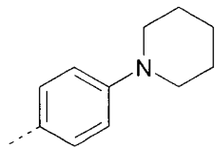
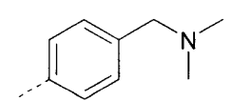
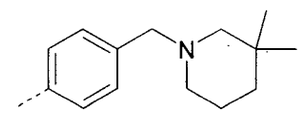
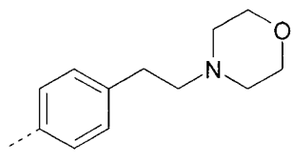
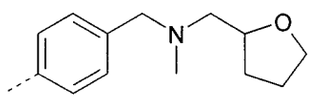
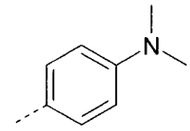
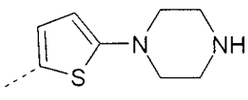
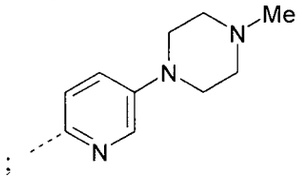
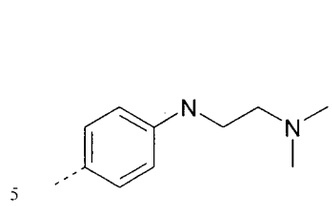
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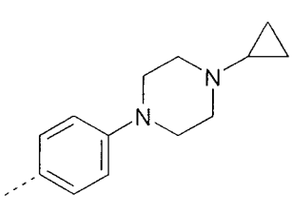
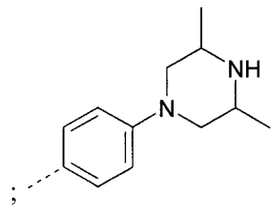
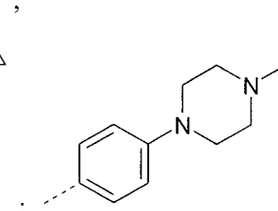
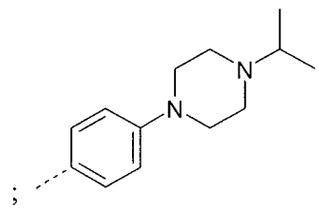
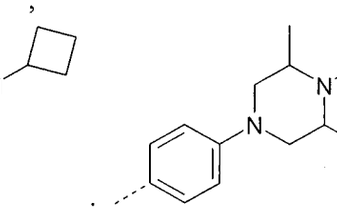
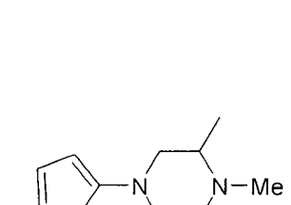
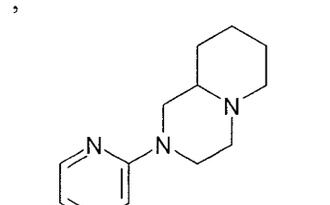
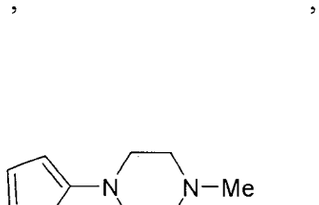
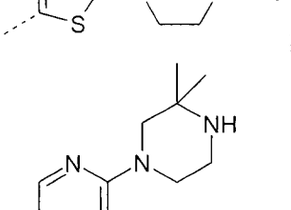
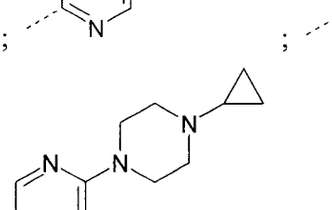
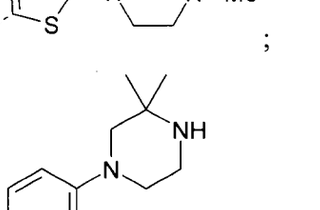
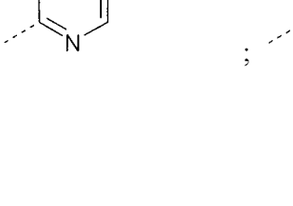
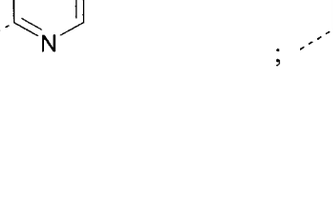
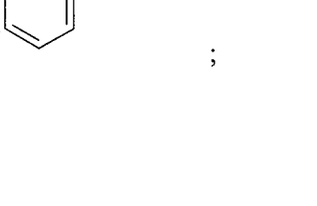
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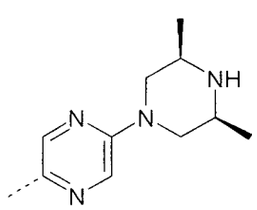
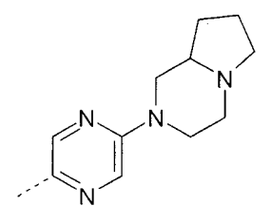
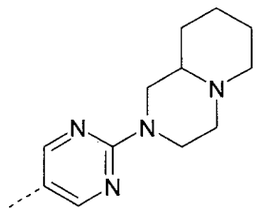
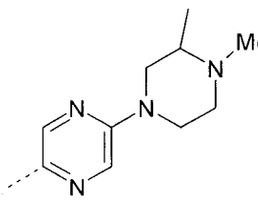
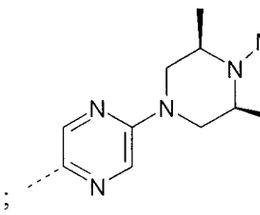
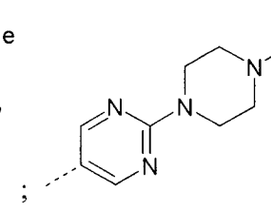
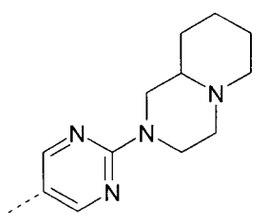
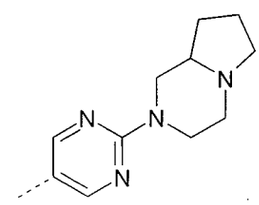
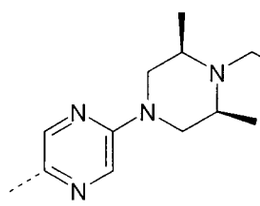
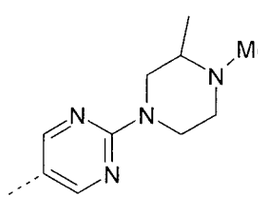
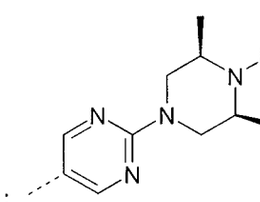
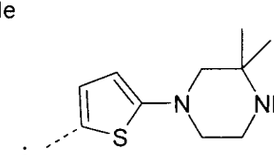
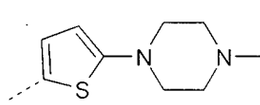
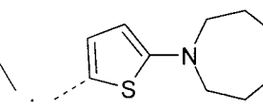
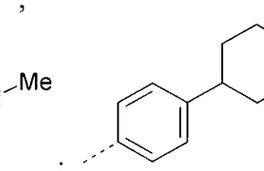
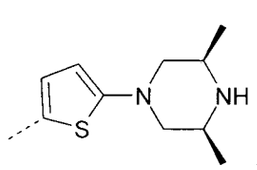
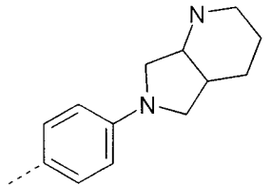
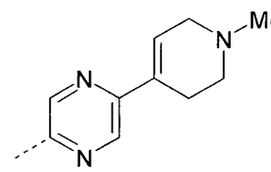
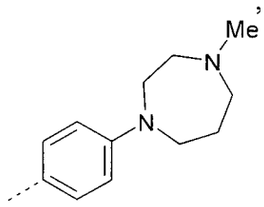
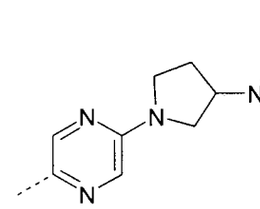
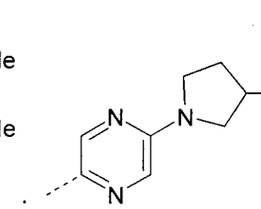
En otro aspecto de la invención, se proporciona un compuesto de fórmula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

-A-$(R^1)_a$ representa un grupo  ; y

-B-$(R^2)_b$ representa un grupo  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; ; ;  ;  ;  ;  ;  ;  ;  ; ; ; ;

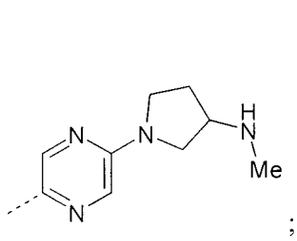
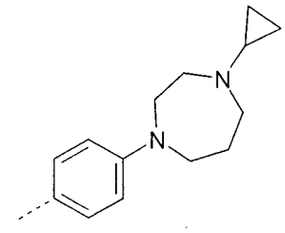
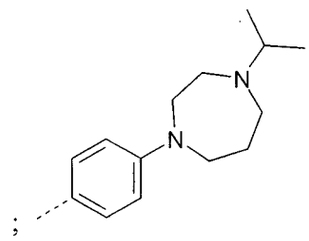
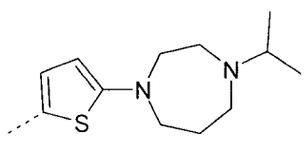
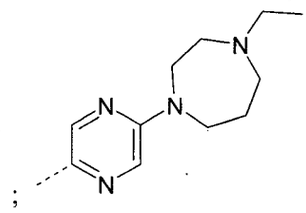
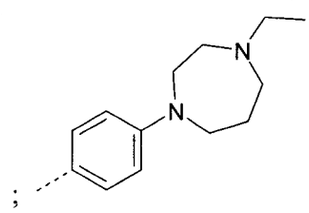
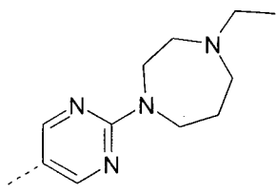
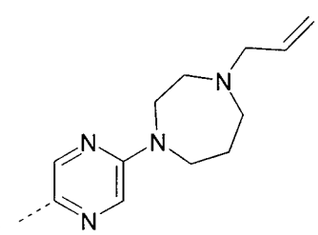
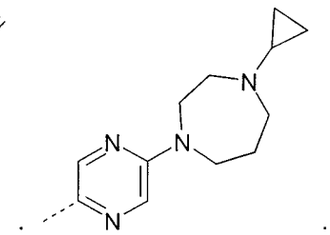
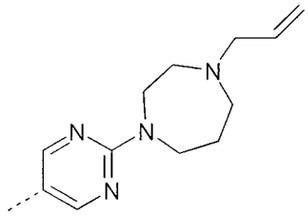
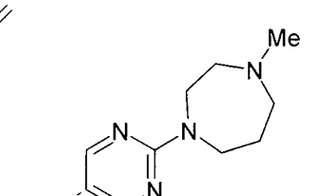
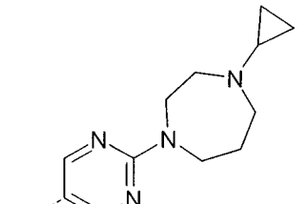
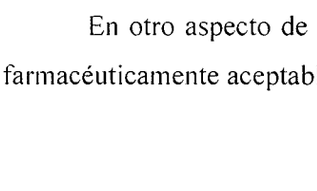
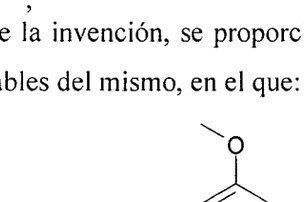
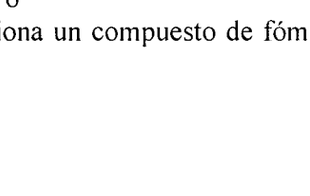
















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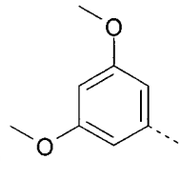
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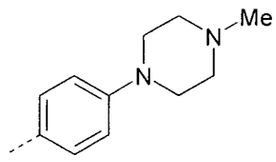
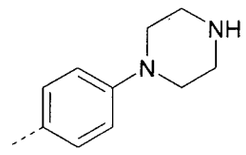
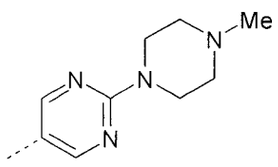
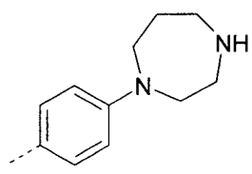
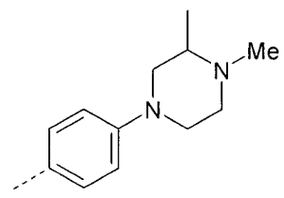
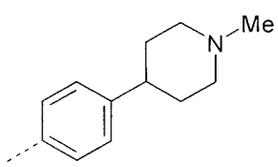
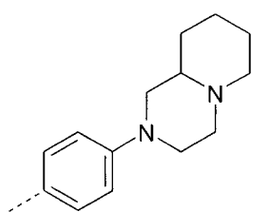
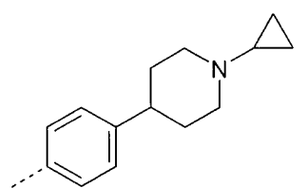
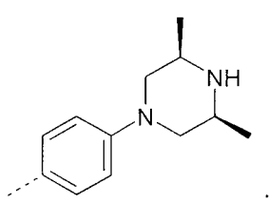
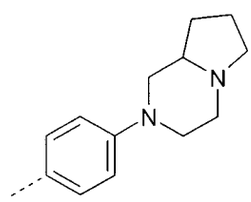
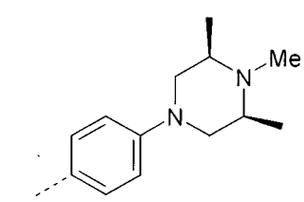
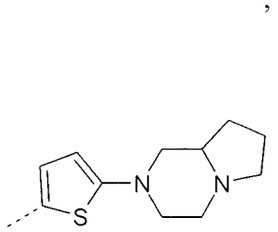
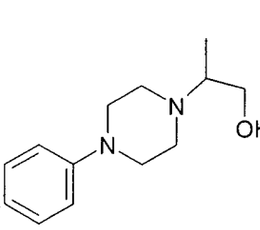
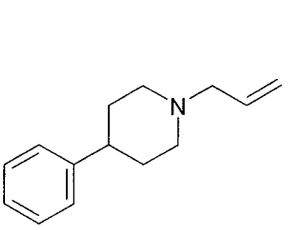
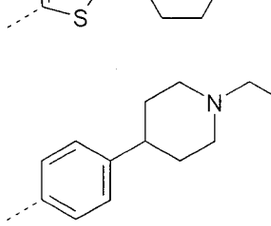
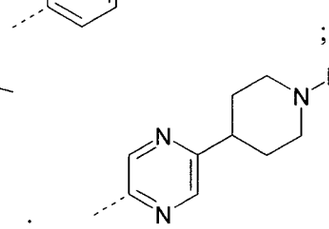
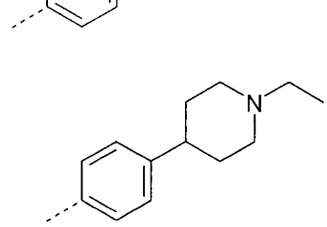
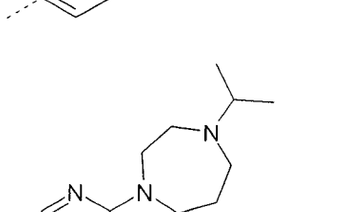
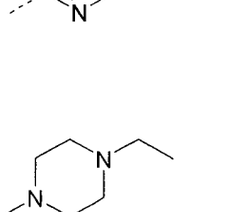
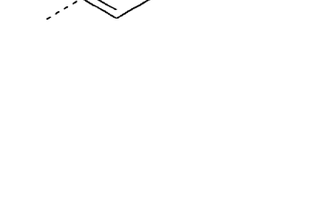
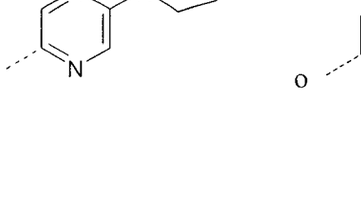
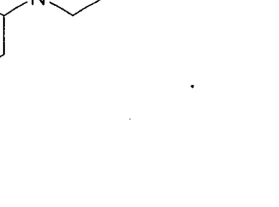
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En otro aspecto de la invención, se proporciona un compuesto de fómula **(I)**, o sales farmacéuticamente aceptables del mismo, en el que:

-A-$(R^1)_a$ representa un grupo  ; y

-B-$(R^2)_b$ representa un grupo  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ;  ; ; ; .

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En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo;

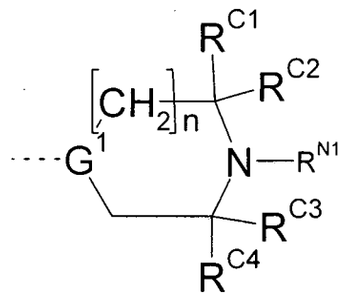
el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil

C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de ciano, halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, -$NR^{59}R^{60}$, -SO_2R^{61} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo

C_1-C_3 alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

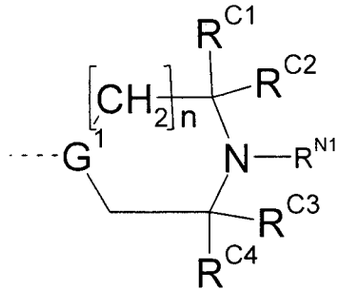
el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3 alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar

opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo furilo, fenilo o piridilo;

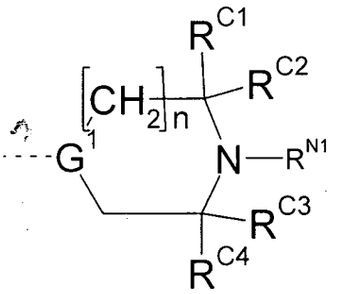
el anillo B representa un anillo fenilo, pirazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

el anillo A representa un anillo fenilo;

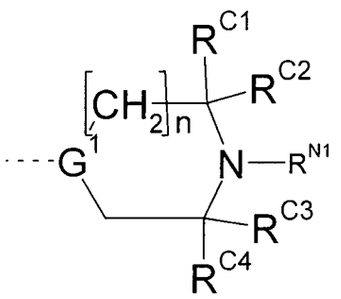
el anillo B representa un anillo fenilo, piraziníilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil

C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, -$NR^{59}R^{60}$, -SO_2R^{61} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterocicilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3,

cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

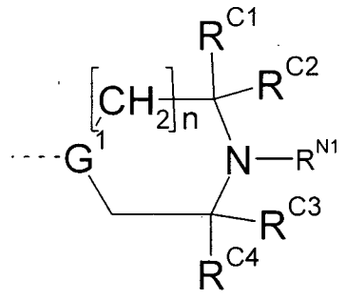
el anillo A representa un anillo fenilo;

el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico de 3 a 5 miembros,

y

R^{N1} se selecciona de alquilo C_1-C_2, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo) e hidrógeno, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

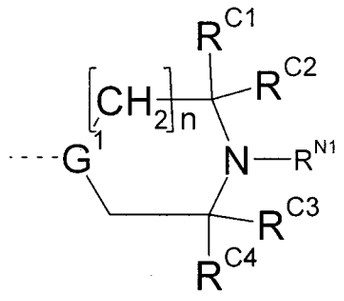
b es 1.

En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

$A(R^1)_a$ representa 3,5-dimetoxifenilo;

el anillo B representa un anillo fenilo, pirazinilo, pirimidinilo o tienilo;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo,

y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo, propenilo, propinilo, propilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2; y

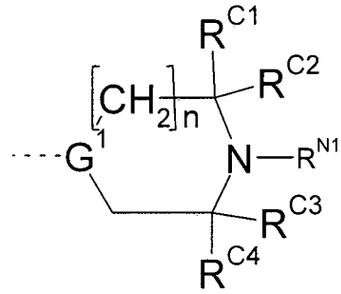
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En otra realización de la invención, se proporciona un subconjunto de compuestos de fórmula **(I)**, o sales farmacéuticamente aceptables de los mismos, en los que:

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en la que

G^1 es C o N,

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R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo,

y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo, propenilo, propinilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2; y

b es 1.

En otra realización de la invención, sólo uno de R^{C1} y R^{C2} o R^{C1} y R^{C3} o R^{C3} y R^{C4} o R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo.

En otra realización de la invención, R^{C1} y R^{C2}, junto con los átomos a los que están unidos, forman un anillo, y sólo uno de R^{C3} y R^{C4} o R^{N1} y R^{C4} puede, junto con los átomos a los que están unidos, formar un anillo.

En otra realización de la invención, R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno y metilo.

Ejemplos de compuestos de la invención incluyen:

4-(4-metilpiperazin-1-il)-N-(5-fenetil-2H-pirazol-3-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-metoxi-benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-morfolin-4-il-benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3-fluoro-1-piperidil)metil]benzamida,

N-[5-[2-[3-(2-Metoxietoxi)fenil]etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

4-(4-Metilpiperazin-1-il)-N-[5-(2-piridin-3-iletil)-2H-pirazol-3-il]benzamida,

N-[5-[2-(2-furil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(3-furil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-6-metil-piridin-3-carboxamida,

6-Metoxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-metilsulfonil-benzamida,
N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-5-metil-pirazin-2-carboxamida,
N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-5-(prop-2-inilamino)piridin-2-carboxamida,
6-Etilamino-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
4-Acetamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)pirazin-2-carboxamida,
4-benzamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
6-(2-metoxietoxi)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
4-ciano-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]bencen-1,4-dicarboxamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-4-pirazol-1-il-benzamida,
6-anilino-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
4-metanosulfonamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
4-(hidroximetil)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
5-formamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-2-carboxamida,
4-(dimetilsulfamoil)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida,
6-hidroxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-6-morfolin-4-il-piridin-3-carboxamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-4-(1,3-oxazol-5-il)benzamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-4-(tetrazol-1-il)benzamida,
N-[5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-il]carbamato de prop-2-enilo,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-4-(1,2,4-triazol-1-il)benzamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-6-pirazol-1-il-piridin-3-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluoro-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-3-metoxi-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-3-morfolin-4-il-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-2-metoxi-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-etoxietoxi)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(1-piperidil)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-piperidilmetoxi)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-piperazin-1-il-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-6-piperazin-1-il-piridin-3-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(dimetilaminometil)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-hidroxietoxi)benzamida,
4-(2-aminopropil)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(3,3-dimetil-1-piperidil)metil]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[4-(2-hidroxietil)piperazin-1-il]benzamida,
4-[(7-ciano-3,4-dihidro-1H-isoquinolin-2-il)metil]-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(3-fluoro-1-piperidil)metil]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-morfolin-4-iletoxi)benzamida,
4-[2-(4,4-difluoro-1-piperidil)etoxi]-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-morfolin-4-iletil)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(metil-(oxolan-2-ilmetil)amino)-metil]benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-piperidil)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-dimetilamino-benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-5-piperazin-1-il-tiofen-2-carboxamida,
6-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-3-carboxilato de metilo,
6-cloro-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
6-ciano-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida,
4-hidroxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-2-carboxamida,
N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-6-(2-pirrolidin-1-iletil)piridin-3-carboxamida,
Ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico,
5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxilato de metilo,
5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxilato de etilo,
N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)piridin-2-carboxamida,
N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(2-dimetilaminoetilamino)benzamida,
N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-metoxi-benzamida,
N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-6-piperazin-1-il-piridin-3-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-1H-pirazol-3-il]-2-(4-metilpiperazin-1-il)pirimidin-5-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-1H-pirazol-3-il]-3-piperazin-1-il-benzamida,

4-(1,4-diazepan-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-1H-pirazol-3-il]benzamida,

N-[5-[2-[5-(dimetilaminometil)-2-furil]etil]-1H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-(2-benzo[1,3]dioxol-5-iletil)-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(2,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(4-metoxi-2-metil-fenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,5-dimetilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-yodo-benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-2-[(3-metil-1,2-oxazol-5-il)metilamino]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-6-(4-metilpiperazin-1-il)piridazin-3-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metilpiperazin-1-il)pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-metilpiperazin-1-carbonil)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-propan-2-ilpiperazin-1-il)benzamida,

4-(4-ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,

4-(4-ciclobutilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,

4-(4-acetilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida,

N-[5-[2-(3-metoxifenil)etil]-1H-pirazol-3-il]-4-(4-metilsulfonilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(1-metil-4-piperidil)benzamida,

4-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

4-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(4-metilpiperazin-1-il)metil]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(3,4,5-trimetilpiperazin-1-il)benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)tiofen-2-carboxamida,

4-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida,

4-(1-Ciclopropilpiperidin-4-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-[(3R,5S)-3,5-dimetilpiperazin-1-il]benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida,

4-[5-[[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]carbamoil]tiofen-2-il]piperazin-1-carboxilato de *terc*-butilo,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(1-metilpiperidin-4-il)benzamida,

4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida,

5-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)tiofen-2-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)tiofen-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3,3-dimetilpiperazin-1-il)pirazin-2-carboxamida,

5-(4-Ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(3,3-dimetilpiperazin-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-[(3R,5S)-3,5-dimetilpiperazin-1-il]pirazin-2-carboxamida,

5-(4-Ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,

5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,

5-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida,

4-(4-ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-Dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metil-4-oxidopiperazin-4-io-1-il)benzamida,

4-(4-Ciclobutilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida,

2-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida,

5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]tiofen-2-carboxamida,

5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]tiofen-2-carboxamida,

5-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[2-(3,5-Dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)pirazin-2-carboxamida,

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirazin-2-carboxamida,

2-(4-ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida,

2-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida,

2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida,

5-[(3R,5S)-4-(cianometil)-3,5-dimetilpiperazin-1-il]-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirazin-2-carboxamida,

5-[(3R,5S)-4-(cianometil)-3,5-dimetilpiperazin-1-il]-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxamida,

2-(4-ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida,

2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[4-(1-hidroxipropan-2-il)piperazin-1-il]benzamida,

N-(3-(3,5-dimetoxibenciloxi)-1H-pirazol-5-il)-2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,3-dimetilpiperazin-1-il)benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,3-dimetilpiperazin-1-il)tiofen-2-carboxamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-etilpiperazin-1-il)tiofen-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metil-1,4-diazepan-1-il)tiofen-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-etil-3-metilpiperazin-1-il)pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-enilpiperidin-4-il)benzamida,

4-(1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-inilpiperidin-4-il)benzamida,

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-[(3S,5R)-3,5-dimetilpiperazin-1-il]tiofen-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[1-(2-metoxietil)piperidin-4-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[(3S)-3-propan-2-ilpiperazin-1-il]pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metil-3-oxopiperazin-1-il)pirimidin-5-carboxamida,

4-(1,2,3,4,4a,5,7,7a-octahidropirrolo[3,4-b]piridin-6-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(1-metilpiperidin-4-il)pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(1-metil-3,6-dihidro-2H-piridin-4-il)pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3R,5S)-3,5-dimetilpiperazin-1-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metil-1,4-diazepan-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3-dimetilaminopirrolidin-1-il)pirazin-2-carboxamida,

5-(3-dietilaminopirrolidin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-etilpiperidin-4-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[3-(metoximetil)piperazin-1-il]pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3-metilaminopirrolidin-1-il)pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(1-metilpiperidin-4-il)pirimidin-5-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metil-1,4-diazepan-1-il)pirazin-2-carboxamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-prop-2-enil-1,4-diazepan-1-il)benzamida,

4-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-propan-2-il-1,4-diazepan-1-il)benzamida,

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-propan-2-il-1,4-diazepan-1-il)pirazin-2-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-propan-2-il-1,4-diazepan-1-il)tiofen-2-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-etil-1,4-diazepan-1-il)pirazin-2-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-etil-1,4-diazepan-1-il)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-etil-1,4-diazepan-1-il)pirimidin-5-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-prop-2-enil-1,4-diazepan-1-il)pirazin-2-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-propan-2-il-1,4-diazepan-1-il)pirimidin-5-carboxamida,
5-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-prop-2-enil-1,4-diazepan-1-il)pirimidin-5-carboxamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metil-1,4-diazepan-1-il)pirimidin-5-carboxamida,
2-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida,
N-[5-[2-[3-(metilcarbamoil)fenil]etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida,
N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(4-etilpiperazin-1-il)benzamida,
N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-etilpiperazin-1-il)benzamida
y sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 1 a 20 o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 1, 2, 3, 4, 5, 10, 11, 12, 20, 42, 43, 44, 45, 46, 47, 48, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 71, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, o 96, o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

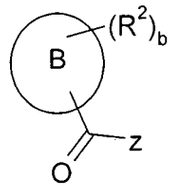
En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 2, 3, 4, 5, 10, 11, 12, 20, 42, 43, 44, 45, 46, 47, 48, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 71, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, o 96, o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 10, 11, 12, 20, 43, 44, 45, 46, 50, 51, 53, 54, 55, 56, 57, 58, 59, 60, 69, 70, 72, 73, 74, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 95, o 96, o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 2, 3, 4, 10, 11, 12, 20, 42, 43, 45, 47, 50, 56, 57, 59, 60, 69, 70, 71, 73, 75, 80, 81, 85, 87, 88, 89, 92, 93, 94, 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 144, 145, 146, 147, 148, 151, 152, 153, 154, 155, 156, 157, 158; 159, 161, 165, 166, 167, 168, 169, 170, 171, 172, 174, 175, 176, 177, 179 o 180, o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

En otro aspecto de la invención, compuestos particulares de la invención son uno cualquiera de los Ejemplos 12, 45, 73, 75, 81, 92, 98, 99, 100, 103, 104, 110, 121, 137, 144, 148, 152, 154, 155, 159, 167, 179 o 180, o sales farmacéuticamente aceptables de uno cualquiera de los mismos.

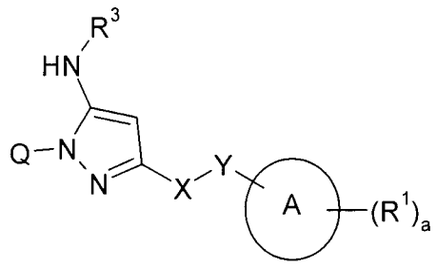
La presente invención proporciona además un procedimiento para la preparación de un compuesto de fórmula **(I)** como se define aquí, o una sal farmacéuticamente aceptable del mismo, que comprende hacer reaccionar un compuesto de fórmula **(II)**



(II)

en la que Z representa un grupo saliente (por ejemplo halógeno, por ejemplo cloro, -CN, $-N_3$, -OH o un grupo –OR, -OC(O)R, $–OCR(NR^aR^b)_2$ o $–OC(=NR)NR^aR^b$ en los que R es un alquilo, arilo, heteroarilo o alcarilo opcionalmente sustituidos, y cada R^a, R^b es independientemente hidrógeno o un alquilo, arilo o alcarilo opcionalmente sustituidos), y B, R^2 y b son como se definen aquí anteriormente para un compuesto de fórmula **(I),**

con un compuesto de fórmula **(III)**



(III)

en la que Q es hidrógeno o un grupo protector (por ejemplo un grupo t-Bu o BOC, o como se describe en "Protective Groups in Organic Synthesis", 2ª edición, T.W. Greene y P.G.M. Wuts, Wiley-Interscience (1991)), y A, R^1, R^3, X, Y y a son como se definen aquí anteriormente para un compuesto de fórmula **(I)**

para dar un compuesto de fórmula **(I),**

y opcionalmente llevar a cabo una o más de las siguientes:

- convertir el compuesto obtenido en un compuesto adicional de la invención
- formar una sal farmacéuticamente aceptable del compuesto.

Los compuestos de fórmula (II) adecuados incluyen ácidos carboxílicos o derivados reactivos de un ácido carboxílico. Los ácidos carboxílicos o derivados reactivos de un ácido carboxílico incluyen haluros de acilo, tal como un cloruro de acilo formado por la reacción del ácido con un cloruro de ácido inorgánico, por ejemplo, cloruro de tionilo; un anhídrido mixto, por ejemplo un anhídrido formado por la reacción del ácido con un cloroformiato, tal como cloroformiato de isobutilo; un éster activo, por ejemplo un éster formado haciendo reaccionar un ácido carboxílico con un fenol, tal como pentafluorofenol, con un éster tal como trifluoroacetato de pentafluorofenilo, o con un alcohol tal como metanol, etanol, isopropanol, butanol o *N*-hidroxibenzotriazol,; una azida de acilo, por ejemplo una azida formada haciendo reaccionar el ácido con una azida, tal como azida difenilfosforílica; un cianuro de acilo, por

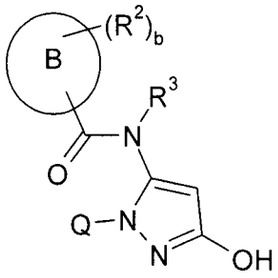
ejemplo un cianuro formado haciendo reaccionar un ácido con un cianuro, tal como cianuro de dietilfosforilo; o el producto de la reacción del ácido con una carbodiimida, tal como diciclohexilcarbodiimida, o con un compuesto de uronio, tal como hexafluorofosfato (V) de 2-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio.

La reacción se puede llevar a cabo convenientemente en presencia de un disolvente o diluyente inerte adecuado, por ejemplo un disolvente halogenado, tal como cloruro de metileno, cloroformo o tetracloruro de carbono, un alcohol o éster tal como metanol, etanol, isopropanol o acetato de etilo, un éter, tal como tetrahidrofurano o 1,4-dioxano, un disolvente aromático, tal como tolueno. La reacción también se puede llevar a cabo en presencia de un disolvente aprótico dipolar, tal como *N,N*-dimetilformamida, *N,N*-dimetilacetamida, *N*-metilpirrolidin-2-ona o dimetilsulfóxido. La reacción se lleva a cabo convenientemente a una temperatura en el intervalo de, por ejemplo, -20°C hasta 100°C, preferiblemente entre 0°C y la temperatura ambiente, dependiendo de la reacción que se esté llevando a cabo y de la naturaleza del grupo saliente Z.

La reacción se puede llevar a cabo típicamente en presencia de una base. Las bases adecuadas incluyen bases de aminas orgánicas, tales como piridina, 2,6-lutidina, *N,N*-diisopropiletilamina, colidina, 4-dimetilaminopiridina, trietilamina, morfolina, *N*-metilmorfolina o diazabiciclo[5.4.0]undec-7-eno, carbonatos o hidróxidos de metales alcalinos o alcalino-térreos, tales como carbonato de sodio, carbonato de potasio, carbonato de calcio, hidróxido de sodio o hidróxido de potasio, amiduros de metales alcalinos, tal como hexametildisilazuro de sodio (NaHMDS), o hidruros de metales alcalinos, tales como hidruro de sodio, dependiendo de la reacción llevada a cabo y de la naturaleza del grupo saliente Z.

La reacción también se puede llevar a cabo en presencia de un ácido de Lewis, por ejemplo trimetilaluminio, dependiendo de la reacción llevada a cabo y de la naturaleza del grupo saliente Z.

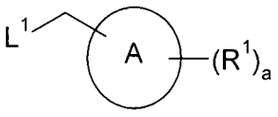
Como alternativa, la presente invención proporciona además un procedimiento para la preparación de un compuesto de fórmula **(I)** como se define aquí, o una sal farmacéuticamente aceptable del mismo, que comprende hacer reaccionar un compuesto de fórmula **(IV)**



(IV)

en la que Q es hidrógeno o un grupo protector (por ejemplo un grupo t-Bu o BOC, o como se describe en "Protective Groups in Organic Synthesis", 2ª edición, T.W. Greene y P.G.M. Wuts, Wiley-Interscience (1991)), y B, R^2, R^3 y b son como se definen aquí anteriormente para un compuesto de fórmula **(I),**

con un compuesto de fórmula **(V)**



(V)

en la que L^1 representa OH o un grupo saliente tal como halógeno o OTs; y A, R^1 y a son como se definen aquí anteriormente para un compuesto de fórmula **(I)**

para dar un compuesto de fórmula **(I),**

y opcionalmente llevar a cabo una o más de las siguientes:

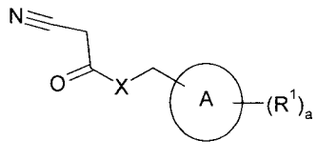
- convertir el compuesto obtenido en un compuesto adicional de la invención
- formar una sal farmacéuticamente aceptable del compuesto.

La reacción se puede llevar a cabo convenientemente en un disolvente adecuado, tal como diclorometano a una temperatura en el intervalo de 0°C hasta la temperatura ambiente. Cuando L^1 es OH, la reacción se puede llevar a cabo típicamente en presencia de azidocarboxilato de diisopropilo y trifenilfosfina. Cuando L^1 es un halógeno o OTs, la reacción se puede llevar a cabo convenientemente en un disolvente adecuado, tal como N,N-dimetilformamida o acetonitrilo, a una temperatura en el intervalo desde la temperatura ambiente hasta 100°C. La reacción se puede llevar a cabo típicamente en presencia de una base inorgánica, tal como carbonato de potasio o hidruro de sodio.

Los compuestos de fórmula **(II)**, **(III)**, **(IV)** o **(V)** están comercialmente disponibles, son conocidos en la bibliografía, o se pueden preparar usando técnicas conocidas.

Los compuestos de fórmula **(II)**, en los que Z es halógeno o –OR, se pueden preparar a partir de compuestos de fórmula (**II**) en los que Z es –OH, mediante métodos conocidos en la bibliografía. Por ejemplo, se pueden emplear métodos conocidos para la preparación de cloruros de ácidos o ésteres a partir de ácidos carboxílicos.

Los compuestos de fórmula **(III)** en los que **X** representa CH_2 se pueden preparar haciendo reaccionar un compuesto de fórmula (VI)

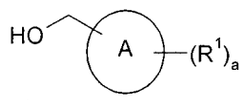


con una hidrazina de fórmula (VII)

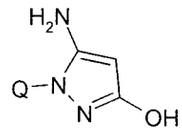


La reacción se puede llevar a cabo convenientemente en un disolvente, tal como etanol, a un intervalo de temperatura de 60 a 80°C.

Como alternativa, los compuestos de fórmula **(III)** en los que **X** representa O se pueden preparar haciendo reaccionar un compuesto de fórmula (VIII)

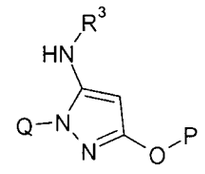


con un compuesto de fórmula (IX)

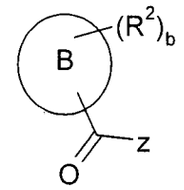


La reacción se puede llevar a cabo convenientemente en un disolvente, tal como diclorometano, a un intervalo de temperatura de 0°C hasta la temperatura ambiente. La reacción se puede llevar a cabo típicamente en presencia de azidocarboxilato de diisopropilo y trifenilfosfina.

Los compuestos de fórmulas **(IV)** se pueden preparar haciendo reaccionar un compuesto de fórmula (X)



con un compuesto de fórmula (II)



en la que Z representa un grupo saliente (por ejemplo halógeno, por ejemplo cloro, -CN, $-N_3$, -OH oun grupo –OR, -OC(O)R, $-OCR(NR^aR^b)_2$ o $-OC(=NR)NR^aR^b$ en el que R es un alquilo, arilo, heteroarilo o alcarilo opcionalmente sustituido, y cada R^a, R^b es independientemente hidrógeno o un alquilo, arilo o alcarilo opcionalmente sustituido);

P representa H o un grupo protector (por ejemplo como se describe en "Protective Groups in Organic Synthesis", 2ª edición, T.W. Greene y P.G.M. Wuts, Wiley-Interscience (1991));

Q es hidrógeno o un grupo protector (por ejemplo un grupo t-Bu o BOC, o como se describe en "Protective Groups in Organic Synthesis", 2ª edición, T.W. Greene y P.G.M. Wuts, Wiley-Interscience (1991)), y

B, R^2, R^3 y b son como se definen aquí anteriormente para un compuesto de fórmula **(I),**

y, cuando P es un grupo protector, eliminar el grupo protector P.

Los compuestos de fórmula **(VI)**, **(VII)**, **(VIII)** y **(IX)** son compuestos comercialmente disponibles, o son conocidos en la bibliografía, o se pueden preparar meidnate procedimientos estándar conocidos en la técnica.

Los compuestos de fórmula **(I)** se pueden convertir en otros compuestos de fórmula **(I)** usando procedimientos estándares. Los ejemplos de los tipos de reacciones de conversion que se pueden usaar incluyen la introducción de un sustituyente por medio de una reacción de sustitución aromática, la reducción de sustituyentes, la alquilación de sustituyentes y la oxidación de sustituyentes. Los reactivos y las condiciones de reacción para tales procedimientos son bien conocidos en la técnica química. Los ejemplos de reacciones de

sustitución aromática incluyen la introducción de un grupo nitro usando ácido nítrico concentrado; la introducción de un grupo acilo usando, por ejemplo, un haluro de acilo y un ácido de Lewis (tal como tricloruro de aluminio) en condiciones de Friedel Crafts; la introducción de un grupo arilo, por ejemplo, usando un haluro de arilo en condiciones de Suzuki; la introducción de un grupo amino usando, por ejemplo, un haluro de arilo y una amina en condiciones de Buchwald; la introducción de un grupo alquilo usando un haluro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) en condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Los ejemplos de reacciones de reducción incluyen la reducción de un grupo nitro a un grupo amino mediante hidrogenación catalítica con un catalizador de níquel o mediante tratamiento con hierro en presencia de ácido clorhídrico y calor; y ejemplos particulares de reacciones de oxidación incluyen la oxidación de alquiltio a alquilsulfinilo o alquilsulfonilo. Estos reactivos y condiciones de reacción descritos anteriormente son bien conocidos en la técnica.

Se apreciará por los expertos en la técnica que, en los procedimientos de la presente invención, puede ser necesario proteger, mediante grupos protectores, ciertos grupos funcionales tales como los grupos hidroxilo o amino en los reactivos de partida o en los compuestos intermedios. De este modo, la preparación de los compuestos de fórmula **(I)** puede implicar, en diversas etapas, la adición y eliminación de uno o más grupos protectores.

La protección y desprotección de grupos funcionales se describe en "Protective Groups in Organic Chemistry", editado por J.W.F. McOmie, Plenum Press (1973) y "Protective Groups in Organic Synthesis", 2ª edición, T.W. Greene y P.G.M. Wuts, Wiley–Interscience (1991).

Los compuestos de la fórmula **(I)** anterior se pueden convertir en una sal farmacéuticamente aceptable, por ejempo una sal de adición de ácidos, tal como una sal de hidrocloruro, hidrobromuro, fosfato, acetato, fumarato, maleato, tartrato, citrato, oxalato, metanosulfonato o *p*–toluenosulfonato, o una sal de metal alcalino, tal como una sal de sodio o potasio.

Ciertos compuestos de fórmula **(I)** son susceptibles de existir en formas estereoisómeras. Se entenderá que la invención abarca el uso de todos los isómeros geométricos y ópticos (incluyendo atropisómeros) de los compuestos de fórmula **(I)** y sus mezclas, incluyendo los racematos. El uso de tautómeros y mezclas de los mismos también forma un aspecto de la presente invención.

Algunos compuestos de fórmula **(I)**, o una sal farmacéuticamente aceptable de los mismos, se pueden aislar como un sólido amorfo o como un sólido cristalino. Si el compuesto está en forma cristalina, puede existir en un número de diferentes formas polimórficas. Los ejemplos de compuestos que se han aislado como sólidos amorfos o cristalinos incluyen: el Ejemplo 10 aislado como una forma cristalina (2-Theta 3,521 (100%), 7,025 (14,8%), 9,274 (16,9%), 9,654 (15,2%), 10,162 (14,8%), 10,508 (19,3%), 11,628 (49,8%), 12,047 (19,3%), 14,516 (21%), 16,242 (26,3%), 17,682 (18,5%), 18,099 (31,3%), 18,615 (92,6%), 19,315 (56,8%), 20,353 (16%), 20,581 (17,3%), 21,192 (10,3%), 22,467 (23%), 23,057 (88,1%), 23,28 (52,3%), 24,261 (34,2%), 25,363 (10,7%), 27,546 (15,6%), 28,285 (14%) y 29,862 (11,9 %); el Ejemplo 75 aislado como un sólido amorfo; el Ejemplo 81 aislado como un un sólido amorfo; el Ejemplo 144 aislado como una forma cristalina (2-Theta 3,62 (100%), 7,247 (4,6%), 10,013 (5,1%), 10,889 (8,1%), 11,294 (7,7%), 12,185 (8,6%), 14,091 (19%), 18,2 (12,7%), 19,102 (8,9%), 19,789 (15,2%) y 20,608 (32,7%); el Ejemplo 99 aislado como una forma cristalina (2-Theta 4,293 (100%), 8,498 (14%), 10,694 (8,1%), 13,078 (4,5%), 15,056 (49,4%), 16,14 (8,1%), 16,298 (11,1%), 17,425 (34,6%), 17,812 (23,1%), 18,157 (9,6%), 19,224 (15%), 20,931 (20,2%), 21,819 (27,9%), 22,248 (16,2%), 22,593 (23,7%), 23,416 (8,8%), 24,726 (26%), 25,295 (11,6%), 25,859 (5,6%), 27,001 (5,9%), 27,754 (5,3%), 28,442 (4,8%), 29,861 (4,3%), 30,89 (3,8%), 32,264 (5,9%) y 32,896 (5,4%); el Ejemplo 147 aislado como una forma cristalina (2-Theta 4,492 (91,3%), 12,465 (23,1%), 13,862 (26,3%), 14,56 (14,4%), 15,811 (16,3%), 17,226 (24,4%), 17,886 (20%), 18,3 (15%), 18,9 (100%), 21,328 (20%), 21,705 (28,1%), 23,263 (27,5%), 23,699 (19,4%), 24,005 (53,8%), 24,333 (37,5%), 25,184 (11,9%), 26,114 (11,3%), 26,573 (10,6%) y 27,803 (16,9%); el Ejemplo 151 aislado como una forma cristalina (2-Theta 3,754 (29,6%), 8,495 (13,9%), 10,235 (19,1%), 10,98 (29,6%), 12,014 (23,5%), 13,38 (18,3%), 14,591 (33%), 15,924 (41,7%), 17,057 (26,1%), 17,379 (30,4%), 18,219 (32,2%), 18,791 (36,5%), 19,201 (100%), 19,577 (47,8%), 20,788 (33%), 21,394 (27%), 22,07 (33%), 23,285 (25,2%), 23,922 (29,6%) y 25,533 (33%); el Ejemplo 154 aislado como una forma cristalina (2-Theta 5,833 (89,6%), 9,786 (21,9%), 10,784 (32,8%), 12,121 (30,7%), 13,394 (35,4%), 13,709 (45,3%), 14,939 (28,1%), 16,799 (35,4%), 17,664 (25%), 18,223 (21,9%), 18,646 (50%), 19,29 (25,5%), 20,563 (35,4%), 21,32 (100%), 22,747 (37,5%), 24,154 (38,5%), 25,197 (23,4%), 25,704 (15,1%), 26,752 (16,7%) y 31,134 (12%); y el Ejemplo 155 aislado como un sólido amorfo. Excepto que se establezca de otro modo, los patrones de difracción de rayos X se determinaron montando una muestra del

material cristalino en montajes de obleas de cristal de silicio único (SSC) Siemens y extendiendo la muestra en una capa delgada con la ayuda de un portaobjetos de microscopio. La muestra se hizo girar a 30 revoluciones por minuto (para mejorar las estadísticas del recuento), y se irradió con rayos X generados mediante un tubo de foco fino de longitud de cobre a 40 kV y 40 mA con una longitud de ondas de 1.5418 Angstroms usando un difractómetro Siemens 5000. La fuente de rayos X colimada se hizo pasar a trvés de una ranura de divergencia variable auomática ajustada a V20, y la radiación reflejada se dirigió a través de una ranura antidispersión de 2 mm y una ranura detectora de 0,2 mm. La muestra se expuso durante 1 segundo por incremento de 2-theta de 0,02 grados (modo de barrido continuo) en el intervalo de 2-theta de 2 grados hasta 40 grados en el modo theta-theta. El instrumento estaba equipado con un contador de centelleos como detector. El control y la captura de datos se realizó por medio de una estación Dell Optiplex 686 NT 4.0 Workstation que funciona con el programa Diffrac+.

La persona experta en la técnica apreciará que los datos del patrón de difracción presentados aquí no se deben de interpretar como absolutos (para más información, véase Jenkins, R y Snyder, R.L. "Introduction to X-Ray Powder Diffractometry" John Wiley & Sons, 1996). Por lo tanto, se debe entender que la forma cristalina no pretende estar limitada a los cristales que proporcionan patrones de difracción de rayos X de polvo idénticos a los patrones de difracción de rayos X de polvo descritos aquí. La presente invención también incluye cualesquiera cristales que proporcionen patrones de difracción de rayos X de polvo sustancialmente iguales a los descritos aquí. Una persona experta en la técnica de difracción de rayos X es capaz de juzgar la similitud sustancial de los patrones de difracción de rayos X de polvo, y entenderá que las diferencias pueden ser el resultado de diversos factores, por ejemplo errores de medida que resultan de las condiciones de medida (tales como el equipo, la preparación de la muestra, o la máquina usada); las variaciones de intensidad, que resultan de las condiciones de medida y preparación de la muestra; las variaciones de intensidad relativa de picos, que resultan de variaciones en el tamaño o relaciones de aspecto no unitarias de los cristales; y la posición de las reflexiones, que se pueden ver afectadas por la altura precisa a la que se coloca la muestra en el difractómetro y la calibración del cero del difractómetro, y la planaridad superficial de la muestra.

Los compuestos de fórmula **(I)** tienen actividad como compuestos farmacéuticos, en particular como moduladores o inhibidores de la actividad de FGFR, y se pueden usar en el

tratamiento de enfermedades/afecciones proliferativas e hiperproliferativas, cuyos ejemplos incluyen los siguientes cánceres:

(1) carcinoma, que incluye el de vejiga, cerebro, mama, colon, riñón, hígado, pulmón, ovario, páncreas, próstata, estómago, cuello uterino, colon, tiroides y piel;

(2) tumores hematopoyéticos de estirpe linfoidea, que incluyen leucemia linfocítica aguda, linfoma de células B y linfoma de Burketts;

(3) tumores hematopoyéticos de estirpe mieloidea, que incluyen leucemias mielogenosas agudas y crónicas y leucemia promielocítica;

(4) tumores de origen mesenquimatoso, que incluyen fibrosarcoma y rabdomiosarcoma; y

(5) otros tumores, que incluyen melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma.

En una realización, los compuestos de la invención son útiles en el tratamiento de tumores de la vejiga, mama y próstata, y mieloma múltiple.

De este modo, la presente invención proporciona un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, para uso en terapia.

Según un aspecto adicional de la presente invención, se proporciona un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí anteriormente, para uso en un método de tratamiento del cuerpo humano o animal mediante terapia.

En un aspecto adicional, la presente invención proporciona el uso de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable, como se define aquí, en la fabricación de un medicamento para uso en terapia.

En el contexto de la presente memoria descriptiva, el término "terapia" también incluye "profilaxis", excepto que haya indicaciones específicas de lo contrario. Los términos "terapéutico" y "terapéuticamente" se deben de interpretar en consecuencia.

La invención también proporciona un método para tratar cáncer, que comprende administrar a un paciente que lo necesite una cantidad terapéuticamente eficaz de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí.

Se ha encontrado que los compuestos definidos en la presente invención, o una sal farmacéuticamente aceptable del mismo, son agentes anticancerígenos eficaces cuya propiedad se cree que surge de la modulación o inhibición de la actividad de FGFR. En

consecuencia, es de esperar que los compuestos de la presente invención sean útiles en el tratamiento de enfermedades o estados médicos mediados solo o en parte por FGFR, es decir, los compuestos se pueden usar para producir un efecto inhibidor de FGFR en un animal de sangre caliente que necesite de tal tratamiento.

De este modo, los compuestos de la presente invención proporcionan un método para tratar cáncer, caracterizado por la inhibición de FGFR, es decir, los compuestos se pueden usar para producir un efecto anticancerígeno mediado solo o en parte por la inhibición de FGFR.

Es de esperar que tal compuesto de la invención posea un amplio intervalo de propiedades anticancerígenas puesto que se han observado mutaciones activantes en FGFR en muchos cánceres humanos, incluyendo pero sin limitarse a mama, vejiga, próstata y mieloma múltiple. De este modo, es de esperar que un compuesto de la invención poseerá actividad anticancerígena frente a estos cánceres. Además, es de esperar que un compuesto de la presente invención poseerá actividad frente a un intervalo de leucemias, neoplasias malignas linfoideas y tumores sólidos tales como carcinomas y sarcomas en tejidos tales como el hígado, el riñón, la vejiga, la próstata, la mama y el páncreas. En una realización, es de esperar que los compuestos de la invención ralenticen ventajosamente el crecimiento de tumores sólidos primarios y recurrentes de, por ejemplo, la piel, colon, tiroides, pulmones y ovarios. Más particularmente, es de esperar que los compuestos de la invención, o una sal farmacéuticamente aceptable de los mismos, inhiban el crecimiento de aquellos tumores que están asociados con FGFR, especialmente aquellos tumores que dependen significativamente de FGFR para su crecimiento y difusión, incluyendo, por ejemplo, ciertos tumores de vejiga, próstata, mama y mieloma múltiple.

De este modo, según este aspecto de la invención, se proporciona un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, para uso como un medicamento.

Según un aspecto adicional de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en la fabricación de un medicamento para uso en la producción de un efecto inhibidor de FGFR en un animal de sangre caliente tal como el hombre.

Según este aspecto de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en la

fabricación de un medicamento para uso en la producción de un efecto anticancerígeno en un animal de sangre caliente tal como el hombre.

Según una característica adicional de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en la fabricación de un medicamento para uso en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer de pulmón, leucemias, neoplasias malignas linfoideas, mieloma múltiple, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama y páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según un aspecto adicional de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en la producción de un efecto inhibidor de FGFR en un animal de sangre caliente tal como el hombre.

Según este aspecto de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en la producción de un efecto anticancerígeno en un animal de sangre caliente tal como el hombre.

Según una característica adicional de la invención, se proporciona el uso de un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer de pulmón, leucemias, neoplasias malginas linfoides, mieloma múltiple, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama y páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios.

Según una característica adicional de este aspecto de la invención, se proporciona un método para producir un efecto inhibidor de FGFR en un animal de sangre caliente, tal como el hombre, que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí.

Según una característica adicional de este aspecto de la invención, se proporciona un método para producir un efecto anticancerígeno en un animal de sangre caliente, tal como el hombre, que necesite de tal tratamiento, que comprende administrar a dicho animal una

cantidad eficaz de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí.

Según una característica adicional de este aspecto de la invención, se proporciona un método para tratar melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer de pulmón, leucemias, neoplasias malginas linfoides, mieloma múltiple, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama y páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios, en un animal de sangre caliente, tal como el hombre, que necesite de tal tratamiento, que comprende administrar a dicho animal una cantidad eficaz de un compuesto de fórmula **(I)** o una sal farmacéuticamente aceptable del mismo como se define aquí.

En otro aspecto de la invención, se proporciona una composición farmacéutica que comprende un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en asociación con un diluyente o vehículo farmacéuticamente aceptable para uso en la producción de un efecto inhibidor de FGFR en un animal de sangre caliente, tal como el hombre.

En otro aspecto de la invención, se proporciona una composición farmacéutica que comprende un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en asociación con un diluyente o vehículo farmacéuticamente aceptable para uso en la producción de un efecto anticancerígeno en un animal de sangre caliente, tal como el hombre.

En otro aspecto de la invención, se proporciona una composición farmacéutica que comprende un compuesto de la fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en asociación con un diluyente o vehículo farmacéuticamente aceptable para uso en el tratamiento de melanoma, tumores papilares de tiroides, colangiocarcinomas, cáncer de colon, cáncer ovárico, cáncer de pulmón, leucemias, neoplasias malignas de linfoides, mieloma múltiple, carcinomas y sarcomas en el hígado, riñón, vejiga, próstata, mama y páncreas, y tumores sólidos primarios y recurrentes de la piel, colon, tiroides, pulmones y ovarios en un animal de sangre caliente, tal como el hombre.

Los compuestos de fórmula **(I)** y sus sales farmacéuticamente aceptables se pueden usar por sí mismos, pero generalmente se administrarán en forma de una composición farmacéutica en la que el compuesto de fórmula **(I)** o sal (ingrediente activo) está en asociación con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

Dependiendo del modo de administración, la composición farmacéutica puede comprender de 0,01 a 99% en peso (porcentaje en peso), de 0,05 a 80% en peso, de 0,10 a 70% en peso, y/o incluso de 0,10 a 50% en peso, de ingrediente activo, basándose todos los porcentajes en peso, en la composición total.

La presente invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, en asociación con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

La invención proporciona además un procedimiento para la preparación de una composición farmacéutica de la invención, que comprende mezclar un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, como se define aquí, con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

Las composiciones farmacéuticas se pueden administrar tópicamente, (por ejemplo, a la piel o al pulmón y/o vías respiratorias) en forma de, por ejemplo, cremas, disoluciones, suspensiones, aerosoles de heptafluoroalcanos y formulaciones en polvo seco; o sistémicamente, por ejemplo mediante administración oral en forma de comprimidos, cápsulas, jarabes, polvos o gránulos; o mediante administración parenteral en forma de disoluciones o suspensiones; o mediante administración subcutánea; o mediante administración rectal en forma de supositorios; o transdérmicamente.

Las composiciones de la invención se pueden obtener mediante procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en la técnica. De este modo, las composiciones destinadas a uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Los excipientes adecuados farmacéuticamente aceptables para una formulación en comprimidos incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y disgregantes tales como almidón de maíz o ácido algínico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido esteárico o talco; agentes conservantes tales como p-hidroxibenzoato de etilo o de propilo, y antioxidantes, tales como ácido ascórbico. Las formulaciones en comprimidos pueden estar recubiertas o no recubiertas, ya sea para modificar su desintegración y la absorción subsiguiente del ingrediente activo en el

tubo digestivo, o para mejorar su estabilidad y/o aspecto, usando en cualquiera de los casos agentes y procedimientos de revestimiento convencionales bien conocidos en la técnica.

Las composiciones para uso oral pueden estar en forma de cápsulas de gelatina duras, en las que el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blandas, en las que el ingrediente activo se mezcla con agua o un aceite, tal como aceite de cacahuete, parafina líquida, o aceite de oliva.

Las suspensiones acuosas generalmente contienen el ingrediente activo en forma de polvo finamente dividido, junto con uno o más agentes de suspensión, tales como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato sódico, polivinilpirrolidona, goma de tragacanto y goma arábiga; agentes dispersantes o humectantes, tales como lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo estearato de polioxietileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con un hexitol, tales como monooleato de polioxietilensorbitol, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con un hexitol, tales como monooleato de polioxietilensorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos con anhídridos de hexitol, por ejemplo monooleato de polietilensorbitán. Las suspensiones acuosas también pueden contener uno o más agentes conservantes (tales como p-hidroxibenzoato de etilo o de propilo), antioxidantes (tales como ácido ascórbico), agentes colorantes, agentes aromatizantes, y/o agentes edulcorantes (tales como sacarosa, sacarina o aspartamo).

Las suspensiones oleosas se pueden formular suspendiendo el ingrediente activo en un aceite vegetal (tal como aceite de cacahuete, aceite de oliva, aceite de sésamo o aceite de coco), o en un aceite mineral (tal como parafina líquida). Las suspensiones oleosas también pueden contener un agente espesante, tal como cera de abeja, parafina dura o alcohol cetílico. Los agentes edulcorantes, tales como los expuestos anteriormente, y los agentes aromatizantes se pueden añadir para proporcionar una preparación oral de sabor agradable. Estas

composiciones se pueden conservar mediante la adición de un antioxidante, tal como ácido ascórbico.

Los polvos y gránulos dispersables, adecuados para la preparación de una suspensión acuosa mediante adición de agua, generalmente contienen el ingrediente activo junto con un agente dispersante o humectante, un agente de suspensión, y uno o más conservantes. Los agentes dispersantes o humectantes y los agentes de suspensión adecuados se ejemplifican mediante los ya mencionados anteriormente. También pueden estar presentes excipientes adicionales tales como agentes edulcorantes, aromatizantes y colorantes.

Las composiciones farmacéuticas de la invención también pueden estar en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de cacahuete, o un aceite mineral, tal como por ejemplo parafina líquida, o una mezcla de cualquiera de estos. Los agentes emulsionantes adecuados pueden ser, por ejemplo, gomas de origen natural, tales como goma arábiga o goma de tragacanto, fosfátidos de origen natural, tales como haba de soja, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos con anhídridos de hexitol (por ejemplo monooleato de sorbitán), y productos de condensación de los mencionados ésteres parciales con óxido de etileno, tales como monooleato de polioxietilensorbitán. Las emulsiones también pueden contener agentes edulcorantes, aromatizantes y conservantes.

Los jarabes y elixires se pueden formular con agentes edulcorantes, tales como glicerina, propilenglicol, sorbitol, aspartamo o sacarosa, y también pueden contener un agente emoliente, un conservante, un aromatizante y/o un colorante.

Las composiciones farmacéuticas también pueden estar en forma de una suspensión acuosa u oleosa estéril inyectable, que se puede formular según procedimientos conocidos usando uno o más de los agentes dispersantes o humectantes y agentes de suspensión apropiados, que se han mencionado anteriormente. Una preparación inyectable estéril también puede ser una disolución o suspensión inyectable estéril en un diluyente o disolvente no tóxico, parenteralmente aceptable, por ejemplo una disolución en 1,3-butanediol.

Las formulaciones de supositorios se pueden preparar mezclando el ingrediente activo con un excipiente no irritante adecuado, el cual es sólido a temperaturas normales, pero es líquido a la temperatura rectal y por lo tanto se fundirá en el recto para liberar el fármaco. Los excipientes adecuados incluyen, por ejemplo, manteca de cacao y polietilenglicoles.

Las formulaciones tópicas, tales como cremas, ungüentos, geles y disoluciones o suspensiones acuosas u oleosas, se pueden obtener generalmente formulando un ingrediente activo con un vehículo o diluyente convencional, tópicamente aceptable, usando procedimientos convencionales bien conocidos en la técnica.

Las composiciones para la administración mediante insuflamiento pueden estar en forma de un polvo finamente dividido que contiene partículas de diámetro medio de, por ejemplo, 30 μm o mucho menos, comprendiendo el propio polvo el ingrediente activo solo o diluido con uno o más vehículos fisiológicamente aceptables, tal como lactosa. El polvo para insuflamiento se retiene entonces convenientemente en una cápsula que contiene, por ejemplo, 1 a 50 mg de ingrediente activo para uso con un dispositivo Turboinhaler, tal como se usa para el insuflamiento del agente conocido cromoglicato sódico.

Las composiciones para la administración mediante inhalación pueden estar en forma de un aerosol a presión convencional, montado para administrar el ingrediente activo ya sea como un aerosol que contiene un sólido finamente dividido o como gotitas líquidas. Se pueden usar propelentes convencionales de aerosoles, tales como hidrocarburos o hidrocarburos fluorados volátiles, y el dispositivo de aerosol se monta convenientemente para administrar una cantidad medida de ingrediente activo.

Para una información adicional sobre la formulación, refiérase el lector al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

El tamaño de la dosis para fines terapéuticos de un compuesto de la invención variará naturalmente de acuerdo con la naturaleza y gravedad de las afecciones, la edad y el sexo del animal o paciente, y la vía de administración, de acuerdo con principios de medicina bien conocidos.

En general, un compuesto de la invención se administrará de tal modo que se reciba una dosis diaria comprendida en el intervalo de, por ejemplo, 0,1 mg a 1000 mg de ingrediente activo por kg de peso corporal, administrada si se requiere en dosis divididas. Sin embargo, la dosis diara variará necesariamente dependiendo del hospedante tratado, de la vía particular de administración y de la gravedad de la enfermedad tratada. En consecuencia, la dosis óptima se puede determinar por el médico que está tratando a un paciente particular. En general, se administrarán dosis menores cuando se emplee una vía parenteral. Así, por ejemplo, para administración intravenosa, se usará generalmente una dosis comprendida en el

intervalo de, por ejemplo, 0,1 mg a 30 mg de ingrediente activo por kg de peso corporal. Análogamente, para administración por inhalación, se usará una dosis comprendida en el intervalo de, por ejemplo, 0,1 mg a 25 mg de ingrediente activo por kg de peso corporal. No obstante, se prefiere la administración oral. Por ejemplo, una formulación destinada a la administración oral a seres humanos contendrá generalmente, por ejemplo, de 0,1 mg a 2 g de ingrediente activo.

Para información adicional sobre Vías de Administración y Regímenes de Dosificación, se remite al lector al Capitulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

El tratamiento anticancerígeno definido aquí anteriormente se puede aplicar como una terapia individual, o puede implicar, además del compuesto de la invención, cirugía convencional o radioterapia o quimioterapia. Tal quimioterapia puede incluir una o más de las siguientes categorías de agentes antitumorales:

(i) otros fármacos antiproliferativos/antineoplásicos, y combinaciones de los mismos, como se usan en oncología médica, tales como agentes alquilantes (por ejemplo cis-platino, oxaliplatino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucilo, busulfán, temozolamida y nitrosoureas); antimetabolitos (por ejemplo, gemcitabina y antifolatos tales como fluoropirimidinas como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, arabinósido de citosina, e hidroxiurea); antibióticos antitumorales (por ejemplo, antraciclinas como adriamicina, bleomicina, doxorrubicina, daunomicina, epirrubicina, idarrubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo, alcaloides de la vinca como vincristina, vinblastina, vindesina y vinorrelbina, y taxoides como taxol y taxotere e inhibidores de polocinasa); e inhibidores de topoisomerasa (por ejemplo, epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecán y camptotecina);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifeno, fulvestrant, toremifeno, raloxifeno, droloxifeno e yodoxifeno), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorrelina y buserelina), progestágenos (por ejemplo acetato de megestrol), inhibidores de aromatasa (por ejemplo como anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α-reductasa tales como finasterida;

(iii) agentes contra la invasión (por ejemplo inhibidores de la familia de c-Src cinasas como 4-(6-cloro-2,3-metilendioxianilino)-7-[2-(4-metilpiperazin-1-il)etoxi]-5-tetrahidropiran-4-iloxiquinazolina (AZD0530; Solicitud de Patente Internacional 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), e inhibidores de metaloproteinasas, como marimastat, e inhibidores de la función del receptor del activador de plasminógeno urocinasa o anticuerpos para heparanasa);

(iv) inhibidores de la función del factor de crecimiento: por ejemplo tales inhibidores incluyen anticuerpos contra el factor de crecimiento, anticuerpos contra el receptor del factor de crecimiento (por ejemplo, el anticuerpo anti-erbB2 trastuzumab [Herceptin™], el anticuerpo anti-EGFR panitumumab, y el anticuerpo anti-erbB1 Cetuximab [Erbitux, C225]), y cualesquiera anticuerpos contra el factor de crecimiento o el receptor del factor de crecimiento descritos por Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, p 11-29); tales inhibidores también incluyen inhibidores de tirosina cinasas, por ejemplo inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo, los inhibidores de tirosina cinasas de la familia del EGFR, tales como N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, AZD1839), 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)), inhibidores de erbB2 tirosina cinasas tales como lapatinib, inhibidores de la familia del factor de crecimiento de hepatocitos, inhibidores de la familia del factor de crecimiento derivado de plaquetas tales como imatinib, inhibidores de serina/treonina cinasas (por ejemplo inhibidores de la señalización de Ras/Raf, tales como inhibidores de farnesil transferasas, por ejemplo sorafenib (BAY 43-9006)), inhibidores de la señalización celular a través de MEK y/o AKT cinasas, inhibidores de la familia del factor de crecimiento de hepatocitos, inhibidores de C-kit, inhibidores de abl cinasas, inhibidores de cinasas del receptor de IGF (factor de crecimiento similar a insulina); inhibidores de aurora cinasas (por ejemplo AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 y AX39459) e inhibidores de cinasas dependientes de ciclinas, tales como inhibidores de CDK2 y/o CDK4;

(v) agentes antiangiogénicos tales como aquellos que inhiben los efectos del factor de crecimiento endotelial vascular [por ejemplo, el anticuerpo anti-factor de crecimiento de células endoteliales vasculares bevacizumab (Avastin™), e inhibidores de tirosina cinasas del

receptor de VEGF, tales como 4-(4-bromo-2-fluoroanilino)-6-metoxi-7-(1-metilpiperidin-4-ilmetoxi)quinazolina (ZD6474; Ejemplo 2 en el documento WO 01/32651), 4-(4-fluoro-2-metilindol-5-iloxi)-6-metoxi-7-(3-pirrolidin-1-ilpropoxi)quinazolina (AZD2171; Ejemplo 240 en el documento WO 00/47212), vatalanib (PTK787; documento WO 98/35985) y SU11248 (sunitinib; documento WO 01/60814), compuestos tales como los descritos en las Solicitudes de Patentes Internacionales WO97/22596, WO 97/30035, WO 97/32856 y WO 98/13354, y compuestos que funcionan mediante otros mecanismos (por ejemplo linomida, inhibidores de la función $\alpha v\beta 3$ de integrina, y angiostatina)];

(vi) agentes que dañan la vasculatura, tales como Combretastatina A4 y los compuestos descritos en las Solicitudes de Patentes Internacionales WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias antisentido, por ejemplo las que van dirigidas contra las dianas enumeradas anteriormente, tales como ISIS 2503, un antisentido anti-ras;

(viii) enfoques de terapia génica, incluyendo, por ejemplo, enfoques para sustituir genes aberrantes, tales como p53 aberrante o BRCA1 or BRCA2 aberrante, enfoques de GDEPT (terapia de profármaco y enzima dirigida por genes), tales como aquellos que usan citosina desaminasa, timidina cinasa o una enzima de nitrorreductasa bacteriana, y enfoques para incrementar la tolerancia del paciente a la quimioterapia o radioterapia, tales como la terapia génica de resistencia a múltiples fármacos; y

(ix) enfoques inmunoterapéuticos, incluyendo, por ejemplo, enfoques ex vivo e in vivo para incrementar la inmunogenicidad de las células tumorales del paciente, tales como la transfección con citocinas tales como interleucina 2, interleucina 4 o el factor estimulador de colonias de granulocitos-macrófagos, enfoques para disminuir la anergia de las células T, enfoques que usan células inmunitarias transfectadas, tales como células dendríticas transfectadas con citocinas, enfoques que usan estirpes celulares tumorales transfectadas con citocinas, y enfoques que usan anticuerpos anti-idiotípicos.

Ejemplos

La invención se describirá ahora adicionalmente con referencia a los siguientes ejemplos ilustrativos, en los que, excepto que se establezca de otro modo:

(i) las temperaturas se dan en grados Celsius (°C); las operaciones se llevaron a cabo a temperatura ambiente, esto es, a una temperatura en el intervalo de 18-25°C;

(ii) las disoluciones orgánicas se secaron sobre sulfato de magnesio anhidro; la evaporación del disolvente se llevó a cabo usando un evaporador giratorio a presión reducida (600-4000 pascales; 4,5-30 mm Hg) con una temperatura del baño de hasta 60°C;

(iii) cromatografía significa cromatografía ultrarrápida sobre gel de sílice; la cromatografía de capa fina (TLC) se llevó a cabo sobre placas de gel de sílice;

(iv) en general, el transcurso de las reacciones fue seguido por TLC, y los tiempos de reacción se dan sólo para ilustración;

(v) los productos finales tuvieron datos de espectros de resonancia magnética nuclear (RMN) protónica y/o de masas satisfactorios;

(vi) los rendimientos se dan sólo para ilustración, y no son necesariamente los que se pueden obtener mediante un desarrollo diligente del procedimiento; las preparaciones se repitieron si se requirió más material;

(vii) cuando se dan, los datos de RMN están en forma de valores de delta para los protones de diagnóstico principales, dados en partes por millón (ppm) con relación a tetrametilsilano (TMS) como patrón interno, determinados a 300 MHz en DMSO-d_6, excepto que se indique de otro modo;

(viii) los símbolos químicos tienen sus significados habituales; se usan las unidades y símbolos del SI;

(ix) las relaciones de disolventes se dan en términos de volumen:volumen (v/v); y

(x) los datos de los espectros de masas (MS) se generaron en un sistema de LC/MS en el que el componente de la HPLC comprendió generalmente un equipo Agilent 1100 o Waters Alliance HT (2790 y 2795) y se llevó a cabo en una columna Phemonenex Gemini C_18 5□m, 50 x 2 mm (o similar), eluyendo con eluyente ácido (por ejemplo, usando un gradiente entre 0 – 95% de agua / acetonitrilo con 5% de ácido fórmico al 1% en una mezcla 50:50 de agua:acetonitrilo (v/v); o usando un sistema disolvente equivalente con metanol en lugar de acetonitrilo), o con un eluyente básico (por ejemplo, usando un gradiente entre 0 – 95% de agua / acetonitrilo con 5% de amoníaco 0,880 al 0,1% en una mezcla de acetonitrilo); el componente de la MS comprendió generalmente un espectrómetro Waters ZQ. Se generaron los cromatogramas para la intensidad del pico base positivo y negativo por electropulverización (ESI) y el cromatograma de absorción total de UV a partir de 220-300 nm, y se dan los valores para m/z; generalmente, sólo se dan los iones que indican la masa

progenitora y, excepto que se establezca de otro modo, el valor dado es el (M+H)+ para el modo de ion positivo, y el $(M-H)^-$ para el modo de ion negativo;

(xi) la HPLC preparative se llevó a cabo en sílice de fase inverse C18, por ejemplo en una columna de fase inversa preparativa Waters "Xterra" (sílice de 5 micrómetros, diámetro de 19 mm, 100 mm de longitud) usando mezclas cada vez menos polares como eluyente, por ejemplo mezclas cada vez menos polares de agua (que contiene 1% de ácido acético o 1% de hidróxido de amonio acuoso (d=0,88) y acetonitrilo;

(xii) se han usado las siguientes abreviaturas:

THF	tetrahidrofurano;
DMF	*N,N*-dimetilformamida;
EtOAc	acetato de etilo;
DCM	diclorometano; y
DMSO	dimetilsulfóxido
DIPEA	*N,N*-diisopropiletilamina (también conocida como N-etil-N-propan-2-il-propan-2-amina)
PBS	disolución salina tamponada con fosfato
HEPES	acido *N*-[2-Hidroxietil]piperazin-*N*'-[2-etanosulfónico]
DTT	ditiotreitol
ATP	trifosfato de adenosina
BSA	seroalbúmina bovina
DMEM	medio de Egle modificado de Dulbecco
MOPS	ácido 3-(N-morfolino)propanosulfónico

(xiii) los compuestos se nombraron usando el programa de nomenclatura patentado: Openeye Lexichem versión 1.4, usando la convención de nomenclatura de la IUPAC;

(xiv) excepto que se especifique de otro modo, los materiales de partida están comercialmente disponibles.

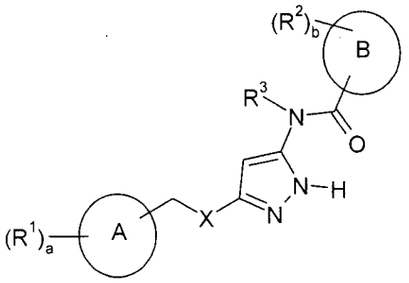
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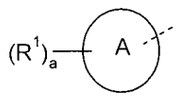
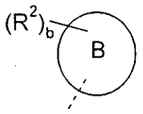
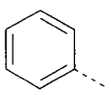
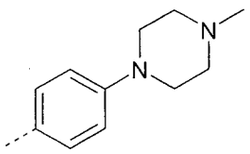
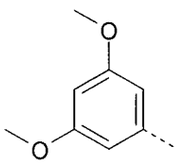
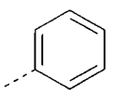
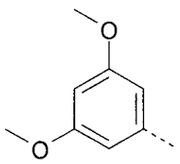
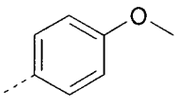
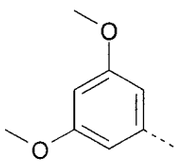
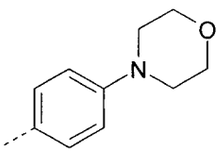
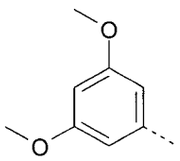
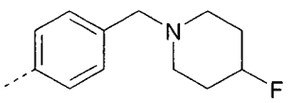
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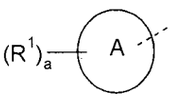
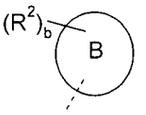
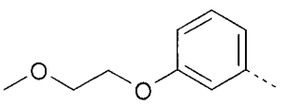
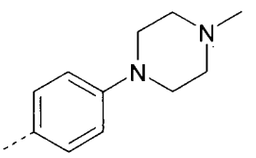
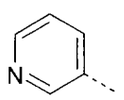
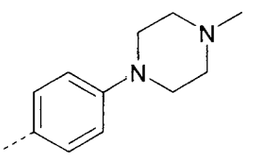
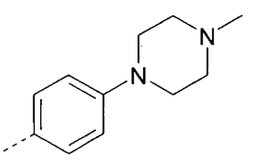
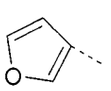
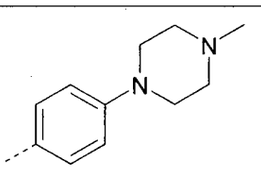
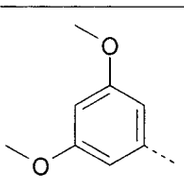
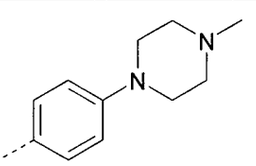
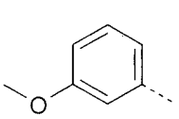
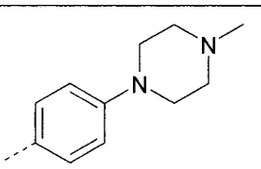
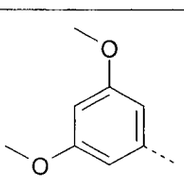
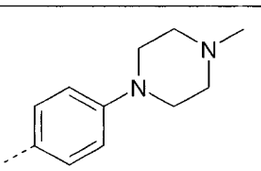
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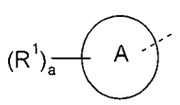
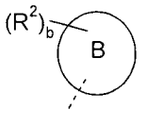
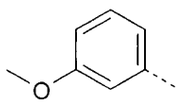
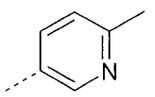
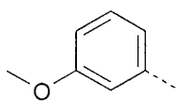
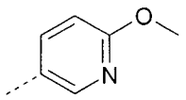
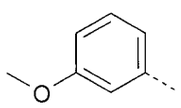
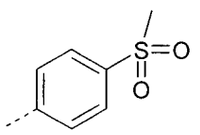
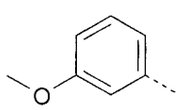
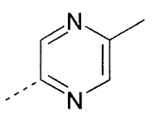
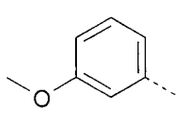
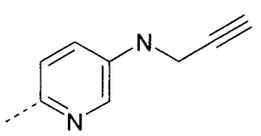
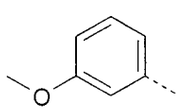
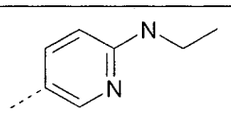
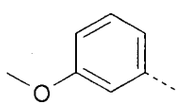
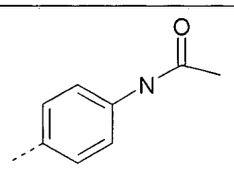
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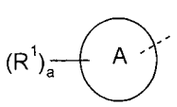
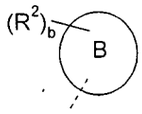
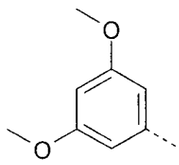
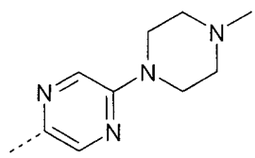
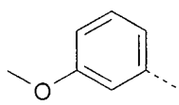
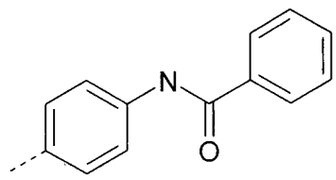
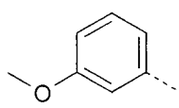
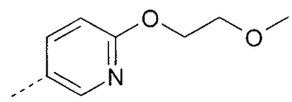
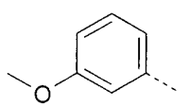
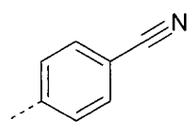
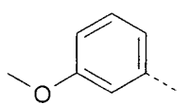
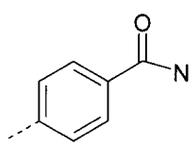
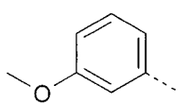
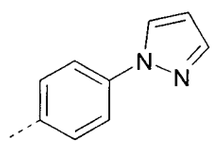
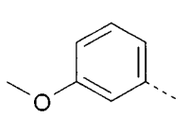
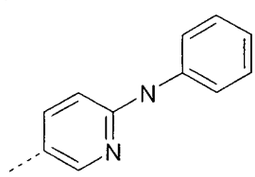
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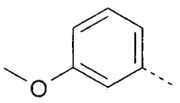
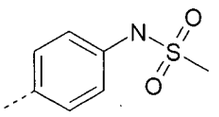
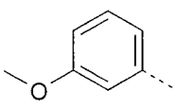
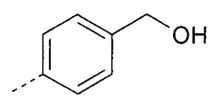
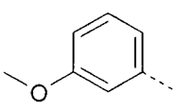
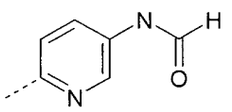
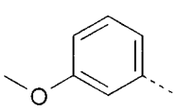
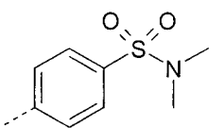
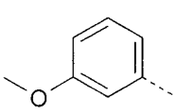
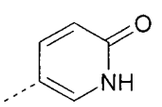
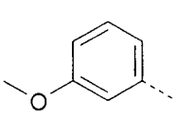
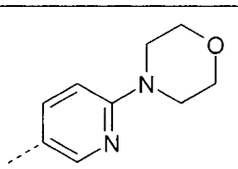
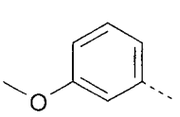
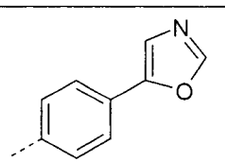


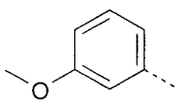
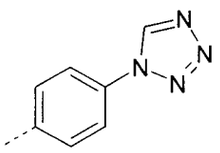
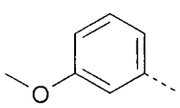
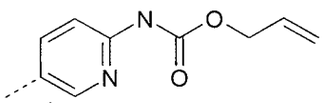
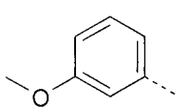
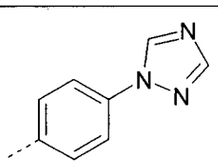
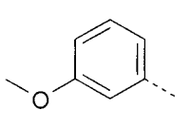
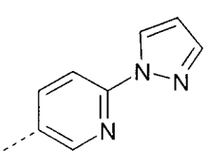
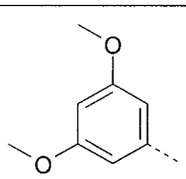
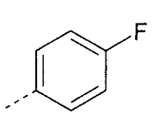
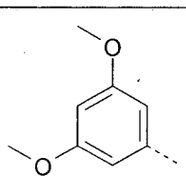
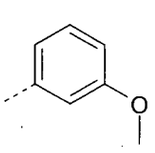
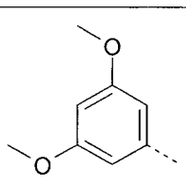
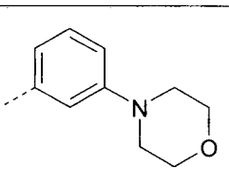
Ejemplo		X		R^3
1		CH_2		H
2		CH_2		H
3		CH_2		H
4		CH_2		H
5		CH_2		H

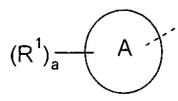
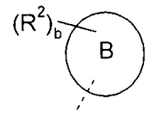
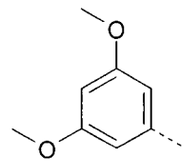
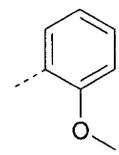
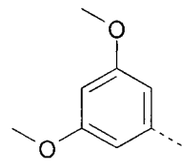
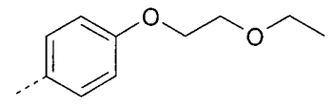
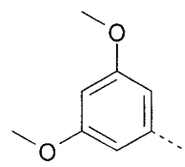
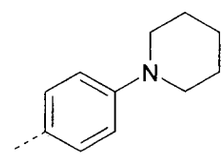
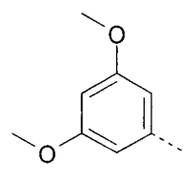
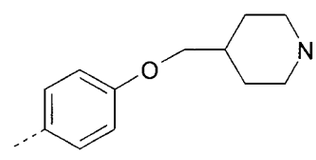
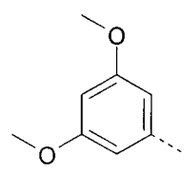
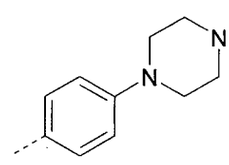
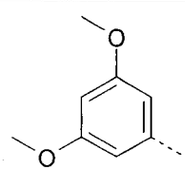
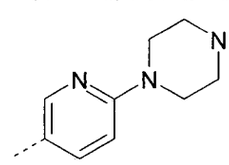
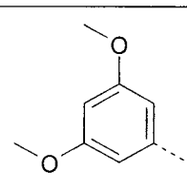
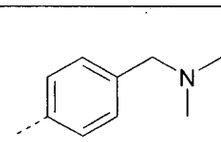
Ejemplo		X		R^3
6		CH_2		H
7		CH_2		H
8		CH_2		H
9		CH_2		H
10		CH_2		H
11		CH_2		H
12		O		H

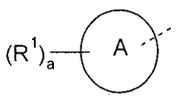
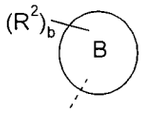
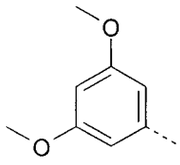
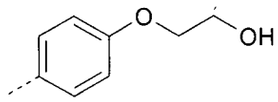
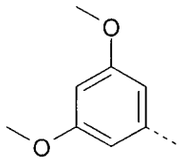
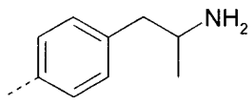
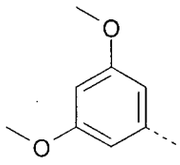
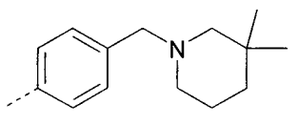
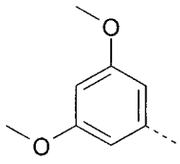
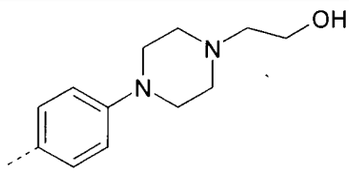
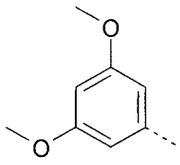
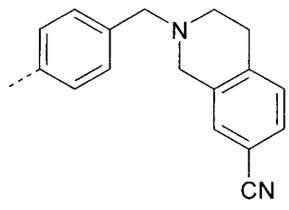
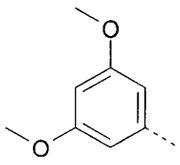
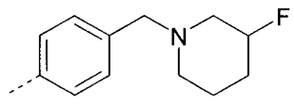
Ejemplo		X		R^3
13		CH_2		H
14		CH_2		H
15		CH_2		H
16		CH_2		H
17		CH_2		H
18		CH_2		H
19		CH_2		H

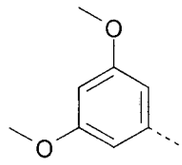
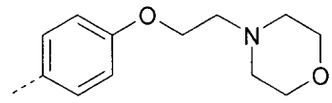
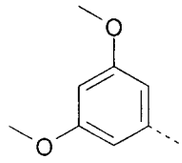
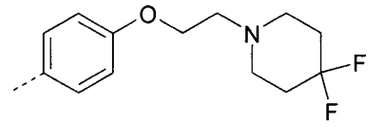
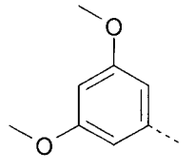
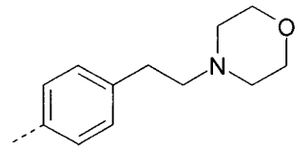
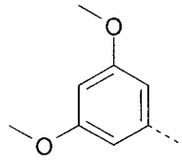
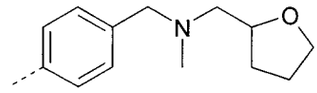
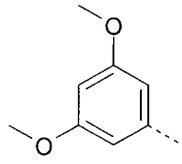
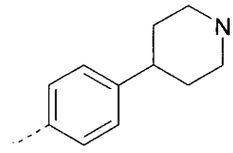
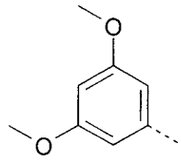
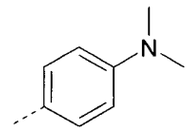
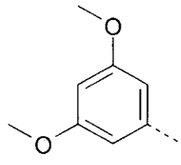
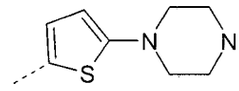
Ejemplo		X		R^3
20		O		H
21		CH_2		H
22		CH_2		H
23		CH_2		H
24		CH_2		H
25		CH_2		H
26		CH_2		H

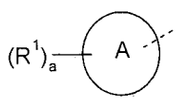
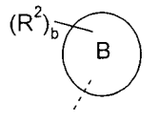
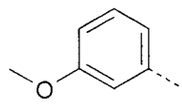
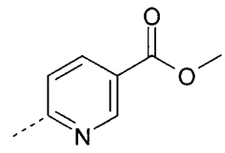
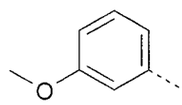
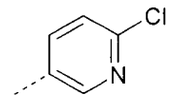
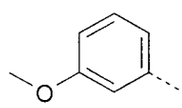
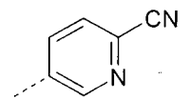
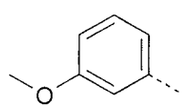
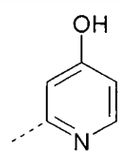
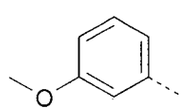
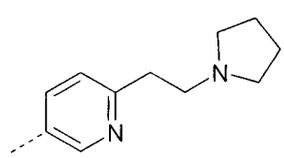
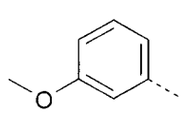
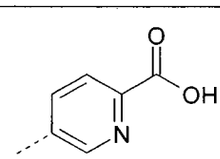
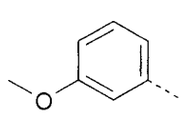
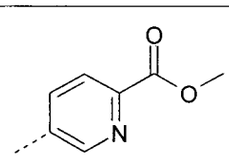
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
27		CH_2		H
28		CH_2		H
29		CH_2		H
30		CH_2		H
31		CH_2		H
32		CH_2		H
33		CH_2		H

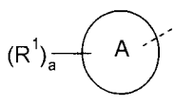
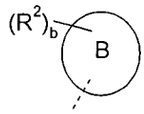
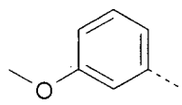
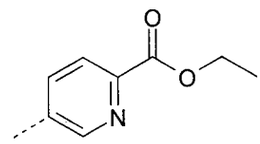
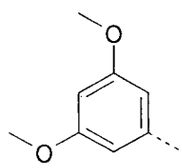
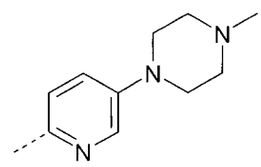
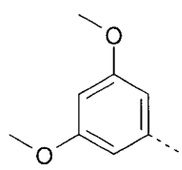
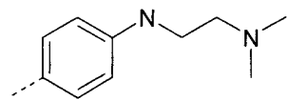
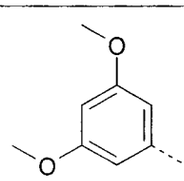
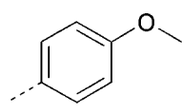
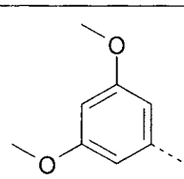
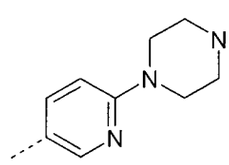
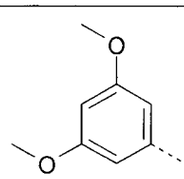
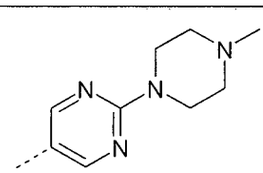
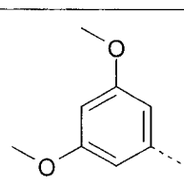
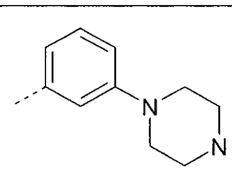
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
34		CH_2		H
35		CH_2		H
36		CH_2		H
37		CH_2		H
38		CH_2		H
39		CH_2		H
40		CH_2		H

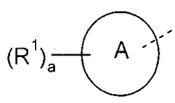
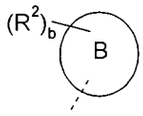
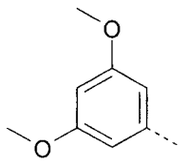
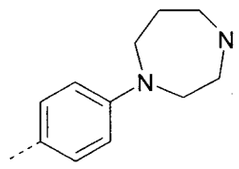
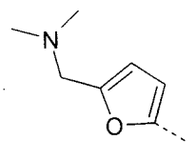
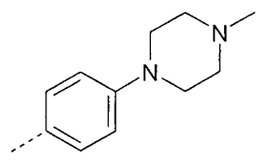
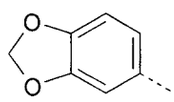
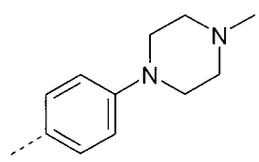
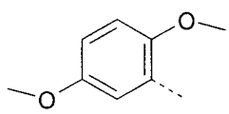
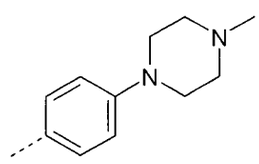
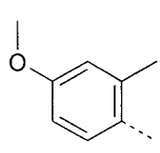
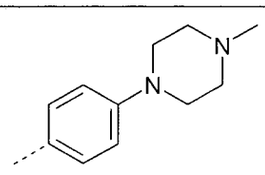
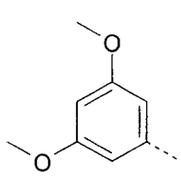
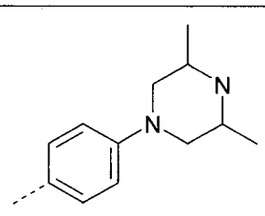
Ejemplo		X		R^3
41		CH_2		H
42		CH_2		H
43		CH_2		H
44		CH_2		H
45		CH_2		H
46		CH_2		H
47		CH_2		H

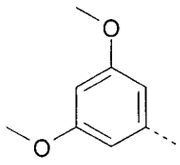
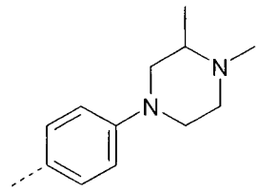
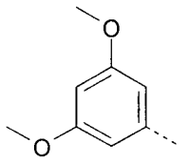
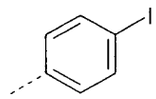
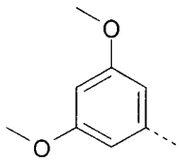
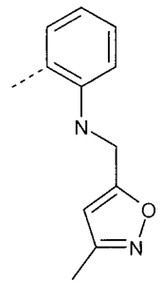
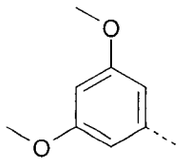
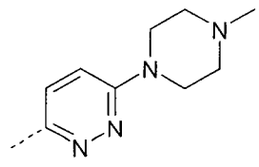
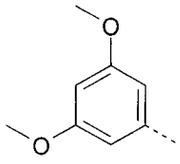
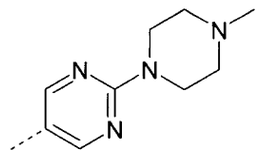
Ejemplo		X		R^3
48		CH_2		H
49		CH_2		H
50		CH_2		H
51		CH_2		H
52		CH_2		H
53		CH_2		H

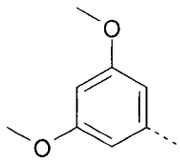
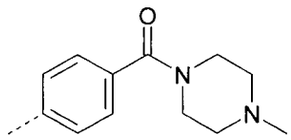
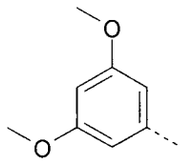
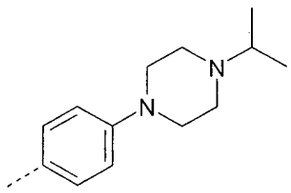
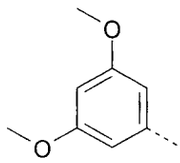
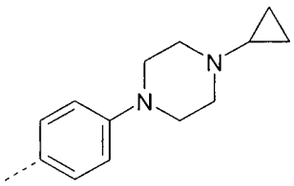
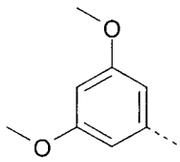
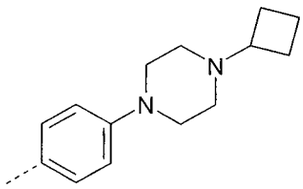
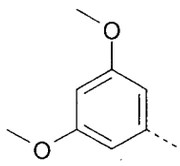
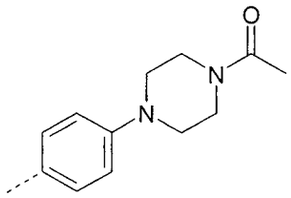
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
54		CH_2		H
55		CH_2		H
56		CH_2		H
57		CH_2		H
58		CH_2		H
59		CH_2		H
60		CH_2		H

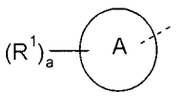
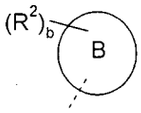
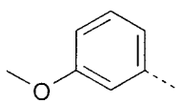
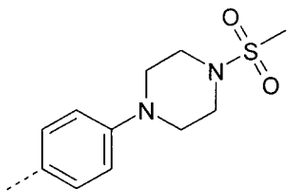
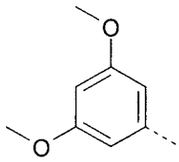
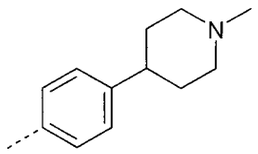
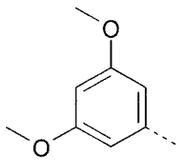
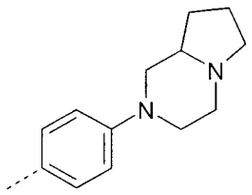
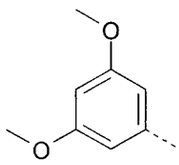
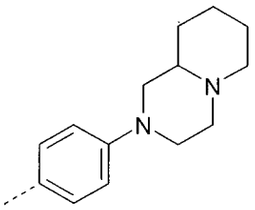
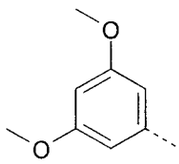
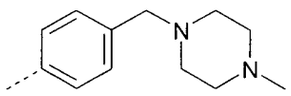
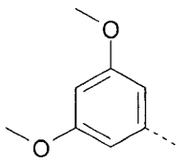
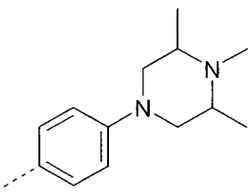
Ejemplo		X		R^3
61		CH_2		H
62		CH_2		H
63		CH_2		H
64		CH_2		H
65		CH_2		H
66		CH_2		H
67		CH_2		H

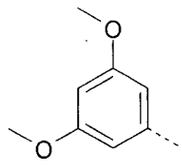
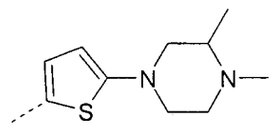
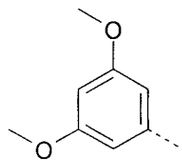
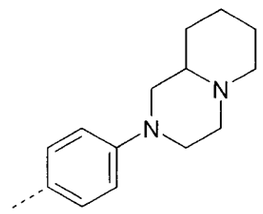
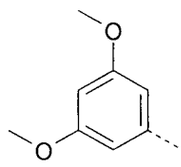
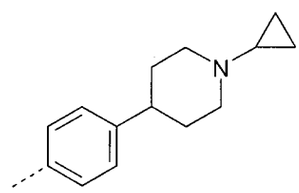
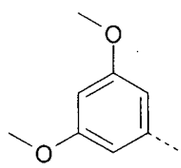
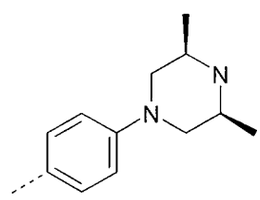
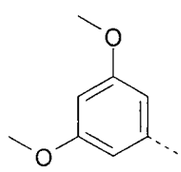
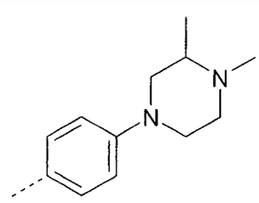
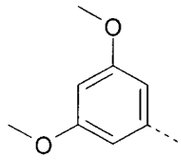
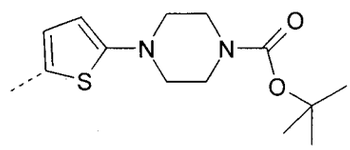
Ejemplo		X		R^3
68		CH_2		H
69		O		H
70		O		H
71		O		H
72		O		H
73		O		H
74		O		H

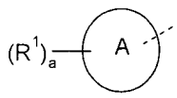
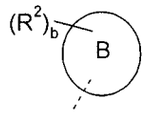
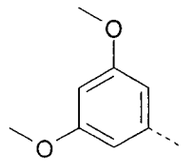
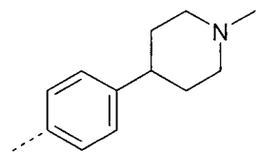
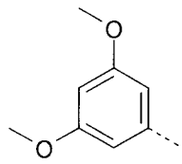
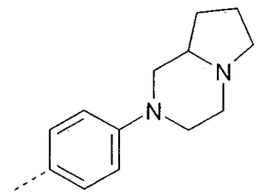
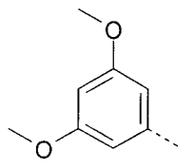
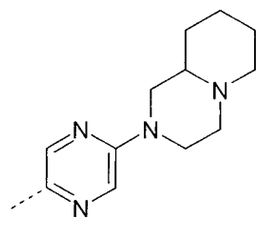
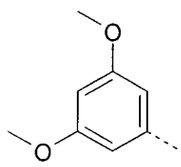
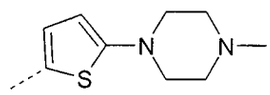
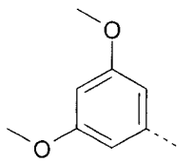
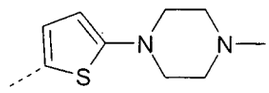
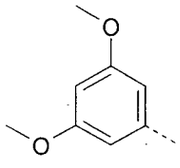
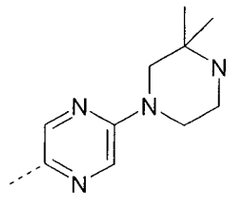
Ejemplo		X		R^3
75		O		H
76		CH_2		H
77		CH_2		H
78		CH_2		H
79		CH_2		H
80		CH_2		H

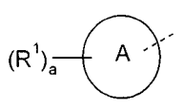
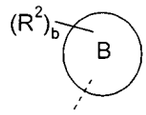
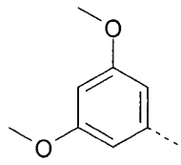
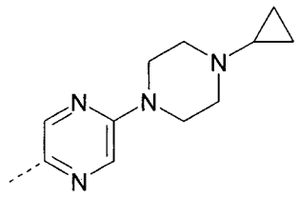
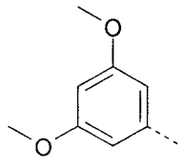
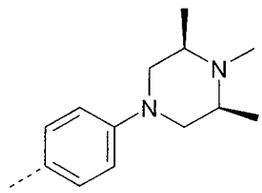
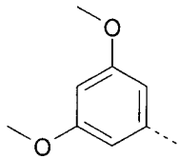
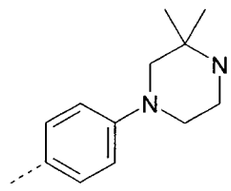
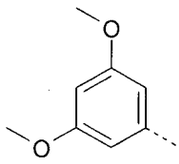
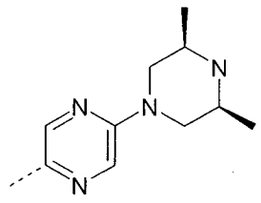
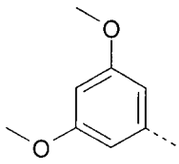
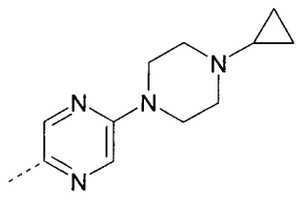
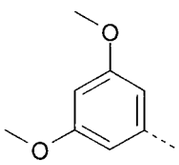
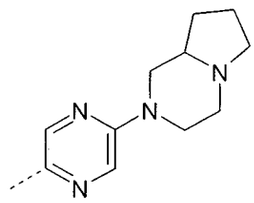
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
81		CH_2		H
82		CH_2		H
83		CH_2		H
84		CH_2		H
85		CH_2		H

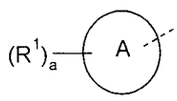
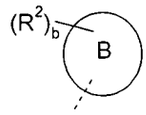
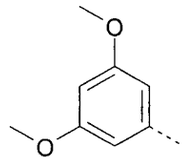
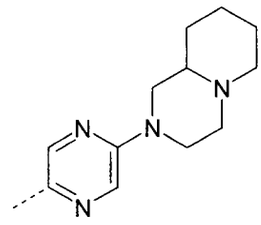
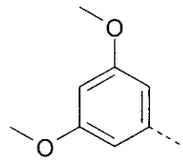
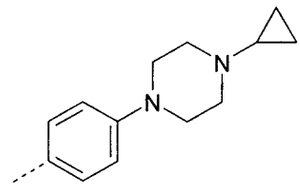
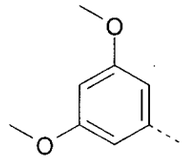
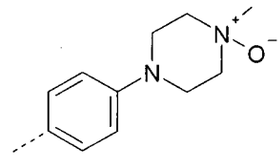
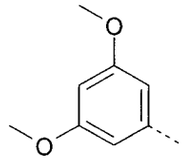
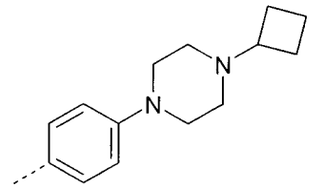
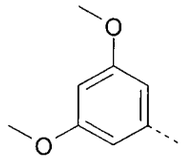
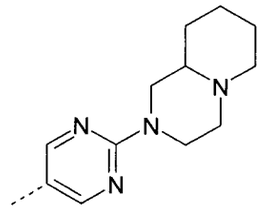
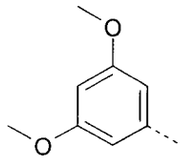
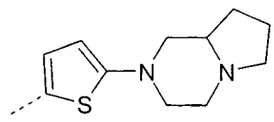
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
86		CH_2		H
87		CH_2		H
88		CH_2		H
89		CH_2		H
90		CH_2		H

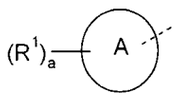
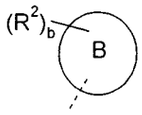
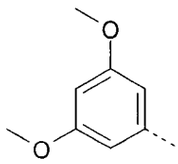
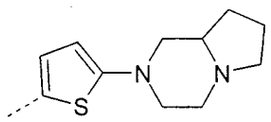
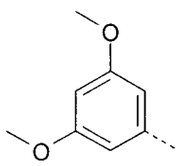
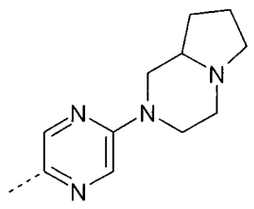
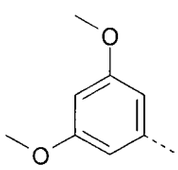
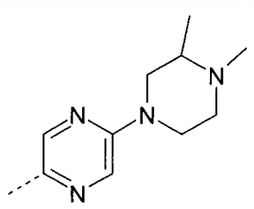
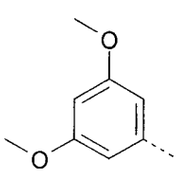
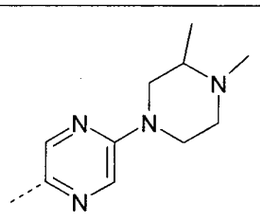
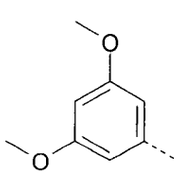
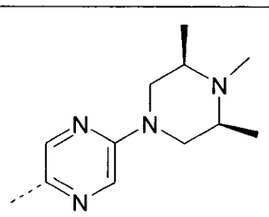
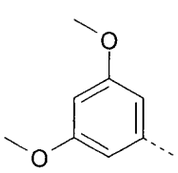
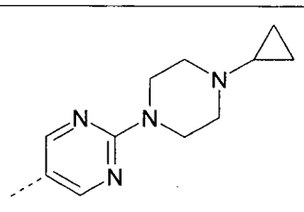
Ejemplo		X		R^3
91		CH_2		H
92		CH_2		H
93		CH_2		H
94		CH_2		H
95		CH_2		H
96		CH_2		H

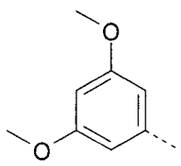
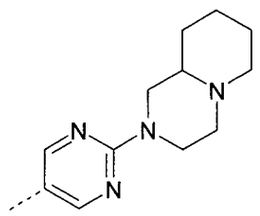
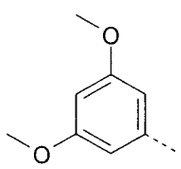
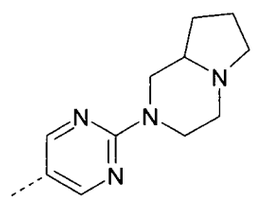
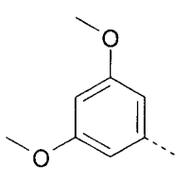
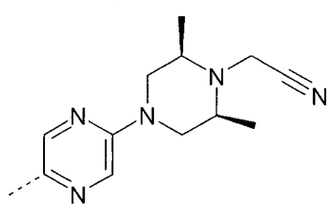
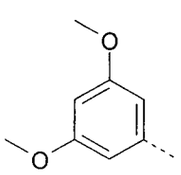
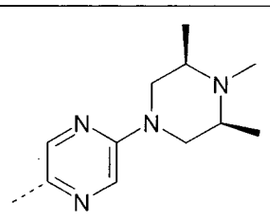
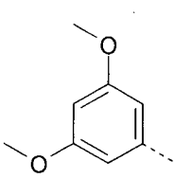
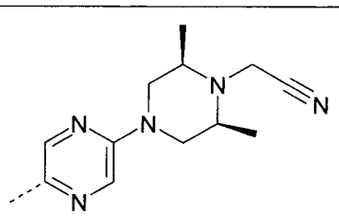
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
97		O		H
98		O		H
99		CH_2		H
100		O		H
101		O		H
102		CH_2		H

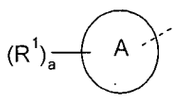
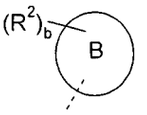
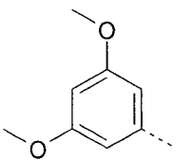
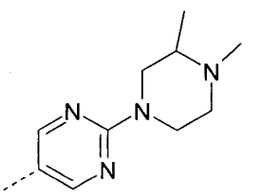
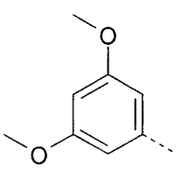
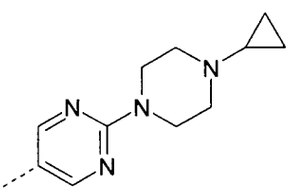
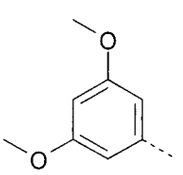
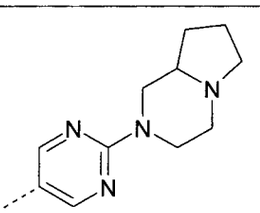
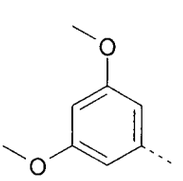
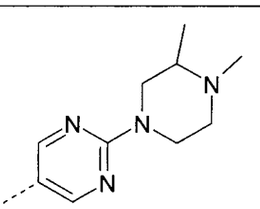
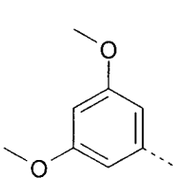
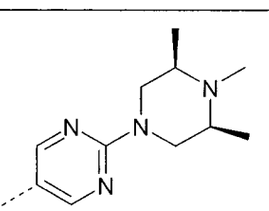
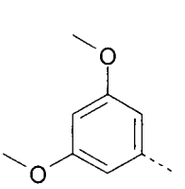
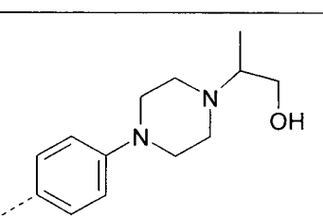
Ejemplo		X		R^3
103		O		H
104		O		H
105		CH_2		H
106		CH_2		H
107		O		H
108		CH_2		H

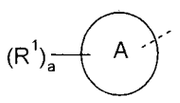
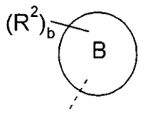
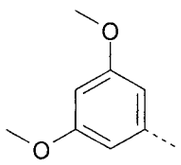
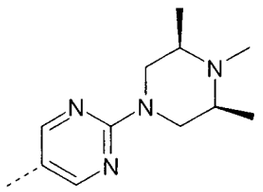
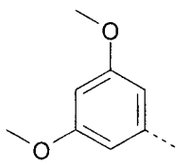
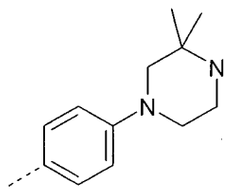
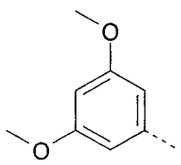
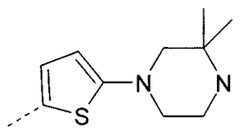
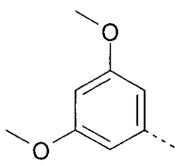
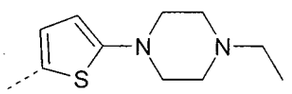
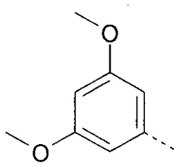
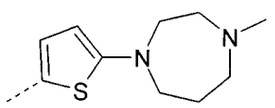
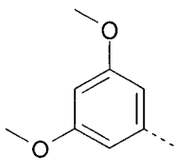
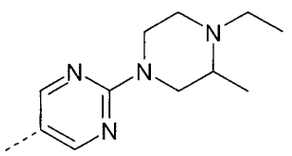
Ejemplo		X		R^3
109		O		H
110		O		H
111		O		H
112		CH_2		H
113		CH_2		H
114		CH_2		H

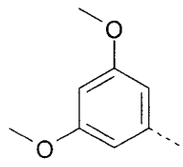
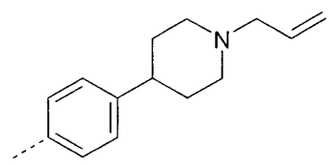
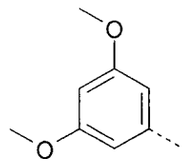
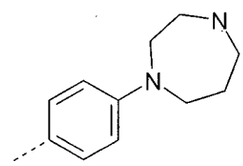
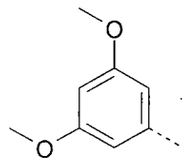
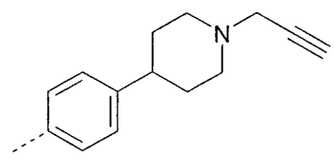
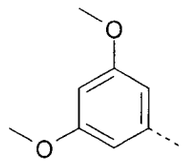
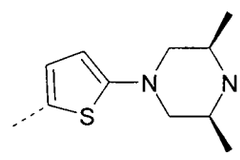
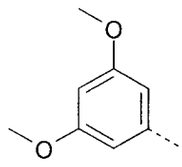
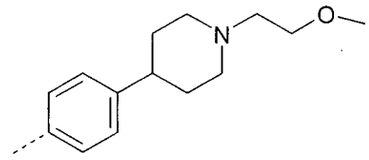
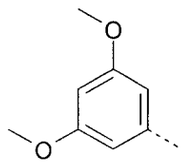
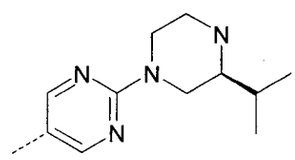
Ejemplo		X		R^3
115		O		H
116		O		H
117		CH_2		H
118		O		H
119		O		H
120		CH_2		H

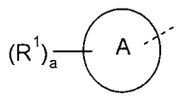
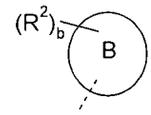
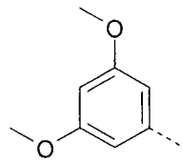
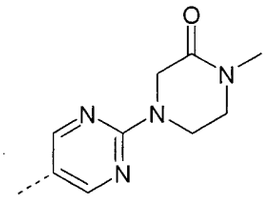
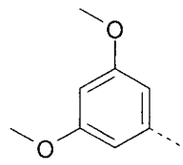
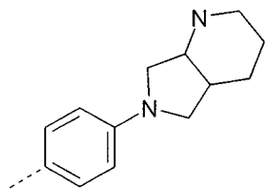
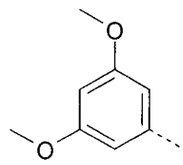
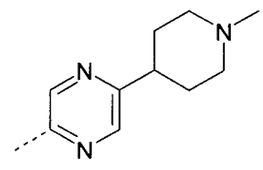
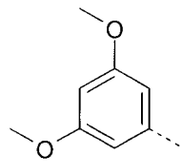
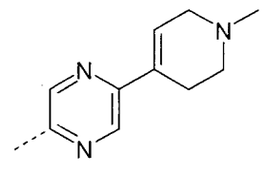
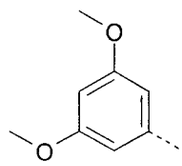
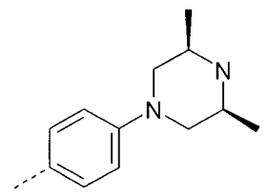
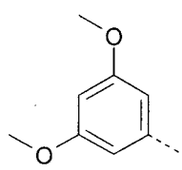
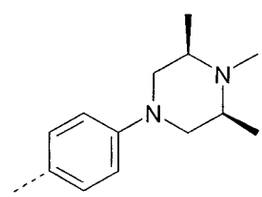
Ejemplo		X		R^3
121		O		H
122		O		H
123		CH_2		H
124		O		H
125		CH_2		H
126		CH_2		H

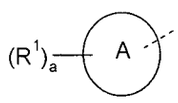
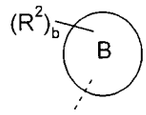
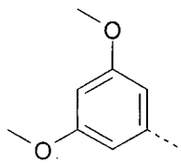
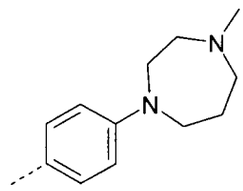
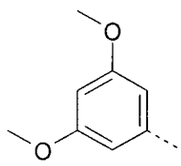
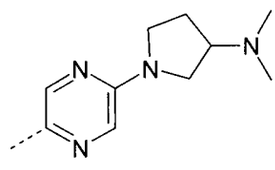
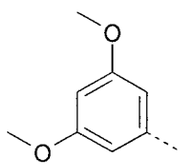
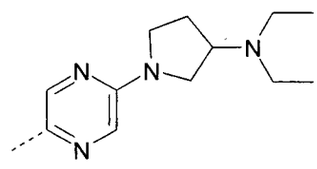
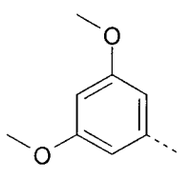
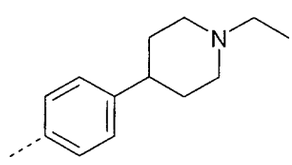
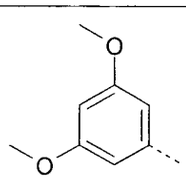
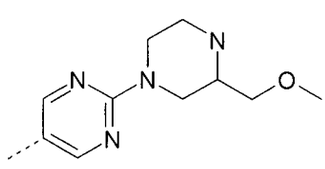
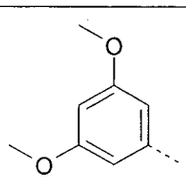
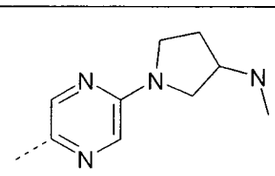
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
127		CH_2		H
128		CH_2		H
129		CH_2		H
130		O		H
131		O		H

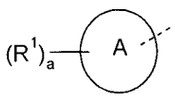
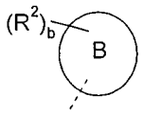
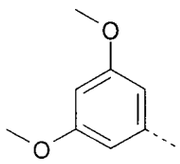
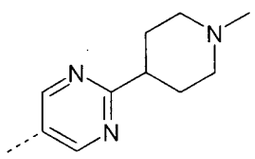
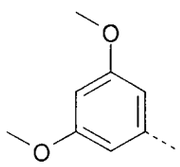
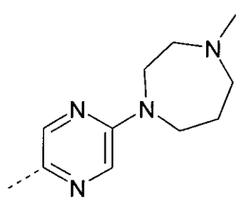
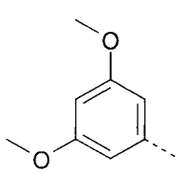
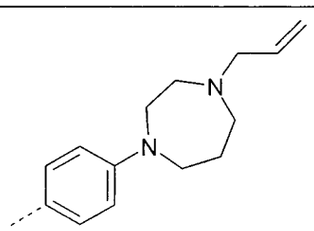
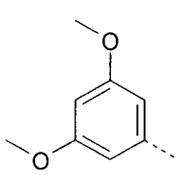
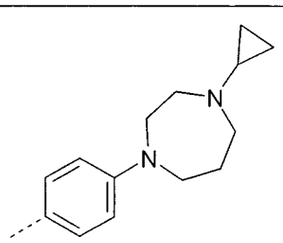
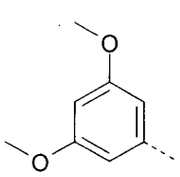
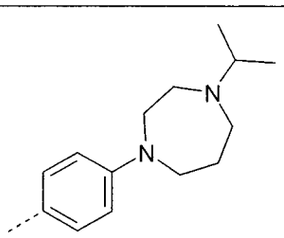
Ejemplo		X		R^3
132		O		H
133		O		H
134		O		H
135		CH_2		H
136		CH_2		H
137		CH_2		H

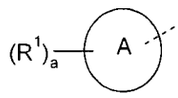
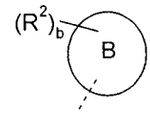
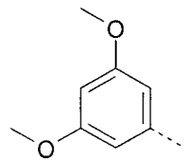
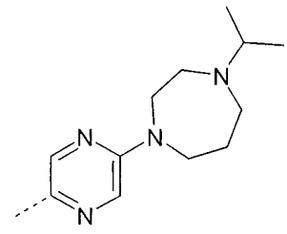
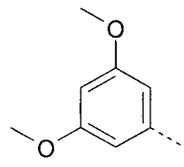
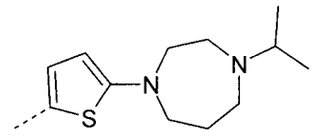
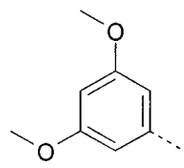
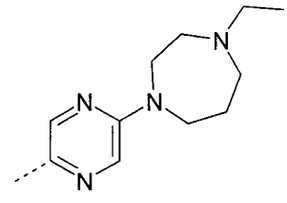
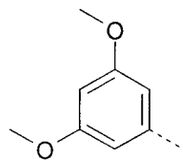
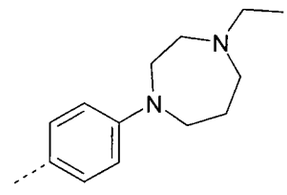
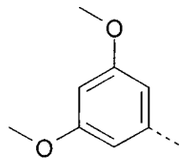
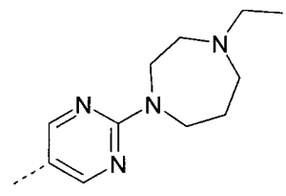
Ejemplo		X		R^3
138		O		H
139		CH_2		H
140		O		H
141		O		H
142		CH_2		H
143		CH_2		H

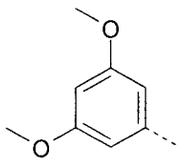
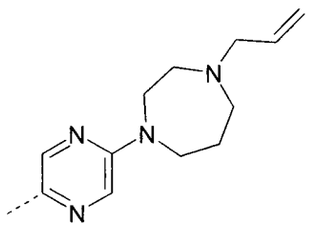
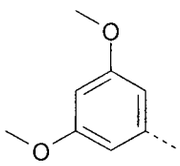
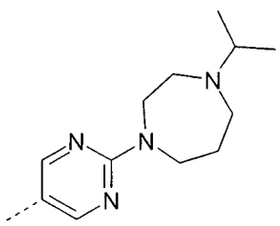
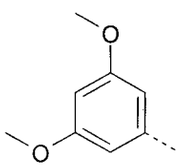
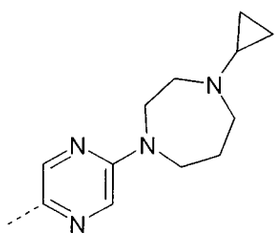
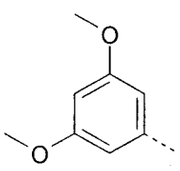
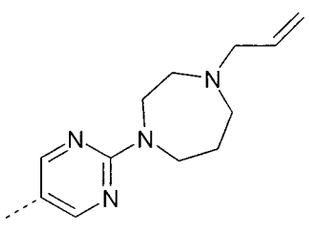
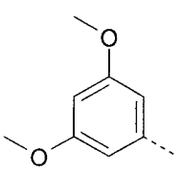
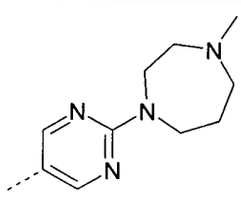
Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
144		CH_2		H
145		CH_2		H
146		CH_2		H
147		O		H
148		CH_2		H
149		CH_2		H

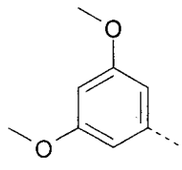
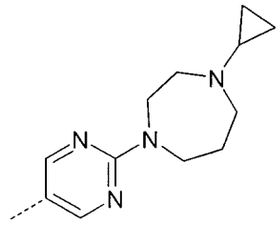
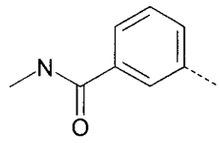
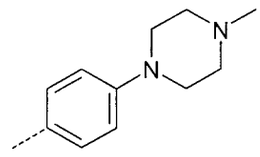
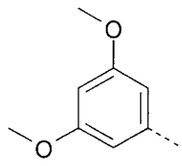
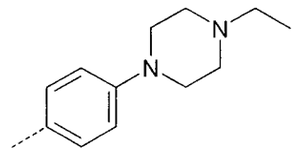
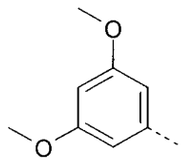
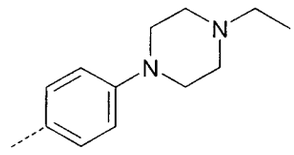
Ejemplo		X		R^3
150		CH_2		H
151		O		H
152		CH_2		H
153		CH_2		H
154		CH_2		H
155		CH_2		H

Ejemplo		X		R^3
156		CH_2		H
157		CH_2		H
158		CH_2		H
159		CH_2		H
160		CH_2		H
161		CH_2		H

Ejemplo		X		R^3
162		CH_2		H
163		CH_2		H
164		CH_2		H
165		CH_2		H
166		CH_2		H

Ejemplo		X		R^3
167		CH_2		H
168		CH_2		H
169		CH_2		H
170		CH_2		H
171		CH_2		H

Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
172		CH_2		H
173		CH_2		H
174		CH_2		H
175		CH_2		H
176		CH_2		H

Ejemplo	$(R^1)_a$—A	X	$(R^2)_b$—B	R^3
177		CH_2		H
178		CH_2		H
179		O		H
180		CH_2		H

Ejemplo 1

4-(4-metilpiperazin-1-il)-N-(5-fenetil-2H-pirazol-3-il)benzamida

Se añadió gota a gota cloruro de oxalilo (2M en DCM, 250 µl, 0,50 mmoles, 1,1 eq) a una mezcla de ácido 4-(4-metilpiperazin-1-il)benzoico (100 mg, 0,45 mmoles, 1 eq) en DCM (5 ml, que contiene unas pocas gotas de DMF) y DIPEA (171 µl, 0,95 mmoles, 2,1 eq) a 0°C. Después de agitar durante 1h a 0°C, se añadió gota a gota una disolución de 5-fenetil-2H-pirazol-3-amina (128 mg, 0,68 mmoles, 1,5 eq) en DCM (2 ml). La mezcla se mantuvo a 0°C durante 2 h, después se dejó calentar gradualmente hasta la temperatura ambiente toda la noche. La mezcla se diluyó con DCM (50 ml), se lavó con disolución de $NaHCO_3$ ac. (50 ml) y la capa acuosa se extrajo con DCM (50 ml). Las capas orgánicas combinadas se

concentraron. El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua (que contiene hidróxido de amonio al 1%) para producir el compuesto del título (8 mg, rendimiento 3%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 2,84 - 2,95 (4H, m), 3,26 - 3,30 (4H, m), 6,41 (1H, s), 6,96 (2H, d), 7,15 - 7,33 (5H, m), 7,89 (2H, d), 10,30 (1H, s), 12,08 (1H, s). MS m/z 390 (MH+)

Ensayo de FGFR cinasa - Elisa, IC_{50} 0,22 μM.

Ejemplo 2

N-[5-[2-(3,5-dimetoxifenil)etil]-2*H*-pirazol-3-il]benzamida

Se añadió gota a gota cloruro de benzoilo (56 μl, 0,47 mmoles, 1,1 eq) a una mezcla de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (150 mg, 0,43 mmoles, 1 eq) y piridina (104 μl, 1,29 mmoles, 3 eq) en DCM (1,5 ml) a temperatura ambiente. Después de agitar a temperatura ambiente durante 2 h, se añadió gota a gota una disolución de TFA (321 μl, 4,32 mmoles, 10 eq) en DCM (2,7 ml), y la agitación se continuó durante a otra 1 h. La mezcla de reacción se concentró, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 33-53% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido espumoso incoloro (100 mg, rendimiento 66%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,81 (4H, s), 3,65 (6H, s), 6,26-6,25 (1H, m), 6,35 (2H, d), 6,41 (1H, s), 7,50-7,39 (3H, m), 7,91 (2H, d), 10,56 (1H, s), 12,07 (1H, s). MS: m/z 352 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,140 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Una disolución de dicarbonato de di-*terc*-butilo (464 mg, 2,12 mmoles, 1,05 eq) en DCM (2 ml) se añadió gota a gota a una mezcla de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (500 mg, 2,02 mmoles, 1 eq) en DCM (18 ml) que contiene disolución ac. de KOH (4,5 N, 3,6 ml; aprox. 16 mmoles, 8 eq). La mezcla de reacción se transfirió a un embudo separador, y las

capas se separaron. La capa orgánica se lavó con agua (10 ml), con salmuera (10 ml), y se secó sobre sulfato de sodio. Después de filtrar, el disolvente se evaporó a presión reducida para producir un aceite amarillo pálido que solidificó al dejar reposar toda la noche para dar un sólido de color crema (704 mg, rendimiento 100%).

RMN ^{1}H (399,902 MHz, DMSO) δ 1,56 (9H, s), 2,68-2,63 (2H, m), 2,80-2,75 (2H, m), 3,73 (6H, s), 5,22 (1H, s), 6,23 (2H, br.s), 6,32-6,31 (1H, m), 6,44 (2H, d). MS: m/z 370 ([M+Na]+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

Se añadió acetonitrilo (2,29 ml, 43,61 mmoles, 1,2 eq) a una suspensión de hidruro de sodio (1,75 g, dispersión en aceite mineral, 43,61 mmoles, 1,2 eq) en tolueno anhidro (70 ml), y la mezcla se agitó a temperatura ambiente durante 30 min. Se añadió 3-(3,5-dimetoxifenil)propanoato de etilo (8,66 g, 36,34 mmoles, 1 eq) en tolueno (60 ml), y la reacción se puso a reflujo durante 18 h. Después de enfriar, la mezcla de reacción se paralizó con agua, y el disolvente se evaporó a presión reducida. El residuo se disolvió en HCl 2M (50 ml). La disolución ácida se extrajo con acetato de etilo. Los extractos orgánicos se combinaron y se lavaron con agua, con salmuera, y se secaron sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó a presión reducida para producir el producto bruto como un aceite amarillo. El aceite se purificó mediante cromatografía en columna de sílice (eluyendo con DCM), y las fraccoines deseadas se combinaron y se evaporaron para producir un sólido de color crema (3,76 g, rendimiento 44%).

Al sólido de color crema (3,72 g, 15,96 mmoles, 1 eq) en etanol (55 ml) se añadió hidrato de hidrazina (852 µl, 17,56 mmoles, 1,1 eq). La reacción se puso a reflujo durante 24 h antes de dejar enfriar. Después de evaporar a presión reducida, el residuo se extrajo en DCM. Las capas orgánicas se lavaron con agua, con salmuera, se secaron con sulfato de magnesio, se filtraron y se evaporaron a presión reducida para dar 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina como un sólido amarillo pálido (3,76 g, 42% a lo largo de 2 etapas).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,64 - 2,82 (4H, m), 3,71 (6H, s), 4,07 - 4,72 (2H, m), 5,20 (1H, s), 6,31 (1H, t), 6,38 (2H, d). MS: m/z 248 (MH+)

Ejemplo 3

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-metoxi-benzamida

Se añadió gota a gota 1-cloro-*N*,*N*,2-trimetilprop-1-en-1-amina (89 µl, 0,63 mmoles, 1,05 eq) a ácido 4-metoxibenzoico (97 mg, 0,63 mmoles, 1 eq) en DCM (1,5 ml) a temperatura ambiente. Después de agitar a temperatura ambiente durante 1,5 h, se añadió una disolución de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (199 mg, 0,57 mmoles, 0,9 eq) y piridina (142 µl, 1,74 mmoles, 2,75 eq) en DCM (2 ml) a la mezcla de reacción, y la agitación se continuó a temperatura ambiente durante otras 3 h. Entonces se añadió una disolución de TFA (386 µl, 5,2 mmoles, 8,25 eq) en DCM (3,5 ml), y la agitación se continuó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 33-53% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido espumoso incoloro (113 mg, rendimiento 52%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,88 (4H, s), 3,73 (6H, s), 3,84 (3H, s), 6,34–6,32 (1H, m), 6,42 (2H, d), 6,47 (1H, s), 7,01 (2H, d), 7,99 (2H, d), 10,48 (1H, br.s), 12,12 (1H, br.s).
MS: m/z 382 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,132 µM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 4

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-morfolin-4-il-benzamida

Preparada de manera análoga al Ejemplo 3 para dar el compuesto del título como un sólido (125 mg, rendimiento 50%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,88 (4H, s), 3,26-3,24 (4H, m), 3,76-3,72 (10H, m), 6,34-6,32 (1H, m), 6,46-6,42 (3H, m), 6,98 (2H, d), 7,92 (2H, d), 10,35 (1H, br.s), 12,10 (1H, br.s).
MS: m/z 437 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,068 µM.

Ejemplo 5

N-[5-[2-(3,5-dimetoxifenil)etil]-2*H*-pirazol-3-il]-4-[(4-fluoropiperidin-1-il)metil]benzamida

Se añadió gota a gota a temperatura ambiente una disolución de NaHMDS en THF (1 M, 0,65 ml, 0,65 mmoles, 1,5 eq) a una mezcla de 5-amino-3-[2-(3,5-dimetoxifenil) etil]pirazol-1-carboxilato *terc*-butilo (150 mg, 0,43 mmoles, 1 eq) y 4-[(4-fluoropiperidin-1-il)metil]benzoato de metilo (131 mg, 0,52 mmoles, 1,2 eq) en THF (0,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Entonces se concentró, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 39-49% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido incoloro (33 mg, rendimiento 16%).

RMN ^{1}H (399,902 MHz, DMSO) δ 1,78-1,67 (2H, m), 1,94-1,80 (2H, m), 2,35-2,29 (2H, m), 2,57-2,55 (2H, m), 2,89 (4H, s), 3,55 (2H, s), 3,73 (6H, s), 4,79-4,61 (1H, m), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,48 (1H, s), 7,40 (2H, d), 7,95 (2H, d), 10,59 (1H, br.s), 12,15 (1H, br.s).

MS: m/z 467 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,063 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El 4-[(4-fluoropiperidin-1-il)metil]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió de una vez hidrocloruro de 4-fluoropiperidina (366 mg, 2,62 mmoles, 1,2 eq) a una mezcla de 4-(bromometil)benzoato de metilo (500 mg, 2,18 mmoles, 1 eq) y carbonato de MP (2,74 mmoles/g, 1,912 g, 5,24 mmoles, 2,4 eq) en MeCN (10 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se añadió de una vez isocinato soportado sobre polímero (1 mmol/g, 500 mg, 0,5 mmoles, 0,5 eq), y la agitación se continuó durante 4 h. La mezcla de reacción se filtró, las resinas se lavaron con MeCN, y el filtrado combinado se concentró para dar un aceite claro, 478 mg, rendimiento 87% a una pureza de 80%.

RMN ^{1}H (399,902 MHz, CDCl3) δ 1,98-1,83 (4H, m), 2,40-2,34 (2H, m), 2,61-2,54 (2H, m), 3,55 (2H, s), 3,91 (3H, s), 4,77-4,60 (1H, m), 7,40 (2H, d), 8,00-7,98 (2H, m). MS: m/z 252 (MH+).

Ejemplo 6

N-[5-[2-[3-(2-metoxietoxi)fenil]etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

A ácido 4-(4-metilpiperazin-1-il)benzoico (440 mg, 2 mmoles, 1 eq) en diclorometano (10 ml) a 0°C se añadieron una pocas gotas de N,N-dimetilformamida, seguido de la adición gota a gota de una disolución 2M de cloruro de oxalilo en diclorometano (1,1 ml, 2,2 mmoles, 1,1 eq). La reacción se mantuvo a 0°C durante 1 h. Entonces se añadió gota a gota 5-[2-[3-(2-metoxietoxi)fenil]etil]-2H-pirazol-3-amina (628 mg, 2,4 mmoles, 1,2 eq) en diclorometano (10 ml), seguido de DIPEA (750 µl, 4,20 mmoles, 2,1 eq). La reacción se mantuvo a 0°C durante una hora adicional antes de permitir calentar hasta la temperatura ambiente toda la noche. La mezcla se diluyó con DCM (50 ml) y se lavó con disolución ac. de $NaHCO_3$ (50 ml). La capa acuosa se extrajo con DCM (50 ml). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de magnesio y se evaporaron a presión reducida. El producto bruto se purificó mediante HPLC prep. de fase inversa ácida. Las fracciones que contienen el producto se capturaron en una columna SCX-2. Después de lavar con metanol, el producto bruto se liberó con amoníaco al 10% en metanol. Después de evaporar a presión reducida, el producto bruto se repurificó sobre la HPLC prep. de fase inversa básica usando un gradiente 20-45% de acetonitrilo en agua que contiene hidróxido de amonio al 1% para producir, después de la evaporación, un sólido blanco (22,9 mg, 2,5%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,22 (3H, s), 2,44 (4H, t),2,88 (4H, s),3,27 (4H, t),3,30 (3H, s),3,64 (2H, dd),4,06 (2H, dd),6,41 (1H, s),6,72 - 6,84 (3H, m),6,95 (2H, d),7,18 (1H, t),7,88 (2H, d),10,30 (1H, s),12,06 (1H, s) MS: m/z 464 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,058 µM.

La 5-[2-[3-(2-metoxietoxi)fenil]etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

A hidruro de sodio (1,065g, 26,57 mmoles, 1,1 eq) se añadió 1,4-dioxano anhidro (40 ml), seguido de acetonitrilo anhidro (1,52 ml, 29 mmoles, 1,2 eq). Entonces se añadió 3-[3-(2-metoxietoxi)fenil]propanoato de 2-metoxietilo (6,82 g, 24,16 mmoles, 1 eq) en 1,4-dioxano

anhidro (35 ml). La reacción se puso a reflujo durante 18h. Después de enfriar, la disolución marrón se paralizó con agua. El disolvente se evaporó a presión reducida, y el residuo acuoso se acidificó con HCl 2M y se extrajo con acetato de etilo. Las capas orgánicas se combinaron, se lavaron con HCl 2M, con agua y con salmuera. Después de secar (sulfato de magnesio), la disolución se filtró y se evaporó a presión reducida. El producto bruto se purificó mediante cromatografía en columna eluyendo con 0-50% de acetato de etilo en hexanos. El intermedio deseado se obtuvo, después de la evaporación, como un aceite amarillo (3,24 g, 54%). A este intermedio (3,24 g, 13,10 mmoles, 1 eq) en etanol (65 ml) se añadió monohidrato de hidrazina (700 µl, 14,41 mmoles, 1,1 eq). La reacción se puso a reflujo a 85°C durante 18h. El disolvente se evaporó a presión reducida. El residuo se extrajo con acetato de etilo, se lavó con agua y salmuera,se secó (sulfato de magnesio), se filtró y se evaporó a presión reducida para producir un aceite amarillo (2,78 g, 81%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,68 - 2,84 (4H, m),3,31 (3H, s),3,65 (2H, dd),4,06 (2H, dd),4,40 (2H, s),5,19 (1H, s),6,71 - 6,81 (3H, m),7,17 (1H, t),11,08 (1H, s); MS: m/z 262 (MH+).

El 3-[3-(2-metoxietoxi)fenil]propanoato de 2-metoxietilo usado como material de partida se preparó según lo siguiente:

A ácido 3-(3-hidroxifenil)propiónico (8,31 g, 50 mmoles, 1 eq) en N,N-dimetilformamida (150 ml) se añadió carbonato de potasio (17,28 g, 125 mmoles, 3 eq) seguido de 2-bromoetilmetiléter (10,34 ml, 110 mmoles, 2,20 eq). La mezcla de reacción se agitó toda la noche a temperatura ambiente. La mezcla de reacción se evaporó hasta sequedad. El residuo se extrajo en acetato de etilo, se lavó con agua y salmuera, se secó con sulfato de magnesio, se filtró y se evaporó para producir un aceite amarillo ~ 11,38g. La mezcla de reacción se purificó mediante cromatografía en columna usando un gradiente de 0-30% de acetato de etilo en hexanos. A este intermedio (9,82 g, 43,76 mmoles, 1 eq) se añadió N,N-dimetilformamida (50 ml) seguido de carbonato de potasio (9,1 g, 65,64 mmoles, 2,5 eq) y 2-bromoetilmetiléter (4.94 ml, 52,5 mmoles, 1,2 eq). La mezcla de reacción se calentó a 60°C durante 18h. La mezcla de reacción se diluyó con N,N-dimetilformamida (50 ml) y se añadieron otros 4,55 g de carbonato de potasio, seguido de 2-bromoetilmetiléter (2,45 ml). La mezcla de reacción se calentó toda la noche a 60°C durante otras 20h. Después de enfriar hasta la temperatura ambiente, los inorgánicos se filtraron, y el disolvente se evaporó a presión reducida. El

residuo se extrajo en acetato de etilo, y las capas orgánicas se lavaron con agua, con hidrogenocarbonato de sodio saturado y con salmuera. Después de secar (sulfato de magnesio) y filtrar, las capas orgánicas se evaporaron a presión reducida para producir un aceite amarillo. El producto bruto se purificó mediante cromatografía en columna, eluyendo con un gradiente de 0-50% de acetato de etilo en hexanos. El producto deseado se obtuvo como un aceite amarillo claro (8,755 g, 71%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,63 (2H, t), 2,82 (2H, t), 3,25 (3H, s), 3,31 (3H, s), 3,50 (2H, m), 3,65 (2H, m), 4,06 (2H, m), 4,13 (2H, dd), 6,73 - 6,82 (3H, m), 7,18 (1H, t); MS: m/z 283 (MH+).

Ejemplo 7

4-(4-metilpiperazin-1-il)-N-[5-(2-piridin-3-iletil)-2H-pirazol-3-il]benzamida

Preparada de manera análoga al Ejemplo 1 pero partiendo de 5-(2-piridin-3-iletil)-2H-pirazol-3-amina (189 mg, 1 mmol, 1,5 eq) para dar el compuesto del título anterior como un sólido blanco (15 mg, rendimiento 6%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 2,89 - 2,98 (4H, m), 3,28 (4H, t), 6,40 (1H, s), 6,96 (2H, d), 7,28 - 7,33 (1H, m), 7,65 (1H, dt), 7,89 (2H, d), 8,40 (1H, dd), 8,45 (1H, d), 10,31 (1H, s), 12,09 (1H, s). MS m/z 391 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,047 μM.

La 5-(2-piridin-3-iletil)-2H-pirazol-3-amina usado como material de partida se preparó según lo siguiente:

Se añadió acetonitrilo (2,9 ml, 54,8 mmoles, 1,3 eq) a una suspensión de hidruro de sodio (2,2 g, 54,8 mmoles, 1,3 eq) en 1,4-dioxano anhidro (50 ml). A esto se añadió entonces una disolución de 3-piridin-3-ilpropanoato de metilo (6,96 g, 42 mmoles, 1 eq) en 1,4-dioxano anhidro (50 ml). La reacción se calentó a reflujo durante 18h. Después de enfriar, se añadió etanol (5 ml), seguido de hidrazina.HCl (3181 mg, 46,43 mmoles, 1,1 eq). La mezcla de reacción se calentó a 100°C durante 20h, se dejó enfriar hasta la temperatura ambiente y entonces se evaporó a presión reducida. El residuo naranja se disolvió en agua (50 ml) y se repartió con acetato de etilo (2x75 ml). Las capas orgánicas se combinaron y se lavaron con HCl 2M. Las capas ácidas acuosas se combinaron y se lavaron con acetato de etilo. La capa acuosa se separó, se basificó mediante adición de disolución de amoníaco 8N y se extrajo con

acetato de etilo. La capa orgánica se lavó con salmuera, se secó con sulfato de magnesio, se filtró y se evaporó a presión reducida para producir el compuesto del título como un aceite naranja. El aceite se disolvió en acetonitrilo (10 ml) y se purificó en hplc de fase inversa básica usando un gradiente 2-20% de acetonitrilo en agua (que contiene hidróxido de amonio al 1%). Las fracciones deseadas se combinaron y se evaporaron para producir el compuesto del título (348 mg , rendimiento 5%).

RMN ^{1}H (400,132 MHz, DMSO) δ 2,74 (2H, t), 2,87 (2H, t), 4,43 (2H, s), 5,17 (1H, s), 7,29 (1H, ddd), 7,61 (1H, dddd), 8,39 (1H, dd), 8,42 (1H, d), 11,08 (1H, s). MS; m/z 189 (MH+).

Se obtuvo más producA una partir de la capa acuosa basificada, mediante purificación usando HPLC prep. de fase inversa básica. Después de la evaporación de las fracciones deseadas a presión reducida hast un volumen bajo, la disolución se acidificó usando HCl 2M. El producto se capturó en una columna SCX-2. El producto se eluyó de la columna usando disolución de amoníaco al 10% en metanol. Después de evaporar a presión reducida, se obtuvo un aceite amarillo (657 mg, rendimiento 9%).

Ejemplo 8

N-[5-[2-(2-furil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Preparada de manera análoga al Ejemplo 1, pero partiendo de 5-[2-(2-furil)etil]-2H-pirazol-3-amina (178 mg, 1 mmol, 1,5 eq) para dar el compuesto del título anterior como un sólido bronceado (24,8 mg, rendimiento 10%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 2,89 - 2,98 (4H, m), 3,28 (4H, t), 6,40 (1H, s), 6,96 (2H, d), 7,28 - 7,33 (1H, m), 7,65 (1H, dt), 7,89 (2H, d), 8,40 (1H, dd), 8,45 (1H, d), 10,31 (1H, s), 12,09 (1H, s). MS; m/z 380 (MH+).

Media de n= 1, ensayo de FGFR cinasa - Elisa, IC_{50} 0,0795 μM.

La 5-[2-(2-furil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

a) Una mezcla de 2-trifenilfosforanilidenacetato de etilo (34,84 g, 100 mmoles, 1 eq) y furan-2-carbaldehído (9609 mg, 100 mmoles, 1 eq) en THF anhidro (200 ml) se agitó a temperatura ambiente durante 24h. El disolvente se evaporó a presión reducida, y el residuo se trituró con éter para producir una disolución marrón y un precipitado. El sólido se filtró, se lavó y se eliminó. Entonces se evaporó el filtrado. El producto se purificó mediante cromatografía en

columna sobre sílice, eluyendo con 0-20% de acetato de etilo en hexanos. Las fracciones desedas se evaporaron para producir una mezcla cis/trans de (E)-3-(2-furil)prop-2-enoato de etilo como un aceite amarillo pálido (la RMN sugirió un producto principalmente trans) (15,5 g, 93%).

b) Una mezcla cis/trans de (E)-3-(2-furil)prop-2-enoato de etilo (15,5 g, 93,27 mmoles, 1 eq) se agitó en etanol (120 ml) que contiene paladio al 10% sobre carbón (775 mg, 5% en peso). La mezcla de reacción se agitó en hidrógeno durante 4h. Se añadió una cantidad adicional de Pd al 10%/C (775 mg, 5% en peso). La reacción se agitó en hidrógeno durante 95 min adicionales. La reacción se filtró y se evaporó a presión reducida. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 20% de acetato de etilo en hexanos. Las fracciones desedas se evaporaron a presión reducida y se obtuvo 3-(2-furil)propanoato de etilo como un aceite claro (3,69 g, rendimiento 24%).

RMN ^{1}H (300,132 MHz, CDCl3) δ 1,25 (3H, t), 2,64 (2H, t), 2,97 (2H, t), 4,15 (2H, q), 6,02 (1H, td), 6,27 (1H, dd), 7,30 (1H, dd)

Entonces se preparó 5-[2-(2-furil)etil]-2H-pirazol-3-amina (2,09 g, 54% a lo largo de 2 etapas) de manera análoga a la descrita para el material de partida para el Ejemplo 2 (5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina), usando 3-(2-furil)propanoato de etilo (6,33 g, 37,64 mmoles, 1 eq) como material de partida.

RMN ^{1}H (300,132 MHz, CDCl3) δ 2,98 (4H, t), 3,45 (2H, s), 6,04 (1H, d), 6,28 (1H, dd), 7,30 (1H, dd). MS m/z 178 (MH+).

Ejemplo 9

N-[5-[2-(3-furil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Preparada de manera análoga al Ejemplo 1, pero partiendo de 5-[2-(3-furil)etil]-2H-pirazol-3-amina (178 mg, 1 mmol, 1,5 eq) para dar el compuesto del título como un sólido bronceado (17,3 mg, rendimiento 7%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,45 (4H, t), 2,67 - 2,89 (4H, m), 3,28 (4H, t), 6,39 (1H, d), 6,43 (1H, s), 6,96 (2H, d), 7,45 (1H, s), 7,56 (1H, t), 7,89 (2H, d), 10,29 (1H, s), 12,07 (1H, s). MS m/z 380 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,137 μM.

La 5-[2-(3-furil)etil]-2H-pirazol-3-amina (3,94 g, 59% a lo largo de 2 etapas finales), usada como material de partida, se preparó de manera análoga a la síntesis de la 5-[2-(2-furil)etil]-2H-pirazol-3-amina mostrada en el Ejemplo 8.

Ejemplo 10

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Preparada de manera análoga al Ejemplo 1, pero partiendo de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (566 mg, 2,30 mmoles, 1,5 eq) para dar el compuesto del título como un sólido beige (183,5 mg, rendimiento 27%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 2,86 (4H, s), 3,27 (4H, t), 3,72 (6H, s), 6,32 (2H, t), 6,35 - 6,42 (3H, m), 6,96 (2H, d), 7,89 (2H, d), 10,31 (1H, s), 12,08 (1H, s). MS: m/z 450 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00085 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 11

N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Preparada de manera análoga al Ejemplo 1, pero partiendo de 5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina (148 mg, 0,68 mmoles, 1,5 eq) para dar el compuesto del título como un sólido (8,2 mg, rendimiento 4%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 2,89 (4H, s), 3,26 - 3,31 (4H, m), 3,73 (3H, s), 6,16 (1H, s), 6,69 - 6,86 (3H, m), 6,96 (2H, d), 7,20 (1H, t), 7,89 (2H, d), 10,31 (1H, s), 12,08 (1H, s). MS m/z 420 (MH+)

Media de n= 1, ensayo de FGFR cinasa - Elisa, IC_{50} 0,0828 μM.

La 5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:-

Se añadió acetonitrilo (3,36 ml, 64,25 mmoles, 1 eq) a una suspensión de hidruro de sodio (2,57g, dispersión en aceite mineral, 64,25 mmoles, 1 eq) en 1,4-dioxano anhidro (50 ml), y la mezcla se agitó a temperatura ambiente durante 20 min. Se añadió 3-(3-

metoxifenil)propanoato de metilo (10,4 g, 53,54 mmoles, 1 eq) en 1,4-dioxano (25 ml), y la reacción se puso a reflujo durante 2h. La mezcla de reacción se enfrió y se paralizó con agua. El residuo se disolvió en HCl 2M y se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con HCl 2M, agua y salmuera, y se secó sobre sulfato de magnesio. La evaporación a presión reducida dio paso a un aceite amarillo, que se purificó mediante cromatografía en columna de sílice, eluyendo con una mezcla de 0-50% de acetato de etilo en hexanos. Las fracciones que contienen el producto se combinaron y se evaporaron para dejar 5-(3-metoxifenil)-3-oxo-pentanonitrilo (5,37 g, rendimiento 49%).

RMN ^{1}H (300,132 MHz, CDCl3) δ 2,86 (4H, s), 3,32 (2H, s), 3,73 (3H, s), 6,64 - 6,72 (3H, m), 7,14 (1H, t)

A 5-(3-metoxifenil)-3-oxo-pentanonitrilo (5,37 g, 26,42 mmoles, 1 eq) en etanol (80 ml) se añadió hidrato de hidrazina (1,41 ml, 29,06 mmoles, 1,1 eq). La reacción se puso a reflujo durante 3,5 h, y después se dejó enfriar. La mezcla se evaporó a presión reducida. El residuo se disolvió en acetato de etilo, y la capa orgánica se lavó con agua, con salmuera, se secó con sulfato de magnesio, se filtró y se evaporó para producir un aceite amarillo (que solidificó al dejar reposar). Éste se acidificó y purificó mediante cromatografía en columna SCX-3. El compuesto se eluyó con amoníaco al 10% en metanol. Después de la evaporación se obtuvo 5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina (5,48 g, rendimiento 96%).

RMN ^{1}H (300,132 MHz, DMSO): δ 2,64 - 2,87 (4H, m), 3,73 (3H, s), 4,40 (1H, s), 5,19 (1H, s), 6,71 - 6,82 (3H, m), 7,18 (1H, t), 11,07 (1H, s). MS; m/z 218 (MH+)

Ejemplo 12

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Preparada de manera análoga al Ejemplo 1, pero partiendo de hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina para dar el compuesto del título como un sólido beige (34 mg, rendimiento 13%).

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (3H, s), 2,44 (4H, t), 3,27 - 3,32 (4H, m), 3,75 (6H, s), 5,07 (2H, s), 5,57 (1H, s), 6,44 - 6,45 (1H, m), 6,59 (2H, d), 7,01 (2H, d), 7,85 (2H, d), 10,64 (1H, s), 11,54 (1H, s). MS m/z 452 (MH+)

Media de n = 3, ensayo de FGFR cinasa - Elisa, IC_{50} 0,06μM.

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó según lo siguiente:

3-Amino-5-hidroxipirazol (8 g, 80,74 mmoles) y trifenilfosfina (25,45 g, 96,88 mmoles) se agitaron en DCM (110 ml) en nitrógeno, y la mezcla se enfrió en un baño de hielo. Se añadió gota a gota azodicarboxilato de diisopropilo (19,08 ml, 96,88 mmoles) (temperatura <10°C), y la mezcla de reacción se agitó en el baño de hielo durante 1h. Se añadió gota a gota alcohol 3,5-dimetoxibencílico (16,30 g, 96,88 moles) en DCM (35 ml), la mezcla de reacción se dejó calentar hasta la temperatura ambiente y se agitó en nitrógeno durante 4 días. La mezcla se filtró, se lavó con DCM y el filtrado se extrajo con HCl 1M (ac.) (3 x 50 ml). Los extractos acuosos combinados se lavaron con DCM (50 ml), dando como resultado la precipitación del producto. El producto se recogió por filtración, se lavó con agua, DCM y se secó a vacío para dar el compuesto del título como un sólido blanco (358 mg, rendimiento 1,8%). Una segunda cosecha de producto se obtuvo tras la precipitación de la capa de DCM inicial al dejar reposar a temperatura ambiente. El producto sólido se recogió por filtración, se lavó con DCM y se secó a vacío para dar un sólido blanquecino (1,127 g, rendimiento 5,6%).

RMN ^{1}H (300,132 MHz, DMSO) δ 3,75 (s, 6H), 5,18 (s, 2H), 5,26 (s, 1H), 6,50 (t, 1H), 6,60 (d, 2H). MS:m/z 250 (MH+)

Ejemplo 13

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-6-metil-piridin-3-carboxamida

Se disolvió 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina (0,2 g, 0,73 mmoles) en tolueno (10 ml), y a esto se añadió 6-metilpiridin-3-carboxilato de metilo (122 mg, 0,73 mmoles) y $AlMe_3$ (0,93 ml, 1,8 mmoles). La mezcla de reacción se agitó toda la noche. La mezcla de reacción se diluyó con DCM (15 ml) y se paralizó con sulfito de sodio húmedo (precaución); la reacción se agitó durante 20 min antes de filtrarla, y el disolvente se eliminó *a vacío* para producir una goma amarilla. Ésta se disolvió en ácido fórmico (12 ml), y se calentó a 82°C toda la noche. La mezcla de reacción se evaporó hasta sequedad, y el producto resultante se hizo pasar a través de una columna SCX, eluyendo inicialmente con metanol seguido de amoníaco 2N/metanol. Después de la eliminación del disolvente se obtuvo un sólido amarillo, que se trituró con acetonitrilo caliente para dar un sólido blanco. El sólido se filtró y se secó (117 mg, 48%).

RMN ^{1}H (400,132 MHz, DMSO) δ 2,54 (s, 3H), 2,91 (s, 4H), 3,74 (s, 3H), 6,45 (s, 1H), 6,76 (d, 1H), 6,83-6,82 (m, 2H), 7,20 (t, 1H), 7,36 (d, 1H), 8,21 (dd, 1H), 9,01 (s, 1H), 10,81 (s, 1H), 12,21 (s, 1H); MS: m/z 409 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,95 μM.

La 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

El 5-(3-metoxi-fenil)-3-oxo-pentanonitrilo bruto (10 g, 0,049 moles), *t*-butilhidrazina HCl (7,29 g, 0,059 moles) y TEA (8,20 ml, 0,059 moles) se disolvieron en etanol (300 ml) y se calentaron a reflujo durante 3 h. La mezcla de reacción se enfrió, y el disolvente se eliminó *a vacío* para producir un aceite marrón viscoso; éste se paralizó con agua (100 ml), se extrajo con éter dietílico (3 x 200 ml), se secó ($MgSO_4$) y el disolvente se eliminó *a vacío* para producir un aceite naranja oscuro. Éste se purificó vía destilación a 165°C a 0,40 mbares, para dar un aceite viscoso claro que solidificó al dejar reposar.

RMN ^{1}H (400,132 MHz, CDCl3) δ 1,55 (s, 9H), 2,76-2,71 (m, 2H), 2,85-2,80 (m, 2H), 3,40 (brs, 2H), 3,72 (s, 3H), 5,31 (s, 1H), 6,66 (dd, 1H), 6,71 (s, 1H), 6,76 (d, 1H), 7,11 (t, 1H); MS: m/z 274 (MH+).

El 5-(3-Metoxi-fenil)-3-oxo-pentanonitrilo usado como material de partida se preparó según lo siguiente:

Se añadió LDA (34 ml, 0,068 moles) a THF (300 ml), y se enfrió hasta–78°C en una atmósfera de nitrógeno; a esto se le añadió lentamente acetonitrilo (2,8 g, 0,068 moles) en THF (20 ml). La reacción se agitó durante 10 min a –78°C antes de la adición rápida de 3-(3-metoxifenil)propanoato de metilo (10 g, 0,052 moles). La reacción se agitó durante 30 min antes de dejar calentar hasta la temperatura ambiente. La reacción se paralizó con HCl 1,0 N (100 ml), se extrajo con éter dietílico (2 x 200 ml), se secó ($MgSO_4$) y el disolvente se eliminó *a vacío* para producir una goma amarilla. Ésta pareció descomponerse lentamente, y se usó inmediatamente en la siguiente etapa.

Ejemplo 14

6-Metoxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

Preparada de manera análoga al Ejemplo 13m excepto usando 6-metoxipiridin-3-carboxilato de metilo como material de partida (168 mg, 65%).

RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,74 (s, 3H), 3,93 (s, 3H), 6,45 (s, 1H), 6,77-6,75 (m, 1H), 6,83-6,81 (m, 2H), 6,90 (d, 1H), 7,20 (t, 1H), 8,25 (dd, 1H), 8,81 (d, 1H), 10,70 (s, 1H), 12,17 (s, 1H); MS: m/z 353 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,61 μM.

Ejemplo 15

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-metilsulfonil-benzamida

Preparada de manera análoga al Ejemplo 13, excepto usando 4-metilsulfonilbenzoato de etilo como material de partida (82 mg, 28%).

RMN ^{1}H (400,132 MHz, DMSO) δ 2,91 (s, 4H), 3,28 (s, 3H), 3,74 (s, 3H), 6,49 (s, 1H), 6,78-6,75 (m, 1H), 6,84-6,81 (m, 2H), 7,20 (t, 1H), 8,03 (d, 2H), 8,20 (d, 2H), 10,96 (s, 1H), 12,23 (s, 1H); MS: m/z 400 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,11 μM.

Ejemplo 16

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-5-metil-pirazin-2-carboxamida

Preparada de manera análoga al Ejemplo 13, excepto usando 5-metilpirazin-2-carboxilato de metilo como material de partida (63 mg, 26%).

RMN ^{1}H (400,132 MHz, DMSO) δ 2,62 (s, 3H), 2,91 (s, 4H), 3,73 (s, 3H), 6,48 (s, 1H), 6,77-6,75 (m, 1H), 6,85-6,80 (m, 2H), 7,20 (t, 1H), 8,67 (s, 1H), 9,13 (s, 1H), 10,26 (s, 1H), 12,28 (s, 1H); MS: m/z 338 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,75 μM.

Ejemplo 17

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-5-(prop-2-inilamino)piridin-2-carboxamida

Preparada de manera análoga Ejemplo 13, excepto usando 5-(prop-2-inilamino)piridin-2-carboxilato de metilo como material de partida (39 mg, 14%).

RMN ^{1}H (400,132 MHz, CDCl3) δ 2,28 (t, 1H), 2,96 (s, 4H), 3,77 (s, 3H), 4,00 (s, 2H), 4,56 (s, 1H), 6,47 (s, 1H), 6,76-6,73 (m, 2H), 6,78 (d, 1H), 7,04 (dd, 1H), 7,21-7,17 (m, 1H), 7,96 (d, 1H), 8,09 (d, 1H), 10,14 (s, 1H), NH ausente; MS: m/z 376 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,66 μM.

Ejemplo 18

6-Etilamino-*N*-{5-[2-(3-metoxi-fenil)-etil]-2*H*-pirazol-3-il}-nicotinamida

Preparada de manera análoga al Ejemplo 13, excepto usando éster metílico del ácido 6-etilamino-nicotínico como material de partida (44 mg, 16%).

RMN ^{1}H (400,132 MHz, DMSO) δ 1,15 (t, 3H), 2,89 (s, 4H), 3,35-3,30 (m, 2H), 3,74 (s, 3H), 6,46-6,42 (m, 2H), 6,77-6,75 (m, 1H), 6,82-6,81 (m, 2H), 7,06 (s, 1H), 7,20 (t, 1H), 7,93 (d, 1H), 8,65 (s, 1H), 10,28 (s, 1H), 12,06 (s, 1H); MS: m/z 366 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,54 μM.

Ejemplo 19

4-Acetamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Se disolvió 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina (0,2 g, 0,73 mmoles) en THF/piridina (5 ml/1 ml); a esto se añadió cloruro de 4-acetamidobenzoilo (190 mg, 0,95 mmoles), y la mezcla de reacción se agitó toda la noche. La mezcla de reacción se evaporó hasta sequedad, se purificó mediante cromatografía en columna, eluyendo con 0-5% de MeOH en DCM, y se evaporó para dar una espuma blanca. El residuo se disolvió en ácido fórmico (12 ml), y se calentó a 82°C toda la noche. La mezcla de reacción se evaporó hasta sequedad, y el producto se purificó mediante una columna SCX. La eliminación del disolvente dio un sólido amarillo, que se trituró con acetonitrilo caliente para dar un sólido blanco. El sólido se filtró y se secó *a vacío* (16 mg, 6%); MS: m/z 378 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,40 μM.

La 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina usada como material de partida se preparó como se indica en el Ejemplo 13.

Ejemplo 20

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)pirazin-2-carboxamida

Se añadió gota a gota NaHMDS (disolución 1M en THF, 0,645 ml, 0,644 mmoles, 1,5 eq) a una suspensión agitada de 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de

terc-butil (150 mg, 0,429 mmoles, 1 eq) y 5-(4-metilpiperazin-1-il)pirazin-2-carboxilato de metilo (122 mg, 0,515 mmoles, 1,2 eq) en THF seco (2,5 ml) en nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 50 min, y después se neutralizó con NH_4Cl ac. saturado, y se diluyó con agua (5 ml). La fase acuosa se extrajo con acetato de etilo (3 x 8 ml), y los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El sólido residual se purificó mediante HPLC prep. de fase inversa usando un gradiente de 31-51% de acetonitrilo en agua que contiene hidróxido de amonio al 1%, para dar el producto como un sólido blanco (88 mg, 45%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,24 (s, 3H), 2,41 - 2,46 (m, 4H), 3,72 - 3,78 (m, 4H), 3,75 (s, 6H), 5,08 (s, 2H), 5,84 (s, 1H), 6,44 (t, 1H), 6,59 (d, 2H), 8,33 (s, 1H), 8,72 (s, 1H), 10,81 (s, 1H), 11,35 (s, 1H). MS: m/z 454 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,046 μM.

El 5-(4-metilpiperazin-1-il)pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se calentaron 5-cloropirazin-2-carboxilato de metilo (100 mg, 0,579 mmoles, 1 eq), 1-metilpiperazina (65 μl, 0579 mmoles, 1 eq) y carbonato de potasio (161 mg, 1,159 mmoles, 2 eq) en DMSO en un reactor de microondas a 120°C durante 5 min. La mezcla de reacción se vertió sobre una columna SCX (10 g), se lavó con metanol y después se eluyó con amoníaco 2M en metanol. La reacción se repitió como antes con 5-cloropirazin-2-carboxilato de metilo (150 mg), 1-metilpiperazina (98 μl) y carbonato de potasio (241 mg) en DMSO (3 ml). Las fracciones del producto procedentes de ambas reacciones se combinaron y se evaporaron a vacío para dar el producto como un sólido amarillo (283 mg, 83%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,23 (s, 3H), 2,42 (t, 4H), 3,73 (t, 4H), 3,82 (s, 3H), 8,38 (d, 1H), 8,66 (d, 1H). MS: m/z 237 (MH+).

Ejemplo 21

4-Benzamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Se disolvió 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina (0,2 g, 0,73 mmoles) en tolueno (10 ml), y a esto se añadió 4-benzamidobenzoato de metilo (200 mg, 0,80 mmoles) y $AlMe_3$ (0,93 ml, 1,8 mmoles). La reacción se agitó toda la noche. La reacción se diluyó con

DCM (15 ml) y se paralizó con sulfito de sodio húmedo. La mezcla de reacción se agitó durante 20 min antes de filtrarla, y el disolvente se eliminó *a vacío* para producir una goma amarilla. Esta goma se disolvió en ácido fórmico (12 ml) y se calentó a 82°C toda la noche. La reacción se evaporó hasta sequedad, y el producto resultante se hizo pasar a través de una columna SCX, eluyendo inicialmente con metanol seguido de amoníaco 2N/metanol. Después de la eliminación del disolvente, se obtuvo un sólido amarillo que se trituró con acetonitrilo caliente para dar un sólido blanco. El sólido se filtró y se secó (66 mg, 21%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,91 (s, 4H), 3,74 (s, 3H), 6,46 (brs, 1H), 6,77 (d, 1H), 6,83 (s, 2H), 7,20 (t, 1H), 7,64-7,54 (m, 3H), 7,90 (d, 2H), 8,02-7,97 (m, 4H), 10,46 (s, 1H), 10,55 (s, 1H), 12,15 (s, 1H); MS: m/z 441 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 231 μM.

Ejemplo 22

6-(2-Metoxietoxi)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

Se añadió 6-cloro-N-[5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-il]piridin-3-carboxamida (0,15 g, 0,36 mmoles) a un tubo y se disolvió en 2-metoxietanol (15 ml). Se añadió NaH (51 mg, 1,0 mmoles), y la reacción se calentó a 80°C toda la noche. La mezcla de reacción se evaporó hasta sequedad, y se hizo pasar a través una columna SCX, eluyendo inicialmente con metanol seguido de amoníaco 2N/metanol. El eluyente se evaporó hasta sequedad. La goma obtenida se disolvió entonces en ácido fórmico, y se calentó a 80°C toda la noche. La reacción se evaporó hasta sequedad y se hizo pasar a través una columna SCX, eluyendo inicialmente con metanol seguido de amoníaco 2N/metanol. El eluyente se evaporó hasta sequedad y la goma resultante se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. El producto se obtuvo como un sólido (19 mg, 13%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,31 (s, 3H), 3,69 - 3,67 (m, 2H), 3,74 (s, 3H), 4,47 - 4,44 (m, 2H), 6,45 (s, 1H), 6,76 (d, 1H), 6,82 (s, 2H), 6,90 (d, 1H), 7,20 (t, 1H), 8,25 (d, 1H), 8,78 (s, 1H), 10,69 (s, 1H), 12,17 (s, 1H); MH+ 397.

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,72 μM.

La 6-cloro-N-[5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-il]piridin-3-carboxamida, usada como material de partida, se preparó según el Ejemplo 21 usando 6-cloropiridin-3-carboxilato

de metilo (1,02 g, 33%); RMN ^{1}H (400,132 MHz, CDCl3) δ 1,65 (s, 9H), 2,98 - 2,88 (m, 4H), 3,79 (s, 3H), 6,20 (brs, 1H), 6,73 (dd, 1H), 6,79 (s, 1H), 6,83 (d, 1H), 7,19 (t, 1H), 7,52 - 7,47 (m, 2H), 8,12 (brs, 1H), 8,83 (brs, 1H); MS: m/z 413 (MH+).

Ejemplo 23

4-Ciano-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Se añadió 5-[(4-cianobenzoil)amino]-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo a acetonitrilo (5 ml) y HCl 6,0 N en propan-2-ol (10 ml). La mezcla de reacción se agitó toda la noche para dar un sólido blanco, que se filtró y disolvió en metanol/agua. La disolución se hizo pasar entonces a través de una columna SCX. Al eliminar el disolvente *a vacío*, se obtuvo un sólido blanco (0,29 g, 67%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,91 (s, 4H), 3,74 (s, 3H), 6,48 (s, 1H), 6,76 (d, 1H), 6,83 (s, 2H), 7,20 (t, 1H), 7,97 (d, 2H), 8,12 (d, 2H), 10,95 (s, 1H), 12,24 (s, 1H); MH+ 347.

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 28,6 μM.

El 5-[(4-cianobenzoil)amino]-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se disolvió 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (0,4 g, 1,26 mmoles) en DCM/piridina (6 ml, 5:1), y a esto se le añadió cloruro de 4-cianobenzoilo (0,27 g, 0,95 mmoles). La mezcla de reacción se agitó toda la noche. La mezcla de reacción se evaporó hasta sequedad para dar una goma oscura que se usó en la siguiente etapa sin ninguna purificación adicional.

El 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se disolvieron 5-[2-(3-metoxi-fenil)-etil]-2*H*-pirazol-3-ilamina (5 g, 23 mmoles) y anhídrido de Boc (6,5 g, 30 mmoles) en DCM (200 ml), y se agitaron toda la noche a temperatura ambiente. La mezcla de reacción se evaporó hasta sequedad y se disolvió en éter dietílico. A esto se añadió iso-hexano, y el disolvente se eliminó lentamente *a vacío* hasta que fue visible un sólido. La disolución se raspó y se sometió a ultrasonidos para dar 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (6,3 g, 86%) como un sólido blanco;

RMN ^{1}H (400,132 MHz, CDCl3) δ 7,20 (t, 1H), 6,82 (d, 1H), 6,79 (s, 1H), 6,74 (d, 1H), 5,22 (s, 1H), 3,79 (s, 3H), 2,93 - 2,88 (m, 2H), 2,86 - 2,81 (m, 2H), 1,65 (s, 9H); MH+ 318.

Ejemplo 24

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]benceno-1,4-dicarboxamida

Se añadieron 4-ciano-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida (Ejemplo 23) (0,2 g, 0,58 mmoles) y NaOH (69 mg, 1,73 mmoles) a una disolución de etanol/agua (20 ml, 3:1), y se calentó a 80°C hasta que se observó que el material de partida se había consumido completamente. Es necesrio tener cuidado, ya que la amida se hidroliza posteriormente al ácido carboxílico. La reacción se extrajo con DCM (3 x 50 ml), se secó, y el disolvente se eliminó *a vacío* para producir un sólido blanco. Éste se trituró con DCM para dar un sólido blanco (20 mg, 10%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,75 (s, 3H), 6,42 (s, 1H), 6,82 - 6,75 (m, 3H), 7,20 (t, 1H), 7,46 (s, 1H), 7,95 (d, 2H), 8,16 - 8,03 (m, 3H), 10,82 (s, 1H), 12,18 (s, 1H); MH+ 366.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,43 μM.

Ejemplo 25

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-pirazol-1-il-benzamida

Se disolvió 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina (0,2 g, 0,73 mmoles) en tolueno (10 ml), y a esto se añadió 4-pirazol-1-ilbenzoato de metilo (177 mg, 0,88 mmoles) y $AlMe_3$ (0,93 ml, 1,8 mmoles). La mezcla de reacción se agitó toda la noche. La mezcla de reacción se diluyó con DCM (15 ml), se paralizó con sulfito de sodio húmedo y se agitó adicionalmente durante 20 min antes de filtrarla. El disolvente se eliminó *a vacío* para producir una goma amarilla. Esta goma se disolvió en ácido fórmico (12 ml) y se calentó a 82°C toda la noche. La mezcla de reacción se evaporó hasta sequedad, y el producto resultante se hizo pasar a través de una columna SCX, eluyendo inicialmente con metanol seguido de amoníaco 2N/metanol. Después de la eliminación del disolvente, se obtuvo un sólido amarillo que se trituró con acetonitrilo caliente para dar un sólido blanco. El sólido se filtró y se secó (155 mg, 55%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,92 (s, 4H), 3,74 (s, 3H), 6,48 (s, 1H), 6,60 (s, 1H), 6,77 (d, 1H), 6,84 - 6,82 (m, 2H), 7,20 (t, 1H), 7,81 (s, 1H), 7,96 (d, 2H), 8,14 (d, 2H), 8,63 (s, 1H), 10,69 (s, 1H), 12,18 (s, 1H); MS: m/z 388 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,94 μM.

Ejemplo 26

6-Anilino-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 6-anilinopiridin-3-carboxilato de metilo (200 mg, 0,88 mmoles) para dar el compuesto del título (106 mg, 35%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,74 (s, 3H), 6,44 (s, 1H), 6,76 (d, 1H), 6,87 - 6,82 (m, 3H), 6,97 (t, 1H), 7,20 (t, 1H), 7,31 (t, 2H), 7,70 (d, 2H), 8,11 (d, 1H), 8,79 (s, 1H), 9,41 (s, 1H), 10,51 (s, 1H), 12,13 (s, 1H); MH+414

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 64 μM.

Ejemplo 27

4-Metanosulfonamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-metanosulfonamidobenzoato de metilo (200 mg, 0,88 mmoles) para dar el compuesto del título (125 mg, 41%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,06 (s, 3H), 3,74 (s, 3H), 6,42 (s, 1H), 6,76 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 7,24 (d, 2H), 7,97 (d, 2H), 10,54 (s, 1H), 12,09 (vbrs, 1H); MH+ 416

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,26 μM.

Ejemplo 28

4-(Hidroximetil)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-(hidroximetil)benzoato de metilo (146 mg, 0,88 mmoles) para dar el compuesto del título (136 mg, 53%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,74 (s, 3H), 4,57 (d, 2H), 5,28 (t, 1H), 6,45 (s, 1H), 6,76 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 7,41 (d, 2H), 7,95 (d, 2H), 10,58 (s, 1H), 12,14 (s, 1H); MH+ 352.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,074 μM.

Ejemplo 29

5-Formamido-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-2-carboxamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 5-[(2-metilpropan-2-il)oxicarbonilamino]piridin-2-carboxilato de metilo (222 mg, 0,88 mmoles) para dar el

compuesto del título (72 mg, 27%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,91 (s, 4H), 3,73 (s, 3H), 6,47 (s, 1H), 6,76 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 8,12 (d, 1H), 8,26 (dd, 1H), 8,44 (s, 1H), 8,87 (s, 1H), 10,13 (vbrs, 1H), 10,74 (s, 1H), 12,23 (s, 1H); MH+ 366

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,87 μM.

Ejemplo 30

4-(Dimetilsulfamoil)-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-(dimetilsulfamoil)benzoato de metilo (214 mg, 0,88 mmoles) para dar el compuesto del título (126 mg, 40%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,66 (s, 6H), 2,91 (s, 4H), 3,74 (s, 3H), 6,49 (s, 1H), 6,77 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 7,85 (d, 2H), 8,20 (d, 2H), 10,93 (s, 1H), 12,23 (s, 1H); MH+ 429.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,80 μM.

Ejemplo 31

6-Hidroxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 6-hidroxipiridin-3-carboxilato de metilo (147 mg, 0,88 mmoles) para dar el compuesto del título (28 mg, 11%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,89 (s, 4H), 3,73 (s, 3H), 6,37 - 6,34 (m, 2H), 6,76 (d, 1H), 6,82 - 6,80 (m, 2H), 7,19 (t, 1H), 7,97 (dd, 1H), 8,18 (d, 1H), 10,44 (s, 1H), 12,03 (vbrs, 1H); MH+ 339

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 1,05 μM.

Ejemplo 32

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-6-morfolin-4-il-piridin-3-carboxamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 6-morfolin-4-ilpiridin-3-carboxilato de metilo (195 mg, 0,88 mmoles) para dar el compuesto del título (140 mg, 47%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,59 - 3,57 (m, 4H), 3,71 - 3,69 (m, 4H), 3,74 (s, 3H), 6,44 (s, 1H), 6,76 (d, 1H), 6,82 - 6,81 (m, 2H), 6,86 (d, 1H), 7,20 (t, 1H), 8,13 (d, 1H), 8,76 (s, 1H), 10,45 (s, 1H), 12,11 (s, 1H); MH+ 408

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,027 μM.

El 6-morfolin-4-ilpiridin-3-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadieron ácido 6-morfolin-4-ilpiridin-3-carboxílico (2,56 g, 13,6 mmoles) y carbonato de potasio (2,8 g, 20,4 mmoles) a DMF (40 ml), y a esto se añadió MeI (0,97 ml, 15 mmoles). La mezcla de reacción se calentó a 50°C durante 3 h. El disolvente se eliminó *a vacío* para producir un sólido oscuro, que se paralizó con NaOH 2,0N (100 ml), se extrajo con DCM (3 X 100 ml), se secó ($MgSO_4$) y el disolvente se eliminó *a vacío* para producir un sólido marrón. Este sólido se disolvió en acetonitrilo caliente, y se dejó enfriar para dar un sólido blanco, que se filtró, y el proceso se repitió sobre el licor madre para obtener el compuesto del título (1,8 g, 60%); RMN ^{1}H (400,132 MHz, CDCl3) 3,65 (t, 4H), 3,81 (t, 4H), 3,87 (s, 3H), 6,53 (d, 1H), 8,04 (dd, 1H), 8,80 (d, 1H); MH+ 223.

Ejemplo 33

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-(1,3-oxazol-5-il)benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-(1,3-oxazol-5-il)benzoato de metilo (177 mg, 0,88 mmoles) para dar el compuesto del título (28 mg, 10%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,91 (s, 4H), 3,74 (s, 3H), 6,48 (s, 1H), 6,77 (d, 1H), 6,82 (m, 2H), 7,20 (t, 1H), 7,87 - 7,83 (m, 3H), 8,10 (d, 2H), 8,51 (s, 1H), 10,73 (s, 1H), 12,18 (s, 1H); MH+ 389.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 1,2 μM.

Ejemplo 34

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-(tetrazol-1-il)benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-(tetrazol-1-il)benzoato de metilo (179 mg, 0,88 mmoles) para dar el compuesto del título (16 mg, 6%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,92 (s, 4H), 3,74 (s, 3H), 6,50 (s, 1H), 6,77 (d, 1H), 6,84 - 6,82 (m, 2H), 7,21 (t, 1H), 8,06 (d, 2H), 8,25 (d, 2H), 10,19 (s, 1H), 10,89 (s, 1H), 12,22 (s, 1H); MH+ 390.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 1 μM.

Ejemplo 35

N-[5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-il]carbamato de prop-2-enilo

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 6-(prop-2-enoxicarbonilamino)piridin-3-carboxilato de metilo (208 mg, 0,88 mmoles) para dar el compuesto del título (38 mg, 12%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,90 (s, 4H), 3,74 (s, 3H), 4,66 (d, 2H), 5,25 (d, 1H), 5,40 (d, 1H), 6,02 - 5,95 (m, 1H), 6,46 (s, 1H), 6,76 (d, 1H), 6,84 - 6,80 (m, 2H), 7,20 (t, 1H), 7,91 (d, 1H), 8,32 (d, 1H), 8,87 (s, 1H), 10,56 (s, 1H), 10,74 (s, 1H), 12,17 (s, 1H); MH+ 422.

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 76 μM.

El 6-(prop-2-enoxicarbonilamino)piridin-3-carboxilato de metilo usado como material de partida se preparó de manera análoga a la síntesis de 6-morfolin-4-ilpiridin-3-carboxilato de metilo en el Ejemplo 32, pero partiendo de carboxilato del ácido 6-(prop-2-enoxicarbonilamino)piridin-3-carboxílico (880 mg, 3,96 mmoles) para dar el compuesto del título (0,35 g, 37%); RMN ^{1}H (400,132 MHz, CDCl3) 3,93 (s, 3H), 4,75 (dt, 2H), 5,32 (dq, 1H), 5,41 (dq, 1H), 6,09-5,99 (m, 1H), 8,07 (d, 1H), 8,30 (dd, 1H), 8,97 (d, 1H), 9,45 (brs, 1H); MH+ 237.

Ejemplo 36

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-4-(1,2,4-triazol-1-il)benzamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 4-(1,2,4-triazol-1-il)benzoato de metilo (177 mg, 0,88 mmoles) para dar el compuesto del título (83 mg, 29%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,92 (s, 4H), 3,74 (s, 3H), 6,48 (s, 1H), 6,77 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 8,00 (d, 2H), 8,19 (d, 2H), 8,29 (s, 1H), 9,42 (s, 1H), 10,79 (s, 1H), 12,20 (s, 1H); MH+ 389.

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,66 μM.

Ejemplo 37

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-6-pirazol-1-il-piridin-3-carboxamida

Preparada usando un método análogo al Ejemplo 25, pero partiendo de 6-pirazol-1-ilpiridin-3-carboxilato de metilo (177 mg, 0,88 mmoles) para dar el compuesto del título (151 mg, 54%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,92 (s, 4H), 3,74 (s, 3H), 6,49 (s, 1H), 6,63 (dd, 1H), 6,77 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 7,90 (s, 1H), 8,01 (d, 1H), 8,52 (d, 1H), 8,70 (s, 1H), 9,03 (s, 1H), 10,95 (s, 1H), 12,23 (s, 1H); MH+ 389.

Media de n = 3, ensayo de FGFR cinasa – Caliper, IC_{50} 69 μM.

El 6-pirazol-1-ilpiridin-3-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió pirazol (2,4 g, 35,4 mmoles) a DMA (100 ml), y a esto se le añadió lentamente NaH (1,85 g, 38,6 mmoles). La mezcla de reacción se agitó durante 10 min en una atmósfera de nitrógeno. Al anión resultante se le añadió 6-cloropiridin-3-carboxilato de metilo (5,5 g, 32,2 mmoles), y la reacción se calentó a 95°C toda la noche. La mezcla de reacción se evaporó hasta sequedad, se paralizó con NaOH 2,0 N (100 ml), se extrajo con DCM (3 x 100 ml), se secó ($MgSO_4$) y el disolvente se eliminó *a vacío* para producir un sólido marrón. Este sólido se purificó vía cromatografía en columna de sílice, eluyendo con 0-40% de éter dietílico en iso-hexano. Se obtuvo un sólido blanco, que se disolvió en iso-hexano caliente. Al enfriar se obtuvo un sólido blanco, que se filtró y se secó (2,6 g, 40%); RMN ^1H (400,132 MHz, CDCl3) δ 3,96 (s, 3H), 6,50 (s, 1H), 7,77 (s, 1H), 8,05 (d, 1H), 8,40 (dd, 1H), 8,62 (d, 1H), 9,02 (d, 1H); MH+ 203.

Ejemplo 38

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluoro-benzamida

Se añadió gota a gota cloruro de oxalilo (2M en DCM, 1,40 ml, 2,75 mmoles, 1,1 eq) a una mezcla de ácido 4-fluorobenzoico (350 mg, 2,50 mmoles, 1 eq) en diclorometano (15 ml) a 0°C que contiene unas pocas gotas de DMF (10 μl, 0,12 mmoles, 0,05 eq) y DIPEA (937 μl, 5,25 mmoles, 2,1 eq). Después de agitar durante 60 min a 0°C, se añadió gota a gota una disolución de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (742 mg, 3 mmoles, 1,2 eq) en DCM (10 ml) durante 15 min. La mezcla se mantuvo a 0°C durante otras 2 h, después se dejó calentar gradualmente hasta la temperatura ambiente toda la noche. La mezcla se diluyó con DCM (50 ml), y se lavó con disolución acuosa de $NaHCO_3$ (50 ml). La capa acuosa se extrajo con DCM (50 ml). Las capas orgánicas combinadas se recogieron y se concentraron. El producto bruto se purificó mediante HPLC prep de fase inversa usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones desedas se evaporaron para dar el compuesto del título como un sólido beige. (31,5 mg, rendimiento 3%)

RMN ^1H (300,132 MHz, DMSO) δ 2,87 (4H, s),3,72 (6H, s),6,32 (1H, t),6,42 (2H,

d),6,46 (1H, s),7,31 (2H, t),8,06 (2H, m),10,69 (1H, s),12,16 (1H, s). MS: m/z 370 (MH+)
Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,165 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se muestra en la preparación del material de partida en el Ejemplo 2.

Ejemplo 39

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-3-metoxi-benzamida

Se añadió gota a gota 1-cloro-*N*,*N*,2-trimetilprop-1-en-1-amina (89 μl, 0,67 mmoles, 1,05 eq) a ácido 3-metoxibenzoico (97 mg, 0,63 mmoles, 1 eq) en DCM (1,5 ml) a temperatura ambiente. Después de agitar a temperatura ambiente durante 1,5 h, a la mezcla de reacción se añadió una disolución de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (199 mg, 0,57 mmoles, 0,9 eq) y piridina (142 μl, 1,74 mmoles, 2,75 eq) en DCM (2 ml), y la agitación se continuó a temperatura ambiente durante otras 3 h. Entonces se añadió una disolución de TFA (386 μl, 5,2 mmoles, 8,25 eq) en DCM (3,5 ml), y la agitación se continuó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido incoloro (129 mg, rendimiento 59%). RMN ^{1}H (399,902 MHz, DMSO) δ 2,89 (4H, s), 3,73 (6H, s), 3,84 (3H, s), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,48 (1H, s), 7,12-7,10 (1H, m), 7,42-7,37 (1H, m), 7,59-7,56 (2H, m), 10,65 (1H, br.s), 12,16 (1H, br.s). MS: m/z 382 (MH+).
Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,37 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 40

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-3-morfolin-4-il-benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 3-morfolin-4-ilbenzoico (130 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (105 mg, rendimiento 42%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,89 (4H, s), 3,21-3,19 (4H, m), 3,73 (6H, s), 3,79-

3,76 (4H, m), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,48 (1H, s), 7,12 (1H, d), 7,35-7,31 (1H, m), 7,43 (1H, d), 7,57 (1H, s), 10,62 (1H, br.s), 12,15 (1H, br.s). MS: m/z 437 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,71 μM.

Ejemplo 41

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-2-metoxi-benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 2-metoxibenzoico (95,8 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (100 mg, rendimiento 46%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,89 (4H, s), 3,73 (6H, s), 3,97 (3H, s), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,49 (1H, s), 7,12-7,07 (1H, m), 7,21 (1H, d), 7,56-7,51 (1H, m), 7,85-7,82 (1H, m), 10,16 (1H, br.s), 12,14 (1H, br.s). MS: m/z 382 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 2,61 μM.

Ejemplo 42

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-etoxietoxi)benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 4-(2-etoxietoxi)benzoico (132 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (126 mg, rendimiento 50%); RMN ^{1}H (399,902 MHz, DMSO) δ 1,15 (3H, t), 2,88 (4H, s), 3,52 (2H, q), 3,73 (8H, s), 4,19-4,16 (1H, m), 6,34-6,32 (1H, m), 6,43 (2H, d), 6,46 (1H, s), 7,02 (2H, d), 7,98 (2H, d), 10,47 (1H, br.s), 12,11 (1H, br.s). MS: m/z 440 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,075μM.

Ejemplo 43

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(1-piperidil)benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 4-(1-piperidil)benzoico (129 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (97,5 mg, rendimiento 39%);

RMN ^{1}H (399,902 MHz, DMSO) δ 1,60 (6H, s), 2,88 (4H, s), 3,33-3,31 (6H, m), 3,73 (1H, s), 6,33-6,32 (2H, m), 6,42 (1H, d), 6,45 (2H, s), 6,94 (2H, d), 10,26 (1H, br.s), 12,07 (1H, br.s). MS: m/z 435 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,438 μM.

Ejemplo 44

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-piperidilmetoxi)benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 4-[[1-[(2-metilpropan-2-il)oxicarbonil]-4-piperidil]metoxi]benzoico (211 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (40 mg, rendimiento 15%); RMN ^{1}H (399,902 MHz, DMSO) δ1,72-1,67 (2H, m), 1,87-1,79 (2H, m), 2,48-2,45 (1H, m), 2,88 (4H, s), 2,98-2,94 (2H, m), 3,73 (6H, s), 3,88 (2H, d), 6,34 (1H, s), 6,46-6,42 (3H, m), 7,00 (2H, d), 7,97 (2H, d), 10,48 (1H, br.s), 12,14 (1H, br.s). MS: m/z 465 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,025 μM.

Ejemplo 45

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-piperazin-1-il-benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 4-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]benzoico (193 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (100 mg, rendimiento 40%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,84-2,82 (4H, m), 2,88 (4H, s), 3,21-3,15 (4H, m), 3,73 (6H, s), 6,33 (1H, s), 6,46-6,42 (3H, m), 6,94 (2H, d), 7,89 (2H, d), 10,30 (1H, br.s), 12,09 (1H, br.s). MS: m/z 436 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,026 μM.

Ejemplo 46

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-6-piperazin-1-il-piridin-3-carboxamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 6-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]piridin-3-carboxílico (193 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (96 mg, rendimiento 39%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,79-2,76 (4H, m), 2,88 (4H, s), 3,56-3,53 (4H, m), 3,73 (6H, s), 6,34-6,32 (1H, m), 6,45-6,42 (3H, m), 6,82 (1H, d), 8,10-8,07 (1H, m), 8,73 (1H, d), 10,43 (1H, br.s), 12,12 (1H, br.s). MS: m/z 437 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,040 μM.

Ejemplo 47

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(dimetilaminometil)benzamida

Se añadió gota a gota cloruro de oxalilo (61 µl, 0,69 mmoles, 1,1 eq) a ácido 4-(dimetilaminometil)benzoico (113 mg, 0,63 mmoles, 1 eq) en DCM (2,5 ml) que contiene 1 gota de DMF. Después de agitar a temperatura ambiente durante 1,5 h, a la mezcla de reacción se añadió una disolución de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butil (196 mg, 0,56 mmoles, 0,9 eq) y piridina (137 µl, 1,69 mmoles, 2,70 eq) en DCM (2 ml), y la agitación se continuó a temperatura ambiente durante otras 2 h. Entonces se añadió una disolución de TFA (384 µl, 5,16 mmoles, 8,25 eq) en DCM (3,5 ml), y la agitación se continuó a temperatura ambiente durante 18 h. La mezcla de reacción se concentró, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido incoloro (65 mg, rendimiento 25%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,09 (6H, s), 2,81 (4H, s), 3,38 (2H, s), 3,65 (6H, s), 6,26-6,25 (1H, m), 6,35 (2H, d), 6,40 (1H, s), 7,31 (2H, d), 7,87 (2H, d), 10,51 (1H, br.s), 12,07 (1H, br.s). MS: m/z 409 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,019 µM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

RMN ^{1}H (399,902 MHz, DMSO) δ1,56 (9H, s), 2,68-2,63 (2H, m), 2,80-2,75 (2H, m), 3,73 (6H, s), 5,22 (1H, s), 6,23 (2H, br.s), 6,32-6,31 (1H, m), 6,44 (2H, d). MS: m/z 370 ([M+Na]+).

Ejemplo 48

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-hidroxietoxi)benzamida

Se añadió gota a gota a temperatura ambiente una disolución de NaHMDS en THF (1 M, 1,15 ml, 1,15 mmoles, 2 eq) a una mezcla de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (200 mg, 0,58 mmoles, 1 eq) y 4-(2-hidroxietoxi)benzoato de metilo (136 mg, 0,69 mmoles, 1,2 eq) en THF (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Ésta se concentró entonces, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se

evaporaron para dar el compuesto del título como un sólido incoloro (29 mg, rendimiento 12%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,89 (4H, s), 3,77-3,72 (8H, m), 4,07 (2H, t), 4,88 (1H, t), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,46 (1H, s), 7,01 (2H, d), 7,98 (2H, d), 10,46 (1H, br.s), 12,12 (1H, br.s). MS: m/z 412 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,039 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 49

4-(2-Aminopropil)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

Se añadió gota a gota a temperatura ambiente una disolución de NaHMDS en THF (1 M, 0,86 ml, 0,86 mmoles, 1,5 eq) a una mezcla de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (200 mg, 0,58 mmoles, 1 eq) y 4-(2-aminopropil)benzoato de metilo (133 mg, 0,69 mmoles, 1,2 eq) en THF (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Ésta se concentró entonces, y el producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como una goma amarilla pálida (10 mg, rendimiento 4%); RMN ^{1}H (399,902 MHz, DMSO) δ 0,89 (3H, d), 2,53-2,47 (2H, m), 2,80 (4H, s), 3,01-2,93 (1H, m), 3,65 (6H, s), 6,25-6,24 (1H, m), 6,34 (2H, d), 6,40 (1H, s), 7,21 (2H, d), 7,84 (2H, d), 10,47 (1H, br.s), 12,06 (1H, br.s). MS: m/z 409 (MH+)

FGFR1 celular, IC_{50} 1,47μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 50

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(3,3-dimetil-1-piperidil)metil]-benzamida

Preparada de manera análoga al Ejemplo 49, partiendo de 4-[(3,3-dimetil-1-piperidil)metil]benzoato de metilo (180 mg, 0,69 mmoles) para dar el compuesto del título

como un sólido incoloro (44 mg, rendimiento 16%); RMN ^{1}H (399,902 MHz, DMSO) δ 0,92 (3H, s), 1,23-1,20 (2H, m), 1,59-1,52 (2H, m), 2,01-1,99 (2H, m), 2,35-2,29 (2H, m), 2,89 (4H, s), 3,48 (2H, s), 3,73 (6H, s), 6,34-6,32 (1H, m), 6,43 (2H, d), 6,48 (1H, s), 7,40 (2H, d), 7,94 (2H, d), 10,57 (1H, br.s), 12,14 (1H, br.s). MS: m/z 477 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,001 μM.

El 4-[(3,3-dimetil-1-piperidil)metil]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió de una vez 3,3-dimetilpiperidina (170 mg, 1,5 mmoles, 1,5 eq) a una mezcla de 4-(bromometil)benzoato de metilo (230 mg, 1 mmol, 1 eq) y carbonato de MP (2,74 mmoles/g, 1,46 g, 4 mmoles, 4 eq) en MeCN (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se añadió de una vez isocianato soportado sobre polímero (1 mmol/g, 1 g, 1 mmol, 1 eq), y la agitación se continuó durante 4 h. La mezcla de reacción se filtró, las resinas se lavaron con MeCN, y el filtrado combinado se concentró para dar un líquido claro (216 mg, rendimiento 83%); RMN ^{1}H (399,902 MHz, DMSO) δ 0,91 (6H, s), 1,22-1,19 (2H, m), 1,58-1,52 (2H, m), 1,99 (2H, s), 2,33-2,28 (2H, m), 3,49 (2H, s), 3,85 (3H, s), 7,46 (2H, d), 7,92 (2H, d). MS: m/z 262 (MH+)

Ejemplo 51

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[4-(2-hidroxietil)piperazin-1-il]benzamida

Preparada de manera análoga al Ejemplo 49, partiendo de 4-[4-(2-hidroxietil)piperazin-1-il]benzoato de metilo (182 mg, 0,69 mmoles) para dar el compuesto del título como un sólido incoloro (11 mg, rendimiento 4%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,45 (2H, t), 2,58-2,55 (4H, m), 2,88 (4H, s), 3,29-3,26 (4H, m), 3,58-3,53 (2H, m), 3,73 (6H, s), 4,42 (1H, t), 6,34-6,32 (1H, m), 6,42 (2H, d), 6,45 (1H, s), 6,96 (2H, d), 7,90 (2H; d), 10,30 (1H, br.s), 12,08 (1H, br.s). MS: m/z 480 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,081 μM.

El 4-[4-(2-hidroxietil)piperazin-1-il]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota disolución de trimetilsilildiazometano (2M en hexanos, 1,2 ml, 2,4 mmoles, 1,2 eq) a ácido 4-(4-[2-hidroxietil]piperazin-1-il)benzoico (501 mg, 2 mmoles, 1 eq) en tolueno (14 ml) y metanol (4 ml) a temperatura ambiente. La mezcla de reacción se dejó agitar durante 5 h, el disolvente se eliminó a presión reducida y el residuo se secó a alto vacío para dar 4-(2-bromoetoxi)benzoato de metilo como un sólido de color crema (342 mg, rendimiento 65%). MS: m/z 265 (MH+)

Ejemplo 52

4-[(7-Ciano-3,4-dihidro-1H-isoquinolin-2-il)metil]-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de 4-[(7-ciano-3,4-dihidro-1H-isoquinolin-2-il)metil]benzoato de metilo (211 mg, 0,69 mmoles) para dar el compuesto del título como una goma amarilla pálida (45 mg, rendimiento 15%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,67-2,64 (2H, m), 2,81 (4H, s), 2,86-2,83 (2H, m), 3,54 (2H, s), 3,67-3,64 (8H, m), 6,26-6,24 (1H, m), 6,35 (2H, d), 6,41 (1H, s), 7,26 (1H, d), 7,39 (2H, d), 7,51-7,47 (2H, m), 7,91 (2H, d), 10,53 (1H, br.s), 12,07 (1H, br.s). MS: m/z 522 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,486 μM.

El 4-[(7-ciano-3,4-dihidro-1H-isoquinolin-2-il)metil]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió de una vez hidrocloruro de 1,2,3,4-tetrahidroisoquinolin-7-carbonitrilo (292 mg, 1,5 mmoles, 1,5 eq) a una mezcla de 4-(bromometil)benzoato de metilo (230 mg, 1 mmol, 1 eq) y carbonato de MP (2,74 mmoles/g, 1,46 g, 4 mmoles, 4 eq) en MeCN (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se añadió de una vez isocianato soportado sobre polímero (1 mmol/g, 1 g, 1mmol, 1 eq), y la agitación se continuó durante 4 h. La mezcla de reacción se filtró, las resinas se lavaron con MeCN, y el filtrado combinado se concentró para dar un aceite amarillo pálido que solidificó al dejar reposar toda la noche (292 mg, rendimiento 95%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,70–2,63 (2H, m), 2,89–2,82 (2H, m), 3,53 (2H, s), 3,68 (2H, s), 3,78 (3H, s), 7,25 (1H, d), 7,51-7,38 (4H, m), 7,89-7,86 (2H, m). MS: m/z 307 (MH+)

Ejemplo 53

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(3-fluoro-1-piperidil)metil]benzamida

Se añadió gota a gota a temperatura ambiente una disolución de NaHMDS en THF (1 M, 0,86ml, 0,86 mmoles, 1,5 eq) a una mezcla de 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (200 mg, 0,58 mmoles, 1 eq) y 4-[(3-fluoro-1-piperidil)metil]benzoato de metilo (174 mg, 0,69 mmoles, 1,2 eq) en THF (1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró entonces, y el producto bruto se purificó mediante HPLC prep. de fase inversa (acidic) usando un gradiente de acetonitrilo en agua que contiene 0,1% de TFA. Las fracciones limpias se recogieron y se evaporaron. El residuo se disolvió en una mezcla 3:1 de DCM:MeCN (4 ml) y se añadió carbonato de MP (2,74 mmoles/g, 1 g, 2,74 mmoles). La mezcla se agitó durante 4 h, se filtró y el filtrado se evaporó para dar el compuesto del título como una goma amarilla pálida (43 mg, rendimiento 16%); RMN ^{1}H (399,902 MHz, DMSO) δ 1,46-1,34 (2H, m), 1,82-1,61 (2H, m), 2,36-2,28 (2H, m), 2,66-2,56 (2H, m), 2,81 (4H, s), 3,50 (2H, s), 3,65 (6H, s), 4,66-4,47 (1H, m), 6,26-6,24 (1H, m), 6,35 (2H, d), 6,40 (1H, s), 7,32 (2H, d), 7,88 (2H, d), 10,51 (1H, br.s), 12,07 (1H, br.s). MS: m/z 467 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,090 μM.

El 4-[(3-fluoro-1-piperidil)metil]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió de una vez hidrocloruro de 3-fluoropiperidina (210 mg, 1,5 mmoles, 1,5 eq) a una mezcla de 4-(bromometil)benzoato de metilo (230 mg, 1 mmol, 1 eq) y carbonato de MP (2,74 mmoles/g, 1,46 g, 4 mmoles, 4 eq) en MeCN (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se añadió de una vez isocianato soportado sobre polímero (1 mmol/g, 1 g, 1 mmol, 1 eq), y la agitación se continuó durante 4 h. La mezcla de reacción se filtró, las resinas se lavaron con MeCN, y el filtrado combinado se concentró para dar un aceite claro, 217 mg, rendimiento 86%.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,59-1,42 (2H, m), 1,90-1,67 (2H, m), 2,42-2,36 (2H, m), 2,73-2,63 (2H, m), 3,59 (2H, s), 3,86 (3H, s), 4,73-4,56 (1H, m), 7,46 (2H, d), 7,93 (2H, d). MS: m/z 252 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 54

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-morfolin-4-iletoxi)benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de 4-(2-morfolin-4-iletoxi)benzoato de metilo (183 mg, 0,69 mmoles) para dar el compuesto del título como una goma amarilla pálida (21 mg, rendimiento 7,5%); RMN ^{1}H (399,902 MHz, CDCl3) δ 2,59-2,57 (4H, m), 2,81 (2H, t), 2,99-2,90 (4H, m), 3,75-3,72 (4H, m), 3,77 (6H, s), 4,14 (2H, t), 6,36-6,32 (4H, m), 6,67 (1H, br.s), 6,96 (2H, d), 7,83 (2H, d), 8,53 (1H, br.s). MS: m/z 481 (MH+)
Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,096 μM.

El 4-(2-morfolin-4-iletoxi)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió carbonato de MP (2,74 mmoles/g, 529 mg, 1,45 mmoles, 1,5 eq) a 4-(2-bromoetoxi)benzoato de metilo (250 mg, 0,96 mmoles, 1 eq), se cargaron morfolina (93 μl, 1,06 mmoles, 1,1 eq), yoduro de sodio (150 mg, 1 mmol, 1,05 eq) y MeCN (5 ml) a una vasija reactora de microondas, y la mezcla de reacción se calentó hasta 120°C en un reactor de microondas durante 10 minutos. La mezcla de reacción se transfirió a un cartucho SCX-2, se eluyó con MeOH seguido de disolución de amoníaco 3,5 N en MeOH. Las últimas fracciones se combinaron y se evaporaron para dar un aceite claro que solidificó al dejar reposar en un sólido de color crema (146 mg, rendimiento 57%). RMN ^{1}H (400,132 MHz, CDCl3) δ 2,59-2,57 (4H, m), 2,82 (2H, t), 3,74-3,72 (4H, m), 3,88 (3H, s), 4,16 (2H, t), 6,93-6,91 (2H, m), 7,99-7,97 (2H, m). MS: m/z 266 (MH+)

Ejemplo 55

4-[2-(4,4-Difluoro-1-piperidil)etoxi]-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de 4-[2-(4,4-difluoro-1-piperidil)etoxi]benzoato de metilo (104 mg, 0,35 mmoles) para dar el compuesto del título como una goma clara (5 mg, rendimiento 1,7%); RMN ^{1}H (399,902 MHz, CDCl3) δ 2,06-1,96 (4H, m), 2,70-2,67 (4H, m), 2,88-2,85 (2H, m), 2,97-2,92 (4H, m), 3,77-3,76 (8H, m),

4,12 (2H, t), 6,33-6,32 (2H, m), 6,35-6,35 (2H, m), 6,65 (1H, br.s), 6,95 (2H, d), 7,83 (2H, d), 8,59 (1H, s). MS: m/z 515 (MH+)

FGFR1 celular, IC_{50} 0,46 μM.

El 4-[2-(4,4-difluoro-1-piperidil)etoxi]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió carbonato de MP (2,74 mmoles/g, 1,234 g, 3,38 mmoles, 2,5 eq) a 4-(2-bromoetoxi)benzoato de metilo (350 mg, 1,35 mmoles, 1 eq), se cargaron hidrocloruro de 4,4-difluoropiperidina (235 mg, 1,49 mmoles, 1,1 eq), yoduro de sodio (212 mg, 1,42 mmoles, 1,05 eq) y MeCN (6 ml) a una vasija reactora de microondas, y la mezcla de reacción se calentó hasta 120°C en un reactor de microondas durante 10 minutos. La mezcla de reacción se transfirió a un cartucho SCX-2, se eluyó con MeOH seguido de disolución de amoníaco 3,5 N en MeOH. Las últimas fracciones se combinaron y se evaporaron para dar un sólido incoloro (104 mg, rendimiento 35%).

RMN ^{1}H (400,132 MHz, CDCl3) δ 2,08-1,98 (4H, m), 2,74-2,71 (4H, m), 2,90 (2H, t), 3,89 (3H, s), 4,16 (2H, t), 6,93-6,91 (2H, m), 8,00-7,98 (2H, m). MS: m/z 300 (MH+)

Ejemplo 56

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(2-morfolin-4-iletil)benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de 4-(2-morfolin-4-iletil)benzoato de metilo (172 mg, 0,69 mmoles) para dar el compuesto del título como una goma clara (42 mg, rendimiento 15,6%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,37-2,35 (4H, m), 2,49-2,45 (2H, m), 2,73 (2H, t), 2,80 (4H, s), 3,50 (4H, t), 3,65 (6H, s), 6,26-6,24 (1H, m), 6,34 (2H, d), 6,40 (1H, s), 7,26 (2H, d), 7,83 (2H, d), 10,47 (1H, br.s), 12,06 (1H, br.s). MS: m/z 465 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,120 μM.

El ácido 4-(2-morfolin-4-iletil)benzoico usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota disolución de trimetilsilildiazometano (2M en hexanos, 1,2 ml, 2,4 mmoles, 1,2 eq) a ácido 4-(2-bromoetil)benzoico (459 mg, 2 mmoles, 1 eq) en tolueno (14 ml) y metanol (4 ml) a temperatura ambiente. La mezcla de reacción se dejó agitar durante 5

h, el disolvente se eliminó a presión reducida y el residuo se secó a alto vacío para dar 4-(2-bromoetoxi)benzoato de metilo como un líquido amarillo pálido (487 mg, rendimiento 100%). RMN ^{1}H (399,902 MHz, DMSO) δ 3,20 (2H, t), 3,76 (2H, t), 3,83 (3H, s), 7,42 (2H, d), 7,89 (2H, d).

Se añadió carbonato de MP (2,74 mmoles/g, 270 mg, 0,74 mmoles, 0,6 eq) a 4-(2-bromoetoxi)benzoato de metilo (300 mg, 1,23 mmoles, 1 eq), se cargaron a una vasija reactora de microondas morfolina (0,12 ml, 1,36 mmoles, 1,1 eq), yoduro de sodio (193 mg, 1,29 mmoles, 1,05 eq) y MeCN (6 ml), y la mezcla de reacción se calentó hasta 120°C en un reactor de microondas durante 10 minutos. La mezcla de reacción se transfirió a un cartucho SCX-2, se eluyó con MeOH seguido de disolución de amoníaco 3,5 N en MeOH. Las últimas fracciones se combinaron y se evaporaron para dar un sólido amarillo pálido (130 mg, rendimiento 52%).

RMN ^{1}H (399,902 MHz, CDCl3) δ 2,53-2,51 (4H, m), 2,64-2,60 (2H, m), 2,88-2,84 (2H, m), 3,75-3,72 (4H, m), 3,90 (3H, s), 7,28-7,26 (2H, m), 7,97-7,94 (2H, m). MS: m/z 250 (MH+)

Ejemplo 57

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(metil-(oxolan-2-ilmetil)amino)metil]benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de 4-[(metil-(oxolan-2-ilmetil)amino)metil]benzoato de metilo (181 mg, 0,69 mmoles) para dar el compuesto del título como una goma clara (56 mg, rendimiento 20%); RMN ^{1}H (399,902 MHz, DMSO) δ 1,56-1,42 (1H, m), 1,81-1,74 (2H, m), 1,98-1,90 (1H, m), 2,20 (3H, s), 2,44 (2H, d), 3,31 (4H, s), 3,66-3,59 (3H, m), 3,73 (6H, s), 4,01-3,94 (2H, m), 6,34-6,33 (1H, m), 6,43 (2H, d), 6,48 (1H, s), 7,40 (2H, d), 7,95 (2H, d), 10,58 (1H, br.s), 12,15 (1H, br.s). MS: m/z 479 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0053 μM.

El 4-[(metil-(oxolan-2-ilmetil)amino)metil]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió carbonato de MP (2,74 mmoles/g, 1,44 g, 4 mmoles, 2 eq) a 4-(bromometil)benzoato de metilo (500 mg, 2 mmoles, 1 eq), *N*-metil-1-(oxolan-2-il)metanamina (231 mg, 2 mmoles, 1 eq) y MeCN (10 ml). La mezcla de reacción se dejó agitar a temperatura ambiente durante 18 h, y después se transfirió a un cartucho SCX-2, se

eluyó con MeOH seguido de disolución de amoníaco 3,5 N en MeOH. Las últimas fracciones se combinaron y se evaporaron para dar un sólido amarillo pálido (355 mg, rendimiento 64%).

RMN ^{1}H (399,902 MHz, CDCl3) δ 1,54-1,47 (1H, m), 1,87-1,80 (2H, m), 2,01-1,93 (1H, m), 2,28 (3H, s), 2,46-2,42 (1H, m), 2,55-2,50 (1H, m), 3,68-3,57 (2H, m), 3,76-3,71 (1H, m), 3,87-3,81 (1H, m), 3,91 (3H, s), 4,08-4,01 (1H, m), 7,41 (2H, d), 7,98 (2H, d). MS: m/z 264 (MH+)

Ejemplo 58

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-piperidil)benzamida

Preparada de manera análoga al Ejemplo 53, partiendo de hidrocloruro de 4-(4-piperidil)benzoato de metilo (176 mg, 0,69 mmoles) para dar el compuesto del título como una goma amarilla pálida (20 mg, redimiento 8%); RMN ^{1}H (399,902 MHz, DMSO) δ 1,69-1,57 (2H, m), 1,84-1,76 (2H, m), 2,76-2,68 (2H, m), 2,93 (4H, s), 3,17-3,12 (2H, m), 3,77-3,76 (7H, m), 6,38-6,37 (1H, m), 6,47 (2H, d), 6,53 (1H, s), 7,38 (2H, d), 7,98 (2H, d), 10,61 (1H, s), 12,20 (1H, s). MS: m/z 435 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,001 μM.

Ejemplo 59

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-dimetilamino-benzamida

Preparada de manera análoga al Ejemplo 39, partiendo de ácido 4-dimetilaminobenzoico (102 mg, 0,63 mmoles) para dar el compuesto del título como un sólido (139 mg, rendimiento 63%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,87 (4H, s), 3,00 (6H, s), 3,73 (6H, s), 6,33-6,32 (1H, m), 6,42 (2H, d), 6,45 (1H, s), 6,72 (2H, d), 7,89 (2H, d), 10,21 (1H, brs), 12,06 (1H, br.s). MS: m/z 395 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,134 μM.

Ejemplo 60

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-5-piperazin-1-il-tiofen-2-carboxamida (sal del ácido 2,2,2-trifluoroacético)

Se disolvió ácido 5-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]tiofen-2-carboxílico (150 mg, mmol) en THF seco (10 ml) en nitrógeno, se añadió 1-cloro-N,N,2-trimetil-prop-1-

en-1-amina (177 µl, mmol), y la mezcla se agitó a temperatura ambiente durante 3,5 h. Seañadieron 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (167 mg, mmol) y piridina (47 µl, mmol), y la reacción se calentó hasta 65°C durante 18 h. La mezcla de reacción se enfrió entonces hasta la temperatura ambiente, y se añadió HCl 4M en dioxano (2,0 ml, 2,0 mmoles). La mezcla se agitó toda la noche a temperatura ambiente, se evaporó, y el residuo se purificó mediante HPLC prep. ácida, eluyendo con un gradiente de 24-32% de MeCN en 0,1% de TFA en agua. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido verde pálido (28,7 mg, 11 %); RMN ^{1}H (399,902 MHz, DMSO) δ 2,79 (s, 4H), 3,21 (s, 4H), 3,34 (s, 4H), 3,64 (s, 6H), 6,29 (m, 5H), 7,77 (m, 1H), 8,71 (s, 1H), 10,37 (s, 1H) MS: m/z = 442 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,022 µM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]pirazol-1-carboxilato *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El ácido 5-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]tiofen-2-carboxílico usado como material de partida se preparó según lo siguiente:

Se añadió de una vez una disolución de 4-(5-formiltien-2-il)piperazin-1-carboxilato de terc-butilo (2,51 g, 8,50 mmoles) en etanol (85 ml) a una disolución de nitrato de plata (I) (10,0 g, 58,8 mmoles) e hidróxido sódico (4,83 g, 120,6 mmoles) en agua (85 ml). Esta mezcla se agitó y se calentó a 65°C durante 22 h. La mezcla se enfrió mediante adición de hielo, y después se filtró para eliminar las sales de plata. El filtrado se evaporó con cuidado para eliminar el etanol, y la disolución acuosa resultante se filtró nuevamente a través de una almohadilla de fibra de vidrio para eliminar el material alquitranoso. El filtrado se diluyó entonces con agua hasta un volumen total de 400 ml, y después se acidificó hasta pH 5 con ácido acético. El precipitado se separó por filtración, se lavó con agua y después se secó en un horno de vacío a 45°C toda la noche para dar ácido 5-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]tiofen-2-carboxílico (1,88 g, 71%).

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,41 (9H, s), 3,18 (4H, m), 3,45 (4H, m), 6,20 (1H, d), 7,43 (1H, d)

MS: m/z 313 (MH+)

El 4-(5-formiltien-2-il)piperazin-1-carboxilato de terc-butilo usado como material de partida se preparó según lo siguiente:

Una mezcla de 5-bromotiofen-2-carboxaldehído (3,82 g, 20,0 mmoles), piperazin-1-carboxilato de terc-butilo (4,1 g, 22,0 mmoles), N-etil-N,N-diisopropilamina (7,0 ml, 40,0 mmoles) y dimetilsulfóxido (5,0 ml) se agitó a 130ºC en una atmósfera de nitrógeno durante 18 h. La mezcla enfriada se repartió entre acetato de etilo y agua. Los orgánicos se lavaron con agua, con salmuera, se secaron sobre sulfato de magnesio y se evaporaron. El sólido rojo oscuro resultante se purificó mediante cromatografía en columna de sílice, eluyendo con diclorometano seguido de acetato de etilo/diclorometano (15%) para dar 4-(5-formiltien-2-il)piperazin-1-carboxilato de terc-butilo (4,3 g, 73%).

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,41 (9H, s), 3,34 (4H, m), 3,47 (4H, m), 6,36 (1H, d), 7,70 (1H, d), 9,49 (1H, s)

MS: m/z 297 (MH+)

Ejemplo 61

6-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-3-carboxilato de metilo

Se añadió ácido 5-metoxicarbonilpiridin-2-carboxílico (0,285 g, 1,58 mmoles) a DCM (40 ml); a esto se añadió cloruro de oxalilo (0,165 ml, 1,90 mmoles) y una pocas gotas de DMF anhidra. La mezcla de reacción se agitó durante 30 min antes de añadir 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo (0,50 g, 1,58 mmoles) y piridina (2,0 ml). La reacción se agitó toda la noche. La reacción se evaporó hasta sequedad para dar paso a una goma. A esta goma se añadió ácido fórmico. La mezcla de reacción se agitó durante 1 h antes de evaporarla hasta sequedad. La goma resultante se paralizó con carbonato de potasio saturado (30 ml), se extrajo con DCM (3 x 50 ml), se secó ($MgSO_4$) y el disolvente se eliminó *a vacío* para producir una goma viscosa. La trituración con acetonitrilo dio el producto deseado como un sólido ligeramente amarillo (24 mg, 4%); RMN ^{1}H (400,132 MHz, DMSO) δ 2,92 (s, 4H), 3,74 (s, 3H), 3,95 (s, 3H), 6,50 (s, 1H), 6,76 (d, 1H), 6,83 - 6,82 (m, 2H), 7,20 (t, 1H), 8,26 (d, 1H), 8,53 (d, 1H), 9,17 (s, 1H), 10,38 (s, 1H), 12,31 (s, 1H); MH+ 381.

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 68 μM.

El 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 23.

El cloruro de 4-(4-metilpiperazin-1-il)benzoilo usado como material de partida se preparó según lo siguiente:

A una suspensión de ácido 4-(4-metilpiperazin-1-il)benzoico (500 mg, 2,27 mmoles, 1 eq) en DCM (20 ml) se añadió DMF (1 gota) seguido de cloruro de oxalilo (219 µl, 2,50 mmoles, 1,1 eq) añadido gota a gota. La mezcla se dejó agitar durante 18 horas, después de lo cual la mezcla se concentró hasta sequedad y se llevó a la siguiente etapa sin ninguna purificación o caracterización adicional.

Ejemplo 62

6-Cloro-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

Se disolvió ácido 6-bromopiridin-3-carboxílico (122 mg, 0,82 mmoles, 1,3 eq) en DCM (5 ml) y se añadió gota a gota cloruro de oxalilo (72 µl, 0,82 mmoles, 1,3 eq) seguido de una gota de DMF. La reacción se agitó durante 1 h a temperatura ambiente, después se añadió N,N-dietiletanamina (1 ml, 1,89 mmoles, 3 eq) seguido de 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de terc-butilo (200 mg, 0,63 mmoles, 1 eq). La reacción se agitó durante 2 h, después se diluyó con DCM y se lavó con agua, con salmuera, se secó ($MgSO_4$), se filtró y se evaporó para dar el compuesto bruto protegido mediante Boc como una goma amarilla. La goma se disolvió en 2-propanol (5 ml), y se añadió una disolución de HCl 6M en 2-propanol (4 ml). La disolución se agitó a temperatura ambiente toda la noche, y después se evaporó hasta sequedad y se cargó en una columna SCX-2. La columna se lavó con metanol, y el producto se eluyó con amoníaco 2N en metanol para dar un sólido naranja. La trituración con un pequeño volumen de metanol dio 6-cloro-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida (39 mg, 17%) como un sólido blanco; RMN ^1H (400,13MHz, DMSO) δ 2,89 (4H, s), 3,74 (3H, s), 6,46 (1H, s), 6,75 (1H, m), 6,81 (2H, m), 7,20 (1H, t), 7,65 (1H, d), 8,35 (1H, m), 8,95 (1H, d), 10,99 (1H, s), 12,23 (1H, s) MS m/z 357 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 4,54 µM.

El 5-amino-3-[2-(3-metoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como se esquematiza en el Ejemplo 23.

Ejemplo 63

6-Ciano-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-3-carboxamida

La preparación fue análoga a la descrita para el Ejemplo 62, excepto usando ácido 6-cianopiridin-3-carboxílico (122 mg, 0,82 mmoles, 1,3 eq) como material de partida. Después de la purificación mediante columna SCX, el material se purificó adicionalmente mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido de color crema. (58 mg, 27% yield); RMN ^{1}H (400,13MHz, DMSO) δ 2,9 (4H, s), 3,74 (3H, s), 6,48 (1H, s), 6,75 (1H, m), 6,8 (2H, m), 7,2 (1H, t), 8,15 (1H, d), 8,52 (1H, m), 9,22 (1H, d), 11,19 (1H, s), 12,26 (1H, s) MS m/z 348 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 3,77 μM.

Ejemplo 64

4-Hidroxi-N-[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]piridin-2-carboxamida

La preparación fue análoga a la descrita para el Ejemplo 62, excepto usando ácido 4-hidroxipiridin-2-carboxílico (114 mg, 0,82 mmoles, 1,3 eq) como material de partida. Después de la purificación mediante columna SCX, el material se purificó adicionalmente mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (10 mg, rendimiento 5%); RMN ^{1}H (400,13MHz, DMSO) δ 2,9 (4H, s), 3,73 (3H, s), 6,47 (1H, s), 6,75 (1H, m), 6,8 (2H, m), 6,92 (1H, s), 7,19 (1H, t), 7,47 (1H, s), 8,32 (1H, s), 10,2 (1H, s), 12,21 (1H, s) MS m/z 339 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 5 μM.

Ejemplo 65

N-[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]-6-(2-pirrolidin-1-iletil)piridin-3-carboxamida

La preparación fue análoga a la descrita para el Ejemplo 62, excepto usando ácido 6-(2-pirrolidin-1-iletil)piridin-3-carboxílico (180 mg, 0,82 mmoles, 1,3 eq) como material de partida. Después de la purificación mediante columna SCX, el material se purificó

adicionalmente mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (5 mg, rendimiento 2%); RMN ^{1}H (400,13MHz, DMSO) δ 1,66 (4H, m), 2,77 (2H, t), 2,89 (4H, s), 2,94 (2H, t), 3,27 (4H, m), 3,73 (3H, s), 6,46 (1H, s), 6,75 (1H, m), 6,82 (1H, m), 7,19 (1H, t), 7,40 (1H, d), 8,21 (1H, m), 9,01 (1H, d), 10,79 (1H, s), 12,17 (1H, s) MS m/z 420 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,24 μM.

Ejemplo 66

Ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico

La preparación fue análoga a la descrita para el Ejemplo 62, excepto usando ácido 6-metoxicarbonilpiridin-3-carboxílico (149 mg, 0,82 mmoles, 1,3 eq) como material de partida. Después de la purificación mediante columna SCX, el material se purificó adicionalmente mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Durante esta purificación, el éster se hidrolizó al producto del ácido. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (66 mg, rendimiento 40%); RMN ^{1}H (400,13MHz, DMSO) δ 2,90 (4H, s), 3,74 (3H, s), 6,46 (1H, s), 6,75 (1H, m), 6,83 (2H, m), 7,19 (1H, t), 8,01 (1H, d), 9,12 (1H, d), 11,01 (1H, s), 12,2 (1H, s) MS m/z 367 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 1,02 μM.

Ejemplo 67

5-[[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxilato de metilo

A una suspensión agitada de ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico (55 mg, 0,15 mmoles, 1 eq) en metanol (0,5 ml) se añadió cloruro de tionilo (23 ul, 0,32 mmoles, 2,1 eq) gota a gota. La disolución resultante se calentó a 50°C durante 3 h. La mezcla se concentró *a vacío* para producir un sólido naranja. Éste se disolvió en DCM y se lavó con hidrogenocarbonato de sodio acuoso saturado y salmuera. Las capas orgánicas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar el producto bruto como un sólido amarillo. La trituración con éter dietílico dio el compuesto del título como un sólido blanco 27 mg (47%); RMN ^{1}H (400,13MHz, DMSO) δ 2,92 (4H, s),

3,74 (3H, s), 3,92 (3H, s), 6,49 (1H, s), 6,25 (1H, m), 6,82 (2H, m), 7,19 (1H, t), 8,14 (1H, d), 8,46 (1H, m), 9,20 (1H, d), 11,11 (1H, s), 12,25 (1H, s) MS m/z 381 (MH+)
Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 2,86 μM.

El ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico usado como material de partida se preparó como se esquematiza en el Ejemplo 66.

Ejemplo 68

5-[[5-[2-(3-Metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxilato de etilo

La preparación fue análoga a la descrita para el Ejemplo 67, excepto usando ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico acid (55 mg, 0,15 mmoles, 1 eq) en etanol (0,5 ml) para dar el compuesto del título como un sólido blanco (9 mg, rendimiento 15%); RMN ^{1}H (400,13MHz, DMSO) δ 1,40 (3H, t), 2,97 (4H, s), 3,79 (3H, s), 4,44 (2H, q), 6,54 (1H, s), 6,8 (1H, m), 6,87 (2H, m), 7,25 (1H, t), 8,19 (1H, d), 8,52 (1H, m), 9,25 (1H, s), 11,17 (1H, s), 12,3 (1H, s) MS m/z 395 (MH+)
Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,724 μM.

El ácido 5-[[5-[2-(3-metoxifenil)etil]-2H-pirazol-3-il]carbamoil]piridin-2-carboxílico usado como material de partida se preparó como se esquematiza en el Ejemplo 66.

Ejemplo 69

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)piridin-2-carboxamida

Se añadió gota a gota NaHMDS (disolución 1M en THF, 0,45 ml, 0,451 mmoles, 1,5 eq) a una suspensión agitada de 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (105 mg, 0,301 mmol, 1 eq) y 5-(4-metilpiperazin-1-il)piridin-2-carboxilato de metilo (85 mg, 0,361 mmol, 1,2 eq) en THF seco (2,5 ml) en nitrógeno. La disolución se agitó a temperatura ambiente durante 1h. La disolución se neutralizó con NH_4Cl satd. ac., y se diluyó con agua (5 ml). La fase acuosa se extrajo con acetato de etilo (3 x 8 ml), y los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. La reacción se repitió como antes en una escala de 0,338 mmoles. Los extractos brutos se combinaron con los anteriores, y se purificaron mediante cromatografía en columna de sílice,

eluyendo con 0-6% de MeOH en DCM, para dar el compuesto del título como un sólido marrón pálido (92 mg, rendimiento 35%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,25 (s, 3H), 2,45 - 2,50 (m, 4H), 3,37 - 3,43 (m, 4H), 3,75 (s, 6H), 5,08 (s, 2H), 5,88 (bs, 1H), 6,45 (t, 1H), 6,60 (d, 2H), 7,45 - 7,49 (m, 1H), 7,94 (d, 1H), 8,35 (d, 1H), 10,89 (bs, 1H), 11,36 (bs, 1H) MS: m/z 453 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,122 μM.

El 5-(4-metilpiperazin-1-il)piridin-2-carboxilato usado como material de partida se preparó según lo siguiente:-

Se agitaron 5-bromo-2-carboxilato de metilo (250 mg, 1,16 mmoles, 1 eq), fosfato de potasio (334 mg, 1,62 mmoles, 1,4 eq), S-Phos (96 mg, 0,231 mmoles, 0,2 eq) y Pd_2dba_3 (13 mg, 0,058 mmoles, 0,05 eq) en tolueno (5 ml) en nitrógeno. Se añadió N-metilpiperazina (155 μl, 1,39 mmoles, 1,2 eq), y la mezcla se agitó a 100°C durante 48h, después se dejó enfriar hasta la temperatura ambiente y se agitó durante otras 48h. La mezcla de reacción se vertió en una columna SCX y se lavó a través de ella con MeOH, después con NH_3 2M en MeOH para eluir el producto. Las fracciones del producto se evaporaron para dar 5-(4-metilpiperazin-1-il)piridin-2-carboxilato como un aceite naranja, el cual cristalizó al dejar reposar (194 mg, rendimiento 72%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,24 (s, 3H), 2,43 - 2,48 (m, 4H), 3,35 - 3,40 (m, 4H), 3,81 (s, 3H), 7,32 - 7,37 (m, 1H), 7,88 (d, 1H), 8,38 (d, 1H). MS: m/z 236 (MH+)

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como se esquematiza en el Ejemplo 70.

Ejemplo 70

Hidrocloruro de N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(2-dimetilaminoetilamino)benzamida

Se disolvieron 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (150 mg, 0,429 mmoles) y 4-[2-dimetilaminoetil-[*terc*-butoxicarbonil]amino]benzoato de metilo (166 mg, 0,515 mmoles) en THF seco (2,5 ml). Se añadió gota a gota NaHMDS (1 M en THF, 0,645 ml) en nitrógeno y la mezcla se agitó durante 1h a temperatura ambiente. La mezcla se neutralizó con NH_4Cl (aq), se diluyó con agua y se extrajo con acetato de etilo. Los

extractos se combinaron, se secaron y se evaporaron. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-8% de MeOH en DCM. Las fracciones puras se combinaron y se evaporaron para dar un aceite marrón (74 mg). El aciete se disolvió en THF (10 ml), y se añadió HCl 4 M en dioxano (2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18h. El sólido se recogió por filtración, se lavó (hexano) y se secó para dar hidrocloruro de N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(2-dimetilaminoetilamino)benzamida (38,6 mg, rendimiento global 20%) como un sólido blanco; RMN ^{1}H (399,902 MHz, DMSO) δ 2,84 (d, J = 4,0 Hz, 6H), 3,25 (m, 2H), 3,75 (s, 6H), 5,08 (s, 2H), 5,67 (s, 1H), 6,45 (t, J = 2,2 Hz, 1H), 6,60 (d, J = 2,2 Hz, 2H), 6,72 (d, J = 8,8 Hz, 2H), 7,83 (d, J = 8,8 Hz, 2H), 9,85 (s, 1H), 10,53 (s, 1H). MS: m/z = 440 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,031 μM.

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadió hidróxido de potasio (11,19 g, 199,4 mmoles) disuelto en agua (44,8 ml) a una disolución de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (7,121 g) disuelta en diclorometano (40 ml). Se añadió carbonato de (2-metilpropan-2-il)oxicarbonil terc-butilo (6,8 g, 31,2 mmoles) disuelto en DCM (35 ml), y la mezcla de reacción se agitó vigorosamente a temperatura ambiente durante 4 h. La mezcla de reacción se separó, y la capa orgánica se lavó con agua (2 x 15 ml), con salmuera (2 x 15 ml), se secó sobre sulfato de sodio, se filtró, se evaporó y se secó *a vacío* para dar 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (8,70 g, 99%) como un sólido de color crema.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,55 (s, 9H), 3,75 (s, 6H), 4,93 (s, 1H), 5,06 (s, 2H), 6,38 (s, 2H), 6,45 (t, J = 2,2 Hz, 1H), 6,60 (d, J = 2,3 Hz, 2H). MS: m/z = 350 (MH+)

El 4-[2-dimetilaminoetil-[*terc*-butoxicarbonil]amino]benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se disolvió 4-(2-[dimetilamino]etilamino)benzoato de metilo (1,00 g, 4,50 mmoles) en THF (30 ml). Se añadió carbonto de (2-metilpropan-2-il)oxicarbonil terc-butilo (1,035 g, 4,72 mmoles), y la disolución se puso a reflujo durante 3h. El disolvente entonces se evaporó, el

residuo se disolvió en DCM, se lavó con disolución de cloruro amónico sat. ac., se secó sobre sulfato de sodio, se filtró y se evaporó para dar 4-[2-dimetilaminoetil-[*terc*-butoxicarbonil]amino]benzoato de metilo (1,07g, 74 %) como un aceite marrón.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,41 (s, 9H), 2,13 (s, 6H), 2,34 (t, *J* = 6,9 Hz, 2H), 3,73 (t, *J* = 6,8 Hz, 2H), 3,86 (s, 3H), 7,43 (d, *J* = 8,5 Hz, 2H), 7,94 (d, *J* = 8,5 Hz, 2H). MS: m/z = 323 (MH+)

El 4-(2-[dimetilamino]etilamino)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se disolvió 4-yodobenzoato de metilo (1,19 g, 4,54 mmoles, 1,0 eq) en dimetilformamida seca (10 ml). Se añadieron *N,N*-dimetiletano-1,2-diamina (400 mg, 4,54 mmoles, 1,0 eq), carbonato de cesio (2,69 g, 9,08 mmoles, 2,0 eq), 2-acetilciclohexanona (120 µl, 0,908 mmoles, 0,20 eq [20% en moles]) y yoduro de cobre (I) (44 mg, 0,227 mmoles, 0,05 eq [5% en moles]), y la mezcla se agitó en nitrógeno a 90°C durante 18 h. La mezcla de reacción se concentró, se disolvió en metanol y se adsorbió sobre una columna de resina de intercambio catiónico SCX-2. La columna se lavó con metanol, y el producto se eluyó con amoníaco 2M en metanol. Las fracciones se evaporaron para dar 4-(2-[dimetilamino]etilamino)benzoato de metilo (1,00 g, 99%) como una goma marrón.

RMN ^{1}H (399,902 MHz, DMSO) δ 2,19 (s, 6H), 2,44 (t, *J* = 6,3 Hz, 5H), 3,17 (m, 2H), 3,75 (s, 3H), 6,33 (t, *J* = 5,3 Hz, 1H), 6,62 (d, *J* = 8,9 Hz, 2H), 7,69 (d, *J* = 8,7 Hz, 2H). MS: m/z = 223 (MH+)

Ejemplo 71

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-metoxi-benzamida

Se añadió gota a gota cloruro de 4-metoxibenzoilo (54 mg, 0,315 mmoles, 1,1 eq) en THF (2 ml) a una disolución de 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (100 mg, 0,286 mmoles, 1 eq) en THF (3 ml) en nitrógeno, y la disolución se calentó a reflujo durante un total de 14h, después se agitó a temperatura ambiente durante 16h. El disolvente se evaporó, y el residuo se purificó mediante HPLC prep., usando un gradiente de 55-75% de MeCN en H_2O (que contiene hidróxido de amonio al 1%). Las fracciones del producto se evaporaron hasta sequedad y se recogieron en DCM (4 ml). Se añadió HCl 4M en dioxano (1 ml), y la mezcla se agitó a temperatura ambiente durante 1h, después se evaporó

hasta sequedad. El residuo se repartió entre acetato de etilo (6 ml) y $NaHCO_3$ acuoso (6 ml), las capas se separaron, y la capa acuosa se reextrajo con acetato de etilo (3 x 6 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se evaporaron para dar el compuesto del título como un sólido blanquecino (22 mg, rendimiento 20%); RMN ^1H (400,132 MHz, DMSO) δ 3,74 (s, 6H), 3,82 (s, 3H), 5,06 (s, 2H), 5,59 (s, 1H), 6,43 (t, 1H), 6,59 (d, 2H), 7,00 (d, 2H), 7,96 (d, 2H) MS: m/z 384 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,157 μM.

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo, usado como material de partida se preparó como se esquematiza en el Ejemplo 70.

Ejemplo 72

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-6-piperazin-1-il-piridin-3-carboxamida

Se disolvió ácido 6-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]piridin-3-carboxílico (150 mg, 0,412 mmoles) en THF seco (10 ml), se añadió 1-cloro-N,N,2-trimetil-prop-1-en-1-amina (65 μl, 0,412 mmoles) y la mezcla se agitó a temperatura ambiente en nitrógeno toda la noche. Se añadieron piridina (40 μl, 0,412 mmoles) y 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (142 mg, 0,343 mmoles), y la mezcla se agitó a 65°C durante 18h. La mezcla se enfrió entonces hasta la temperatura ambiente y se agitó toda la noche con HCl 4 M en dioxano (1,8 ml, 7,20 mmoles). La mezcla se filtró entonces, y el sólido se lavó con hexano. El producto se purificó en HPLC prep. ácida, eluyendo con un gradiente de 16-26% de MeCN en agua (que contiene 0,1% de TFA). Las fracciones que contienen el producto se neutralizaron con $NaHCO_3$ ac., y el acetonitrilo se eliminó a vacío. El producto precipitó y se recogió por filtración. Éste se lavó posteriormente con agua y se secó *a vacío* para dar el compuesto del título (39 mg, 26 %) como un sólido blanco; RMN ^1H (399,902 MHz, DMSO) δ 2,82 (t, J = 5,1 Hz, 4H), 3,61 (t, J = 4,8 Hz, 4H), 3,80 (s, 6H), 5,13 (s, 2H), 5,62 (bs, 1H), 6,50 (s, 1H), 6,65 (d, J = 2,2 Hz, 2H), 6,92 (d, J = 8,9 Hz, 1H), 8,09 (d, J = 9,3 Hz, 1H), 8,76 (d, J = 2,3 Hz, 1H), 10,74 (bs, 1H), 11,64 (bs, 1H). MS: m/z = 439 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,025 μM.

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadió hidróxido de potasio (11,19 g, 199,4 mmoles) disuelto en agua (44,8 ml) a una disolución de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (7,121 g) disuelta en diclorometano (40 ml). Se añadió una disolución de carbonato de (2-metilpropan-2-il)oxicarbonil terc-butilo (6,8 g, 31,2 mmoles) en DCM (35 ml), y la mezcla de reacción se agitó vigorosamente a temperatura ambiente durante 4 h. La mezcla de reacción se separó, y la capa orgánica se lavó con agua (2 x 15 ml) y salmuera (2 x 15 ml), se secó sobre sulfato de sodio, se filtró, se evaporó y se secó *a vacío* para dar 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de terc-butilo (8,70 g, 99%) como un sólido de color crema.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,55 (s, 9H), 3,75 (s, 6H), 4,93 (s, 1H), 5,06 (s, 2H), 6,38 (s, 2H), 6,45 (t, J = 2,2 Hz, 1H), 6,60 (d, J = 2,3 Hz, 2H). MS: m/z = 350 (MH+)

Ejemplo 73

N-[5-[(3,5-Dimetoxifenil)metoxi]-1H-pirazol-3-il]-2-(4-metilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota NaHMDS (disolución 1M en THF, 0,39 ml, 0,386 mmoles, 1,5 eq) a una disolución agitada de 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (90 mg, 0,258 mmoles, 1 eq) y 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo (74 mg, 0,309 mmoles, 1,2 eq) en THF seco (5 ml) en nitrógeno. La disolución se agitó a temperatura ambiente durante 1h, después se neutralizó con NH_4Cl satd. ac., se diluyó con agua (15 ml) y se extrajo con acetato de etilo (3 x 15 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron para dar una goma naranja. La goma se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-2,5% de MeOH en DCM. El material bruto, que contiene 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo de partida, se redisolvió en THF (5 ml) en nitrógeno. se añadió 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (50 mg, 0,143 mmoles), seguido de la adición gota a gota de NaHMDS (disolución 1M en THF, 0,32 ml, 0,32 mmoles). La disolución se agitó a temperatura ambiente durante 45 min, se neutralizó con NH_4Cl satd. ac., se diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 x 10 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El

residuo gomoso se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-8% de MeOH en DCM, para dar el compuesto del título como un sólido marrón pálido (16 mg, rendimiento 14%); RMN ^{1}H (399,9 MHz, DMSO-d_6 + d4-AcOD) δ 2,42 (3H, s), 2,67 - 2,70 (4H, m), 3,75 (6H, s), 3,91 - 3,94 (4H, m), 5,08 (2H, s), 5,75 (1H, s), 6,45 (1H, t), 6,59 (2H, d), 8,90 (2H, s). MS: m/z 454 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,044 μM.

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como se esquematiza en el Ejemplo 70.

El 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se suspendió ácido 2-cloropirimidin-5-carboxílico (100 mg, 0,631 mmoles, 1 eq) en una mezcla de tolueno (3 ml) y metanol (0,8 ml) en nitrógeno, y se enfrió en un baño de hielo. Se añadió gota a gota trimetilsilildiazometano (disolución 2M en hexanos, 0,347 ml, 0,694 mmoles, 1,1 eq). La disolución se agitó a 0°C durrante 10 min, después se dejó calentar hasta la temperatura ambiente y se agitó durante otra 1h. Se añadieron gota a gota 1-metilpiperazina (70 μl, 0,631 mmoles, 1 eq) y trietilamina (88 μl, 0,631 mmoles, 1 eq), y la agitación se continuó a temperatura ambiente durante 2h. El disolvente se evaporó y el residuo se recogió en acetato de etilo (20 ml) y agua (15 ml). Las capas se separaron y la acuosa se extrajo con porcoines adicionales de acetato de etilo (2 x 10 ml). Los extractos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. La reacción se repitió como antes, y los extractos se combinaron con los anteriores para dar 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo como un sólido amarillo gomoso (76 mg, rendimiento 25%).

RMN ^{1}H (399,902 MHz, DMSO) δ 2,12 (s, 3H), 2,27 (t, 4H), 3,70 (s, 3H), 3,75 (t, 4H), 8,68 (s, 2H). MS: m/z 237 (MH+)

Ejemplo 74

N-[5-[(3,5-Dimetoxifenil)metoxi]-1H-pirazol-3-il]-3-piperazin-1-il-benzamida

Se añadió gota a gota 1-cloro-*N,N*-2-trimetil-1-propenilamina (78 μl, 0,588 mmoles, 1,2 eq) a una disolución agitada de ácido 3-[4-(*terc*-butoxicarbonil)piperazin-1-il]benzoico (150 mg, 0,588 mmoles, 1,2 eq) en THF (10 ml) en nitrógeno. La mezcla se agitó a temperatura

ambiente toda la noche. Se añadieron 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (172 mg, 0,490 mmoles, 1 eq) y piridina (48 µl, 0,588 moles, 1,2 eq), y la mezcla se calentó a 65°C toda la noche. La mezcla se dejó enfriar hasta la temperatura ambiente, y se añadió HCl 4M en dioxano (2 ml). La agitación se continuó a temperatura ambiente toda la noche. El sólido amarillo que precipitó se recogió por filtración y se lavó con THF. El sólido se trituró con $NaHCO_3$ ac (4 ml) y DCM (2 ml). Una pequeña cantidad de una goma marrón permaneción fuera de la disolución. La goma se recogió por filtración y se lavó con agua y éter. El filtrado acuoso se extrajo con acetato de etilo (3 x 10 ml), y los extractos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto extraido se combinó con la goma procedente de la filtración, y se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 10-12% de MeOH en DCM. Las fracciones del producto se evaporaron para dar el compuesto del título como un sólido blanco (27 mg, rendimiento 10%); RMN ^1H (399,902 MHz, DMSO + d4-AcOD) δ 3,13 - 3,21 (m, 4H), 3,33 - 3,40 (m, 4H), 3,68 (s, 6H), 5,02 (s, 2H), 5,71 (s, 1H), 6,38 (t, 1H), 6,52 (d, 2H), 7,12 - 7,17 (m, 1H), 7,33 (t, 1H), 7,37 - 7,41 (m, 1H), 7,46 - 7,49 (m, 1H). MS: m/z 438 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,130 µM.

Ejemplo 75

Hidrocloruro de 4-(1,4-diazepan-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-1H-pirazol-3-il]benzamida

Se disolvieron 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (176 mg, 0,50 mmoles) y 4-(4-metoxicarbonilfenil)-1,4-diazepan-1-carboxilato de *terc*-butilo (168 mg, 0,60 mmoles) en THF seco (5 ml). Se añadió gota a gota NaHMDS (1 M en THF, 0,754 ml) en nitrógeno, y la mezcla se agitó durante 1 h a temperatura ambiente. Se añadió una cantidad adicional de NaHMDS (1M en THF, 0,754 ml), y la mezcla de reacción se agitó en nitrógeno durante 30 min. La mezcla de reacción se neutralizó con NH_4Cl saturado (ac), se diluyó con agua (20 ml) y se extrajo con acetato de etilo (3 x 30 ml). Los extractos se combinaron, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El residuo se purificó mediante cromatografía en columna de sílice, eluyendo con 0-3% de MeOH en DCM. Las fracciones se evaporaron para dar un aceite marrón (51 mg), que se repurificó mediante cromatografía en columna de sílice, eluyendo con 0-1% de MeOH en DCM. Las fracciones

puras se combinaron, se evaporaron, y el residuo se disolvió en THF (10 ml). Se añadió HCl 4M en dioxano (1,5 ml, 1,5 mmoles), y la disolución se agitó a temperatura ambiente toda la noche. El precipitado se recogió por filtración, se lavó con hexano y se secó *a vacío* para dar el compuesto del título (18,7 mg, 6,5 %) como un sólido blanco; RMN ^{1}H (399,902 MHz, DMSO) δ 2,01 (m, 2H), 3,08 (m, 2H), 3,20 (m, 2H), 3,53 (m, 2H), 3,68 (s, 6H), 3,72 (t, J = 5,2 Hz, 2H), 5,01 (s, 2H), 5,60 (s, 1H), 6,38 (t, J = 2,4 Hz, 1H), 6,52 (d, J = 2,3 Hz, 2H), 6,81 (d, J = 9,2 Hz, 2H), 7,82 (d, J = 8,9 Hz, 2H), 8,69 (s, 1H), 10,49 (s, 1H). MS: m/z = 452 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,0085 μM.

El 4-(4-metoxicarbonilfenil)-1,4-diazepan-1-carboxilato *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se disolvió 4-yodobenzoato de metilo (1,00 g, 3,82 mmoles, 1,0 eq) en DMF y se añadieron 1,4-diazepan-1-carboxilato de *terc*-butilo (765 mg, 3,82 mmoles, 1,0 eq), carbonato de cesio (2,49 g, 7,63 mmoles, 2,0 eq), 2-acetilciclohexanona (101 μl, 0,76 mmoles, 0,20 eq [20% en moles]) y yoduro de cobre (37 mg, 0,19 mmoles, 0,05 eq [5% en moles]). La mezcla de reacción se agitó a 90°C en nitrógeno durante 7 h. La mezcla de reacción se evaporó, se disolvió en DCM (50 ml), se lavó con agua (20 ml), con disolución saturada de cloruro de amonio (20 ml), se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 0-1% de MeOH en DCM. Las fracciones que contienen el producto se combinaron, se evaporaron y se secaron *a vacío* para dar 4-(4-metoxicarbonilfenil)-1,4-diazepan-1-carboxilato de *terc*-butilo (168 mg, 13%) como un aceite amarillo.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,12 (s, 5H), 1,24 (s, 4H), 1,72 (m, 2H), 3,12 (m, 1H), 3,42 (m, 1H), 3,49 (m, 3H), 3,59 (m, 2H), 3,69 (s, 3H), 6,72 (d, J = 9,1 Hz, 2H), 7,67 (d, J = 9,0 Hz, 2H) MS: m/z = 335 (MH+)

El 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo se preparó según lo siguiente:

Se añadió hidróxido de potasio (11,19 g, 199,4 mmoles) disuelto en agua (44,8 ml) a una disolución de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (7,121 g) disuelta en diclorometano (40 ml). Se añadió carbonato de (2-metilpropan-2-il)oxicarbonil terc-butilo (6,8 g, 31,2 mmoles) disuelto en DCM (35 ml), y la mezcla de reacción se agitó

vigorosamente a temperatura ambiente durante 4 h. La mezcla de reacción se separó, y la capa orgánica se lavó con agua (2 x 15 ml) y con salmuera (2 x 15 ml), se secó sobre sulfato de sodio, se filtró, se evaporó y se secó *a vacío* para dar 5-amino-3-[(3,5-dimetoxifenil)metoxi]pirazol-1-carboxilato de *terc*-butilo (8,70 g, 99%) como un sólido de color crema.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,55 (s, 9H), 3,75 (s, 6H), 4,93 (s, 1H), 5,06 (s, 2H), 6,38 (s, 2H), 6,45 (t, J = 2,2 Hz, 1H), 6,60 (d, J = 2,3 Hz, 2H). MS: m/z = 350 (MH+)

Ejemplo 76

N-[5-[2-[5-(Dimetilaminometil)-2-furil]etil]-1H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Se añadió una disolución de hidróxido de potasio (4,5M en agua, 1,8 ml, 8,10 mmoles, 8,10 eq) a una disolución agitada de 5-(2-{5-[(dimetilamino)metil]-2-furil}etil)-1H-pirazol-3-amina (235 mg, 1,0 mmoles, 1,0 eq) en diclorometano a temperatura ambiente. Entonces se añadió una disolución de dicarbonato de di-terc-butilo (230 mg, 1,05 mmoles, 1,05 eq) en diclorometano (2,0 ml), y la mezcla de reacción se agitó vigorosamente durante 18 h. La mezcla de reacción se vertió en un embudo separador, y las capas se separaron. La capa de diclorometano se lavó con agua (10 ml) y salmuera saturada (10 ml), se secó sobre sulfato de sodio anhidro, se filtró y el disolvente se eliminó *a vacío* para dar 5-amino-3-(2-{5-[(dimetilamino)metil]-2-furil}etil)-1H-pirazol-1-carboxilato de terc-butil como un aceite dorado, (320 mg).

Una porción de este material se usó sin purificación adicional según lo siguiente:

Se añadió gota a gota una disolución de bis(trimetilsilil)amiduro de sodio (1,0 M en tetrahidrofurano, 0,7 ml, 0,69 mmoles, 1,50 eq) a temperatura ambiente a una disolución agitada de 5-amino-3-(2-{5-[(dimetilamino)metil]-2-furil}etil)-1H-pirazol-1-carboxilato de terc-butilo (bruto, 154 mg, 0,46 mmoles, 1,0 eq) y 4-(4-metilpiperazin-1-il)benzoato de metilo (130 mg, 0,55 mmoles, 1,20 eq) en tetrahidrofurano seco (1,0 ml) en nitrógeno. La mezcla se dejó reposar a temperatura ambiente toda la noche, y entonces el disolvente se evaporó a presión reducida para dar el producto bruto como una goma marrón. Esta goma se disolvió en metanol (5 ml), y la disolución se aplicó a una columna SCX-2. La columna se lavó con metanol que contiene 10% de agua. La columna se eluyó entonces con amoníaco anhidro 2,0M en metanol. Las fracciones que contienen el producto se combinaron y se evaporaron

para dar una goma marrón, 235 mg. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente 3–10% de metanol (que contiene amoníaco a 2M) en diclorometano. Las fracciones del producto puro se combinaron y se evaporaron para dar una goma marrón clara, 32,9 mg. Este material se purificó adicionalmente mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido. (8 mg, rendimiento 4%); RMN ^{1}H (500,13 MHz, DMSO-d6) δ 2,17 (6H, d), 2,26 (3H, s), 2,48 (4H, t), 2,88 – 2,96 (4H, m), 3,30 (4H, t), 3,39 (2H, s), 6,03 (1H, d), 6,12 (1H, d), 6,95 (2H, d), 7,88 (2H, d), 9,95 (1H, s ancho), 11,80 (1H, s ancho). MS: m/z 437 (MH+)
Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,34 μM.

La 5-(2-{5-[(dimetilamino)metil]-2-furil}etil)-1H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

Se añadió acetonitrilo (0,258 ml, 4,88 mmoles) a una suspensión de hidruro de sodio (196 mg dispersión en aceite mineral, 4,88 mmoles) en dioxano anhhidro (15 ml), y la mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 5 min. Entonces se añadió 3-{5-[(dimetilamino)metil]-2-furil}propanoato de etilo (917 mg, 4,07 mmoles), y la reacción se puso a reflujo durante 18 h. La mezcla se enfrió hasta la temperatura ambiente, y se añadió etanol (1,9 ml), seguido de hidrocloruro de hidrazina (558 mg, 8,14 mmoles). La mezcla se puso a reflujo durante 1 h. Después de enfriar, el disolvente se evaporó a presión reducida. El residuo se disolvió en diclorometano que contiene 10% de metanol (50 ml), y las impurezas insolubles se separaron por filtración. El filtrado se evaporó para dar el producto bruto como un aceite dorado, 1,07 g. Este material se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente 0–10% de metanol (que contiene amoníaco a 2M) en diclorometano. Las fracciones del producto puro se combinaron y se evaporaron para dar un aceite claro. (520 mg, rendimiento 55%); RMN ^{1}H (399,9 MHz, DMSO-d6) δ2,16 (6H, s), 2,70 - 2,74 (2H, m), 2,81 - 2,85 (2H, m), 3,40 (2H , s), 5,20 (1H, s), 6,03 (1H, d), 6,15 (1H, d). MS: m/z 235 (MH+)

El 3-{5-[(dimetilamino)metil]-2-furil}propanoato de etilo usado como material de partida se preparó según lo siguiente:

Una mezcla de 3-(2-furanil)propionato de etilo (12,11 g, 72,0 mmoles), cloruro de dimetilamonio (6,76 g, 82,8 mmoles), formaldehído acuoso al 37% (6,43 g, 79,2 mmoles) en ácido acético (75 ml) se agitó a temperatura ambiente hasta que se formó una disolución. La disolución se dejó reposar durante 44 h. La mezcla se evaporó hasta un aceite. Éste se suspendió en agua y se extrajo con acetato de etilo (2 x 250 ml). La capa acuosa (que contiene el producto) se basificó hasta pH 11 con disolución de hidróxido sódico 4M, y después se extrajo con acetato de etilo (2 x 250 ml). Estos extractos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio y se evaporaron para dar el producto bruto como un aceite marrón oscuro, 6,5 g. Este material se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente 0–10% de metanol (que contiene amoníaco a 2M) en diclorometano. Las fracciones que contienen el producto se combinaron y se evaporaron para dar un aceite marrón claro (3,44 g). Este material se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente 0–5% de metanol (que contiene amoníaco a 2M) en diclorometano. Las fracciones que contienen el producto se combinaron y se evaporaron para dar un aceite marrón claro (1,36 g, rendimiento 8%).

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,24 (3H, t), 2,29 (6H, s), 2,62 - 2,65 (2H, m), 2,95 (2H, t), 3,47 (2H, s), 4,11 - 4,15 (2H, m), 5,95 (1H, d), 6,11 (1H, d). MS: m/z 226 (MH+)

Ejemplo 77

N-[5-(2-Benzo[1,3]dioxol-5-iletil)-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

A una disolución agitada de 5-amino-3-(2-benzo[1,3]dioxol-5-iletil)pirazol-1-carboxilato de *terc*-butilo (229 mg, 0,69 mmoles, 1,0 eq) en piridina (5 ml) a 5°C se añadió cloruro de 4-(4-metilpiperazin-1-il)benzoilo (181 mg, 0,76 mmoles, 1,1 eq). La mezcla de reacción se agitó hasta 60°C durante 24 h. Después de este tiempo, la mezcla se concentró y se redisolvió en DCM (10 ml). Se añadió ácido trifluoroacético (464 µl, 6,25 mmoles, 8,25 eq), y la mezcla de reacción se agitó durante 2 h a 25°C. La mezcla de reacción se concentró entonces. El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 30-50% de acetonitrilo en agua que contiene disolución de hidróxido de amonio al 1%. Las fracciones limpias se combinaron y se evaporaron para dar el compuesto del título como un sólido blanco. (12 mg, 4%); RMN ^{1}H (300,132 MHz, DMSO) δ 2,28 (s, 3H), 2,49 (t, 2H), 2,89 (s, 2H), 3,31 - 3,37 (m, 8H), 6,01 (s, 2H), 6,43 (s, 1H), 6,74 (d, 1H), 6,86 (d, 2H), 7,01 (d, 2H), 7,94 (d, 2H), 10,36 (s, 1H), 12,11 (s, 1H); MS: m/z 434 (MH+).

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,14 μM.

El 5-amino-3-(2-benzo[1,3]dioxol-5-iletil)pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

A una disolución agitada de 5-(2-benzo[1,3]dioxol-5-iletil)-2H-pirazol-3-amina en DCM (10 ml) se añadió disolución ac. de KOH 4,5M (1,9 ml, 8,66 mmoles, 8 eq). Entones se añadió una disolución de BOC_2O (464 mg, 2,12 mmoles, 1,05 eq) en DCM (2 ml), y la mezcla de reacción se agitó vigorosamente durante 3 h. La mezcla de reacción se vertió en un embudo separador, y las capas se separaron. La capa orgánica se lavó con agua (10 ml), con salmuera (10 ml), se secó (Na_2SO_4), se filtró y el disolvente se evaporó para dar el compuesto del título como un sólido blanco. (325 mg, 91%); RMN ^{1}H (300,132 MHz, DMSO) δ 1,55 (s, 9H), 2,58 - 2,64 (m, 2H), 2,73 - 2,78 (m, 2H), 5,19 (s, 1H), 5,95 (s, 2H), 6,21 (s, 2H), 6,68 - 6,71 (m, 1H), 6,80 (d, 1H), 6,85 (d, 1H)

La 5-(2-benzo[1,3]dioxol-5-iletil)-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

La 5-(2-benzo[1,3]dioxol-5-iletil)-2H-pirazol-3-amina usada como material de partida se preparó de manera similar a 5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina en el Ejemplo 11. El producto se obtuvo como un aceite amarillo. (3,04 g, rendimiento 44%).

RMN ^{1}H (300,132 MHz, DMSO): δ 2,63-2,79 (m, 4H), 4,40 (s, 2H), 5,18 (s, 1H), 5,95 (s, 2H), 6,66 (dd, 1H), 6,77-6,81 (m, 2H). MS: m/z 232 (MH+).

Ejemplo 78

N-[5-[2-(2,5-Dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Obtenida de manera análoga al compuesto en el Ejemplo 77, usando 5-amino-3-[2-(2,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butil (240 mg, 0,69 mmoles, 1 eq) como material de partida para dar el compuesto del título como un sólido blanco. (27 mg, 9%);

RMN ^{1}H (300,132 MHz, DMSO) δ 2,23 (s, 3H), 2,43 - 2,46 (m, 4H), 2,80 - 2,88 (m, 4H), 3,26 - 3,29 (m, 4H), 3,68 (s, 3H), 3,76 (s, 3H), 6,43 (s, 1H), 6,72 - 6,77 (m, 2H), 6,88 (d, 1H), 6,96 (d, 2H), 7,89 (d, 2H), 10,29 (s, 1H), 12,06 (s, 1H)

MS: m/z 450 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,47 μM.

El 5-amino-3-[2-(2,5-dimetoxifenil)etil]pirazol-1-carboxilato de *terc*-butilo, usado como material de partida se obtuvo de manera análoga al 5-amino-3-(2-benzo[1,3]dioxol-5-iletil)pirazol-1-carboxilato de *terc*-butilo en el Ejemplo 77, usando 5-[2-(2,5-dimetoxifenil)etil]-2H-pirazol-3-amina (200 mg, 0,87 mmoles, 1 eq) como material de partida para dar el compuesto del título como un sólido blanco. (283 mg, 94%).

RMN ^{1}H (300,132 MHz, DMSO) δ 1,60 (s, 9H), 2,61 - 2,67 (m, 2H), 2,79 - 2,84 (m, 2H), 3,73 (s, 3H), 3,79 (s, 3H), 5,25 (s, 1H), 6,26 (s, 2H), 6,75 - 6,79 (m, 1H), 6,84 (d, 1H), 6,92 (d, 1H)

La 5-[2-(2,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

Se añadió hidruro de sodio (60%, 0,240 g, 6 mmoles) a una disolución agitada de 3-(2,5-dimetoxifenil)propanoato de metilo (1,125 g, 5 mmoles) en 1,4-dioxano (25 ml) en acetonitrilo seco (0,314 ml, 6 mmoles) en nitrógeno. La mezcla se agitó a r.t. durante 10 min, y después se calentó a reflujo en nitrógeno durante 18 h. Después de este tiempo, la mezcla se enfrió hasta r.t., con lo que se formó un precipitado. Se añadió etanol (2 ml), seguido de monohidrocloruro de hidrazina (0,686 g, 10 mmoles). La mezcla se calentó a reflujo durante 4 h. En este tiempo, el precipitado pasó a la disolución, y apareció un precipitado. Después de filtrar, la mezcla de reacción se concentró *a vacío* y se repartió entre HCl 2N y acetato de etilo (25ml cada uno). La capa acuosa se basificó con disolución de hidróxido de amonio hasta pH 8, se extrajo con acetato de etilo y se secó con MgSO4. Esto se filtró, y los disolventes se evaporaron *a vacío* para dar un aceite naranja (0,690 g, 56 %).

El cloruro de 4-(4-metilpiperazin-1-il)benzoilo usado como material de partida se preparó según el Ejemplo 61.

Ejemplo 79

N-[5-[2-(4-Metoxi-2-metil-fenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Obtenida de manera análoga al compuesto en el Ejemplo 77, usando 5-amino-3-[2-(4-metoxi-2-metil-fenil)etil]pirazol-1-carboxilato de *terc*-butilo (229 mg, 0,69 mmoles, 1 eq) como material de partida para dar el compuesto del título como un sólido blanco. (15 mg, 5%);

RMN ^{1}H (300,132 MHz, DMSO) δ 2,26 (s, 3H), 2,72 - 2,83 (m, 5H), 2,88 (t, 4H), 3,41 (t, 4H), 3,69 (s, 3H), 5,70 (s, 1H), 6,41 (s, 1H), 6,65 - 6,73 (m, 2H), 6,99 (d, 2H), 7,06 (d, 1H), 7,91 (d, 2H) [*Nota: con D4-Acético añadido*]

MS: m/z 434 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,2 μM.

El 5-amino-3-[2-(4-metoxi-2-metil-fenil)etil]pirazol-1-carboxilato de *terc*-butilo usado como material de partida se obtuvo de manera análoga a 5-amino-3-(2-benzo[1,3]dioxol-5-iletil)pirazol-1-carboxilato de *terc*-butilo en el Ejemplo 77, usando 5-[2-(4-metoxi-2-metil-fenil)etil]-2H-pirazol-3-amina (214 mg, 0,87 mmoles, 1 eq) como material de partida para dar el compuesto del título como un sólido blanco. (256 mg, 89%).

RMN ^{1}H (300,132 MHz, DMSO) δ 1,60 (s, 9H), 2,30 (s, 3H), 2,58 - 2,64 (m, 2H), 2,76 - 2,81 (m, 2H), 3,75 (s, 3H), 5,26 (s, 1H), 6,26 (s, 2H), 6,70 - 6,74 (m, 1H), 6,77 (d, 1H), 7,13 (d, 1H)

La 5-[2-(4-metoxi-2-metil-fenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó según lo siguiente:

La 5-[2-(4-metoxi-2-metil-fenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó en un método análogo al uso para sintetizar 5-[2-(3-metoxifenil)etil]-2H-pirazol-3-amina en el Ejemplo 11, usando 3-(4-metoxi-2-metil-fenil)propanoato de metilo como material de partida para dar 5-[2-(4-metoxi-2-metil-fenil)etil]-2H-pirazol-3-amina como un sólido rojo. MS: m/z 232 (MH+).

El cloruro de 4-(4-metilpiperazin-1-il)benzoilo, usado como material de partida se preparó según el Ejemplo 61.

Ejemplo 80

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,5-dimetilpiperazin-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,5-dimetilpiperazin-1-il)benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(3,5-dimetilpiperazin-1-il)benzoato de metilo (221 mg, 0,84 mmol), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (244 mg, 0,7 mmoles) y NaHMDS 1M (1,13 ml, 1,13 mmoles) en THF (5 ml).

El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 34-54% de acetonitrilo en agua que contiene amoníaco 0,880 al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (34 mg, 10%); RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,04 (6H, d), 2,22 (2H, t), 2,53 (2H, d), 2,82 (2H, t), 2,87 (4H, s), 3,71 (1H, s), 3,73 (7H, s), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 6,94 (2H, d), 7,89 (2H, d), 10,27 (1H, s), 12,07 (1H,s).

MS: m/z 464 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,011 μM.

Se añadió 2,6-dimetilpiperazina (3,43 g, 30,00 mmoles) a 4-fluorobenzoato de etilo (1,101 ml, 7,5 mmoles) en DMSO (10 ml) calentado hasta 120°C en nitrógeno. La disolución resultante se agitó a 120°C durante 20 h. La mezcla de reacción se enfrió, y el disolvente se evaporó. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con metanol al 10% en diclorometano que contiene amoníaco 0,880 al 1%. Las fracciones puras se evaporaron hasta sequedad para dar 4-(3,5-dimetilpiperazin-1-il)benzoato de etilo (1,490 g, 76 %) como un sólido incoloro. RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,15 (6H, d), 1,37 (3H, t), 2,39 (1H, d), 2,42 (1H, d), 2,97 - 3,05 (2H, m), 3,65 - 3,69 (2H, m), 4,33 (2H, q), 6,84 - 6,87 (2H, m), 7,90 - 7,93 (2H, m) – NH no observado. MS: m/z = 264 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 81

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(3,4-dimetilpiperazin-1-il)benzoato de metilo (221 mg, 0,84 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (244 mg, 0,7 mmoles) y NaHMDS 1M (1,13 ml, 1,13 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 38-58% de acetonitrilo en agua que contiene hidróxido de amonio 0,880 al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (63 mg, 19%); RMN ^{1}H (500,13 MHz, DMSO-d_6) δ 1,12 (3H, d), 1,89

- 1,90 (3H, m), 2,32 (3H, s), 2,35 - 2,40 (1H, m), 2,64 - 2,68 (1H, m), 2,86-2,91 (1H, m), 2,89 (4H, t), 3,00 (1H, s), 3,64 - 3,68 (2H, m), 3,74 (6H, s), 6,32 (1H, s), 6,33 (1H, t), 6,42 (2H, d), 6,94 - 6,96 (2H, m), 7,86 - 7,88 (2H, m). MS: m/z 464 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,04 μM.

Se disolvieron 1,2-dimetil-piperazina (0,914 g, 8,00 mmoles) y 4-fluorobenzoato de etilo (0,587 ml, 4 mmoles) en DMA (6 ml), y se encerraron en un tubo de microondas. La reacción se calentó hasta 150°C durante 90 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. La mezcla de reacción se evaporó, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM (que contiene amoníaco 0,880 al 0,1%). Las fracciones puras se evaporaron hasta sequedad para dar 4-(3,4-dimetilpiperazin-1-il)benzoato de etilo (0,380 g, 36,2 %) como un sólido ceroso incoloro.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,15 (3H, d), 1,37 (3H, t), 2,20 - 2,25 (1H, m), 2,34 (3H, s), 2,37 - 2,41 (1H, m), 2,61 - 2,67 (1H, m), 2,87 - 2,92 (1H, m), 2,99 - 3,06 (1H, m), 3,58 - 3,62 (1H, m), 3,65 - 3,70 (1H, m), 4,33 (2H, q), 6,83 - 6,87 (2H, m), 7,90 - 7,94 (2H, m). MS: m/z = 263 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 82

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-yodo-benzamida

Se añadió de una vez ácido trifluoroacético (3,85 ml, 50,02 mmoles) a 3-(3,5-dimetoxifenetil)-5-(4-yodobenzamido)-1H-pirazol-1-carboxilato de terc-butilo (288 mg, 0,5 mmoles) en DCM (10 ml) a temperatura ambiente. La disolución resultante se agitó durante 24 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (5 ml). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/metanol, y las fracciones puras se evaporaron hasta sequedad para dar un sólido bronceado. El sólido se trituró con DCM para dar el compuesto del título (58,0 mg, 24,3 %) como un sólido blanco;

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,88 (4H, s), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,47 (1H, s), 7,77 (2H, d), 7,87 (2H, d), 10,73 (1H, s), 12,17 (1H, s).

MS m/z: 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,021 μM.

El 3-(3,5-dimetoxifenetil)-5-(4-yodobenzamido)-1H-pirazol-1-carboxilato de terc-butilo usado como material de partida se preparó según lo siguiente:

Se añadió cloruro de 4-yodobenzoilo (1,332 g, 5,00 mmoles) a 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (1,737 g, 5 mmoles) y piridina (0,445 ml, 5,50 mmoles) en DCM (15 ml). La suspensión resultante se agitó a 25ºC durante 24 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en EtOAc (25 ml), y se lavó secuencialmente con agua (10 ml) y salmuera saturada (10 ml). La capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar un producto bruto.

El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 5-20% de EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para dar 3-(3,5-dimetoxifenetil)-5-(4-yodobenzamido)-1H-pirazol-1-carboxilato de terc-butilo (1,187 g, 41,1 %) como un sólido blanco. RMN ^{1}H (399,9 MHz, CDCl3) δ 1,70 (9H, s), 2,95 (4H, s), 3,78 (6H, s), 6,32 (1H, t), 6,42 (2H, d), 6,91 (1H, s), 7,64 - 7,67 (2H, m), 7,88 - 7,90 (2H, m), 11,13 (1H, s). MS m/z: 478 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 83

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-2-[(3-metil-1,2-oxazol-5-il)metilamino]benzamida

Se añadió gota a gota NaHMDS (disolución 1M en THF, 0,83 ml, 0,828 mmoles, 2,5 eq) a una disolución de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (90 mg, 0,364 mmoles, 1,1 eq) y 2-{[(3-metilisoxazol-5-il)metil]amino}-benzoato de metilo (115 mg, 0,331 mmoles, 1 eq), agitada en THF (4 ml) en nitrógeno. La disolución se agitó a temperatura ambiente durante 50 min. La disolución se paralizó con NH_4Cl satd. ac., se diluyó con agua (5 ml) y se extrajo con acetato de etilo (3 x 8 ml). El producto bruto se

purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-1,5% de MeOH en DCM. Las fracciones que contienen el producto se evaporaron y se purificaron adicionalmente mediante purificación por HPLC prep. de fase inversa, eluyendo con un gradiente de MeCN/H_2O + 0,1% de TFA para dar el compuesto del título como un sólido blanquecino (16 mg, rendimiento 10%); RMN ^{1}H (399,902 MHz, DMSO) δ 2,20 (s, 3H), 2,88 (s, 4H), 3,73 (s, 6H), 4,57 (s, 2H), 6,21 (s, 1H), 6,33 (t, 1H), 6,41 (bs, 1H), 6,43 (d, 3H), 6,65 (t, 1H), 6,77 (d, 1H), 7,28 - 7,34 (m, 1H), 7,75 - 7,79 (m, 1H), 8,10 (bs, 1H), 10,50 (s, 1H). MS: m/z 462 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 1,0 μM.

El 2-{[(3-metilisoxazol-5-il)metil]amino}-benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se agitaron 1-(3-metilisoxazol-5-il)metanamina (155 mg, 1,37 mmoles, 1,2 eq), fosfato de potasio (341 mg, 1,60 mmoles, 1,4 eq), S-Phos (95 mg, 0,230 mmoles, 0,2 eq) y Pd_2dba_3 (13 mg, 0,06 mmoles, 0,05 eq) en tolueno (5 ml) en nitrógeno. Se añadió 2-yodobenzoato de metilo (300 mg, 1,14 mmoles, 1 eq), y la mezcla se agitó a temperatura ambiente durante 3 días, después a 90°C durante 6h. La mezcla de reacción se dejó enfriar, se vertió en agua (100 ml) y se extrajo con acetato de etilo (3 x 60 ml). Los extractos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El aceite gomoso residual se trituró con éter, dando como resultado la precipitación de una pequeña cantidad de un sólido amarillo que se separó por filtración. El filtrado se evaporó y se trituró nuevamente con metanol, y se eliminó por filtración un segundo precipitado. El filtrado se evaporó, después se purificó mediante cromatografía en columna de sílice, eluyendo con DCM. Las fracciones del producto se evaporaron para dar 2-{[(3-metilisoxazol-5-il)metil]amino}-benzoato de metilo como una goma oleosa amarilla (128 mg, rendimiento 45%); RMN ^{1}H (399,902 MHz, $CDCl_3$) δ 2,25 (s, 3H), 3,88 (s, 3H), 4,53 (d, 2H), 5,99 (s, 1H), 6,62 - 6,70 (m, 2H), 7,32 - 7,38 (m, 1H), 7,92 - 7,96 (m, 1H), 8,19 (t, 1H). MS: m/z 247 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 84

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-6-(4-metilpiperazin-1-il)piridazin-3-carboxamida

Se añadió una disolución de NaHMDS (1,500 ml, 1,50 mmoles) en THF (1,0M) a una disolución agitada de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (0,347 g, 1,0 mmoles) y 6-(4-metilpiperazin-1-il)piridazin-3-carboxilato de metilo (0,284 g, 1,20 mmoles) en THF (5,00 ml) enfriado a 0°C en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 70 min. La mezcla se repartió entonces entre acetato de etilo y disolución acuosa saturada de cloruro de amonio diluida con agua (1:2). Un sólido se separó por filtración para dar producto bruto como un sólido blanco. Éste se purificó mediante LCMS preparativa usando mezclas cada vez menos polares de agua (que contiene 0,1% de TFA) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,127 g, 28,1 %) como un sólido blanco; RMN ^{1}H (500,13 MHz, DMSO-d_6, CD_3CO_2D) δ 2,69 (3H, s), 2,89 - 2,95 (4H, m), 3,07 - 3,08 (4H, m), 3,75 (6H, s), 3,92 - 3,97 (4H, m), 6,34 (1H, s), 6,42 (3H, s), 7,41 (1H, d), 8,00 (1H, d)

MS: m/z 452 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,39 μM.

El 6-(4-metilpiperazin-1-il)piridazin-3-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

A suspensión de 6-(4-metilpiperazin-1-il)piridazin-3-carboxamida (221 mg, 1,00 mmoles) en hidróxido sódico (2,0M acuoso) (10,000 ml, 20,00 mmoles) se agitó a reflujo durante 3 h y después se dejó enfriar hasta la temperatura ambiente. La mezcla de reacción se ajustó hasta pH 7 mediante adición de HCl 2M (10 ml) y NaHCO3 saturado. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El producto deseado se eluyó de la columna usando metanol, y las fracciones se evaporaron hasta sequedad para dar ácido 6-(4-metilpiperazin-1-il)piridazin-3-carboxílico como un sólido blanco. Este material se suspendió en metanol (10,00 ml) a 0°C, y se trató con cloruro de tionilo (0,729 ml, 10,00 mmoles), durante un periodo de 5 min. La suspensión resultante se agitó a temperatura ambiente durante 18 h. Se añadió disolución de bicarbonato de sodio hata basicidad, y después la mezcla se extrajo con acetato de etilo (2 x 75 ml). La disolución se

extrajo adicionalmente con 1-butanol (100 ml). Los extractos orgánicos se combinaron y se evaporaron hasta sequedad para dar 6-(4-metilpiperazin-1-il)piridazin-3-carboxilato de metilo como un sólido blanco, 212 mg.

1RMN 1H (399,9 MHz, DMSO-d_6) δ 2,24 (3H, s), 2,43 (4H, t), 3,74 (4H, t), 3,88 (3H, s), 7,30 (1H, d), 7,84 (1H, d)

MS: m/z 237 (MH+)

La 6-(4-metilpiperazin-1-il)piridazin-3-carboxamida, usada como material de partida, se preparó según lo siguiente:

Se suspendieron 6-cloropiridazin-3-carboxamida (0,315 g, 2 mmoles) y 1-metilpiperazina (0,555 ml, 5,00 mmoles) en 2-propanol (2,000 ml) y se encerraron en un tubo de microondas. La reacción se calentó hasta 130°C durante 30 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. El precipitado resultante se recogió por filtración, se lavó con 2-propanol (10 ml) y se secó a vacío para dar 6-(4-metilpiperazin-1-il)piridazin-3-carboxamida (0,333 g, 75 %) como un sólido blanco, que se usó sin purificación adicional. Una muestra (100 mg) del producto bruto se purificó mediante LCMS preparativa usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar 6-(4-metilpiperazin-1-il)piridazin-3-carboxamida (54 mg) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,24 (3H, s), 2,44 (4H, t), 3,71 (4H, t), 7,34 (1H, d), 7,50 (1H, s), 7,84 (1H, d), 8,11 (1H, s)

MS: m/z 222 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 85

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió una disolución de NaHMDS (2,100 ml, 2,10 mmoles) en THF (1,0M) a una disolución agitada de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (0,486 g, 1,4 mmoles) y 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo

(0,397 g, 1,68 mmoles) en THF (7,00 ml, enfriado hasta -20°C), durante un periodo de 5 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla se calentó a reflujo durante 90 min, y después se enfrió hasta la temperatura ambiente. Se añadió más NaHMDS (2,100 ml, 2,10 mmoles), y la mezcla se agitó durante 70 min. La mezcla se dejó reposar durante 96 h, y después se repartió entre acetato de etilo y ácido clorhídrico acuoso 2,0M. La capa acuosa se separó y basificó con disolución acuosa de hidróxido sódico al 50%, y después se extrajo con acetato de etilo (75 ml). La capa orgánica se lavó con salmuera saturada (50 ml) y después se secó sobre MgSO4, se filtró y se evaporó para dar producto bruto. El producto bruto se purificó mediante LCMS preparativa usando mezclas cada vez menos polares de agua (que contiene 1% de amoníaco) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (4,00 mg, 0,633 %) como un sólido blanco; RMN ^{1}H (500,13 MHz, DMSO-d_6, CD_3CO_2D) δ 2,34 (3H, s), 2,53 (4H, t), 2,90 (4H, t), 3,74 (6H, s), 3,89 (4H, t), 6,33 (1H, t), 6,35 (1H, s), 6,42 (2H, d), 8,89 (2H, s)

MS: m/z 452 (MH+)

Ensayo de FGFR cinasa – Caliper, IC_{50} 0,118 μM.

Ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0149 μM.

El 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se suspendieron 2-cloropirimidin-5-carboxilato de metilo (0,863 g, 5,0 mmoles), N,N-dietiletanamina (0,697 ml, 5,00 mmoles) y 1-metilpiperazina (0,565 ml, 5,09 mmoles) en 2-propanol (10,00 ml) y se encerraron en un tubo de microondas. La reacción se calentó hasta 100°C durante 10 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. El precipitado se recogió por filtración, se lavó con EtOH (5 ml) y se secó a vacío para dar 2-(4-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo (0,405 g, 34,3%) como un sólido blanco, que se usó sin purificación adicional.

MS: m/z 237 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 86

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-metilpiperazin-1-carbonil)benzamida

Se añadió gota a gota una disolución de NaHMDS (1M en THF) (2,86 ml, 2,86 mmoles) a una disolución agitada de 4-(4-metilpiperazin-1-carbonil)benzoato de metilo (0,250 g, 0,95 mmoles) y 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-1-carboxilato de *terc*-butilo (0,397 g, 1,14 mmoles) en THF (2 ml), durante un periodo de 10 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió en NH_4Cl saturado (25 ml), se extrajo con EtOAc (2 x 25 ml), se lavó con salmuera saturada y se secó sobre $MgSO_4$, se filtró y se evaporó para dar el producto bruto (0,501 g) como una goma amarilla. El producto bruto se purificó mediante HPLC preparativa usando mezclas cada vez menos polares de agua (que contiene hidróxido de amonio al 1%) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,257 g, 56,5%) como un sólido amarillo; RMN ^1H (399,9 MHz, DMSO-d6) δ 2,21 (3H, s), 2,25 - 2,40 (4H, m), 2,89 (4H, s), 3,16 - 3,20 (1H, d), 3,32 (4H, s), 3,72 (6H, d), 6,33 (1H, m), 6,42 - 6,44 (2H, d), 7,46 - 7,50 (2H, d), 8,02 - 8,06 (2H, d)

MS: m/z 478 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,096 μM.

El 4-(4-metilpiperazin-1-carbonil)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota cloruro de oxalilo (0,533 ml, 6,11 mmol) a una suspensión agitada de ácido 4-(metoxicarbonil)benzoico (1 g, 5,55 mmoles) en DCM (20 ml) en nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 30 min. Se añadió gota a gota DMF (0,05 ml) en nitrógeno. La suspensión resultante se agitó durante 90 min. Una disolución de 1-metilpiperazina (0,554 ml, 5,00 mmoles) y piridina (1,211 ml, 14,99 mmoles) en DCM (15 ml) se añadió gota a gota a 0°C, durante un periodo de 60 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se evaporó hasta sequedad para dar el producto bruto (1,791 g) como un sólido naranja oscuro. El sólido se redisolvió en DCM y se lavó con $NaHCO_3$. La capa orgánica se evaporó hasta

sequedad para dar 4-(4-metilpiperazin-1-carbonil)benzoato de metilo (0,890 g, 61,1%) como una goma naranja, que solidificó al dejar reposar. Se usó sin purificación adicional.
RMN ^{1}H (399,9 MHz, CDCl3) δ 2,78 (4H, s), 3,43 (4H, s), 7,42 - 7,45 (2H, m), 8,04 - 8,06 (2H, m)
MS: m/z 263 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 87

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(4-propan-2-ilpiperazin-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-propan-2-ilpiperazin-1-il)benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(4-propan-2-il-piperizin-1-il)benzoato de metilo (263 mg, 0,84 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-1-carboxilato de *terc*-butilo (244 mg, 0,7 mmoles) y NaHMDS 1M (1,13 ml, 1,13 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 38-58% de acetonitrilo en agua que contiene amoníaco 0,880 al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (18 mg, 5%); RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,02 (6H, d), 2,55 - 2,61 (4H, m), 2,65 - 2,76 (1H, m), 2,89 (2H, s), 3,21 – 3,28 (4H, s), 3,31 (2H, s), 3,72 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,45 (1H, s), 6,95 (2H, d), 7,90 (2H, d), 10,29 (1H, s), 12,07 (1H, s)
MS: m/z 478 (MH+).
Media de n = 5, ensayo de FGFR cinasa – Caliper, IC_{50} 0,0004 μM.

El 4-(4-propan-2-il-piperizin-1-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:
Se añadió tris(dibencilidenacetona)dipaladio(0) (0,014 g, 0,02 mmoles) a una suspensión desoxigenada de 1-isopropilpiperazina (0,151 g, 1,18 mmoles), 4-bromobenzoato de metilo (0,215 g, 1 mmol), carbonato de potasio (0,193g, 1,4 mmoles) y 2-diciclohexilfosfino-2'-(N,N-dimetilamino)bifenilo (0,012 g, 0,03 mmoles) en DME (4 ml), y se encerró en un tubo de microondas. La reacción se calentó hasta 130°C durante 10 min en el reactor de

microondas, y se enfrió hasta la temperatura ambiente. La mezcla de reacción se evaporó hasta sequedad, se redisolvió en EtOAc (25 ml) y se lavó secuencialmente con agua (15 ml) y salmuera saturada (15 ml). La capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar producto bruto. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-propan-2-il-piperizin-1-il)benzoato de metilo (0,170 g, 64,8 %) como un sólido bronceado.

1RMN 1H (399,9 MHz, CDCl3) δ 1,09 (6H, d), 2,66 (4H, t), 2,73 (1H, q), 3,34 (4H, t), 3,86 (3H, s), 6,84 - 6,88 (2H, m), 7,89 - 7,93 (2H, m). MS: m/z 264 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 88

4-(4-Ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

La 4-(4-ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(4-ciclopropilpiperazin-1-il)benzoato de etilo (193 mg, 0,7 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (292 mg, 0,84 mmoles) y NaHMDS 1M (1,23 ml, 1,23 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (acidic) usando un gradiente 16-36% de acetonitrilo en agua que contiene 0,1% de TFA. Las fracciones limpias se neutrailzaron y se evaporaron para dar el compuesto del título como un sólido blanco (40 mg, 12%); ^{1}RMN 1H (500,13 MHz, DMSO-d_6 + d_4 Acético Acid) δ 0,46 (2H, d), 0,50 (2H, d), 1,79 – 1,84 (1H, m), 2,78 (4H, t), 2,90 (4H, s), 3,24-3,31 (4H, m), 3,75 (6H, s), 6,32 (1H, s), 6,33 (1H, t), 6,42 (2H, d), 6,94 – 6,96 (2H, m), 7,86 – 7,88 (2H, m).

Ensayo de FGFR cinasa – Caliper, IC_{50} 0,156 μM.

Ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00077 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El 4-(4-ciclopropilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se recogieron 4-fluorobenzoato de etilo (0,153 ml, 1,04 mmoles) y 1-ciclopropilpiperazina (0,2637 g, 2,09 mmoles) en DMA (2 ml), y se encerraron en un tubo de microondas. La reacción se calentó hasta 150°C durante 90 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. La mezcla de reacción se evaporó para dar una goma marrón, que solidificó al dejar reposar. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 10% de MeOH (que contiene amoníaco acuoso al 0,1%) en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el producto impuro como un sólido amarillo. El producto impuro se purificó nuevamente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-2,5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-ciclopropilpiperazin-1-il)benzoato de etilo (0,096 g, 33,6 %) como un sólido beige.

IRMN 1H (399,9 MHz, CDCl3) δ 0,45 - 0,52 (5H, m), 1,36 (3H, t), 2,75 (4H, t), 3,29 (4H, t), 4,32 (2H, q), 6,84 - 6,88 (2H, m), 7,90 - 7,93 (2H, m)

m/z (ES+) (M+H)+ = 275

La 1-ciclopropilpiperazina usada como material de partida se preparó según lo siguiente:

Una disolución de 4-ciclopropilpiperazin-1-carboxilato de terc-butilo (0,792 g, 3,50 mmoles) en HCl 4M en 1,4-dioxano (4,37 ml, 17,50 mmoles) se agitó a temperatura ambiente durante 3 h en nitrógeno. La mezcla de reacción se filtró y se lavó con éter para dar 1-ciclopropilpiperazina bruta (0,659 g) como un sólido blanco. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 1-ciclopropilpiperazina (0,264 g, 59,7 %) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,25 - 0,30 (2H, m), 0,35 - 0,40 (2H, m), 1,54 - 1,60 (1H, m), 2,43 (4H, t), 2,60 - 2,65 (4H, t), 3,30 (1H, s)

El 4-ciclopropilpiperazin-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadieron MeOH (0,3 ml), ((1-etoxiciclopropil)oxi)trimetilsilano (2 g, 11,47 mmoles) y ácido acético (1,051 ml, 18,35 mmoles) a una disolución agitada de piperazin-1-carboxilato de terc-butilo (1,068 g, 5,735 mmoles) en THF (40 ml) en nitrógeno. Se añadió en porciones cianoborohidruro de sodio (0,541 g, 8,60 mmoles) durante un periodo de 10 min. La mezcla resultante se agitó a 60°C durante 24 h. La mezcla de reacción se evaporó hasta sequedad y se mezcló con agua (80 ml) y HCl 1M (25 ml). Esta disolución se lavó con EtOAc (2 x 50 ml), la capa acuosa se basificó con K_2CO_3, y se extrajo con EtOAc (2 x 30 ml). Las capas orgánicas se combinaron, se lavaron con salmuera saturada (30 ml), se secaron sobre MgSO4, se filtraron y se evaporaron para dar 4-ciclopropilpiperazin-1-carboxilato de terc-butilo (0,792 g, 61,1 %) como un aceite incoloro, que cristalizó al dejar reposar.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,30 - 0,34 (2H, m), 0,40 - 0,44 (2H, m), 1,41 (9H, s), 1,60 - 1,65 (1H, m), 2,47 (4H, t), 3,26 (4H, t)

Ejemplo 89

4-(4-Ciclobutilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

La 4-(4-ciclobutilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(4-ciclobutillpiperazin-1-il)benzoato de etilo (202 mg, 0,7 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (292 mg, 0,84 mmoles) y NaHMDS·1M (1,23 ml, 1,23 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 39-59% de acetonitrilo en agua que contiene amoníaco 0,880 al 1%. Las fracciones limpias se combinaron y se evaporaron para dar el compuesto del título (21 mg, 6%); RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,61-1,71 (2H, m), 1,81 - 1,86 (2H, m), 1,99 - 2,02 (2H, m), 2,38 (4H, t), 2,75 (1H, s), 2,85 - 2,87 (4H, m), 3,26 - 3,27 (4H, m), 3,72 (6H, d), 6,33 (1H, t), 6,42 - 6,43 (2H, m), 6,45 (1H, s), 6,95 (2H, d), 7,90 (2H, d), 10,29 (1H, s), 12,07 (1H, s). MS = m/z 490 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,009 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El 4-(4-ciclobutilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se recogieron 4-fluorobenzoato de etilo (0,225 ml, 1,53 mmoles) y 1-ciclobutilpiperazina (0,430 g, 3,07 mmoles) en DMA (3 ml), y se encerraron en un tubo de microondas. La reacción se calentó hasta 150°C durante 90 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. La reacción no estaba terminada, de forma que se volvió a calentar a 150°C durante otra 1h. La mezcla de reacción se evaporó hasta sequedad, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0-2,5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-ciclobutilpiperazin-1-il)benzoato de etilo (0,050 g, 11,31 %) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,29 (3H, t), 1,65 - 1,70 (2H, m), 1,86 (2H, t), 2,00 (2H, q), 2,41 (4H, d), 2,68 - 2,75 (1H, m), 3,27 (4H, t), 4,25 (2H, q), 6,79 (2H, d), 7,85 (2H, d). MS= m/z = 289 (MH+).

La 1-ciclobutilpiperazina, usada como material de partida, se preparó según lo siguiente:

Se añadió ácido trifluoroacético (7,84 ml, 101,73 mmoles) a una disolución agitada de 4-ciclobutilpiperazin-1-carboxilato de terc-butilo (2,445 g, 10,17 mmoles) en DCM (25 ml) enfriado hasta 0°C en nitrógeno, y se agitó a 20°C durante 24 h. La mezcla de reacción se evaporó hasta sequedad y se diluyó con DCM (30 ml). Éste se lavó entonces con NaHCO3 saturado (2 x 10 ml), y las capas orgánicas se evaporaron hasta sequedad. Todvía había producto en la capa acuosa, de forma que esta se basificó con NaOH 2M y se extrajo con DCM (3 x 10 ml) y EtOAc (1 x 10 ml). Las fracciones orgánicas se combinaron y se evaporaron hasta sequedad para dar 1-ciclobutilpiperazina (0,430 g, 30,1 %). RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,60 - 1,67 (2H, m), 1,72 - 1,80 (2H, m), 1,93 - 1,97 (2H, m), 2,25 (4H, s), 2,57 - 2,60 (1H, d), 2,82 (4H, t)

El 4-ciclobutilpiperazin-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadieron agua (0,3 ml), ciclobutanona (2,000 g, 28,53 mmoles) y ácido acético (3,48 ml, 60,86 mmoles) a una disolución agitada de piperazin-1-carboxilato de terc-butilo (3,54 g, 19,02 mmoles) en THF (40 ml) en nitrógeno. Se añadió en porciones cianoborohidruro de sodio (1,793 g, 28,53 mmoles) durante un periodo de 10 min. La mezcla resultante se agitó a

60°C durante 19 h. La mezcla de reacción se evaporó hasta sequedad y se mezcló con agua (80 ml) y HCl 1M (25 ml). La disolución se lavó con EtOAc (2 x 50 ml), se basificó con K_2CO_3 y se extrajo con EtOAc (2 x 30 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre MgSO4, se filtró y se evaporó para dar 4-ciclobutilpiperazin-1-carboxilato de terc-butilo puro (2,445 g, 53,5 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,40 (9H, s), 1,60 - 1,65 (2H, m), 1,75 - 1,80 (1H, m), 1,90 - 2,00 (2H, m), 2,17 (1H, t), 2,65 - 2,75 (1H, m), 3,30 (4H, d). MS = m/z 241 (MH+).

Ejemplo 90

4-(4-Acetilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]benzamida

La 4-(4-acetilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(4-acetilpiperazin-1-il)benzoato de metilo (221 mg, 0,84 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-1-carboxilato de *terc*-butilo (244 mg, 0,7 mmoles) y NaHMDS 1M (1,13 ml, 1,13 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 31-51% de acetonitrilo en agua, que contiene amoníaco 0,880 al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (3 mg, 1,0%); RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,06 (3H, s), 2,78 (4H, s), 3,28 (2H,s) 3,25 (2H, t), 3,49 – 3,56(4H, m), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,45 (1H, s), 6,99 (2H, d), 7,92 (2H, d), 10,32 (1H, s), 12,08 (1H, s).

MS: m/z 478 (MH+).

Media de n = 5, ensayo de FGFR cinasa – Caliper, IC_{50} 0,056 μM.

Una suspensión desoxigenada de 1-acetilpiperazina (0,308 g, 2,40 mmoles), 4-bromobenzoato de metilo (0,430 g, 2 mmoles), ortofosfato de tripotasio (0,594 g, 2,80 mmoles), 2-diciclohexilfosfino-2',6'-dimetoxi-1,1'-bifenilo (0,164 g, 0,40 mmoles) y tris(dibencilidenacetona)dipaladio (0) (0,092 g, 0,10 mmoles) en tolueno (10 ml) se agitó a 100°C, durante un periodo de 24 h en nitrógeno. La mezcla de reacción enfriada se filtró y se evaporó para dar producto bruto. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente 0 - 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-acetilpiperazin-1-il)benzoato de metilo (0,295 g, 56,2 %) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, CDCl3) δ 2,07 (3H, s), 3,24 - 3,30 (4H, m), 3,56 (2H, t), 3,70 - 3,72 (2H, m), 3,80 (3H, s), 6,78 - 6,81 (2H, m), 7,85 - 7,89 (2H, m). MS: m/z 263 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 91

N-[5-[2-(3-Metoxifenil)etil]-1H-pirazol-3-il]-4-(4-metilsulfonilpiperazin-1-il)benzamida

Una disolución de ácido fórmico (5 ml, 130,36 mmoles) y N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(4-(metilsulfonil)piperazin-1-il)benzamida (255 mg, 0,47 mmoles) se agitó a 85°C durante 2 h. La mezcla de reacción se enfrió y se evaporó hasta sequedad. El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 36-46% de acetonitrilo en agua, que contiene amoníaco 0,880 al 1%. Las fracciones limpias se combinaron y se evaporaron para dar el compuesto del título (43,0 mg, 18,82 %) como un sólido blanco; RMN ^{1}H (499,9 MHz, $DMSO_d6$ + CD_3CO_2D) δ 2,87 (3H, s), 2,88 –2,92 (4H, m), 3,28 – 3,32 (4H, m), 3,39 – 3,42 (4H, m), 3,73 (3H, s), 6,30 (1H, s), 6,71 – 6,74 (1H, m), 6,77 (1H, s0, 6,80 (2H, d), 6,94 – 6,98 (2H, m), 7,16 (1H, t), 7,85 – 7,89 (2H, m).

MS: m/z = 484 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,25 μM.

La N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(4-(metilsulfonil)piperazin-1-il)benzamida usada como material de partida se preparó según lo siguiente:

Se añadió cloruro de metanosulfonilo (0,042 ml, 0,55 mmoles) a 0°C a una disolución de N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(piperazin-1-il)benzamida (0,231 g, 0,5 mmoles) y N,N-dietiletanamina (0,077 ml, 0,55 mmoles) en DCM (4 ml). La disolución resultante se agitó a 20°C durante 1 h. La mezcla de reacción se diluyó con hidrogenocarbonato de sodio saturado (10 ml), se filtró, y el sólido se lavó con DCM (2 x 10 ml). Las capas orgánicas se combinaron y se lavaron con agua (20 ml) y salmuera saturada (20 ml). Los orgánicos se secaron (MgSO4), se filtraron y se evaporaron para dar producto bruto. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 - 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta

sequedad para dar N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(4-(metilsulfonil)-piperazin-1-il)benzamida (0,255 g, 94 %) como un sólido blanco. MS: m/z = 540 (MH+).

La N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(piperazin-1-il)benzamida se preparó según lo siguiente:

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (6,25 ml, 12,50 mmoles) a una disolución agitada de 1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-amina (1,367 g, 5,00 mmoles) y 4-(piperazin-1-il)benzoato de etilo (1,171 g, 5 mmoles) en tolueno (20 ml) a 4°C, durante un periodo de 5 min en nitrógeno. La disolución resultante se agitó a 20°C durante 18 h. La mezcla de reacción se paralizó con metanol (20 ml), se filtró y se evaporó para dar un sólido bronceado. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de MeOH en DCM y 0,1% de amoníaco. Las fracciones puras se evaporaron hasta sequedad para dar N-(1-terc-butil-3-(3-metoxifenetil)-1H-pirazol-5-il)-4-(piperazin-1-il)benzamida (0,520 g, 22,53 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,59 (9H, s), 2,81 - 2,91 (4H, m), 2,96 - 2,99 (4H, m), 3,23 (3H, t), 3,25 - 3,42 (1H, m), 3,72 (3H, s), 6,17 (1H, s), 6,64 - 6,68 (1H, m), 6,73 (1H, t), 6,78 (1H, d), 6,84 - 6,88 (2H, m), 7,12 (1H, t), 7,38 (1H, s), 7,67 - 7,71 (2H, m).

Se añadió piperazina (17,23 g, 200,00 mmoles) a 4-fluorobenzoato de etilo (7,34 ml, 50 mmoles) en DMSO (50 ml) calentado a 120°C en nitrógeno. La disolución resultante se agitó a 120°C durante 20 h. La mezcla de reacción se enfrió y el disolvente se evaporó. El producto se repartió entre disolución saturada ac. de hidrogenocarbonato de sodio (100 ml) y acetato de etilo (100 ml). Esto se extrajo con acetato de etilo (2 x 75 ml), se lavó con disolución de salmuera, se secó sobre MgSO4, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con metanol al 10% en diclorometano que contiene amoníaco 0,880 al 0,1%. Las fracciones puras se evaporaron hasta sequedad para dar el producto como un sólido. El sólido insoluble se suspendió en DCM (500 ml) y se agitó durante 1 h. Esta disolución se filtró y la disolución orgánica se secó sobre MgSO4, se filtró y se evaporó para dar el grueso del producto como un sólido. Los sólidos se combinaron para dar 4-(piperazin-1-il)benzoato de etilo (9,53 g, 81 %). RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,28 - 1,32 (3H, m), 2,94 - 2,96 (4H, m), 3,20 - 3,22 (4H, m), 4,26 (2H, q), 6,77 - 6,81 (2H, m), 7,84 - 7,87 (2H, m). MS: m/z = 236 (MH+)

La 5-[2-(3-metoxifenil)etil]-2-terc-butil-pirazol-3-amina se preparó como se esquematiza en el Ejemplo 13.

Ejemplo 92

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(1-metil-4-piperidil)benzamida

Se añadió gota a gota una disolución de NaHMDS (1M en THF) (5,91 ml, 5,91 mmol) a una disolución agitada de 4-(1-metilpiperidin-4-il)benzoato de metilo (0,4594 g, 1,97 mmoles) y 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-1-carboxilato de *terc*-butilo (0,821 g, 2,36 mmoles) en THF (4 ml), durante un periodo de 10 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió en NH_4Cl saturado (25 ml), se extrajo con EtOAc (2 x 25 ml), se lavó con salmuera saturada y se secó sobre $MgSO_4$, se filtró y se evaporó para dar el producto bruto (1,0719 g) como una goma naranja. El producto bruto se purificó mediante HPLC preparativa usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,142 g, 16,08 %) como un sólido blanco;

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,64 - 1,78 (4H, m), 1,97 - 2,01 (2H, m), 2,22 (3H, s), 2,53 - 2,58 (1H, m), 2,88 - 2,91 (6H, m), 3,73 (6H, s), 6,33 (1H, t), 6,42 - 6,44 (3H, m), 7,35 (2H, d), 7,93 (2H, d), 10,57 (1H, s), 12,08 (1H, s)

MS: m/z 449 (MH+)

Media de n = 1, ensayo de FGFR cinasa - Caliper, IC_{50} 0,0079 μM.

El 4-(1-metilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadieron agua (0,2 ml), paraformaldehído (0,470 g, 15,64 mmoles) y ácido acético (0,895 ml, 15,64 mmoles) a una suspensión agitada de cloruro de 4-(4-(metoxicarbonil)fenil)piperidinio (1 g, 3,91 mmoles) en THF (20 ml) en nitrógeno. Se añadió en porciones cianoborohidruro de sodio (0,369 g, 5,87 mmoles) durante un periodo de 10 min. La mezcla resultante se agitó a 60°C durante 19 h. La mezcla de reacción se evaporó hasta sequedad y se mezcló con agua (20 ml) y HCl 1M (5 ml). La disolución se lavó con EtOAc (2 x 15 ml), se basificó con K_2CO_3 y se extrajo con EtOAc (2 x 15 ml). La capa orgánica se

lavó con salmuera saturada y se secó sobre MgSO4, se filtró y se evaporó para dar 4-(1-metilpiperidin-4-il)benzoato de metilo puro (0,459 g, 50,4%) como un aceite incoloro, que cristalizó al dejar reposar.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,63 - 1,72 (2H, m), 1,73 - 1,77 (2H, m), 1,96 - 2,03 (2H, m), 2,21 (3H, s), 2,87 - 2,90 (2H, m), 3,85 (3H, s), 4,30 - 4,31 (1H, m), 7,40 (2H, d), 7,88 - 7,91 (2H, m)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 93

4-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida

La 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida se preparó como en el Ejemplo 94, pero partiendo de 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)benzoato de metilo (193 mg, 0,7 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (292 mg, 0,84 mmoles) y NaHMDS 1M (1,23 ml, 1,23 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 33-53% de acetonitrilo en agua, que contiene amoníaco 0,880 al 1%. Las fracciones limpias se combinaron y se evaporaron para dar el compuesto del título (34 mg, 10%); RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,37 - 1,41 (1H, m), 1,67 - 1,77 (2H, m), 1,84 - 1,88 (1H, m), 1,99 - 2,06 (1H, m), 2,09 (1H, t), 2,18 - 2,25 (1H, m), 2,80 - 2,84 (1H, m), 2,87 (4H, s), 3,01 - 3,06 (2H, m), 3,73 (6H, s), 3,80 - 3,83 (1H, m), 3,96 - 3,98 (1H, m), 6,33 (1H, t), 6,42 - 6,45 (3H, m), 6,97 (2H, d), 7,90 (2H, d), 10,28 (1H, s), 12,07 (1H, s)

MS = m/z 476 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,037 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadieron 4-yodobenzoato de metilo (2,076 g, 7,92 mmoles), carbonato de cesio (5,16 g, 15,85 mmoles), 2-acetilciclohexanona (0,209 ml, 1,58 mmoles) y yoduro de cobre (I) (0,075 g, 0,40 mmoles) a una disolución agitada de 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (1 g, 7,92 mmoles) en DMF (20 ml) en nitrógeno. La suspensión resultante se agitó a 90°C durante 20 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en una mezcla de metanol y agua. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,243 g, 60,2 %) como una goma marrón.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,33 - 1,43 (1H, m), 1,57 - 1,79 (3H, m), 1,81 - 1,89 (1H, m), 1,99 - 2,03 (1H, m), 2,07 (1H, q), 2,16 - 2,23 (1H, m), 2,56 (1H, t), 2,83 - 2,95 (2H, m), 3,00 - 3,05 (2H, m), 3,06 - 3,09 (1H, m), 3,75 - 3,78 (3H, m), 3,86 (1H, t), 3,98 - 4,01 (1H, m), 6,98 - 7,02 (2H, m), 7,77 - 7,80 (2H, m).

MS = m/z 261 (MH+).

Ejemplo 94

4-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida

Se añadió una disolución 1M de NaHMDS en THF (1,13 ml, 1,05 mmoles) a una disolución agitada de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (244 mg, 0,7 mmoles) y 4-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)benzoato de metilo (231 mg, 0,84 mmoles) en THF (5 ml) a 0°C en nitrógeno, durante 5 minutos. La mezcla de reacción se agitó durante 5 minutos adicionales a 0°C, después se agitó a 20°C durante 18 h. Se añadió una cantidad adicional de 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (80 mg, 0,23 mmol) con NaHMDS 1M en THF (1,13 ml, 1,13 mmoles). La mezcla de reacción se agitó durante 3 h adicionales. La mezcla de reacción se paralizó con cloruro de amonio saturado (20 ml), y se extrajo con acetato de etilo (3 x 20 ml). Los extractos se lavaron con disolución saturada de salmuera (15 ml), se secaron (MgSO4) y se evaporaron para dar producto bruto. El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 38-58% de acetonitrilo en agua que contiene 1% de

hidróxido de amonio 0,880. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (32 mg, 9%); RMN ^{1}H (500,13 MHz, DMSO-d_6) δ 1,25 (1H, s), 1,62 (2H, t), 1,72 (1H, d), 1,93 - 1,95 (2H, m), 2,19 - 2,20 (1H, m), 2,44 (1H, s), 2,81 (3H, q), 2,87 (4H, s), 3,28 (1H, s), 3,69 (1H, s), 3,72 (6H, s), 3,77 (1H, d), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 6,96 (2H, d), 7,89 (2H, d), 10,29 (1H, s), 12,07 (1H, s). MS: m/z 490 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,081 μM.

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

El 4-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Una disolución de 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (5 g) en una mezcla de metanol y agua (1:1) se convirtió en la base libre mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,5224 g, 10,86 mmoles) como un sólido amarillo.

Seañadieron 4-yodobenzoato de metilo (2,84 g, 10,86 mmoles), carbonato de cesio (7,07 g, 21,71 mmol), 2-acetilciclohexanona (0,286 ml, 2,17 mmoles) y yoduro de cobre (I) (0,103 g, 0,54 mmoles) a una disolución agitada de 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (1,5224 g, 10,86 mmoles) en DMF (30 ml) en nitrógeno. La suspensión resultante se agitó a 90°C durante 20 h. La mezcla de reacción se evaporó hasta sequedad y se disolvió en metanol. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar una goma marrón. Ésta se purificó nuevamente mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH (que contiene 0,1% de hidróxido de amonio) en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,503 g, 16,8 %) como un sólido naranja. RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,29 - 1,33 (1H, m), 1,26 - 1,40 (1H, m), 1,62 (1H, d), 1,64 (1H, d), 1,65 - 1,68 (1H, m), 1,69 (1H, s), 1,80 - 1,82 (1H, m), 2,04 - 2,10 (2H, m), 2,32 - 2,39 (1H,

m), 2,61 (1H, d), 2,89 (2H, d), 3,01 - 3,08 (1H, m), 3,58 - 3,63 (1H, m), 3,70 - 3,75 (1H, m), 3,86 (3H, s), 6,83 - 6,87 (2H, m), 7,89 - 7,93 (2H, m). MS m/z = 275 (MH+).

Ejemplo 95

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-[(4-metilpiperazin-1-il)metil]benzamida

Se añadió gota a gota una disolución de NaHMDS (1M en THF) (2,83 ml, 2,83 mmoles) a una disolución agitada de 4-((4-metilpiperazin-1-il)metil)benzoato de metilo (0,351 g, 1,41 mmol) y 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-1-carboxilato de *terc*-butilo (0,589 g, 1,70 mmoles) en THF (3 ml), durante un periodo de 10 min en nitrógeno. Se añadió DMA (3 ml). La disolución resultante se agitó a temperatura ambiente durante 60 h. Se añadió gota a gota una alícuota adicional de NaHMDS (1,415 ml, 1,415 mmoles), y la disolución se agitó a temperatura ambiente durante otros 90 min. La mezcla de reacción se vertió en NH_4Cl saturado (25 ml), se extrajo con EtOAc (2 x 25 ml), se lavó con salmuera saturada y se secó sobre $MgSO_4$, se filtró y se evaporó para dar el producto bruto (0,8776 g) como una goma naranja. El producto bruto se purificó mediante HPLC preparativa usando mezclas cada vez menos polares de agua (que contiene 1% de NH_3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,034 g, 5,19 %) como un sólido blanco; RMN ^1H (500,0 MHz, DMSO-d6) δ 2,18 (3H, s), 2,34 - 2,37 (2H, m), 3,54 (2H, s), 3,73 (3H, s), 6,32 - 6,33 (1H, t), 6,41 - 6,42 (2H, d), 7,38 - 7,39 (1H, d), 7,90 - 7,92 (1H, d), 10,02 (1H, s), 11,79 (1H, s)

MS: m/z 464 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper, IC_{50} 0,14 μM.

El 4-((4-metilpiperazin-1-il)metil)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota una disolución de (trimetilsilil)diazometano ((0,611 ml, 3,84 mmoles) 2,0M en éter dietílico) a una suspensión agitada de ácido 4-((4-metilpiperazin-1-il)metil)benzoico (0,75 g, 3,20 mmoles) en tolueno (21 ml) y metanol (7 ml) durante un periodo de 10 min en nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 3 h. Se añadió gota a gota una alícuota adicional de (trimetilsilil)diazometano (1,222 ml, 7,68 mmoles), y la disolución se agitó a temperatura ambiente durante otras 18 h. La

mezcla de reacción se evaporó hasta sequedad para dar el producto bruto (0,723 g) como un sólido blanco. Éste se recogió en DCM, y los insolubles se separaron por filtración. El filtrado se evaporó hasta sequedad para dar el producto bruto. Éste se recogió en DCM nuevamente, y se separaron por filtración más insolubles para dar 4-((4-metilpiperazin-1-il)metil)benzoato de metilo (0,351 g, 44,2 %), que se usó sin purificación.

RMN ^{1}H (399,9 MHz, CDCl3) δ 2,60 - 2,61 (3H, m), 2,77 (4H, t), 2,99 (4H, s), 3,58 (1H, s), 3,62 (1H, s), 3,85 (2H, d), 7,29 - 7,38 (2H, m), 7,92 - 7,80 (2H, m)

MS: m/z 249 (MH+)

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 96

N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(3,4,5-trimetilpiperazin-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-1H-pirazol-3-il]-4-(3,4,5-trimetilpiperazin-1-il)benzamida se preparó siguiendo el procedimiento como en el Ejemplo 94, pero partiendo de 4-(3,4,5-trimetilpiperazin-1-il)benzoato de etilo (310 mg, 0,86 mmoles), 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo (225 mg, 0,65 mmoles) y NaHMDS 1M (2,59 ml, 2,59 mmoles) en THF (5 ml). El producto bruto se purificó mediante HPLC prep. de fase inversa (básica) usando un gradiente 38-58% de acetonitrilo en agua que contiene amoníaco 0,880 al 1%. Las fracciones limpias se recogieron y se evaporaron para dar el compuesto del título como un sólido blanco (23 mg, 5,6%); RMN ^{1}H (399,99 MHz, $CDCl_3$) δ1,09 (6H, d), 2,17-2,28 (2H, m), 2,22 (3H, s), 2,56 (2H, t), 2,81 – 2,90 (4H, m), 3,48 (2H, d), 3,68 (6H, s), 6,22 (1H, t), 6,28 (2H, s), 6,56 (1H, s), 6,78 (2H, d), 7,68 (2H, d0, 8,86 (1H, s), 9,65 (1H, s). MS: m/z 464 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00054 μM.

El 4-(3,4,5-trimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió isopropóxido de titanio (IV) (0,598 ml, 2,00 mmoles) a 4-(3,5-dimetilpiperazin-1-il)benzoato de etilo (0,262 g, 1 mmol), y paraformaldehído (0,120 g, 4,00 mmoles) en etanol (5 ml). La disolución resultante se agitó a 60°C en nitrógeno durante 30 min. Ésta se enfrió

hasta 20°C y se añadió de una vez borohidruro de sodio (0,095 g, 2,5 mmoles). La disolución se calentó a 60°C durante 24 h. La mezcla de reacción se paralizó con amoníaco 0,880 (0,5 ml), se filtró, se lavó con éter dietílico (2 x 5 ml) y los extractos orgánicos se evaporaron. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 - 5% de MeOH en DCM que contiene amoníaco al 0,1%. Las fracciones se evaporaron hasta sequedad para dar un aceite. Éste se disolvió en acetonitrilo (20 ml), se añadió resina de isocianato soportada sobre polímero (1 mmol/g, 2g), y la suspensión se agitó toda la noche. La resina se separó por filtración, y la disolución se evaporó hasta sequedad para dar 4-(3,4,5-trimetilpiperazin-1-il)benzoato de etilo (0,310 g, 112 %) como un sólido blanco. MS: m/z 278 (MH+).

El 5-amino-3-[2-(3,5-dimetoxifenil)etil]-1*H*-pirazol-1-carboxilato de *terc*-butilo usado como material de partida se preparó como en el Ejemplo 2.

Ejemplo 97

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 5-(3,4-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,268 g, 1 mmol) e hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,286 g, 1,00 mmoles) en tolueno (7,14 ml) a 80°C en nitrógeno durante 4 h, y después a 70°C durante 18 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y se eliminó la capa acuosa. La capa de acetato de etilo se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como una goma amarilla. El producto bruto se purificó mediante LCMS preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,036 g, 7,63 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6) δ 1,07 (3H, d), 2,26 - 3,12 (4H, m), 3,38 -3,47 (3H, m), 3,78 (6H, s), 5,09 (2H, s), 5,55 (1H, s), 6,17 (1H, d), 6,45 (1H, s), 6,61 (2H, d), 7,64 (1H, s).

MS: m/z 472 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00046 µM.

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

El 5-(3,4-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (0,112 g, 0,50 mmoles) a una mezcla de 5-bromotiofen-2-carboxilato de etilo (0,571 g, 5 mmoles), 1,2-dimetil-piperazina (1,175 g, 5 mmoles), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,311 g, 0,50 mmoles) y carbonato de cesio (2,281 g, 7,00 mmoles) en tolueno (50,0 ml) a 20°C en nitrógeno. La suspensión resultante se agitó a 110°C durante 23 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El material bruto se disolvió en metanol y después se aplicó a la columna. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad para dar el producto bruto como un aceite marrón. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 1 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 5-(3,4-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,640 g, 47,7 %) como un sólido marrón claro.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,11 - 1,13 (3H, m), 1,33 (3H, t), 2,24 - 2,29 (1H, m), 2,33 (3H, s), 2,37 - 2,44 (1H, m), 2,73 (1H, d), 2,82 - 2,87 (1H, m), 3,08 - 3,14 (1H, m), 3,36 - 3,40 (1H, m), 3,43 - 3,48 (1H, m), 4,28 (2H, q), 6,01 (1H, d), 7,54 (1H, d)

MS: m/z 269 (MH+)

Ejemplo 98

4-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (0,853 ml, 1,71 mmol) a una disolución agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,170 g, 0,68 mmoles) y 4-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)benzoato de metilo (0,187 g, 0,68 mmoles) en tolueno (10 ml), durante un periodo de 5 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La reacción estaba sin

terminar, de forma que se añadió gota a gota más trimetilaluminio (0,853 ml, 1,71 mmoles) durante un periodo de 5 min, y la disolución se agitó a 60°C durante 4 h. La mezcla de reacción se enfrió y se vertió en acetona (50 ml), se paralizó con sulfito de sodio húmedo, se filtró y se evaporó hasta sequedad. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad hasta el compuesto del título (0,105 g, 31,3 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6) δ 1,21 - 1,26 (1H, m), 1,30 - 1,33 (1H, m), 1,53 - 1,57 (1H, m), 1,63 (1H, d), 1,65 (1H, d), 1,76 (1H, d), 1,98 (1H, d), 1,98 - 2,03 (1H, m), 2,22 - 2,27 (1H, m), 2,55 (1H, d), 2,79 (1H, t), 2,83 (2H, d), 3,68 - 3,70 (1H, m), 3,78 (7H, s), 5,10 (2H, s), 5,67 (1H, s), 6,46 (1H, t), 6,61 - 6,62 (2H, m), 6,97 (2H, d), 7,84 (2H, d), 10,20 (1H, s), 11,15 (1H, s). MS: m/z 492 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,003 μM.

El 4-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Una disolución de dihidrocloruro de 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (5 g) en metanol (20 ml) y agua (10 ml) se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (1,5224 g, 10,86 mmoles) como un sólido amarillo.

Se añadieron 4-yodobenzoato de metilo (2,84 g, 10,86 mmoles), carbonato de cesio (7,07 g, 21,71 mmol), 2-acetilciclohexanona (0,286 ml, 2,17 mmoles) y yoduro de cobre (I) (0,103 g, 0,54 mmoles) a una disolución agitada de 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (1,5224 g, 10,86 mmoles) en DMF (30 ml) en nitrógeno. La suspensión resultante se agitó a 90°C durante 20 h. La mezcla de reacción se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones se evaporaron hasta sequedad para dar el producto bruto como una goma marrón impura. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH, amoníaco acuoso al 0,1% en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,681 g, 22,87 %) como un sólido naranja.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,29 - 1,33 (1H, m), 1,26 - 1,40 (1H, m), 1,62 (1H, d), 1,64 (1H, d), 1,65 - 1,68 (1H, m), 1,69 (1H, s), 1,80 - 1,82 (1H, m), 2,04 - 2,10 (2H, m), 2,32 - 2,39 (1H, m), 2,61 (1H, d), 2,89 (2H, d), 3,01 - 3,08 (1H, m), 3,58 - 3,63 (1H, m), 3,70 - 3,75 (1H, m), 3,86 (3H, s), 6,83 - 6,87 (2H, m), 7,89 - 7,93 (2H, m). MS: m/z 275 (MH+).

Ejemplo 99

4-(1-Ciclopropilpiperidin-4-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida

Se trató 4-(1-ciclopropilpiperidin-4-il)benzoato de metilo (0,259 g, 1 mmol), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1,00 mmoles) en tolueno (10 ml) con una disolución 2M de trimetilaluminio (1,250 ml, 2,50 mmoles) en tolueno, en nitrógeno. La mezcla de reacción se calentó a 60°C durante 18 h. La mezcla de reacción se enfrió, y la reacción se paralizó con metanol (40 ml) y se acidificó con HCl 2N (1 ml). La mezcla de reacción bruta se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto bruto se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/metanol en DCM. Las fracciones puras se evaporaron hasta sequedad, y el producto cristalizó en DCM/éter dietílico para dar el compuesto del título (0,170 g, 35,8 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,31 - 0,33 (2H, m), 0,43 - 0,45 (2H, m), 1,58 - 1,66 (3H, m), 1,74 (1H, d), 1,77 (1H, s), 2,25 - 2,30 (2H, m), 2,55 (1H,d), 2,88 (4H, s), 3,05 (2H, d), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,47 (1H, s), 7,34 (2H, d), 7,92 (2H, d), 10,54 (1H, s), 12,13 (1H, s). MS: m/z 475 (MH+).

Media de n = 3, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00091 μM.

El 4-(1-ciclopropilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se disolvió 4-piperidin-4-ilbenzoato de metilo (1,279 g, 5 mmoles) en una mezcla de THF (15 ml) y metanol (1 ml). Se añadió [(1-etoxiciclopropil)oxi]trimetilsilano (2,001 ml, 10,00 mmoles), seguido de ácido acético (0,916 ml, 16,00 mmoles). Se añadió DCM (15,00 ml) para ayudar a la solubilidad. Se añadió en porciones cianoborohidruro de sodio sólido (0,471 g, 7,50 mmoles) durante 5 min. La reacción se agitó a 60°C durante 18 h. Ésta se enfrió, se paralizó con disolución saturada de cloruro de amonio (5 ml), se diluyó con metanol (20 ml) y

se purificó parcialmente mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar un aceite. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,548 g, 42,3 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,42 - 0,50 (4H, m), 1,60 - 1,65 (2H, m), 1,70 - 1,75 (1H, m), 1,80 - 1,85 (2H, m), 2,25 - 2,32 (2H, m), 2,55 - 2,61 (1H, m), 3,15 - 3,18 (2H, m), 3,89 (3H, s), 7,27 - 7,30 (2H, m), 7,94 - 7,97 (2H, m). MS: m/z 260 (MH+).

El 4-piperidin-4-ilbenzoato de metilo se preparó según lo siguiente:

El hidrocloruro de 4-(piperidin-4-il)benzoato de metilo (5,0g, 17 mmoles) se convirtió en la base libre mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 4-(piperidin-4-il)benzoato de metilo (4,20g, 95%) como un sólido blanco. MS: m/z 260 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 100

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-[(3R,5S)-3,5-dimetilpiperazin-1-il]benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (1,875 ml, 3,75 mmoles) a una suspensión agitada de 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo (0,394 g, 1,50 mmoles) y 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,374 g, 1,5 mmoles) en tolueno (10 ml) a 20°C, durante un periodo de 5 min en nitrógeno. La disolución resultante se agitó a 60°C durante 5 h. La mezcla de reacción se enfrió y la reacción se paralizó diluyendo con acetona (100 ml), y se añadió en porciones un exceso de sulfito de sodio húmedo. Se agitó durante 60 min. El sólido resultante se separó por filtración, se lavó con metanol al 10% en DCM. El filtrado se evaporó para dar producto bruto. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de

0 a 5% de amoníaco 2M / MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (0,287 g, 41,1 %) como un sólido blanco. RMN ^{1}H (500,13 MHz, DMSO-d6) δ 1,08 (6H, d), 2,31 (2H, t), 3,70 - 3,73 (2H, m), 3,78 (6H, s), 5,10 (2H, s), 5,64 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 6,95 - 6,97 (2H, m), 7,83 - 7,85 (2H, m), 10,21 (1H, s), 11,09 (1H, s). MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0014 μM.

El 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente.

Se añadió (2S,6R)-2,6-dimetilpiperazina (6,85 g, 60,00 mmoles) a 4-fluorobenzoato de etilo (2,201 ml, 15 mmoles), en DMSO (40 ml) calentado hasta 120°C en nitrógeno. La disolución resultante se agitó a 120°C durante 20 h. La mezcla de reacción se enfrió, y el disolvente se evaporó. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de metanol en diclorometano que contiene amoníaco 0,880 al 1%. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (2,83 g, 71,9 %) como un aceite marrón. RMN ^{1}H (399,9 MHz, CDCl3) δ 1,15 (6H, d), 1,37 (3H, t), 2,38 (1H, d), 2,41 (1H, d), 2,96 - 3,04 (2H, m), 3,65 - 3,69 (2H, m), 4,33 (2H, q), 6,84 - 6,87 (2H, m), 7,89 - 7,93 (2H, m). MS: m/z 263 (MH+).

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina se preparó según lo siguiente:

Se añadió carbonato de MP (2,74 mmoles/g) (12,00 g, 32,88 mmoles) a hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (5 g, 17,50 mmoles) en metanol (200 ml) y agua (20 ml). La suspensión resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se filtró y el carbonato de MP se lavó con 10% de MeOH en DCM. Éste se evaporó hasta sequedad para dar 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (2,94 g, 67,5 %) como un sólido ceroso naranja. RMN ^{1}H (399,9 MHz, DMSO-d6) δ 3,74 (6H, s), 4,76 (1H, s), 4,97 (2H, s), 6,42 (1H, t), 6,55 (2H, d).

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

Ejemplo 101

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida

La N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(3,4-dimetilpiperazin-1-il)benzamida se preparó siguiendo el procedimiento para el Ejemplo 100, pero partiendo de 4-(3,4-dimetilpiperazin-1-il)benzoato de etilo (0,394 g, 1,50 mmoles), 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,374 g, 1,5 mmoles) y trimetilaluminio 2M en tolueno (1,875 ml, 3,75 mmoles). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (0,301 g, 43,1 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6) δ 1,06 - 1,10 (3H, m), 2,22 - 2,30 (1H, m), 2,20 - 2,63 (4H, m), 2,61 - 2,65 (1H, m), 2,83 - 2,86 (1H, m), 2,96 - 3,02 (1H, m), 3,63 - 3,70 (2H, m), 3,78 (6H, s), 5,11 (2H, s), 5,66 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 6,96 - 6,98 (2H, m), 7,83 - 7,86 (2H, m), 10,15 (1H, s), 11,07 (1H, s). MS: m/z 466 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,021 μM.

El 4-(3,4-dimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se disolvieron 1,2-dimetilpiperazina (2,284 g, 20,00 mmoles) y 4-fluorobenzoato de etilo (1,467 ml, 10 mmoles) en DMA (12 ml), y se encerraron en un tubo de microondas. La reacción se calentó hasta 150°C durante 90 min en el reactor de microondas, y se enfrió hasta la temperatura ambiente. La mezcla de reacción se calentó durante otros 30 min a 150°C, y se enfrió hasta la temperatura ambiente. La mezcla de reacción se evaporó, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM con amoníaco 0,880 al 0,1%. Las fracciones puras se evaporaron hasta sequedad para dar 4-(3,4-dimetilpiperazin-1-il)benzoato de etilo (0,853 g, 32,5 %) como un sólido ceroso incoloro.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,14 (3H, d), 1,37 (3H, t), 2,20 - 2,25 (1H, m), 2,33 (3H, s), 2,34 - 2,41 (1H, m), 2,62 (1H, t), 2,87 - 2,91 (1H, m), 2,99 - 3,05 (1H, m), 3,57 - 3,62 (1H, m), 3,65 - 3,70 (1H, m), 4,33 (2H, q), 6,83 - 6,87 (2H, m), 7,90 - 7,94 (2H, m). MS: m/z 263.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, usada como material de partida, se preparó como en el Ejemplo 100.

Ejemplo 102

4-[5-[[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]carbamoil]tiofen-2-il]piperazin-1-carboxilato de *terc*-butilo

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 4-(5-(metoxicarbonil)tiofen-2-il)piperazin-1-carboxilato de terc-butilo (0,326 g, 1 mmol) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1,00 mmoles) en tolueno (7,14 ml) a 20°C en nitrógeno. La mezcla de reacción se agitó a 20°C durante 20 h. La temperatura se incrementó hasta 60°C, y la mezcla de reacción se agitó durante 20 h y después se dejó enfriar. La mezcla de reacción se diluyó con acetona (10 ml) y se paralizó con sulfito de sodio sólido húmedo. La mezcla se agitó durante 30 min, y después se añadió una disolución de metanol al 10% en DCM (10 ml) y la mezcla se agitó otros 30 min. La suspensión se filtró, y el sólido se lavó con metanol al 10% en DCM (20 ml); los filtrados combinados se evaporaron para dar una espuma amarilla. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 1 a 10% de amoníaco 2M/metanol en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el producto bruto. Éste se purificó adicionalmente mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar 4-[5-[[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]carbamoil]tiofen-2-il]piperazin-1-carboxilato de *terc*-butilo (0,272 g, 50,2 %) como una película seca blanca.

RMN ^{1}H (500,13 MHz, DMSO-d6) δ 1,46 (9H, s), 2,89 - 2,90 (6H, m), 3,22 (4H, t), 3,52 (4H, t), 3,75 (6H, s), 6,18 (1H, d), 6,27 (1H, s), 6,34 (1H, t), 6,42 - 6,42 (2H, m), 7,72 (1H, d), 9,81 (1H, s), 11,71 (1H, s); MS: m/z 542 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,028 μM.

El 4-(5-(metoxicarbonil)tiofen-2-il)piperazin-1-carboxilato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota disolución 2,0M de (trimetilsilil)diazometano en éter (0,525 ml, 1,05 mmoles) a una disolución agitada de ácido 5-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]tiofen-2-carboxílico (0,312 g, 1 mmol) en metanol (2,000 ml), y la mezcla se agitó a temperatura ambiente durante 20 h. Se añadió más disolución 2,0M de

(trimetilsilil)diazometano en éter (0,500 ml, 1,00 mmoles), y la mezcla se agitó durante 2 h. La mezcla se evaporó, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 1 a 3% de EtOAc en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,141 g, 43,2 %) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,48 (9H, s), 3,22 (4H, t), 3,58 (4H, t), 3,82 (3H, s), 6,06 (1H, d), 7,55 (1H, d). MS: m/z 327 (MH+)

El ácido 5-[4-[(2-metilpropan-2-il)oxicarbonil]piperazin-1-il]tiofen-2-carboxílico usado como material de partida se puede preparar mediante el método descrito en la bibliografía (Stokes, Elaine Sophie Elizabeth; Waring, Michael James; Gibson, Keith Hopkinson. Preparation of amides as inhibitors of histone deacetilase. Documento WO2003/092686).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 103

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(1-metilpiperidin-4-il)benzamida

La N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(1-metilpiperidin-4-il)benzamida se preparó siguiendo el procedimiento como en el Ejemplo 159, pero partiendo de 4-(1-metilpiperidin-4-il)benzoato de metilo (0,25 g, 1,07 mmoles), 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,267 g, 1,07 mmoles) y trimetilaluminio 2M en tolueno (2,14 ml, 4,29 mmoles). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 8% de NH3 2,5M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad, se redisolvieron en DCM, se trituraron con éter y se evaporaron hasta sequedad para dar el compuesto del título (0,225 g, 46,5 %) como un sólido blanco. RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,69 (1H, d), 1,73 (2H, d), 1,77 (1H, s), 1,95 - 2,02 (2H, m), 2,21 (3H, s), 2,88 (2H, d), 3,76 (6H, s), 5,09 (2H, s), 5,62 (1H, s), 6,45 (1H, s), 6,60 (2H, s), 7,41 - 7,42 (2H, m), 7,89 - 7,91 (2H, m), 10,85 (1H, s), 11,58 (1H, s). MS: m/z 451 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00094 μM.

El 4-(1-metilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadieron agua (0,4 ml), paraformaldehído (0,742 g, 24,71 mmol) y ácido acético (1,415 ml, 24,71 mmol) a una suspensión agitada de cloruro de 4-piperidin-1-io-4-ilbenzoato de metilo (1,58 g, 6,18 mmoles) en THF (40 ml) en nitrógeno. Se añadió en porciones cianoborohidruro de sodio (0,582 g, 9,27 mmoles) durante un periodo de 10 min. La mezcla resultante se agitó a 60°C durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se mezcló con agua (30 ml) y HCl 1M (10 ml). La disolución se lavó con acetato de etilo (2 x 25 ml), se basificó con carbonato de potasio sólido y se extrajo con acetato de etilo (2 x 25 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre MgSO4, se filtró y se evaporó para dar 4-(1-metilpiperidin-4-il)benzoato de metilo puro (0,784 g, 54,4 %) como un aceite incoloro que solidificó al dejar reposar.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,62 - 1,71 (2H, m), 1,72 - 1,74 (2H, m), 1,95 - 2,02 (2H, m), 2,21 (3H, s), 2,54 - 2,59 (1H, m), 2,88 (2H, d), 3,85 (3H, s), 7,39 - 7,42 (2H, m), 7,88 - 7,91 (2H, m). MS: m/z 234 (MH+).

Ejemplo 104

4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida

La 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida se preparó siguiendo el procedimiento como en el Ejemplo 159, pero partiendo de 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)benzoato de metilo (0,25 g, 0,96 mmoles), 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,239 g, 0,96 mmoles) y trimetilaluminio 2M en tolueno (1,2 ml, 2,4 mmoles). El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,124 g, 27 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,37 - 1,44 (1H, m), 1,67 - 1,74 (2H, m), 1,83 - 1,89 (1H, m), 1,99 - 2,04 (1H, m), 2,08 (1H, q), 2,18 - 2,25 (1H, m), 2,82 - 2,89 (1H, m), 3,01 - 3,06 (2H, m), 3,75 (6H, s), 3,85 (1H, d), 3,99 - 4,02 (1H, m), 5,08 (2H, s), 5,57 (1H, s), 6,44 (1H,

s), 6,59 - 6,60 (2H, m), 7,04 (2H, d), 7,85 (2H, d), 10,61 (1H, s), 11,49 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0013 μM.

El 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadieron 4-yodobenzoato de metilo (2,076 g, 7,92 mmoles), carbonato de cesio (5,16 g, 15,85 mmoles), 2-acetilciclohexanona (0,209 ml, 1,58 mmoles) y yoduro de cobre (I) (0,075 g, 0,40 mmoles) a una disolución agitada de 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (1 g, 7,92 mmoles) en DMF (20 ml) en nitrógeno. La suspensión resultante se agitó a 90°C durante 20 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en una mezcla de metanol y agua. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 4-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)benzoato de metilo (1,243 g, 60,2 %) como una goma marrón.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,33 - 1,43 (1H, m), 1,57 - 1,79 (3H, m), 1,81 - 1,89 (1H, m), 1,99 - 2,03 (1H, m), 2,07 (1H, q), 2,16 - 2,23 (1H, m), 2,56 (1H, t), 2,83 - 2,95 (2H, m), 3,00 - 3,05 (2H, m), 3,06 - 3,09 (1H, m), 3,75 - 3,78 (3H, m), 3,86 (1H, t), 3,98 - 4,01 (1H, m), 6,98 - 7,02 (2H, m), 7,77 - 7,80 (2H, m). MS: m/z 261(MH+).

Ejemplo 105

5-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina (477 mg, 3,40 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (659 mg, 1,70 mmoles) en dimetilsulfóxido anhidro (1,70 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de ácido fórmico) y MeCN como eluyentes. La muestra se hizo pasar a través de un

sistema de HPLC básica, para obtener la base libre. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (395 mg, 47%) como un sólido de color crema.

RMN ^{1}H (500,133 MHz, DMSO) δ 1,19 - 1,35 (3H, m), 1,51 - 1,60 (1H, m), 1,64 (1H, t), 1,73 - 1,79 (1H, m), 1,93 - 2,08 (2H, m), 2,17 - 2,25 (1H, m), 2,73 (1H, dd), 2,81 - 2,93 (6H, m), 3,13 (1H, td), 3,73 (6H, s), 4,28 - 4,33 (1H, m), 4,37 - 4,42 (1H, m), 6,32 (1H, t), 6,38 - 6,41 (3H, m), 8,26 (1H, d), 8,70 (1H, d), 9,59 (1H, br s), 11,82 (1H, br s). MS: m/z 492 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing; IC_{50} 0,13 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida usada como material de partida se preparó según lo siguiente:

Se añadió gota a gota trimetilaluminio (2M en tolueno, 9,64 ml, 19,28 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (1,91 g, 7,71 mmoles) y 5-cloropirazin-2-carboxilato de metilo (1,33 g, 7,71 mmol) en tolueno anhidro (38,6 ml) a temperatura ambiente. La disolución resultante se agitó entonces en nitrógeno a temperatura ambiente durante 18 h. La reacción no estaba terminada, de forma que la temperatura se incrementó hasta 60°C y la mezcla de reacción se agitó otras 3 h. La mezcla de reacción se paralizó con metanol (10 ml) y HCl (disolución acuosa 2M). La mezcla se diluyó con EtOAc (100 ml) y agua (250 ml), y después se acidificó con HCl (disolución acuosa 2N). La capa orgánica se eliminó, y la acuosa se extrajo adicionalmente con EtOAc (2 x 100 ml). Los orgánicos combinados se lavaron con agua (200 ml), con salmuera (200 ml), se secaron sobre MgSO4 y se concentraron a presión reducida. Al concentrar, se formó un precipitado. El precipitado se recogió por filtración, se lavó con MeOH (10 ml) y se secó al aire para dar el compuesto deseado (1,88 g, 63%) como un sólido amarillo, que se usó sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,88 - 2,89 (4H, m), 3,73 (6H, s), 6,33 (1H, t), 6,43 (2H, d), 6,49 (1H, s), 8,93 (1H, s), 9,09 (1H, s), 10,44 (1H, s), 12,31 (1H, s). MS: m/z 388 (MH+).

Ejemplo 106

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 5-(4-metilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,254 g, 1 mmol) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1,00 mmoles) en tolueno (7,14 ml) a 20°C en nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 16 h, y después se calentó a 65°C durante 24 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y la capa acuosa se eliminó. La capa de acetato de etilo se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como un sólido amarillo. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,154 g, 33,8 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 2,32 (3H, d), 2,58 (4H, t), 2,88 (4H, s), 3,26 (4H, t), 3,73 (3H, s), 3,74 (3H, s), 6,13 (1H, d), 6,25 (1H, s), 6,32 (1H, d), 6,40 (2H, d), 7,68 - 7,69 (1H, m); MS: m/z 456 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,001 μM.

El 5-(4-metilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (0,225 g, 1,00 mmoles) a 5-bromotiofen-2-carboxilato de etilo (2,351 g, 10 mmoles), 1-metilpiperazina (1,331 ml, 12,00 mmoles), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,623 g, 1,00 mmoles) y carbonato de cesio (4,56 g, 14,00 mmoles) en tolueno (100 ml) a 20°C en nitrógeno. La suspensión resultante se agitó a 110°C durante 23 h. La mezcla se filtró a través de celita, y el filtrado se evaporó hasta sequedad para dar un aceite marrón. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar el producto bruto como una goma marrón. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 3% de metanol en

DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,380 g, 54,3 %) como un aceite naranja.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,33 (3H, t), 2,34 (3H, s), 2,54 (4H, t), 3,28 (4H, t), 4,28 (2H, q), 6,02 (1H, d), 7,55 (1H, d); MS: m/z 255 (MH+)

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 107

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-metilpiperazin-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 5-(4-metilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,254 g, 1 mmol) e hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,286 g, 1,00 mmoles) en tolueno (7,14 ml) a 20°C en nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 18 h, y después se calentó a 65°C durante 6 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y la capa acuosa se eliminó. La capa de acetato de etilo se lavó con salmuera saturada y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como un sólido amarillo. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,147 g, 32,1 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 2,29 (3H, s), 2,53 - 2,55 (4H, m), 3,25 - 3,28 (4H, m), 3,77 (6H, s), 5,09 (2H, s), 5,63 (1H, s), 6,16 (1H, d), 6,45 (1H, t), 6,60 (2H, d), 7,64 (1H, d); MS: m/z 458 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0011 μM.

El 5-(4-metilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó como se esquematiza en el Ejemplo 106.

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

Ejemplo 108

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3,3-dimetilpiperazin-1-il)pirazin-2-carboxamida

Se añadió de una vez 2,2-dimetilpiperazina (343 mg, 3,00 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (388 mg, 1 mmol) en dimetilsulfóxido anhidro (1,00 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (217 mg, 47%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,06 (6H, s), 2,04 (1H, s), 2,82 - 2,88 (6H, m), 3,51 (2H, s), 3,65 (2H, t), 3,72 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,32 (1H, s), 8,66 (1H, s), 9,71 (1H, s), 12,17 (1H, s). MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,002 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 109

5-(4-Ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (390 mg, 1,00 mmoles) a 1-ciclopropilpiperazina, 2HCl (398 mg, 2,00 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,52 ml, 3,00 mmoles) en dimetilsulfóxido anhidro (1,00 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El

producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en DCM. Las fracciones que contienen producto deseado se evaporaron hasta sequedad para dar un sólido amarillo. El sólido se recogió en DCM y se trituró con Et_2O para dar un sólido que se recogió por filtración y se secó a vacío para dar el compuesto del título (130 mg, 27%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,38 - 0,40 (2H, m), 0,45 - 0,49 (2H, m), 1,66 - 1,70 (1H, m), 2,66 (4H, t), 3,71 (4H, t), 3,75 (6H, s), 5,08 (2H, s), 5,84 (1H, s), 6,45 (1H, s), 6,59 (2H, s), 8,33 (1H, s), 8,72 (1H, s), 10,80 (1H, s), 11,35 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,003 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida usada como material de partida se preparó según lo siguiente:

Se añadió gota a gota trimetilaluminio (2M en tolueno, 7,44 ml, 14,88 mmoles) a una suspensión agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (1,70 g, 5,95 mmoles) y 5-cloropirazin-2-carboxilato de metilo (1,03 g, 5,95 mmoles) en tolueno anhidro (29,8 ml) a temperatura ambiente. La disolución resultante se agitó entonces en nitrógeno a temperatura ambiente durante 18 h. La mezcla de reacción se paralizó con metanol (5 ml) y HCl (disolución acuosa 2M), se diluyó con agua (200 ml) y se extrajo con EtOAc (3 x 150 ml). Los orgánicos se lavaron con agua (200 ml), con salmuera (200 ml), se secaron sobre MgSO4, se filtraron y se concentraron. Al evaporar, se formó un precipitado que se recogió por filtración, se lavó con MeOH (20 ml) y se secó al aire para dar el compuesto deseado (1,65 g, 71%) como un sólido naranja, que se usó sin purificación adicional.

RMN ^{1}H (500,13 MHz, DMSO-d6, 373K) δ 3,78 (6H, s), 5,12 (2H, s), 5,94 (1H, s), 6,46 (1H, s), 6,62 (2H, s), 8,87 (1H, s), 9,09 (1H, s), 10,99 (1H, s), 11,24 (1H, s). MS: m/z 390 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,060 μM.

Ejemplo 110

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]benzamida

La N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]benzamida se preparó siguiendo el procedimiento para el Ejemplo 100, pero partiendo de 4-

((3R,5S)-3,4,5-trimetilpiperazin-1-il)benzoato de etilo (0,276 g, 1,00 mmoles) y 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,249 g, 1 mmol) y una disolución 2M de trimetilaluminio en tolueno (1,25 ml, 2,5 mmoles). El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,027 g, 5,63 %) como un sólido blanco.

RMN ^{1}H (500,133 MHz, DMSO-d6 + CD3COOD) δ: 1,13 (6H, d), 2,31 (3H, s), 2,60 - 2,68 (2H, m), 3,19 (2H, s), 3,70 (1H, s), 3,65 (6H, s), 5,08 (2H, s), 5,68 (1H, s), 6,40 - 6,44 (1H, m), 6,58 (2H, s), 6,97 (2H, d), 7,82 (2H, d). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00068 μM.

El 4-((3R,5S)-3,4,5-trimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió isopropóxido de titanio (IV) (2,99 ml, 10,00 mmoles) a 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo (1,312 g, 5,00 mmoles) y formaldehído (0,601 g, 20,00 mmoles) en etanol (25 ml) calentado hasta 60°C durante un periodo de 45 min en nitrógeno. La disolución resultante se enfrió hasta 20°C, y se añadió de una vez borohidruro de sodio (0,473 g, 12,50 mmoles) y la suspensión se agitó a 60°C durante 18 h. La reacción se paralizó con amoníaco (2 ml). El sólido se separó por filtración y se lavó con 10% de MeOH en DCM (2 x 50 ml). La capa orgánica se evaporó hasta sequedad, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM que contiene 0,1% de amoníaco. Las fracciones se evaporaron hasta sequedad para dar un aceite. Éste se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto deseado (0,320 g, 23,16 %) como un sólido blanco cristalino.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,11 (6H, d), 1,29 (3H, t), 2,24 (3H, s), 2,25 - 2,30 (2H, m), 2,59 (1H, d), 2,62 (1H, d), 3,53 - 3,57 (2H, m), 4,26 (2H, q), 6,75 - 6,79 (2H, m), 7,82 - 7,86 (2H, m). MS: m/z 277 (MH+).

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, usada como material de partida, se preparó como en el Ejemplo 100.

Ejemplo 111

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(3,3-dimetilpiperazin-1-il)benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (0,691 ml, 1,38 mmoles) a una disolución agitada de 4-(3,3-dimetilpiperazin-1-il)benzoato de etilo (145 mg, 0,55 mmoles) y 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (138 mg, 0,55 mmoles) en tolueno (5 ml) a 20°C, durante un periodo de 5 min en nitrógeno. La disolución resultante se agitó a 20°C durante 24 h. Ésta se diluyó con acetona (25 ml) y se añadió un exceso de sulfito de sodio sólido húmedo. La mezcla se agitó durante 1 h, y el sólido se separó por filtración. El sólido se lavó con 10% de MeOH/DCM y los orgánicos combinados se evaporaron hasta sequedad. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (27,0 mg, 10,49 %) como una goma incolora.

RMN ^{1}H (500,13 MHz, DMSO-d6 a 373K) δ: 1,11 (6H, s), 2,85-2,91 (2H, m), 3,03 (2H, s), 3,18 - 3,22 (2H, m), 3,78 (6H, s), 5,09 (2H, s), 5,62 (1H, s), 6,44 (1H, t), 6,60 (2H, s), 6,92 (2H, d), 7,82 (2H, d), 10,19 (1H, s), 11,12 (1H, s). MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00076 μM.

El 4-(3,3-dimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se disolvieron 4-fluorobenzoato de etilo (0,151 ml, 1 mmol), 2,2-dimetilpiperazina (0,137 g, 1,20 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,349 ml, 2,00 mmoles) en DMA (2 ml), y se encerraron en un tubo de microondas. La reacción se calentó hasta 200°C durante 4 h en el reactor de microondas, y se enfrió hasta la temperatura ambiente. La mezcla bruta se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando amoníaco 3,5M en metanol, las fracciones se evaporaron hasta sequedad para dar un aceite. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% amoníaco 2M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(3,3-

dimetilpiperazin-1-il)benzoato de etilo (0,145 g, 55,3 %) como un sólido blanco. RMN ^{1}H (399,9 MHz, CDCl3) δ 1,15 (6H, d), 1,37 (3H, t), 2,38 (1H, d), 2,41 (1H, d), 2,96 - 3,04 (2H, m), 3,65 - 3,69 (2H, m), 4,33 (2H, q), 6,84 - 6,87 (2H, m), 7,89 - 7,93 (2H, m). MS: m/z 266 (MH+).

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, usada como material de partida, se preparó como en el Ejemplo 100.

Ejemplo 112

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-[(3R,5S)-3,5-dimetilpiperazin-1-il]pirazin-2-carboxamida

Se añadió de una vez (2S,6R)-2,6-dimetilpiperazina (228 mg, 2,00 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (388 mg, 1,00 mmoles) en dimetilsulfóxido anhidro (1,00 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (164 mg, 35%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,05 - 1,06 (6H, d), 2,43 - 2,50 (2H, m), 2,72 - 2,78 (2H, m), 2,88 (4H, s), 3,72 (6H, s), 4,39 (2H, d), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,34 (1H, d), 8,69 (1H, d), 9,73 (1H, s), 12,18 (1H, s), no NH observed. MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0017 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 113

5-(4-Ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (388 mg, 1,00 mmoles) a 1-ciclopropilpiperazina, 2HCl (398 mg, 2,00 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,52 ml, 3,00 mmoles) en dimetilsulfóxido anhidro (1,00 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (45 mg, 9%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,39 (2H, t), 0,46 - 0,48 (2H, m), 1,67 - 1,70 (1H, m), 2,66 (4H, q), 2,88 (4H, s), 3,69 - 3,72 (4H, m), 3,72 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,35 (1H, d), 8,71 (1H, d), 9,76 (1H, s), 12,18 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0023 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 114

5-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (429 mg, 3,40 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (659 mg, 1,70 mmoles) en dimetilsulfóxido anhidro (1,70 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de TFA) y MeCN como eluyentes. El material se hizo pasar a través de HPLC básica para obtener la base libre. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (438 mg, 54%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,35 - 1,45 (1H, m), 1,63 - 1,80 (2H, m), 1,82 - 1,91 (1H, m), 1,93 - 2,01 (1H, m), 2,09 (1H, q), 2,16 - 2,20 (1H, m), 2,70 - 2,76 (1H, m), 2,88 (4H, s), 3,04 - 3,11 (3H, m), 3,72 (6H, s), 4,47 (1H, d), 4,63 (1H, d), 6,33 (1H, t), 6,42 (2H, d), 6,47 (1H, s), 8,36 (1H, d), 8,71 (1H, d), 9,76 (1H, s), 12,18 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0016 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 115

5-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (585 mg, 1,50 mmoles) a 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina, HCl (530 mg, 3,00 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (1,04 ml, 6,00 mmoles) en dimetilsulfóxido anhidro (1,50 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (302 mg, 41 %) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,21 - 1,29 (2H, m), 1,49 - 1,67 (1H, m), 1,60 - 1,64 (2H, m), 1,74 (1H, d), 1,90 (1H, t), 1,93 - 2,00 (1H, m), 2,10 - 2,17 (1H, m), 2,67 - 2,73 (1H, m), 2,82 (2H, d), 3,06 - 3,13 (1H, m), 3,75 (6H, s), 4,38 (1H, d), 4,46 (1H, d), 5,08 (2H, s), 5,84 (1H, s), 6,44 (1H, s), 6,59 (2H, d), 8,34 (1H, s), 8,71 (1H, s), 10,79 (1H, s), 11,35 (1H, s). MS: m/z 494 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0023 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se esquematiza en el Ejemplo 109.

Ejemplo 116

4-(4-ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida

La 4-(4-ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-benzamida se preparó siguiendo el procedimiento según se esquematiza para el Ejemplo 100, partiendo de 4-(4-ciclopropilpiperazin-1-il)benzoato de etilo (0,329 g, 1,2 mmoles), hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,343 g, 1,20 mmoles) y trimetilaluminio 2M en tolueno (1,500 ml, 3,00 mmoles). El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,022 g, 3,84 %) como un sólido blanco. RMN ^{1}H (500,13 MHz, DMSOd6) δ 0,34 - 0,40 (2H, m), 0,45 - 0,50 (2H, m), 1,67 - 1,75 (1H, m), 2,67 - 2,73 (4H, m), 3,24 - 3,32 (4H, m), 3,78 (6H, s), 5,08 (2H, s), 5,68 (1H, s), 6,42 - 6,46 (1H, m), 6,58 - 6,61 (2H, m), 6,95 (2H, d), 7,83 (2H, d), 10,30 (1H, s), 11,01 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00093 μM.

El 4-(4-ciclopropilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó siguiendo el procedimiento como se esquematiza para 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo (Ejemplo 100), partiendo de 4-fluorobenzoato de etilo (0,880 ml, 6 mmoles) y 1-ciclopropilpiperazina (1,666 g, 13,20 mmoles) en DMSO (15 ml) El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 8% de amoníaco 2,5M / MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,405 g, 85 %) como un sólido beige.

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,43 - 0,52 (4H, m), 1,34 - 1,39 (3H, m), 1,63 - 1,68 (1H, m), 2,75 (4H, t), 3,29 (4H, t), 4,32 (2H, q), 6,84 - 6,88 (2H, m), 7,90 - 7,97 (2H, m). MS: m/z 275 (MH+).

La 1-ciclopropilpiperazina usada como material de partida se preparó según lo siguiente:

Se disolvió dihidrocloruro de 1-ciclopropilpiperazina (1,493 g, 7,5 mmoles) en agua (5,00 ml) y metanol (5,00 ml), y se convirtió en su base libre mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando 3,5M

amoníaco en metanol, y las fracciones puras se evaporaron hasta sequedad para dar 1-ciclopropilpiperazina (0,796 g, 84 %) como un aceite.

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,31 - 0,39 (4H, m), 1,51 - 1,56 (1H, m), 1,63 - 1,67 (1H, m), 2,51 (4H, s), 2,77 (4H, t).

El dihidrocloruro de 1-ciclopropilpiperazina se preparó según lo siguiente:

Se añadió HCl 4,0M en dioxano (42,7 ml, 170,78 mmoles) a una disolución agitada de 4-ciclopropilpiperazin-1-carboxilato de terc-butilo (7,73 g, 34,16 mmoles) en una mezcla de metanol (50,0 ml) y acetato de etilo (200 ml). La suspensión resultante se agitó a temperatura ambiente durante 24 h en nitrógeno. El sólido blanco se separó por filtración para dar dihidrocloruro de 1-ciclopropilpiperazina (6,30 g, 93 %).

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,73 - 0,86 (2H, m), 1,07 - 1,18 (2H, m), 2,85 - 2,99 (1H, m), 3,30 - 3,40 (4H, m), 3,52 - 3,65 (4H, m), 9,89 (2H, s), 11,99 (1H, s).

El 4-ciclopropilpiperazin-1-carboxilato *terc*-butilo se preparó según lo siguiente:

Una disolución de piperazin-1-carboxilato de terc-butilo (9,31 g, 50 mmoles), [(1-etoxiciclopropil)oxi]trimetilsilano (20,11 ml, 100,00 mmoles) y ácido acético (14,31 ml, 250,00 mmoles) en tetrahidrofurano (100 ml), metanol (10 ml) se trató con cianoborohidruro de sodio (4,71 g, 75,00 mmoles) a 20°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción se enfrió, se filtró y se evaporó hasta sequedad. Se añadieron HCl 1N (40 ml) y agua (60 ml), y la disolución se extrajo con acetato de etilo (3 x 50 ml). La capa acuosa se basificó hasta pH 10 con carbonato de potasio sólido, y se extrajo con acetato de etilo (4 x 50 ml). Los extractos orgánicos se lavaron con disolución saturada de cloruro de sodio (50 ml) y se secaron sobre $MgSO_4$, se filtraron y se evaporaron hasta sequedad para dar 4-ciclopropilpiperazin-1-carboxilato de terc-butilo (7,73 g, 68,3 %) como un sólido ceroso blanco.

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,33 - 0,40 (4H, m), 1,39 (9H, s), 1,52 - 1,55 (1H, m), 2,48 (4H, t), 3,31 (4H, t).

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

Ejemplo 117

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metil-4-oxidopiperazin-4-io-1-il)benzamida

Se añadió de una vez ácido 3-cloroperoxibenzoico (129 mg, 0,53 mmoles) a N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida (225 mg, 0,50 mmoles) en acetona (15 ml) a temperatura ambiente. La disolución resultante se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró sobre sílice, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en DCM hasta metanol 100%. El residuo se purificó adicionalmente mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar el compuesto del título (183 mg, 79%) como un sólido de color crema.

RMN ^{1}H (700,034 MHz, DMSO) δ 2,85 (4H, s), 2,94 (2H, d), 3,09 (3H, s), 3,44 (2H, td), 3,53 (2H, td), 3,65 (2H, d), 3,70 (6H, s), 6,31 (1H, t), 6,37 (1H, s), 6,40 (2H, d), 7,00 (2H, d), 7,90 (2H, d), 10,37 (1H, s), 12,00 (1H, s). MS: m/z 466 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0013 μM.

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida se preparó como se esquematiza en el Ejemplo 10.

Ejemplo 118

4-(4-Ciclobutilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida

La 4-(4-ciclobutilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida se preparó siguiendo el procedimiento como se esquematiza para el Ejemplo 100, partiendo de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,173 g, 0,69 mmoles), 4-(4-ciclobutilpiperazin-1-il)benzoato de etilo (0,2 g, 0,69 mmoles) y una disolución 2M de trimetilaluminio en tolueno (1,387 ml, 2,77 mmoles) en tolueno (10 ml) a temperatura ambiente durante 20 h. La mezcla de reacción se vertió en acetona (20 ml), se paralizó con exceso de sulfito de sodio húmedo, se filtró y se evaporó para dar un sólido amarillo. Se añadió acetonitrilo (10 ml), y éste se filtró para dar el compuesto del título (0,079 g, 23,17 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,63 - 1,66 (1H, m), 1,67 - 1,70 (1H, m), 1,78 - 1,89 (2H, m), 1,97 - 2,03 (2H, m), 2,38 (4H, t), 2,75 (1H, t), 3,75 (6H, s), 5,08 (2H, s), 5,58 (1H, s), 6,45 (1H, s), 6,60 - 6,60 (2H, m), 7,01 (2H, d), 7,86 (2H, d), 10,61 (1H, s), 11,49 (1H, s). MS: m/z 492 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0011 μM.

El 4-(4-ciclobutilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió 4-fluorobenzoato de etilo (0,753 g, 4,48 mmoles) a una disolución de 1-ciclobutilpiperazina (0,571 g, 4,07 mmoles) y carbonato de potasio (0,563 g, 4,07 mmoles) en DMSO (8 ml) en nitrógeno. La disolución resultante se agitó a 100°C durante 18 h, y se evaporó hasta sequedad. El residuo se trituró con éter dietílico, se filtró, y se evaporó, y el producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 2,5% de MeOH 2,5N en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-ciclobutilpiperazin-1-il)benzoato de etilo (0,387 g, 32,9 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,28 - 1,32 (3H, t), 1,62 -1,70 (2H, m), 1,77 - 1,88 (2H, m), 1,95 - 2,04 (2H, m), 2,35 - 2,39 (4H, t), 2,70 - 2,78 (1H, m), 3,28 - 3,32 (4H, t), 4,22 - 4,27 (2H, m), 6,96 - 6,98 (2H, d), 7,66 - 7,80 (2H, d). MS: m/z 289 (MH+).

La 1-ciclobutilpiperazina usada como material de partida se preparó según lo siguiente:

Se añadieron agua (0,15 ml), ciclobutanona (1 g, 14,27 mmoles) y ácido acético (1,742 ml, 30,44 mmoles) a una disolución agitada de piperazin-1-carboxilato de terc-butilo (1,772 g, 9,51 mmol) en THF (20 ml) en nitrógeno. Se añadió en porciones cianoborohidruro de sodio (0,897 g, 14,27 mmoles) durante un periodo de 10 min. La mezcla resultante se agitó a 60°C durante 20 h. La mezcla de reacción se evaporó hasta sequedad y se mezcló con agua (40 ml) y HCl 1M (15 ml). La disolución se lavó con EtOAc (2 x 25 ml), se basificó con K_2CO_3 sólido, y se extrajo con EtOAc (2 x 15 ml). La capa orgánica se lavó con salmuera saturada y se secó sobre MgSO4, se filtró y se evaporó para dar 4-ciclobutilpiperazin-1-carboxilato de terc-butilo puro (1,155 g, 50,5 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,40 (9H, s), 1,62 - 1,65 (2H, m), 1,75 - 1,80 (2H, m), 1,92 - 1,98 (2H, m), 2,17 (4H, t), 2,68 (1H, t), 3,28 - 3,30 (4H, s).

Una disolución de 4-ciclobutilpiperazin-1-carboxilato de terc-butilo (1,1553 g, 4,81 mmoles) en acetato de etilo (10 ml) y metanol (10,00 ml) se trató con una disolución 4M de cloruro de hidrógeno en dioxano (1,669 ml, 48,07 mmoles) y se agitó a temperatura ambiente durante 40 h en nitrógeno. La reacción no estaba terminada, de forma que se añadió más disolución 4M de cloruro de hidrógeno en dioxano (10 ml), y la disolución se agitó a temperatura ambiente durante otras 2 h. La mezcla de reacción se evaporó hasta sequedad para dar un sólido. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 1-ciclobutilpiperazina (0,571 g, 85 %) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,64 (2H, s), 1,74 - 1,75 (2H, m), 1,92 (2H, s), 2,14 (4H, s), 2,63 - 2,66 (4H, m), 3,18 (1H, s).

Ejemplo 119

2-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 2,15 ml, 4,30 mmoles) a una suspensión agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (491 mg, 1,72 mmoles) y 2-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo (475 mg, 1,72 mmoles) en tolueno (8,6 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después a 60°C durante 2 h. La mezcla de reacción se paralizó con cuidado con metanol (20 ml) y se trató con HCl (disolución acuosa 2N, hasta que se obtuvo una disolución libremente agitada). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto bruto. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (361 mg, 43%) como un sólido.

RMN ^{1}H (500,13 MHz, DMSO-d6, 373K) δ 1,21 - 1,27 (1H, m), 1,28 - 1,35 (1H, m), 1,52 - 1,59 (1H, m), 1,59 - 1,64 (2H, m), 1,76 (1H, d), 1,85 - 1,91 (1H, m), 1,98 - 2,03 (1H, m), 2,10 - 2,15 (1H, m), 2,68 - 2,73 (1H, m), 2,80 - 2,84 (2H, m), 3,08 - 3,13 (1H, m), 3,78 (6H, s),

4,57 - 4,61 (1H, m), 4,67 - 4,71 (1H, m), 5,11 (2H, s), 5,70 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 8,86 (2H, s), 10,30 (1H, s), 11,30 (1H, s). MS: m/z 494 (MH+).
Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0033 μM.

El 2-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo se preparó como se esquematiza en el Ejemplo 127.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

Ejemplo 120

5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,525 ml, 3,05 mmoles) en tolueno a una disolución agitada de 5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)tiofen-2-carboxilato de etilo (0,342 g, 1,22 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,302 g, 1,22 mmoles) en tolueno (8,71 ml) a 20°C en nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 18 h, y después se agitó y se calentó a 65°C durante 20 h. Se añadió con cuidado acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y la capa acuosa se eliminó. La capa de acetato de etilo se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como una goma amarilla, 640 mg. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de TFA) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar la sal de TFA del producto. Éste se disolvió en metanol y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad y después se trituraron con acetonitrilo para dar el compuesto del título (0,174 g, 29,6 %) como un sólido.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 1,41 - 1,43 (1H, m), 1,73 - 1,78 (2H, m), 1,87 - 1,91 (2H, m), 2,16 - 2,23 (2H, m), 2,34 - 2,38 (1H, m), 2,68 - 2,72 (1H, m), 2,89 (4H, s), 3,00 - 3,08 (3H, m), 3,50 - 3,53 (1H, m), 3,66 - 3,69 (1H, m), 3,74 (6H, d), 6,12 (1H, d), 6,25 (1H, s), 6,33 (1H, t), 6,41 (2H, d), 7,70 (1H, t); MS: m/z 482 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00098 μM.

El 5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (0,112 g, 0,50 mmoles) a 5-bromotiofen-2-carboxilato de etilo (1,175 g, 5 mmoles), 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (0,631 g, 5,00 mmoles), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,311 g, 0,50 mmoles) y carbonato de cesio (2,281 g, 7,00 mmoles) en tolueno (50,0 ml) a 20°C en nitrógeno. La suspensión resultante se agitó a 110°C durante 23 h. La mezcla se filtró a través de celita, haciéndola pasar mediante lavado con acetato de etilo, y el filtrado se evaporó hasta sequedad para dar un aceite marrón. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El material bruto se disolvió en metanol y después se aplicó a la columna. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad para dar el producto bruto como un sólido marrón. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 4% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,727 g, 51,9 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,33 (3H, t), 1,43 - 1,53 (1H, m), 1,63 (1H, s), 1,73 - 1,93 (3H, m), 2,10 - 2,22 (2H, m), 2,33 - 2,40 (1H, m), 2,74 (1H, t), 3,07 - 3,16 (3H, m), 3,51 - 3,55 (1H, m), 3,67 - 3,71 (1H, m), 4,28 (2H, q), 6,01 (1H, d), 7,55 (1H, d)

MS: m/z 281 (MH+)

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 121

5-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,525 ml, 3,05 mmoles) en tolueno a una disolución agitada de 5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)tiofen-2-carboxilato de etilo (0,342 g, 1,22 mmoles) y 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,304 g, 1,22 mmoles) en tolueno (8,71 ml) a 20°C en nitrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 18 h, y después se calentó a 65°C durante 6 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y se eliminó la capa acuosa. La capa de acetato de etilo se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como una goma amarilla. El producto bruto se purificó mediante LCMS preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de TFA) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar la sal de TFA del producto. Ésta se disolvió en metanol, y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad y después se trituraron con etanol para dar el compuesto del título (0,266 g, 45,1 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 1,40 - 1,44 (1H, m), 1,72 - 1,80 (2H, m), 1,85 - 1,90 (2H, m), 2,17 - 2,22 (2H, m), 2,34 - 2,39 (1H, m), 2,73 (1H, t), 3,03 - 3,09 (3H, m), 3,52 - 3,54 (1H, m), 3,67 - 3,70 (1H, m), 3,77 (6H, s), 5,09 (2H, s), 5,62 (1H, s), 6,16 (1H, d), 6,45 (1H, t), 6,60 (2H, d), 7,64 (1H, d); MS: m/z 484 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00079 μM.

El 5-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)tiofen-2-carboxilato de etilo se preparó como se esquematiza en el Ejemplo 120.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, usada como material de partida, se preparó como en el Ejemplo 100.

Ejemplo 122

5-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (585 mg, 1,50 mmoles) a 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (379 mg, 3,00 mmoles) en dimetilsulfóxido anhidro (1,50 ml) a 25°C. La disolución resultante se agitó a 100°C durante 18 h. El residuo se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar producto impuro como un sólido amarillo. El material impuro se repurificó entonces mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (269 mg, 37 %) como un sólido amarillo.

RMN ^{1}H (500,133 MHz, DMSO, 373K) δ 1,38 - 1,46 (1H, m), 1,67 - 1,82 (2H, m), 1,85 - 1,91 (1H, m), 2,04 - 2,10 (1H, m), 2,17 (1H, q), 2,22 - 2,29 (1H, m), 2,78 (1H, dd), 3,02 - 3,16 (3H, m), 3,76 (6H, s), 4,41 (1H, d), 4,57 (1H, d), 5,09 (2H, s), 5,85 (1H, s), 6,44 (1H, s), 6,59 (2H, d), 8,26 (1H, d), 8,71 (1H, s), 10,42 (1H, s), 11,13 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0013 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 109.

Ejemplo 123

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (388 mg, 1,00 mmoles) a 1,2-dimetil-piperazina (228 mg, 2,00 mmoles) en dimetilsulfóxido anhidro (2,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. El residuo se purificó mediante cromatografía de intercambio iónico,

usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (375 mg, 81%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,07 - 1,09 (3H, d), 2,06 - 2,20 (2H, m), 2,23 (3H, s), 2,76 - 2,86 (2H, m), 2,87 (4H, s), 3,13 - 3,19 (1H, m), 3,72 (6H, s), 4,27 - 4,30 (2H, m), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,35 (1H, d), 8,70 (1H, d), 9,75 (1H, s), 12,18 (1H, s). MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0022 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 124

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,4-dimetilpiperazin-1-il)pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (390 mg, 1,00 mmoles) a 1,2-dimetil-piperazina (228 mg, 2,00 mmoles) en dimetilsulfóxido anhidro (2,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. El residuo se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (392 mg, 84%) como un sólido amarillo.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,08 (3H, d), 2,06 - 2,12 (1H, m), 2,18 (1H, td), 2,23 (3H, s), 2,77 - 2,88 (2H, m), 3,14 - 3,21 (1H, m), 3,75 (6H, s), 4,32 (2H, t), 5,08 (2H, s), 5,84 (1H, s), 6,44 (1H, t), 6,59 (2H, d), 8,34 (1H, s), 8,71 (1H, s), 10,79 (1H, s), 11,35 (1H, s). MS: m/z 468 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0015 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se esquematiza en el Ejemplo 109.

Ejemplo 125

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (271 mg, 0,70 mmoles) a una mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo (180 mg, 1,40 mmoles) en dimetilsulfóxido anhidro (1,40 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. La reacción no estaba terminada, y se añadió N-etil-N-propan-2-ilpropan-2-amina (0,24 ml, 1,40 mmoles) y la disolución se agitó a 60°C durante otras 2 h. La mezcla de reacción se diluyó con metanol (20 ml) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (246 mg, 73%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,10 - 1,12 (6H, d), 2,15 - 2,21 (2H, m), 2,20 (3H, s), 2,75 (2H, t), 2,88 (4H, s), 3,72 (6H, s), 4,37 (2H, d), 6,33 (1H, s), 6,42 - 6,43 (2H, m), 6,46 (1H, s), 8,37 (1H, s), 8,70 (1H, s), 9,75 (1H, s), 12,18 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0017μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

La mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo usada como material de partida se preparó según lo siguiente;

Se añadió metilpoliestirencianoborohidruro de trietilamonio macroporoso (2,31 mmoles/g, 5,05 g, 11,67 mmoles) a éster *terc*-butílico del ácido cis-3,5-dimetil-piperazin-1-carboxílico (1,00 g, 4,67 mmoles), formaldehído acuoso al 37% (6,99 ml, 93,33 mmoles) y ácido acético (0,53 ml, 9,33 mmoles) en metanol (9,33 ml) a 25°C. La suspensión resultante se agitó en

nitrógeno a temperatura ambiente durante 24 h. El metilpoliestirencianoborohidruro de trietilamonio macroporoso se eliminó por filtración, lavando con metanol (50 ml). El filtrado se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad. El residuo se recogió en acetato de etilo (21,00 ml) y metanol (10,00 ml), y se trató con cloruro de hidrógeno (4M en 1,4-dioxano, 4,21 ml, 16,84 mmoles) a 25°C en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 3 días. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar una mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo (645 mg, cuant.) como un aceite incoloro. Éste se usó directamente sin purificación adicional.

Ejemplo 126

2-(4-Ciclopropilpiperazin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,92 ml, 3,85 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (381 mg, 1,54 mmoles) y 2-(4-ciclopropilpiperazin-1-il)pirimidin-5-carboxilato de metilo (404 mg, 1,54 mmoles) en tolueno (7,7 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después se calentó a 60 °C durante 2 h. La mezcla de reacción se paralizó con metanol (20 ml), y se trató con HCl (disolución acuosa 2N). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (100 mg, 14%) como un sólido.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,36 - 0,41 (2H, m), 0,45 - 0,47 (2H, m), 1,65 - 1,68 (1H, m), 2,61 (4H, t), 2,88 (4H, s), 3,72 (6H, s), 3,80 (4H, t), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,90 (2H, s), 10,60 (1H, s), 12,14 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0036 μM.

El 2-(4-ciclopropilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente;

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (900 mg, 5,22 mmoles) en diclorometano (7,50 ml) a una suspensión agitada de 1-ciclopropilpiperazina, 2HCl (1038 mg, 5,22 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (4,10 ml, 23,47 mmoles) en diclorometano (13 ml) a temperatura ambiente en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió sobre hielo (100 ml), se extrajo con diclorometano (3 x 75 ml), la capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar un sólido blanco. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (880 mg, 64%) como un sólido blanco. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,36 - 0,39 (2H, m), 0,45 - 0,47 (2H, m), 1,65 - 1,68 (1H, m), 2,61 (4H, t), 3,81 (3H, s), 3,81-3,84 (4H, t), 8,79 (2H, s). MS: m/z 263 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 127

2-(1,3,4,6,7,8,9,9a-Octahidropirido[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,45 ml, 2,90 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (286 mg, 1,16 mmoles) y 2-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo (320 mg, 1,16 mmoles) en tolueno (5,8 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después a 60°C durante 2 h. La mezcla de reacción se paralizó con metanol (20 ml) y se trató con HCl (disolución acuosa 2N, hasta que se obtuvo una disolución libremente agitada). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material

impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (238 mg, 42%) como un sólido.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,14 - 1,32 (2H, m), 1,46 - 1,55 (1H, m), 1,61 (2H, d), 1,73 (1H, d), 1,80 - 1,83 (1H, m), 1,92 - 1,99 (1H, m), 2,03 - 2,10 (1H, m), 2,64 - 2,70 (1H, m), 2,79 (2H, d), 2,88 (4H, s), 3,02 - 3,09 (1H, m), 3,72 (6H, s), 4,55 - 4,59 (1H, m), 4,65 - 4,68 (1H, m), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,89 (2H, s), 10,59 (1H, s), 12,15 (1H, s). MS: m/z 492 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0029 μM.

El 2-(1,3,4,6,7,8,9,9a-octahidropirido[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente;

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (900 mg, 5,22 mmoles) en diclorometano (7,50 ml) a una suspensión agitada de 2,3,4,6,7,8,9,9a-octahidro-1H-pirido[1,2-a]pirazina, HCl (1106 mg, 6,26 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (3,19 ml, 18,25 mmoles) en diclorometano (13,00 ml) a temperatura ambiente en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió sobre hielo (50 ml), se extrajo con DCM (3 x 50 ml), la capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar un sólido amarillo. El producto bruto se purificó mediante cristalización en IPA para dar el compuesto del título (591 mg, 41%) como un sólido blanco. El filtrado aún contenía algo de producto y se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar una muestra adicional del compuesto del título (402 mg, 28%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,14 - 1,30 (2H, m), 1,46 - 1,55 (1H, m), 1,61 (2H, d), 1,72 (1H, d), 1,81 (1H, t), 1,95 (1H, m), 2,06 (1H, m), 2,67 - 2,70 (1H, m), 2,80 (2H, d), 3,05 - 3,12 (1H, m), 3,81 (3H, s), 4,59 (1H, m), 4,68 (1H, d), 8,79 (2H, s). MS: m/z 277 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 128

2-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 2,55 ml, 5,10 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (504 mg, 2,04 mmoles) y 2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo (535 mg, 2,04 mmoles) en tolueno (10,20 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después a 60°C durante 2 h. La mezcla de reacción se paralizó con metanol (20 ml) y se trató con HCl (disolución acuosa 2N, hasta que se obtuvo una disolución libremente agitada). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (288 mg, 30%) como un sólido.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,36 - 1,40 (1H, m), 1,68 - 1,75 (2H, m), 1,83 - 1,90 (2H, m), 2,07 (2H, q), 2,67 - 2,72 (1H, m), 2,88 (4H, s), 3,01 - 3,08 (3H, m), 3,72 (6H, s), 4,71 - 4,75 (1H, m), 4,87 (1H, d), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,90 (2H, s), 10,59 (1H, s), 12,15 (1H, s). MS: m/z 478 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,003 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente;

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (1,56 g, 9,04 mmoles) en diclorometano (7,50 ml) a una suspensión agitada de 1,2,3,4,6,7,8,8a-octahidropirrolo[1,2-a]pirazina (1,37 g, 10,85 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (3,95 ml, 22,60 mmoles) en diclorometano (22,60 ml) a temperatura ambiente en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió sobre

hielo (100 ml), se extrajo con diclorometano (3 x 100 ml), la capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar un sólido amarillo. La capa acuosa se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto bruto. El producto bruto combinado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,36 g, 57%) como un sólido amarillo.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,33 - 1,44 (1H, m), 1,63 - 1,78 (2H, m), 1,80 - 1,93 (2H, m), 2,04 - 2,11 (2H, m), 2,72 (1H, dd), 3,00 - 3,09 (3H, m), 3,81 (3H, s), 4,74 (1H, d), 4,88 (1H, d), 8,79 (2H, s). MS: m/z 263 (MH+).

Ejemplo 129

5-[(3R,5S)-4-(cianometil)-3,5-dimetilpiperazin-1-il]-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (271 mg, 0,70 mmoles) a una mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo (180 mg, 1,40 mmoles) en dimetilsulfóxido anhidro (1,40 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. La reacción no estaba terminada y se añadió N-etil-N-propan-2-ilpropan-2-amina (0,24 ml, 1,40 mmoles), y la disolución se agitó a 60°C otras 2 h. La mezcla de reacción se diluyó con metanol (20 ml) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (77 mg, 22%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,22 (6H, d), 2,71 - 2,79 (2H, m), 2,84 (1H, d), 2,87 (1H, d), 2,90 - 3,00 (4H, m), 3,77 (6H, s), 3,83 (2H, s), 4,32 - 4,35 (2H, m), 6,33 (1H, t), 6,36 (2H, d), 6,55 (1H, s), 8,01 (1H, d), 8,92 (1H, d), 9,73 (1H, s), One NH not observed. MS: m/z 505 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0035 μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 130

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (273 mg, 0,70 mmoles) a una mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo (180 mg, 1,40 mmoles) en dimetilsulfóxido anhidro (1,40 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. La reacción no estaba terminada y se añadió N-etil-N-propan-2-ilpropan-2-amina (0,24 ml, 1,40 mmoles), y la disolución se agitó a 60°C otras 2 h. La mezcla de reacción se diluyó con metanol (20 ml) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (248 mg, 74 %) como un sólido amarillo.

RMN ^{1}H (500,13 MHz, DMSO-d6, 373K) δ 1,13 - 1,14 (6H, m), 2,24 (3H, s), 2,25 - 2,31 (2H, m), 2,81 (1H, d), 2,83 (1H, d), 3,78 (6H, s), 4,30 - 4,33 (2H, m), 5,11 (2H, s), 5,90 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 8,27 (1H, d), 8,72 (1H, d), 10,3 (1H, s), 11,1 (1H, s). MS: m/z 482 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00059 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se esquematiza en el Ejemplo 109.

Ejemplo 131

5-[(3R,5S)-4-(cianometil)-3,5-dimetilpiperazin-1-il]-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió de una vez 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida (273 mg, 0,70 mmoles) a una mezcla 3:1 de (2R,6S)-1,2,6-trimetilpiperazina y 2-[(2S,6R)-2,6-dimetilpiperazin-1-il]acetonitrilo (180 mg, 1,40 mmoles) en dimetilsulfóxido anhidro (1,40 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. La reacción no estaba terminada y se añadió N-etildiisopropilamina (0,24 ml, 1,40 mmoles), y la disolución se agitó a 60°C otras 2 h. La mezcla de reacción se diluyó con metanol (20 ml) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, para dar material impuro. El eluyente concentrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (65 mg, 18%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,22 (6H, t), 2,72 - 2,77 (2H, m), 2,86 (1H, d), 2,89 (1H, d), 3,80 (6H, s), 3,83 (2H, s), 4,33 - 4,37 (2H, m), 5,18 (2H, s), 5,50 (1H, s), 6,41 (1H, t), 6,61 (2H, d), 7,99 (1H, d), 8,88 (1H, d), 9,62 (1H, s), 10,7 (1H, s). MS: m/z 507 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0035 μM.

La 5-cloro-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se esquematiza en el Ejemplo 109.

Ejemplo 132

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,29 ml, 2,58 mmoles) a una suspensión de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (295 mg, 1,03 mmoles) y 2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo (258 mg, 1,03 mmoles) en tolueno (5,16 ml) a 25°C. La disolución resultante se agitó a 60°C durante 5 h. La mezcla de reacción se vertió en metanol (50 ml) y se acidificó con HCl (disolución acuosa 2M). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH

en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (298 mg, 62%) como un sólido blanco cristalino.

RMN ^{1}H (500,133 MHz, DMSO, 373K) δ 1,05 (3H, d), 2,10 - 2,20 (2H, m), 2,24 (3H, s), 2,81 (1H, dt), 2,91 (1H, dd), 3,24 - 3,29 (1H, m), 3,76 (6H, s), 4,39 - 4,47 (2H, m), 5,09 (2H, s), 5,71 (1H, s), 6,44 (1H, t), 6,60 (2H, d), 8,84 (2H, s), 10,30 (1H, s), 11,28 (1H, s). MS: m/z 468 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0036 μM.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

El 2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (500 mg, 2,90 mmoles) en diclorometano (7,50 ml) a una disolución agitada de 1,2-dimetilpiperazina (331 mg, 2,90 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (1,26 ml, 7,24 mmoles) en diclorometano (7,25 ml) a temperatura ambiente en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se concentró a presión reducida, y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (713 mg, 98%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,04 - 1,06 (3H, m), 1,98 - 2,05 (1H, m), 2,06 - 2,13 (1H, m), 2,21 (3H, s), 2,78 - 2,84 (2H, m), 3,14 - 3,21 (1H, m), 3,81 (3H, s), 4,46 - 4,55 (2H, m), 8,78 (2H, s). MS: m/z 251 (MH+).

Ejemplo 133

2-(4-Ciclopropilpiperazin-1-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 2,00 ml, 4,00 mmoles) a una suspensión agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (459 mg, 1,60 mmoles) y 2-(4-ciclopropilpiperazin-1-il)pirimidin-5-carboxilato de metilo (421 mg, 1,60 mmoles) en tolueno (8,0 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después a 60°C durante 2 h. La mezcla de reacción se paralizó con metanol (20 ml) y se trató con HCl (disolución acuosa 2N, hasta que se obtuvo una disolución libremente agitada). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (94 mg, 12%) como un sólido.

RMN ^{1}H (500,13 MHz, DMSO-d6, 373K) δ 0,40 - 0,43 (2H, m), 0,44 - 0,49 (2H, m), 1,71 - 1,75 (1H, m), 2,65 (4H, t), 3,78 (6H, s), 3,84 (4H, t), 5,11 (2H, s), 5,71 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 8,86 (2H, s), 10,3 (1H, s), 11,3 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0039 μM.

El 2-(4-ciclopropilpiperazin-1-il)pirimidin-5-carboxilato de metilo se preparó como se esquematiza en el Ejemplo 126.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

Ejemplo 134

2-(3,4,6,7,8,8a-Hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 2,50 ml, 5,00 mmoles) a una suspensión agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (572 mg, 2,00 mmoles) y 2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo (525 mg, 2,00 mmoles) en tolueno (10,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h, y después a 60°C durante 2 h. La mezcla de reacción se

paralizó con cuidado con metanol (20 ml) y se trató con HCl (disolución acuosa 2N, hasta que se obtuvo una disolución libremente agitada). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (269 mg, 28%) como un sólido.

RMN ^{1}H (500,13 MHz, DMSO-d6, 373K) δ 1,39 - 1,47 (1H, m), 1,69 - 1,75 (1H, m), 1,76 - 1,82 (1H, m), 1,84 - 1,90 (1H, m), 1,99 - 2,03 (1H, m), 2,13 - 2,21 (2H, m), 2,72 - 2,78 (1H, m), 3,04 - 3,13 (3H, m), 3,78 (6H, s), 4,70 - 4,75 (1H, m), 4,85 - 4,88 (1H, m), 5,11 (2H, s), 5,72 (1H, s), 6,46 (1H, t), 6,62 (2H, d), 8,87 (2H, s), 10,30 (1H, s), 11,30 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0024 μM.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

El 2-(3,4,6,7,8,8a-hexahidro-1H-pirrolo[2,1-c]pirazin-2-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó como se esquematiza en el Ejemplo 128.

Ejemplo 135

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,31 ml, 2,62 mmoles) a una suspensión de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (260 mg, 1,05 mmoles) y 2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo (263 mg, 1,05 mmoles) en tolueno (5,26 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción se vertió en metanol (50 ml) y se acidificó con HCl (disolución acuosa 2M, para obtener una disolución clara que se puede agitar libremente). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para

dar producto impuro. El material impuro se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en diclorometano. Las fracciones que contienen el producto se evaporaron hasta sequedad para dar material que aún estaba impuro. El residuo se repurificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (175 mg, 36%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,05 - 1,07 (3H, m), 1,99 - 2,05 (1H, m), 2,07 - 2,13 (1H, m), 2,22 (3H, s), 2,76 - 2,84 (2H, m), 2,88 (4H, s), 3,12 - 3,19 (1H, m), 3,72 (6H, s), 4,46 - 4,55 (2H, m), 6,33 (1H, t), 6,42 (3H, m), 8,89 (2H, s), 10,60 (1H, s), 12,12 (1H, s). MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0026 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(3,4-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó como se esquematiza en el Ejemplo 132.

Ejemplo 136

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,04 ml, 2,08 mmoles) a una suspensión de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (205 mg, 0,83 mmoles) y 2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo (220 mg, 0,83 mmoles) en tolueno (5,257 ml) a 25ºC. La disolución resultante se agitó a 60ºC durante 18 h. La mezcla de reacción se vertió en metanol (50 ml) y se acidificó con HCl (disolución acuosa 2M, para obtener una disolución clara que se puede agitar libremente). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y

MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (157 mg, 39%) como un sólido blanco.
RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,09 - 1,10 (6H, m), 2,08 - 2,14 (2H, m), 2,20 (3H, s), 2,71 (1H, d), 2,74 (1H, d), 2,87 (4H, s), 3,72 (6H, s), 4,55 - 4,59 (2H, m), 6,33 (1H, t), 6,42 (3H, m), 8,89 (2H, s), 10,61 (1H, s), 12,15 (1H, s). MS: m/z 480 (MH+).
Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0019 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:
Se añadió metilpoliestirencianoborohidruro de trietilamonio macroporoso (2,31 mmoles/g, 3,15 g, 7,29 mmoles) a 2-((3R,5S)-3,5-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo (730 mg, 2,92 mmoles), formaldehído (disolución acuosa al 37%, 4,43 ml, 59,13 mmoles) y ácido acético (0,334 ml, 5,83 mmoles) en metanol (5,83 ml) a 25°C. La suspensión resultante se agitó a temperatura ambiente durante 5 h. El metilpoliestirencianoborohidruro de trietilamonio macroporoso se eliminó por filtración, lavando con metanol (50 ml). El filtrado se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 6% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (474 mg, 62%) como un aceite blanco que solidificó al dejar reposar.
RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,09 (6H, d), 2,07 - 2,15 (2H, m), 2,19 (3H, s), 2,73 - 2,76 (2H, m), 3,81 (3H, s), 4,56 - 4,60 (2H, m), 8,79 (2H, s). MS: m/z 265 (MH+).

El 2-((3R,5S)-3,5-dimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:
Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (535 mg, 3,10 mmoles) en diclorometano (7,50 ml) a una disolución agitada de (2S,6R)-2,6-dimetilpiperazina (354 mg, 3,10 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (1,35 ml, 7,75 mmoles) en

diclorometano (7,24 ml) a temperatura ambiente en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró a presión reducida, y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (740 mg, 95%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,02 - 1,04 (6H, m), 2,33 (1H, s), 2,43 - 2,46 (2H, m), 2,64 - 2,69 (2H, m), 3,81 (3H, s), 4,62 - 4,66 (2H, m), 8,77 (2H, s). MS: m/z 251 (MH+).

Ejemplo 137

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[4-(1-hidroxipropan-2-il)piperazin-1-il]benzamida

Se añadió 2-(piperazin-1-il)propan-1-ol 2HCl (0,274 g, 1,26 mmoles) a N-etil-N-propan-2-ilpropan-2-amina (0,330 ml, 1,89 mmoles) en DMSO (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 10 min. Se añadió N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluorobenzamida (0,233 g, 0,63 mmoles), y la mezcla se calentó a 110°C durante 18 h en nitrógeno. El calentamiento se continuó durante 12 días adicionales. La reacción se enfrió, y la mezcla bruta se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar producto bruto. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,048 g, 15,44 %) como un sólido de color crema.

RMN ^{1}H (500,13 MHz-DMSO-d6 + CD3COOD a 373K): 1,02 (3H, d), 2,70-2,81 (5H, m), 2,89 (4H, s), 3,28-3,34 (4H, m), 3,37-3,44 (1H, m), 3,50-3,55 (1H, m), 3,73 (6H, s), 6,27 - 6,32 (2H, m), 6,40 (2H, s0, 6,92 (2H, d), 7,82 - 7,88 (2H, m). MS: m/z (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00057 μM.

El 2-(piperazin-1-il)propan-1-ol. 2HCl usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota una disolución 1M de complejo de borano-tetrahidrofurano (12,00 ml, 12,00 mmoles) en THF a una suspensión agitada de ácido 2-(1-terc-butoxicarbonilpiperazin-4-il)propionico (2,58 g, 10 mmoles) en tetrahidrofurano (50 ml) a 0°C, durante un periodo de 10 min en nitrógeno. La disolución resultante se agitó a 60°C durante 8 h. Ésta se paralizó con ácido acético/agua (10ml, mezcla 1:2), y se evaporó hasta sequedad. El residuo se disolvió en acetato de etilo (50 ml), se lavó con bicarbonato de sodio saturado (25 ml) y agua, se secó sobre MgSO4, se filtró y se evaporó hasta sequedad para dar 4-(1-hidroxipropan-2-il)piperazin-1-carboxilato de terc-butilo (0,810 g, 33,2 %)

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,83 (3H, d), 1,39 (9H, s), 2,30 (2H, t), 2,51 - 2,57 (3H, m), 2,71 - 2,82 (1H, m), 3,34 - 3,40 (2H, m), 3,35 - 3,39 (4H, m).

Una suspensión de 4-(1-hidroxipropan-2-il)piperazin-1-carboxilato de terc-butilo (0,782 g, 3,2 mmoles) en una mezcla de acetato de etilo (10 ml) y metanol (10,00 ml) se trató gota a gota con HCl 4,0M en dioxano (12,00 ml, 48,00 mmoles) a temperatura ambiente. La mezcla de reacción se agitó durante 18 h. La mezcla de reacción se diluyó con éter, y el sólido blanco se separó por filtración, se lavó con éter y se secó al aire para dar 2-(piperazin-1-il)propan-1-ol (0,525 g, 76 %), como su sal de dihidrocloruro.

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluorobenzamida usada como material de partida se preparó según lo siguiente:

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (3,00 ml, 3,00 mmoles) a una disolución agitada de 4-fluorobenzoato de etilo (0,440 ml, 3,00 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,742 g, 3 mmoles) en tolueno (10 ml) a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se vertió en acetona (50 ml), y se trató con un exceso de sulfito de sodio húmedo. La mezcla de reacción se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar una goma amarilla. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,245 g, 22,11 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,88 (4H, s), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,47 (1H, s), 7,32 (2H, t), 8,05 - 8,09 (2H, m), 10,69 (1H, s), 12,16 (1H, s). MS: m/z 370 (MH+).

Ejemplo 138

N-(3-(3,5-dimetoxibenciloxi)-1H-pirazol-5-il)-2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,04 ml, 2,07 mmoles) a una suspensión de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (237 mg, 0,83 mmoles) y 2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo (219 mg, 0,83 mmoles) en tolueno (4,2 ml) a 25°C. La disolución resultante se agitó a 60°C durante 2 h. La mezcla de reacción se vertió en metanol (50 ml) y se acidificó con HCl (disolución acuosa 2M). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El material impuro se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (158 mg, 40%) como un sólido blanco.

RMN ^{1}H (500,133 MHz, DMSO, 373K) δ 1,10 (6H, d), 2,14 - 2,20 (2H, m), 2,22 (3H, s), 2,74 - 2,79 (2H, m), 3,76 (6H, s), 4,53 - 4,57 (2H, m), 5,08 (2H, s), 5,71 (1H, s), 6,44 (1H, t), 6,59 (2H, d), 8,84 (2H, s), 10,32 (1H, s), 11,31 (1H, s). MS: m/z 482 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0026 μM.

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

El 2-((3R,5S)-3,4,5-trimetilpiperazin-1-il)pirimidin-5-carboxilato de metilo se preparó como se esquematiza en el Ejemplo 136.

Ejemplo 139

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(3,3-dimetilpiperazin-1-il)benzamida

Se agitaron N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluorobenzamida (0,1 g, 0,27 mmoles) y 2,2-dimetilpiperazina (0,124 g, 1,04 mmoles) a 60°C durante 20 min. Se añadieron carbonato de potasio (0,033 ml, 0,54 mmoles) y DMSO (1 ml), y la reacción se agitó a 120°C durante 16 días en un tubo cerrado herméticamente. La mezcla de reacción se enfrió y se evaporó. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (6,00 mg, 2,000 %) como una goma incolora.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,19 (6H, s), 2,92 - 2,95 (4H, m), 3,02 (4H, d), 3,04 (1H, s), 3,17 (2H, t), 3,75 (6H, s), 6,32 - 6,35 (3H, m), 6,84 (2H, d), 7,77 (2H, d), 8,73 (1H, s). MS: m/z 465 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00047 μM.

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-fluorobenzamida usada como material de partida se preparó según lo siguiente:

Se añadió gota a gota una disolución 2M de trimetilaluminio (3,54 ml, 7,08 mmoles) en tolueno a 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,7 g, 2,83 mmoles) en tolueno (35 ml). Entonces se añadió 4-fluorobenzoato de metilo (0,366 ml, 2,83 mmoles), y la disolución resultante se agitó a temperatura ambiente durante 18 h. Se añadió una cantidad adicional de 4-fluorobenzoato de metilo (0,183 ml, 1,42 mmoles), y la disolución se agitó a temperatura ambiente durante otras 20 h. La mezcla de reacción se vertió en acetona (40 ml), y se trató con un exceso de disolución de sulfito de sodio húmedo. La suspensión se agitó durante 2 h, se filtró, y el filtrado se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente 2,5 a 5% de NH_3 2,5N/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado como un aceite beige, que solidificó al dejar reposar (0,147 g, 14,06 %) hasta un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,88 (4H, s), 3,73 (6H, s), 6,33 (1H, t), 6,43 (2H, d), 6,47 (1H, s), 7,31 (2H, t), 8,05 - 8,09 (2H, m), 10,69 (1H, s), 12,16 (1H, s). MS: m/z 370 (MH+).

Ejemplo 140

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(3,3-dimetilpiperazin-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 5-(3,3-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,268 g, 1 mmol) e hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,286 g, 1,00 mmoles) en tolueno (7,14 ml) a 65°C en nitrógeno. La mezcla de reacción se agitó y se calentó a 65°C durante 4 h, después 50°C durante 18 h seguido de 80°C durante 5 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y la capa acuosa se eliminó. La capa de acetato de etilo se lavó con salmuera saturada y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como una goma amarilla. El producto bruto se purificó mediante LCMS preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,073 g, 15,48 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 1,36 (6H, s), 3,24 (4H, s), 3,40 (2H, t), 3,74 (6H, s), 5,06 (2H, s), 5,64 (1H, s), 6,24 (1H, d), 6,41 (1H, s), 6,57 (2H, s), 7,62 - 7,63 (1H, m); MS: m/z 472 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00098 μM.

El 5-(3,3-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (0,112 g, 0,50 mmoles) a 5-bromotiofen-2-carboxilato de etilo (1,175 g, 5 mmoles), 2,2-dimetil-piperazina (0,571 g, 5,00 mmoles), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,311 g, 0,50 mmoles) y carbonato de cesio (2,281 g, 7,00 mmoles) en tolueno (50,0 ml) a 20°C en nitrógeno. La suspensión resultante se agitó a 110°C durante 23 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El material bruto se disolvió en metanol, y después se aplicó a la columna. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad para dar el producto bruto como un sólido marrón. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 4% de MeOH en DCM. Las fracciones puras se

evaporaron hasta sequedad para dar 5-(3,3-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,484 g, 36,1 %) como una goma marrón.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,20 (6H, s), 1,33 (3H, t), 2,98 (2H, s), 3,05 (2H, d), 3,16 - 3,19 (2H, m), 4,28 (2H, q), 6,00 (1H, d), 7,54 (1H, d)

MS: m/z 269 (MH+)

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

Ejemplo 141

N-[5-[(3,5-Dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-etilpiperazin-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio (disolución 2M en tolueno, 1,40 ml, 2,79 mmoles) a una suspensión agitada de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (319 mg, 1,12 mmoles) y 5-(4-etilpiperazin-1-il)tiofen-2-carboxilato de etilo (300 mg, 1,12 mmoles) en tolueno (5,60 ml) a 25°C. La disolución resultante se agitó entonces a 60°C en nitrógeno durante 5 h. La mezcla de reacción se paralizó con cuidado en metanol (100 ml), se acidificó con HCl (disolución acuosa 2M), y la mezcla se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar material impuro. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones se evaporaron hasta sequedad para dar N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-(4-etilpiperazin-1-il)tiofen-2-carboxamida impura como un sólido de color crema. El residuo se repurificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (72 mg, 14%) como un sólido blanco.

RMN ^{1}H (500,133 MHz, DMSO, 373K) δ 1,04 (3H, t), 2,43 (2H, q), 2,53 - 2,54 (4H, m), 3,23 - 3,25 (4H, m), 3,76 (6H, s), 5,07 (2H, s), 5,60 (1H, s), 6,14 (1H, d), 6,44 (1H, t), 6,59 (2H, d), 7,63 (1H, d), 10,05 (1H, s), 11,09 (1H, s). MS: m/z 472 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00086 μM.

El 5-(4-etilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió tris(dibencilidenacetona)dipaladio(0) (183 m,g, 0,20 mmoles), seguido de terc-butóxido de sodio (538 mg, 5,60 mmoles) a 5-bromotiofen-2-carboxilato de etilo (1,034 g, 4,40 mmoles), 1-etilpiperazina (0,51 ml, 4,00 mmoles) y (rac)-(-)-2,2'-bis(difenilfosfino)-1,1'-binaftilo (249 mg, 0,40 mmoles) en tolueno (20,00 ml) a 25°C en nitrógeno. La suspensión resultante se agitó a 110°C durante 18 h. La mezcla de reacción enfriada se diluyó con metanol y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto bruto. El residuo se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 3% de NH3 7M/MeOH en DCM. Las fracciones que contienen producto deseado se evaporaron hasta sequedad para dar un aceite naranja impuro. El material impuro se purificó adicionalmente mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar 5-(4-etilpiperazin-1-il)tiofen-2-carboxilato de etilo (339 mg, 32%) como un aceite amarillo.

RMN ^{1}H (399,902 MHz, DMSO) δ 1,03 (3H, t), 1,25 (3H, t), 2,38 (2H, q), 2,49 (4H, m), 3,24 (4H, m), 4,19 (2H, q), 6,21 (1H, d), 7,51 (1H, d). MS: m/z 269 (MH+)

La 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl se preparó como se esquematiza en el Ejemplo 12.

Ejemplo 142

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metil-1,4-diazepan-1-il)tiofen-2-carboxamida

Se agitaron 5-(4-metil-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo (0,201 g, 0,75 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,185 g, 0,75 mmoles) en tolueno (10 ml) a 20°C, y se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (0,938 ml, 1,88 mmoles). La reacción se agitó en nitrógeno a 60°C durante 18 h. La mezcla de reacción se enfrió y se paralizó vertiéndola en metanol (50 ml), se acidificó con un pocos gotas de ácido clorhídrico 2N. El producto bruto se purificó mediante cromatografía de intercambio

iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,162 g, 46,0 %) como un sólido bronceado. RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,89 - 1,93 (2H, m), 2,28 (3H, s), 2,50 - 2,54 (2H, m), 2,63 (1H, d), 2,64 - 2,65 (1H, m), 2,85 (4H, s), 3,43 (2H, t), 3,50 (2H, t), 3,72 (6H, s), 5,86 (1H, d), 6,32 - 6,34 (2H, m), 6,41 (2H, d), 7,79 (1H, d), 10,15 (1H, s), 12,00 (1H, s). MS: m/z 470 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0021 μM.

El 5-(4-metil-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo se preparó según lo siguiente: se añadió acetato de paladio (II) (0,135 g, 0,60 mmoles) a 5-bromotiofen-2-carboxilato de etilo (1,411 g, 6 mmoles), 1-metil-1,4-diazepano (0,822 g, 7,20 mmoles), BINAP (0,374 g, 0,60 mmoles) y carbonato de cesio (2,74 g, 8,40 mmoles) en dioxano (40 ml) calentado hasta 80ºC durante 18 h en nitrógeno. La mezcla de reacción bruta se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH. Las fracciones se evaporaron hasta sequedad para dar el producto bruto. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 3M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 5-(4-metil-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo (0,204 g, 12,67 %) como una goma amarilla.

RMN ^{1}H (399,9 MHz, CDCl3) δ: 1,34 (3H, t), 1,97 - 2,04 (2H, m), 2,38 (3H, s), 2,55 - 2,61 (2H, m), 2,67 (2H, m), 3,48 (2H, t), 3,54 - 3,57 (2H, m), 4,28 (4H, q), 5,79 (1H, d), 7,55 (1H, d). MS: m/z 269 (MH+).

Ejemplo 143

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-etil-3-metilpiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,65 ml, 3,31 mmol) a una suspensión agitada de 2-(4-etil-3-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo (303 mg, 1,15 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (283 mg, 1,15 mmoles) en

tolueno (5,73 ml) a temperatura ambiente. La disolución resultante se agitó a 60°C toda la noche. La mezcla de reacción se paralizó en metanol (100 ml) y se trató con HCl (disolución acuosa 2N, hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro como una película seca amarilla. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (269 mg, 49%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 0,99 (3H, d), 1,03 (3H, d), 2,20-2,26 (1H, m), 2,35 - 2,43 (2H, m), 2,74 - 2,79 (1H, m), 2,83 (1H, m), 2,88 (4H, s), 3,02 - 3,07 (1H, m), 3,30 - 3,38 (1H, m), 3,72 (6H, s), 4,27 - 4,31 (2H, m), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,89 (2H, s), 10,58 (1H, s), 12,15 (1H, s). MS: m/z 480 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0027 μM.

El 2-(4-etil-3-metilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (300 mg, 1,74 mmoles) en diclorometano (4,30 ml) a una disolución agitada de 1-etil-2-metilpiperazina (223 mg, 1,74 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,75 ml, 4,35 mmoles) en diclorometano (4,40 ml) a 25°C en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró a presión reducida y se diluyó con MeOH (10 ml). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 3% de NH3 7M/MeOH en diclorometano. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (382 mg, 83%) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 0,98 (3H, t), 1,02 (3H, d), 2,20 - 2,27 (1H, m), 2,33 - 2,38 (1H, m), 2,40 - 2,45 (1H, m), 2,71 - 2,79 (1H, m), 2,81 - 2,85 (1H, m), 3,06 - 3,11 (1H, m), 3,35 - 3,42 (1H, m), 3,81 (3H, s), 4,28 - 4,35 (2H, m), 8,78 (2H, s). MS : m/z 265 (MH+)

Ejemplo 144

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-enilpiperidin-4-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-enilpiperidin-4-il)benzamida se preparó siguiendo el procedimiento como se esquematiza para el Ejemplo 99, partiendo de 4-(1-prop-2-enilpiperidin-4-il)benzoato de metilo (0,259 g, 1,00 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1 mmol) y trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno (10 ml). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/metanol en DCM. Las fracciones puras se evaporaron hasta sequedad y el producto se cristalizó en DCM/éter dietílico para dar, al filtrar, el compuesto del título (0,182 g, 38,3 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,66 - 1,70 (2H, m), 1,73 - 1,79 (2H, m), 1,99 - 2,05 (2H, m), 2,55 (1H, d), 2,88 (4H, s), 2,95 (1H, s), 2,99 (3H, d), 3,73 (6H, s), 5,12 - 5,18 (1H, m), 5,22 (1H, t), 5,83 - 5,89 (1H, m), 6,33 (1H, t), 6,43 (2H, d), 6,47 (1H, s), 7,35 (2H, d), 7,93 (2H, d), 10,55 (1H, s), 12,13 (1H, s). MS: m/z 475 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,000041 μM.

El 4-(1-prop-2-enilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota 3-bromoprop-1-eno (0,433 ml, 5,00 mmoles) durante 5 min en nitrógeno a una disolución agitada de 4-piperidin-4-ilbenzoato de metilo (1,096 g, 5 mmoles) y N-etil-N-isopropilpropan-2-amina (2,066 ml, 12,50 mmoles) en DCM (10 ml) a temperatura ambiente. La mezcla de reacción se agitó durante 1 h a temperatura ambiente. Ésta se evaporó hasta sequedad, y se purificó parcialmente en una columna SCX, eluyendo con amoníaco 3,5N en metanol. Las fracciones que contienen el producto se combinaron y se evaporaron hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (1,004 g, 77 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,78 - 1,86 (4H, m), 2,02 - 2,08 (2H, m), 2,53 - 2,57 (1H, m), 3,03 - 3,05 (3H, m), 3,07 (1H, t), 3,90 (3H, s), 5,14 - 5,23 (2H, m), 5,85 - 5,97 (1H, m), 7,28 - 7,31 (2H, m), 7,95 - 7,98 (2H, m). MS: m/z 260 (MH+).

El 4-piperidin-4-ilbenzoato de metilo se preparó como se esquematiza en el Ejemplo 99.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 145

4-(1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida

La 4-(1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida se preparó siguiendo el procedimiento como se esquematiza para el Ejemplo 99, partiendo de 4-(1,4-diazepan-1-il)benzoato de etilo (0,497 g, 2 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,495 g, 2,00 mmoles) y trimetilaluminio 2M (2,50 ml, 5,0 mmoles) en tolueno (10 ml). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de amoníaco 2,5 M/MeOH en DCM. Las fracciones que contienen el producto se evaporaron hasta sequedad, y se purificaron adicionalmente mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,024 g, 2,67 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6 + d4HOAc) δ 2,07 (2H, t), 2,90 (4H, s), 3,10 (2H, t), 3,24 (2H, t), 3,62 (2H, t), 3,74 - 3,76 (8H, m), 6,33 (2H, t), 6,42 (2H, d), 6,81 - 6,83 (2H, m), 7,88 - 7,89 (2H, m). MS: m/z 450 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0007 μM.

El 4-(1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente: 4-fluorobenzoato de etilo (11,01 ml, 75 mmoles) y 1,4-diazepano (30,0 g, 300,00 mmoles) en DMSO (150 ml) calentado hasta 100°C en nitrógeno. La disolución resultante se agitó a 100°C durante 24 h. La mezcla de reacción se enfrió y se evaporó hasta sequedad. La mezcla de reacción se paralizó con NaOH 2M (150 ml), se extrajo con EtOAc (3 x 75 ml), la capa orgánica se lavó con salmuera saturada (100 ml), se secó sobre MgSO4, se filtró y se evaporó para dar 4-(1,4-diazepan-1-il)benzoato de etilo (17,43 g, 94 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,27 - 1,31 (3H, m), 1,71 (1H, s), 1,79 - 1,85 (2H, m), 2,74 (1H, d), 2,74 (1H, d), 2,95 (1H, d), 2,96 (1H, d), 3,51 (2H, t), 3,56 (2H, t), 4,21 - 4,27 (2H, m), 6,56 - 6,60 (2H, m), 7,80 - 7,83 (2H, m). MS: m/z 249 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 146

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-inilpiperidin-4-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-prop-2-inilpiperidin-4-il)benzamida se preparó siguiendo el procedimiento como se esquematiza para el Ejemplo 99, partiendo de 4-(1-prop-2-inilpiperidin-4-il)benzoato de metilo (0,257 g, 1,00 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1 mmol) en tolueno seco (10 ml) con trimetilaluminio 2M (1,250 ml, 2,50 mmoles). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/metanol en DCM. Las fracciones puras se evaporaron hasta sequedad, y el producto se cristalizó en DCM/éter dietílico para dar el compuesto del título (0,245 g, 51,8 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6 + d4HOAc) δ 1,64 - 1,73 (2H, m), 1,79 (2H, d), 2,24 - 2,29 (2H, m), 2,49 - 2,54 (1H, m), 2,88 (4H, s), 2,90 (1H, s), 2,93 (1H, s), 3,15 (1H, t), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 7,36 (2H, d), 7,93 (2H, d), 10,57 (1H, s), 11,95 (4H, s). MS: m/z 473 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0011 μM.

El 4-(1-prop-2-inilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó siguiendo el mismo procedimiento que para 4-(1-prop-2-enilpiperidin-4-il)benzoato de metilo (Ejemplo 144), pero partiendo de 3-bromoprop-1-ino (0,356 ml, 4,00 mmoles) (disolución al 80% en tolueno), 4-piperidin-4-ilbenzoato de metilo (0,877 g, 4 mmoles) y N-etil-N-isopropilpropan-2-amina (1,653 ml, 10,00 mmoles) en DCM (5 ml). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,748 g, 72,7 %) como un sólido blanco. RMN ^{1}H (399,9 MHz, CDCl3) δ 1,81 - 1,90 (4H,

m), 2,27 (1H, t), 2,32 - 2,38 (2H, m), 2,54 - 2,59 (1H, m), 3,00 - 3,04 (2H, m), 3,36 (2H, d), 3,90 (3H, s), 7,27 - 7,30 (2H, m), 7,95 - 7,98 (2H, m). MS: m/z 258 (MH+).

El 4-piperidin-4-ilbenzoato de metilo se preparó como se esquematiza en el Ejemplo 144.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 147

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-5-[(3S,5R)-3,5-dimetilpiperazin-1-il]tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio 2M (1,250 ml, 2,50 mmoles) en tolueno a una disolución agitada de 5-((3R,5S)-3,5-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (0,268 g, 1 mmol) e hidrocloruro 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina (0,286 g, 1,00 mmoles) en tolueno (7,14 ml) a temperatura ambiente, y después la mezcla se calentó a 80°C en nitrógeno durante 4 h y después a 70°C durante 18 h. Se añadió acetato de etilo (5 ml) a la mezcla de reacción, seguido de una disolución de tartrato sódico potásico (5 ml, 20% acuoso). Se añadió más acetato de etilo (50 ml) y agua (25 ml), y la mezcla se filtró a través de celita. El filtrado se transfirió a un embudo separador, y la capa acuosa se eliminó. La capa de acetato de etilo se lavó con salmuera saturada, y después se secó sobre sulfato de magnesio. Después de filtrar, el disolvente se evaporó para dar el producto bruto como una goma amarilla. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,154 g, 32,7 %) como un sólido blanco.

RMN ^{1}H (500,13 MHz, DMSO-d6, CD3CO2D) δ 1,23 (6H, d), 2,79 (2H, t), 3,26 - 3,34 (2H, m), 3,63 - 3,66 (2H, m), 3,76 (6H, s), 5,08 (2H, s), 5,63 (1H, s), 6,25 (1H, d), 6,43 (1H, t), 6,59 (2H, d), 7,66 (1H, d), 11,08 (1H, s)

MS: m/z 472 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0018 μM.

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

El 5-((3R,5S)-3,5-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (0,225 g, 1,00 mmoles) a 5-bromotiofen-2-carboxilato de etilo (2,351 g, 10 mmoles), (2S,6R)-2,6-dimetilpiperazina (1,142 g, 10,00 mmoles), rac-2,2'-bis(difenilfosfino)-1,1'-binaftilo (0,623 g, 1,00 mmoles) y carbonato de cesio (4,56 g, 14,00 mmoles) en dioxano (100 ml) a 20°C en nitrógeno. La suspensión resultante se agitó a 105°C durante 23 h. La mezcla se evaporó hasta sequedad para dar un aceite marrón. Este producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX2. El material bruto se disolvió en metanol, y después se aplicó a la columna. El producto deseado se eluyó de la columna usando NH3 2M en metanol, y las fracciones puras se evaporaron hasta sequedad para dar el producto bruto como un sólido marrón. Este material se purificó adicionalmente mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 5-((3S,5R)-3,5-dimetilpiperazin-1-il)tiofen-2-carboxilato de etilo (1,600 g, 59,6 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,12 - 1,14 (6H, m), 1,33 (3H, t), 2,46 -2,56 (2H, m), 2,98 - 3,07 (2H, m), 3,42 - 3,46 (2H, m), 4,28 (2H, q), 6,00 (1H, d), 7,55 (1H, d)

MS: m/z 269 (MH+)

Ejemplo 148

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[1-(2-metoxietil)piperidin-4-il]benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[1-(2-metoxietil)piperidin-4-il]-benzamida se preparó siguiendo el procedimiento como se esquematiza para el Ejemplo 99, partiendo de 4-(1-(2-metoxietil)piperidin-4-il)benzoato de metilo (0,428 g, 1,25 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,309 g, 1,25 mmoles) y trimetilaluminio 2M (1,56 ml, 3,13 mmoles) en tolueno (10 ml). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/metanol en DCM. Las fracciones puras se evaporaron hasta sequedad, y el producto se

cristalizó en DCM/éter dietílico para dar el compuesto del título (0,215 g, 34,9 %) como un sólido blanquecino.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,76 - 1,91(4H, m), 2,10 - 2,17 (2H, m), 2,54 - 2,58 (1H, m), 2,63 (2H, t), 2,92 - 2,96 (4H, m), 3,10 (2H, d), 3,37 (3H, s), 3,56 (2H, t), 3,76 (6H, s), 6,33 - 6,35 (3H, m), 6,68 (1H, s), 7,32 (2H, d), 7,80 (2H, d), 8,65 (1H, s), 9,28 (1H, s). MS: m/z 493 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00087 μM.

El 4-(1-(2-metoxietil)piperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Una disolución de 4-(piperidin-4-il)benzoato de metilo, HCl (1,279 g, 5 mmoles), N-etil-N-propan-2-ilpropan-2-amina (3,49 ml, 20,00 mmoles) y 1-bromo-2-metoxietano (0,470 ml, 5,00 mmoles) en diclorometano (10 ml) se calentó a 40°C durante 18 h. Se añadieron unas pocas gotas de DMF para ayudar a la solubilidad. La mezcla de reacción se enfrió, se diluyó con DCM (30 ml) y se lavó con agua (2 x 30 ml) y disolución saturada de cloruro de sodio (30 ml). Ésta se secó sobre $MgSO_4$, se filtró y se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(1-(2-metoxietil)piperidin-4-il)benzoato de metilo (0,723 g, 52,1 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,75 (1H, t), 1,81 - 1,90 (3H, m), 2,09 - 2,15 (2H, m), 2,55 (1H, q), 2,60 - 2,63 (2H, m), 3,08 - 3,11 (2H, m), 3,37 (3H, s), 3,53 - 3,56 (2H, m), 3,89 - 3,90 (3H, m), 7,27 - 7,31 (2H, m), 7,95 - 7,98 (2H, m). MS: m/z 278 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 149

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[(3S)-3-propan-2-ilpiperazin-1-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,23 ml, 2,46 mmoles) a una suspensión agitada de (S)-2-(3-propan-2-ilpiperazin-1-il)pirimidin-5-carboxilato de metilo (260 mg, 0,98 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (243 mg, 0,98

mmoles) en tolueno (8,38 ml) a temperatura ambiente. La reacción se agitó entonces a 60°C durante 18 h en una atmósfera de nitrógeno. La mezcla de reacción se paralizó en metanol (100 ml) y se trató con HCl (disolución acuosa 2N, hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (292 mg, 62 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 0,95 - 0,97 (6H, d), 1,63 (1H, m), 2,26 - 2,31 (1H, m), 2,57 - 2,64 (1H, m), 2,68 (1H, d), 2,88 (4H, s), 2,89 - 2,97 (1H, m) 2,98 - 3,02 (1H, m), 3,72 (6H, s), 4,57 (1H, d), 4,66 (1H, d), 6,33 (1H, t), 6,41 - 6,44 (3H, m), 8,88 (2H, s), 10,56 (1H, s), 12,14 (1H, s). MS: m/z 480 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0044 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El (S)-2-(3-propan-2-ilpiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de (2S)-2-propan-2-ilpiperazina (223 mg, 1,74 mmoles) en diclorometano (4,40 ml) a una disolución agitada de 2-cloropirimidin-5-carboxilato de metilo (300 mg, 1,74 mmoles) en diclorometano (4,30 ml) a 25°C. Se añadió N-etil-N-propan-2-ilpropan-2-amina (0,752 ml, 4,35 mmoles). La disolución resultante se agitó a temperatura ambiente durante 18 h en una atmósfera de nitrógeno. La mezcla de reacción se concentró y se diluyó con metanol. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar el compuesto deseado (456,1 mg, 99%) como un aceite amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 0,94 - 0,96 (6H, m), 1,58 - 1,66 (1H, m), 2,25 - 2,30 (1H, m), 2,56 - 2,63 (1H, m), 2,68 - 2,74 (1H, m), 2,95 - 3,02 (2H, m), 3,81 (3H, s), 4,56 - 4,60 (1H, m), 4,64 - 4,68 (1H, m), 8,78 (2H, s). MS: m/z 265 (MH+)

La (2S)-2-propan-2-ilpiperazina, usada como material de partida, se preparó según lo siguiente:

Una disolución de (2S)-2-propan-2-ilpiperazin-1-carboxilato de *terc*-butilo (2 g, 8,76 mmoles) en una mezcla de acetato de etilo (20 ml) y metanol (20,00 ml) se agitó a temperatura ambiente con HCl 4M en dioxano (30 ml) durante 40 h en nitrógeno.La mezcla de reacción se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 3,5M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar (2S)-2-propan-2-ilpiperazina (1,052 g, 94 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,83 - 0,87 (6H, m), 1,39 - 1,47 (1H, m), 2,15 - 2,22 (2H, m), 2,41 - 2,47 (1H, m), 2,53 - 2,59 (1H, m), 2,67 (1H, d), 2,75 - 2,80 (2H, m) – 2 protones no observados.

Ejemplo 150

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metil-3-oxopiperazin-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,23 ml, 2,46 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (243 mg, 0,98 mmoles) y 2-(4-metil-3-oxopiperazin-1-il)pirimidin-5-carboxilato de metilo (246 mg, 0,98 mmoles) en tolueno (5,00 ml) a 25°C. La disolución resultante se agitó a 60°C durante 24 h. La mezcla de reacción se añadió a metanol (100 ml), y después se trató con HCl (disolución acuosa 2N, hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 0,1% de TFA) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (204 mg, 45 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,88 - 2,91 (7H, m), 3,44 (2H, t), 3,72 (6H, s), 4,08 (2H, t), 4,33 (2H, s), 6,33 (1H, t), 6,40 -6,47 (3H, m), 8,95 (2H, s), 10,66 (1H, s), 12,16 (1H, s). MS: m/z 466 (MH+)

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,012 μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(4-metil-3-oxopiperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 1-metilpiperazin-2-ona (198 mg, 1,74 mmoles) en diclorometano (4,00 ml) a una disolución agitada de 2-cloropirimidin-5-carboxilato de metilo (300 mg, 1,74 mmoles) en diclorometano (4,70 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 4 h en nitrógeno. La mezcla de reacción se concentró y se disolvió en acetato de etilo (25 ml) y NaOH (50 ml, disolución acuosa 1M). La capa orgánica se lavó con acetato de etilo (25 ml). Las capas orgánicas se combinaron y se lavaron con salmuera (50 ml), se secaron usando MgSO4, se filtraron y se evaporaron hasta sequedad para dar 2-(4-metil-3-oxopiperazin-1-il)pirimidin-5-carboxilato de metilo (246 mg, 57 %) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,91 (3H, s), 3,44 (2H, t), 3,83 (3H, s), 4,09 (2H, t), 4,35 (2H, s), 8,86 (2H, s). MS: m/z 501 (2MH+)

Ejemplo 151

4-(1,2,3,4,4a,5,7,7a-octahidropirrolo[3,4-b]piridin-6-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida

La 4-(1,2,3,4,4a,5,7,7a-octahidropirrolo[3,4-b]piridin-6-il)-N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]benzamida se preparó siguiendo el procedimiento como en el Ejemplo 115, pero partiendo de 4-(1,2,3,4,4a,5,7,7a-octahidropirrolo[3,4-b]piridin-6-il)benzoato de metilo (0,221 g, 0,85 mmoles) y 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina HCl (0,243 g, 0,85 mmoles) y trimetilaluminio 2M en tolueno (1,06 ml, 2,13 mmoles). El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto

deseado se evaporaron hasta sequedad para dar el compuesto del título (0,124 g, 30,5 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,36 - 1,45 (1H, m), 1,50-1,60 (1H, m), 1,63 - 1,75 (2H, m), 2,12 (1H, s), 2,27 -2,38 (1H, m), 2,83 (1H, d), 3,16 (1H, d), 3,26 - 3,36 (2H, m), 3,37 - 3,45 (2H, m), 3,85 (6H, s), 5,08 (2H, s), 5,54 (1H, s), 6,44 (1H, s), 6,52 (2H, d), 6,57 (2H, s), 7,82 (2H, d), 10,46 (1H, s0, 11,45 (1H, s). 1 protón no observado. MS: m/z 478 (MH+).

Media de n = 3, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0013μM.

El 4-(1,2,3,4,4a,5,7,7a-octahidropirrolo[3,4-b]piridin-6-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se disolvió 2,3,4,4a,5,6,7,7a-octahidro-1H-pirrolo[3,4-b]piridina.2HCl (0,813 g, 5 mmoles) en agua (10 ml), y se coloó en una columna SCX2 (50g). Ésta se lavó con metanol y liberó la base libre de la columna con amoníaco 7N en metanol. La base libre y 4-fluorobenzoato de metilo (0,291 ml, 2,25 mmoles) se disolvieron en DMSO (10 ml), y se calentó a 120ºC durante 12 h. La mezcla de reacción bruta se purificó parcialmente mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de amoníaco 3M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto deseado (0,230 g, 17,67 %) como un sólido blanco.

RMN ^{1}H (700,03MHz, CDCl3)δ: 1,48 - 1,53 (1H, m), 1,57 - 1,68 (2H, m), 1,74 - 1,83 (1H, m), 2,34 - 2,40 (1H, m), 2,66 - 2,70 (1H, m), 2,97 - 3,02 (1H, m), 3,23 - 3,27(1H, m), 3,83 - 3,87 (1H, m), 3,46 - 3,50 (3H, m), 3,85 (3H, s), 6,49 (2H, d), 7,89 (2H, d). MS: m/z 261 (MH+).

Ejemplo 152

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(1-metilpiperidin-4-il)pirazin-2-carboxamida

Se añadió gota a gota trimetilaluminio (2 M en tolueno, 1,73 ml, 3,46 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (247 mg, 1,00 mmoles) y 5-(1-metilpiperidin-4-il)pirazin-2-carboxilato de metilo (235 mg, 1,00 mmoles) en tolueno anhidro (5,00 ml) a temperatura ambiente. La disolución resultante se agitó a 60ºC

durante 18 h. La mezcla de reacción se paralizó en metanol (100 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH. En este momento precipitó un sólido blanco a partir del eluyente. El precipitado se recogió mediante filtración por succión, y se secó a vacío para dar el producto (90 mg, 20%) como un sólido de color crema. El filtrado se concentró y se obtuvo una segunda muestra de producto mediante cristalización en metanol para dar el compuesto del título (93 mg, 21%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,80 - 1,89 (4H, m), 1,98 - 2,04 (2H, m), 2,22 (3H, s), 2,83 - 2,90 (7H, m), 3,73 (6H, s), 6,33 (1H, t), 6,43 (2H, d), 6,50 (1H, d), 8,73 (1H, d), 9,18 (1H, d), 10,27 (1H, s), 12,27 (1H, s). MS: m/z 451 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0013μM.

El 5-(1-metilpiperidin-4-il)pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió triacetoxiborohidruro de sodio (530 mg, 2,50 mmoles) a 5-(piperidin-4-il)pirazin-2-carboxilato de metilo (221 mg, 1,00 mmoles), formaldehído (disolución acuosa al 37%, 1,50 ml, 20,00 mmoles) y ácido acético (0,11 ml, 2,00 mmoles) en metanol (5,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se paralizó con agua (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 5-(1-metilpiperidin-4-il)pirazin-2-carboxilato de metilo (239 mg, 100%) como un sólido ceroso amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,92 - 1,99 (4H, m), 2,07 - 2,13 (2H, m), 2,34 (3H, s), 2,79 - 2,87 (1H, m), 2,99 - 3,03 (2H, m), 4,03 (3H, s), 8,61 (1H, d), 9,21 (1H, d). MS: m/z 236 (MH+).

El 5-(piperidin-4-il)pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió cloruro de hidrógeno (4M en 1,4-dioxano, 0,37 ml, 1,48 mmoles) a 5-[1-[(2-metilpropan-2-il)oxicarbonil]piperidin-4-il]pirazin-2-carboxilato de metilo (120 mg, 0,37

mmoles) en MeOH (3,70 ml). La disolución resultante se agitó a temperatura ambiente durante 24 h. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 5-(piperidin-4-il)pirazin-2-carboxilato de metilo (83 mg, 100%) como un sólido amarillo pálido. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,76 - 1,86 (2H, m), 1,92 - 1,97 (2H, m), 2,80 (2H, d), 2,97 - 3,05 (1H, m), 3,23 - 3,27 (2H, m), 4,04 (3H, s), 8,61 (1H, d), 9,22 (1H, d), NH no observado. MS: m/z 222 (MH+).

El 5-[1-[(2-metilpropan-2-il)oxicarbonil]piperidin-4-il]pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se agitó paladio, 10% sobre carbón (21 mg, 0,20 mmoles) y 5-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirazin-2-carboxilato de metilo (183 mg, 0,57 mmoles) en etanol (5,73 ml) en una atmósfera de hidrógeno a temperatura ambiente y presión atmosférica durante 6 h. La mezcla de reacción se filtró a través de celita y se concentró a presión reducida para dar un aceite amarillo. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 50% de EtOAc en isohexano. Las fracciones puras se evaporaron hasta sequedad para dar 5-[1-[(2-metilpropan-2-il)oxicarbonil]piperidin-4-il]pirazin-2-carboxilato de metilo (126 mg, 68%) como un aceite amarillo.

RMN ^{1}H (DMSO, 399,99 MHz) δ1,43 (9H, s), 1,58 - 1,68 (2H, m), 1,89 (2H, d), 2,88 (2H, s), 3,07 - 3,14 (1H, m), 3,92 (3H, s), 4,07 - 4,11 (2H, m), 8,78 (1H, d), 9,13 (1H, d). MS: m/z 322 (MH+).

El 5-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió disolución saturada de hidrogenocarbonato de sodio acuoso (5,00 ml) a 5-cloropirazin-2-carboxilato de metilo (173 mg, 1,00 mmoles), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-3,6-dihidro-2H-piridin-1-carboxilato de terc-butilo (371 mg, 1,20 mmoles), acetato de paladio (II) (11 mg, 0,05 mmoles) y trifenilfosfina (52 mg, 0,20 mmoles) en 1,2-dimetoxietano (5,00 ml) a 25°C en nitrógeno. La mezcla resultante se agitó a 80°C

durante 4 h. La mezcla de reacción se diluyó con agua (50 ml) y se lavó con EtOAc (50 ml). La capa acuosa se ajustó hasta pH 1 usando HCl (disolución acuosa 2M), y se extrajo con EtOAc (2 x 50 ml). Los orgánicos combinados se secaron sobre MgSO4 y se concentraron a presión reducida para dar ácido 5-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirazin-2-carboxílico (305 mg, 100%) como un sólido amarillo. Éste se usó directamente en la siguiente reacción, sin purificación adicional.

RMN ^{1}H (DMSO, 399,9MHz) δ1,45 (9H, s), 2,64 (2H, d), 3,58 (2H, t), 4,13 (2H, d), 7,02 (1H, s), 9,01 (1H, d), 9,12 (1H, d), 13,40 (1H, br s). MS: m/z 306 (MH+).

Ejemplo 153

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(1-metil-3,6-dihidro-2H-piridin-4-il)pirazin-2-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,74 ml, 3,48 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (343 mg, 1,39 mmoles) y 5-(1-metil-3,6-dihidro-2H-piridin-4-il)pirazin-2-carboxilato de metilo (324 mg, 1,39 mmoles) en tolueno anhidro (6,94 ml) a temperatura ambiente. La disolución resultante se agitó entonces a 60°C durante 18 h. La mezcla de reacción se paralizó en metanol (100 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (152 mg, 24%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,33 (3H, s), 2,63 - 2,64 (4H, m), 2,86 - 2,89 (4H, m), 3,16 (2H, s), 3,73 (6H, s), 6,33 (1H, s), 6,43 - 6,43 (2H, m), 6,50 (1H, s), 7,04 (1H, s), 8,96 (1H, s), 9,17 (1H, s), 10,26 (1H, s), 12,28 (1H, s). MS: m/z 449 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00082μM.

El 5-(1-metil-3,6-dihidro-2H-piridin-4-il)pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió triacetoxiborohidruro de sodio (749 mg, 3,53 mmoles) a 5-(1,2,3,6-tetrahidropiridin-4-il)pirazin-2-carboxilato de metilo (310 mg, 1,41 mmol), formaldehído (disolución acuosa al 37%, 2,10 ml, 28,30 mmoles) y ácido acético (0,16 ml, 2,83 mmoles) en metanol (7,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se paralizó con disolución saturada acuosa de NaHCO3 (5 ml), se diluyó con metanol (10 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar el compuesto deseado (324 mg, 98%) como un sólido ceroso bronceado. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, CDCl3) δ 2,44 (3H, s), 2,69 - 2,75 (4H, m), 3,23 - 3,25 (2H, m), 4,03 (3H, s), 6,89 - 6,91 (1H, m), 8,79 (1H, d), 9,20 (1H, d). MS: m/z 234 (MH+).

El 5-(1,2,3,6-tetrahidropiridin-4-il)pirazin-2-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió cloruro de hidrógeno (4M en 1,4-dioxano, 1,57 ml, 6,29 mmoles) a 5-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirazin-2-carboxilato de metilo (502 mg, 1,57 mmoles) en metanol (15,70 ml) a temperatura ambiente La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con agua (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar el compuesto deseado (316 mg, 92 %) como un sólido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 2,47 - 2,54 (2H, m, parcialmente oscurecido por el pico del disolvente), 2,94 (2H, t), 3,49 (2H, q), 3,92 (3H, s), 7,09 - 7,11 (1H, m), 9,00 (1H, d), 9,12 (1H, d), NH no observado. MS: m/z 261 (M+MeCN+H+).

El 5-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirazin-2-carboxilato de metilo usado como material de partida se preparó como se esquematiza en el Ejemplo 152.

Ejemplo 154

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3R,5S)-3,5-dimetilpiperazin-1-il]benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3R,5S)-3,5-dimetilpiperazin-1-il]-benzamida se preparó siguiendo el procedimiento como en el Ejemplo 155, pero partiendo de 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo (0,525 g, 2 mmoles), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,495 g, 2,00 mmoles) y trimetilaluminio 2M (2,5 ml, 5,0 mmoles en tolueno). La mezcla bruta se cromatografió en una columna SCX, eluyendo con amoníaco 7N en metanol. Las fracciones que contienen el producto se combinaron y se evaporaron para dar un aceite. Este aceite se suspendió en diclorometano (20 ml), y el producto cristalizó lentamente. Éste se filtró para dar el compuesto del título (0,465 g, 50,2 %).

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,04 - 1,05 (6H, m), 1,92 (2H, s), 2,20 - 2,25 (2H, m), 2,80 - 2,82 (1H, m), 2,81 - 2,84 (1H, m), 2,87 (4H, s), 3,71 - 3,74 (2H, m), 3,73 (6H, s), 6,33 (1H, t), 6,40 (1H, s), 6,42 (2H, d), 6,95 (2H, d), 7,89 (2H, d), 10,30 (1H, s). MS: m/z 464 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00075μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 155

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-[(3R,5S)-3,4,5-trimetilpiperazin-1-il]benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio (2,500 ml, 5,00 mmoles) en tolueno a una suspensión agitada de 4-((3R, 5S)-3,4,5-trimetilpiperazin-1-il)benzoato de etilo (0,643 g, 2 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,495 g, 2,00 mmoles) en tolueno (10 ml) a temperatura ambiente. La disolución se calentó entonces a 60°C durante 18 h. La mezcla de reacción se enfrió y se paralizó con metanol (15 ml) y ácido clorhídrico 2N (5 ml). La mezcla de reacción bruta se purificó mediante cromatografía de intercambio iónico en una columna SCX, eluyendo con amoníaco 7N en metanol. Las fracciones apropiadas se evaporaron para dar un aceite. El producto bruto se purificó

mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de amoníaco 2,5N / MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar, al cristalizar en DCM/éter dietílico, el compuesto del título (0,322 g, 33,7 %) como un sólido de color crema.

RMN ^{1}H (500,13MHz, DMSOd + CD3COOD a 373K) δ: 1,16 (6H, d), 2,34 (3H, s), 2,48 - 2,55 (2H, m), 2,66 (2H, t), 2,88 (4H, s), 3,69 - 3,75 (2H, m), 3,73 (3H, s), 6,28 - 6,92 (2H, m), 6,47 - 6,49 (2H, m), 6,92 (2H, d), 7,85 (2H, d). MS: m/z 478 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00045μM.

El 4-((3R,5S)-3,4,5-trimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió triacetoxiborohidruro de sodio (5,30 g, 25,00 mmoles) a 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo (2,62 g, 10 mmoles), y ácido acético (1,145 ml, 20,00 mmoles) en metanol (15 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se paralizó con NaHCO3 saturado (15 ml) hasta pH 7; y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar un aceite. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-((3R,5S)-3,4,5-trimetilpiperazin-1-il)benzoato de etilo (1,960 g, 70,9 %) como un aceite amarillo. MS: m/z 277 (MH+).

El 4-((3R,5S)-3,5-dimetilpiperazin-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió (2S,6R)-2,6-dimetilpiperazina (6,85 g, 60,00 mmoles) a 4-fluorobenzoato de etilo (2,20 ml, 15 mmoles) en DMSO (40 ml), y se calentó hasta 120°C en nitrógeno. La disolución resultante se agitó a 120°C durante 20 h. La mezcla de reacción se enfrió, y el disolvente se evaporó. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de metanol en diclorometano que contiene amoníaco 0,880 al 1%. Las fracciones puras se evaporaron hasta sequedad para dar 4-((3R,5S)-3,5-

dimetilpiperazin-1-il)benzoato de etilo (2,83 g, 71,9 %) como un aceite marrón, que solidificó al dejar reposar.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,15 (6H, d), 1,37 (3H, t), 2,38 (1H, d), 2,41 (1H, d), 2,96 - 3,04 (2H, m), 3,65 - 3,69 (2H, m), 4,33 (2H, q), 6,84 - 6,87 (2H, m), 7,89 - 7,93 (2H, m). MS: m/z 263 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 156

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metil-1,4-diazepan-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-metil-1,4-diazepan-1-il)benzamida se preparó siguiendo el procedimiento como en el Ejemplo 115, pero partiendo de 4-(4-metil-1,4-diazepan-1-il)benzoato de metilo (0,372 g, 1,5 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,371 g, 1,5 mmoles) y trimetilaluminio 2M en tolueno (1,875 ml, 3,75 mmoles). El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de amoníaco 2,5M/ MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad, y el aceite residual cristalizó en DCM/éter dietílico para dar el compuesto del título (0,142 g, 20,42 %) como un sólido blanco. RMN ^{1}H (500,13MHz, DMSOd6 + CD3COOD a 373K) δ: 2,08 - 2,15 (2H, m), 2,69 (3H, s), 2,88 (4H, s), 3,11 (2H, t), 3,19 - 3,24 (2H, m), 3,56 (2H, t), 3,72 (3H, s), 3,74 (2H, t), 6,30 (1H, d), 3,32 (1H,s), 6,49 (2H, s), 6,79 (2H, d), 7,86 (2H, d). MS: m/z 464 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00081μM.

El 4-(4-metil-1,4-diazepan-1-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió 1-metil-1,4-diazepano (15,07 g, 132,00 mmoles) a 4-fluorobenzoato de metilo (7,76 ml, 60 mmoles) en DMA (150 ml). La disolución resultante se agitó a 100ºC durante 40 h. La mezcla de reacción se evaporó y se paralizó con hidróxido sódico 2M (50 ml). Ésta se extrajo con DCM (3 x 50 ml). Los extractos orgánicos combinados se lavaron con salmuera saturada (50 ml), se secaron sobre MgSO4, se filtraron y se evaporaron hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de

0 a 10% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-metil-1,4-diazepan-1-il)benzoato de metilo (3,59 g, 24,10 %) como un sólido ceroso bronceado.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,95 (2H, q), 2,31 (3H, s), 2,48 (2H, d), 2,63 - 2,65 (2H, m), 3,47 (2H, t), 3,54 - 3,56 (2H, m), 3,78 (3H, s), 6,56 - 6,59 (2H, m), 7,79 - 7,83 (2H, m).

Ejemplo 157

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3-dimetilaminopirrolidin-1-il)pirazin-2-carboxamida

Se añadió N,N-dimetilpirrolidin-3-amina (114 mg, 1,00 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (136 mg, 0,35 mmoles) en dimetilsulfóxido anhidro (1,75 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 20 min. La mezcla de reacción se diluyó con metanol (5,00 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro como un aceite marrón. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (130 mg, 80%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,86 (1H, t), 2,16 - 2,21 (1H, m) 2,23 (6H, s), 2,83 - 2,85 (1H, m), 2,88 (4H, s), 3,25 - 3,29 (1H, m), 3,45 - 3,54 (1H, m), 3,72 (6H, s), 3,73 - 3,79 (1H, m), 3,81 - 3,86 (1H, m), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,01 (1H, d), 8,71 (1H, d), 9,73 (1H, s), 12,17 (1H, s). MS: m/z 466 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0024μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 158

5-(3-dietilaminopirrolidin-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió N,N-dietilpirrolidin-3-amina (142 mg, 1,00 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (136 mg, 0,35 mmoles) en dimetilsulfóxido anhidro (1,75 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 50 min. La mezcla de reacción se diluyó con metanol (5,00 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro como una película seca marrón. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (141 mg, 82%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 0,99 (6H, t), 1,80 - 1,90 (1H, m), 2,17 - 2,23 (1H, m), 2,56 - 2,68 (4H, m), 2,88 (4H, s), 3,20 - 3,26 (1H, m), 3,34 - 3,41 (1H, m), 3,43 - 3,50 (1H, m), 3,72 (6H, s), 3,73 - 3,78 (1H, m) 3,82 - 3,87 (1H, m), 6,33 (1H, t), 6,42 (2H, d), 6,46 (1H, s), 8,01 (1H, d), 8,71 (1H, d), 9,73 (1H, s), 12,17 (1H, s). MS: m/z 494 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0029μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 159

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(1-etilpiperidin-4-il)benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio en tolueno (0,413 ml, 0,83 mmoles) a una suspensión de 4-(1-etilpiperidin-4-il)benzoato de metilo (0,082 g, 0,33 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,082 g, 0,33 mmoles) en tolueno (2 ml) a temperatura ambiente. La disolución se calentó entonces a 60°C durante 18 h. La mezcla de reacción se enfrió, se paralizó con metanol (2 ml) y ácido clorhídrico 2N (1 ml). La mezcla de reacción se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y

MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,058 g, 38,0 %) como un sólido blanco. RMN ^{1}H (500,13 MHz, DH4OAcDMSO-d6) δ 1,21 (3H, t), 1,26 (2H, s), 1,84-1,93 (1H, m), 1,95 - 2,04 (2H, m), 2,77 (2H, t), 2,89 (4H, s), 2,94 (2H, q), 3,34 - 3,40 (2H, m), 3,72 (6H, s), 6,30 (1H, d), 6,35 (1H, d), 6,41 (2H, d), 7,34 (2H, d), 7,89 (2H, d). MS: m/z 463 (MH+). Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00097μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 4-(1-etilpiperidin-4-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió en porciones triacetoxiborohidruro de sodio (0,397 g, 1,88 mmoles) a acetaldehído (0,168 ml, 3,00 mmoles), 4-(piperidin-4-il)benzoato de metilo, HCl (0,192 g, 0,75 mmoles) y acetato de sodio (0,062 g, 0,75 mmoles) en metanol (5 ml) a temperatura ambiente. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se paralizó con $NaHCO_3$ saturado (3 ml) hasta pH 7, y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar un aceite. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(1-etilpiperidin-4-il)benzoato de metilo (0,082 g, 44,2 %) como un aceite incoloro. MS: m/z 248 (MH+).

Ejemplo 160

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-[3-(metoximetil)piperazin-1-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,596 ml, 3,19 mmoles) a una disolución de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (314 mg, 1,27 mmoles) y 2-(3-(metoximetil)piperazin-1-il)pirimidin-5-carboxilato de metilo (338 mg, 1,27 mmoles) en tolueno (6,35 ml) a 25°C. La mezcla resultante se agitó a 60°C durante 18 h en nitrógeno. La mezcla de reacción se añadió a metanol (100 ml), y se trató con HCl (disolución acuosa 2N,

hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar el producto bruto como una película seca amarilla. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (348 mg, 57 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 2,72 - 2,77 (2H, m), 2,82 - 2,92 (5H, m), 2,97 - 3,04 (2H, m), 3,24 - 3,28 (1H, m), 3,30 (3H, s), 3,35 - 3,38 (1H, m), 3,69 (6H, s), 4,61 (2H, d), 6,25 - 6,28 (3H, m), 6,61 (1H, s), 8,73 (1H, s), 8,76 (2H, s), 9,6 (1H, s). MS: m/z 482 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0043μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(3-(metoximetil)piperazin-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (300 mg, 1,74 mmoles) en DCM (4,70 ml) a una disolución agitada de 2-(metoximetil)piperazina (226 mg, 1,74 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,752 ml, 4,35 mmoles) en DCM (4,00 ml) a 25°C en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 6 h. La mezcla de reacción se concentró y se diluyó con MeOH. La mezcla resultante se filtró. El filtrado se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar 2-(3-(metoximetil)piperazin-1-il)pirimidin-5-carboxilato de metilo (346 mg, 75 %) como un sólido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 2,72 - 2,79 (2H, m), 2,84 - 2,90 (1H, m), 2,99 - 3,07 (2H, m), 3,25 - 3,30 (1H, m), 3,31 (3H, s), 3,38 - 3,42 (1H, m), 3,80 (3H, s), 4,61 - 4,68 (2H, m), 8,76 (2H, s). MS: m/z 267 (MH+)

La 2-(metoximetil)piperazina usada como material de partida se preparó según lo siguiente:

Se agitaron 1,4-dibencil-2-(metoximetil)piperazina (1,578 g, 5,08 mmoles) y paladio (10% sobre carbón, 0,163 g, 1,53 mmoles) en etanol (50,8 ml) en una atmósfera de hidrógeno a temperatura ambiente durante 3 días. La mezcla de reacción se filtró a través de celita, lavando con etanol. La mezcla resultante se evaporó hasta sequedad para dar producto bruto. El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar 2-(metoximetil)piperazina (0,559 g, 84 %) como un aceite amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 2,37 - 2,43 (1H, m), 2,65 - 2,76 (2H, m), 2,78 - 2,86 (3H, m), 2,89 - 2,92 (1H, m), 3,14 - 3,18 (1H, m), 3,24 - 3,27 (1H, m), 3,27 (3H, s).

La 1,4-dibencil-2-(metoximetil)piperazina usada como material de partida se preparó según lo siguiente:

Se añadió en porciones hidruro de sodio (0,857 g, 21,42 mmoles) a Et_2O agitado (23,0 ml) a 25°C en nitrógeno. Se añadió en porciones una disolución de (1,4-dibencilpiperazin-2-il)metanol (1,411 g, 4,76 mmoles) en DMF (8,0 ml) en nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 1 h. Se añadió gota a gota una disolución de yoduro de metilo (0,454 ml, 7,28 mmoles) en Et_2O (7,0 ml) a la mezcla de reacción a 10°C, en nitrógeno. La mezcla resultante se agitó a temperatura ambiente durante 21 h. La mezcla de reacción se paralizó con agua (35 ml), y se extrajo con Et_2O (3 x 50 ml). Las capas orgánicas se combinaron y se lavaron con agua (50 ml), se secaron sobre MgSO4, se filtraron y se evaporaron para dar 1,4-dibencil-2-(metoximetil)piperazina (1,580 g, 107 %) como un aceite amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,10 - 2,23 (3H, m), 2,44 - 2,48 (1H, m), 2,57 - 2,63 (3H, m), 3,21 (3H, s), 3,35 - 3,39 (1H, m), 3,44 (2H, d), 3,60 - 3,63 (1H, m), 3,95 - 3,99 (1H, m), 7,20 - 7,34 (10H, m). 1H oculto por el pico del agua. MS: m/z 311 (MH+)

Ejemplo 161

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(3-metilaminopirrolidin-1-il)pirazin-2-carboxamida

Se añadió cloruro de hidrógeno (4M en dioxano, 0,57 ml, 2,26 mmoles) a N-[1-[5-[[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]carbamoil]pirazin-2-il]pirrolidin-3-il]-N-metilcarbamato

de terc-butilo (312 mg, 0,57 mmoles) en metanol (2,80 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 48 h. La reacción no estaba terminada y se añadió más cloruro de hidrógeno (4M en dioxano, 0,28 ml, 1,12 mmoles), y la disolución se agitó a temperatura ambiente durante otras 16 h. La mezcla de reacción se diluyó con MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (101 mg, 39 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,85 - 1,93 (1H, m), 2,14 - 2,22 (1H, m), 2,43 (3H, s), 2,84 - 2,92 (4H, m), 3,39 - 3,42 (2H, m), 3,51 - 3,57 (1H, m), 3,63 - 3,68 (2H, m), 3,70 (6H, s), 6,25 - 6,26 (1H, m), 6,30 (2H, d), 6,43 (1H, s), 7,69 (1H, d), 8,85 (1H, d), 9,65 (1H, s). MS: m/z 452 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,003μM.

El N-[1-[5-[[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]carbamoil]pirazin-2-il]pirrolidin-3-il]-N-metilcarbamato de *terc*-butilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de N-metil-N-pirrolidin-3-ilcarbamato de *terc*-butilo (200 mg, 1,00 mmoles) en dioxano (0,75 ml) a una disolución agitada de 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (136 mg, 0,35 mmoles) en dioxano (0,75 ml) y NMP (0,25 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 24 h. La reacción no estaba terminada de forma que se añadió N-etil-N-propan-2-ilpropan-2-amina (0,06 ml, 0,35 mmoles), y la disolución se agitó a temperatura ambiente durante otras 17 h. La mezcla de reacción se diluyó con MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro (312 mg, 162%) como un aceite amarillo. Éste se usó directamente sin purificación adicional.

MS: m/z 552 (MH+)

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 162

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(1-metilpiperidin-4-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,168 ml, 2,34 mmoles) a una suspensión de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (231 mg, 0,93 mmoles) y 2-(1-metilpiperidin-4-il)pirimidin-5-carboxilato de metilo (220 mg, 0,93 mmoles) en tolueno anhidro (4,671 ml) a 25°C. La disolución resultante se agitó a 60°C durante 2 h. La mezcla de reacción se vertió en metanol (100 ml), se acidificó con HCl 2M, y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (166 mg, 39%) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,80 - 1,88 (2H, m), 1,94 (2H, d), 1,98 - 2,03 (2H, m), 2,21 (3H, s), 2,80 - 2,85 (3H, m), 2,89 (4H, s), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,49 (1H, s), 9,20 (2H, s), 11,04 (1H, s), 12,24 (1H, s). MS: m/z 451 (MH+).

Media de n = 4, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,036μM.

El 2-(1-metilpiperidin-4-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió triacetoxiborohidruro de sodio (532 mg, 2,51 mmoles) a 2-(piperidin-4-il)pirimidin-5-carboxilato de metilo (222 mg, 1,00 mmoles), formaldehído (disolución acuosa al 37%, 1,50 ml, 20,07 mmoles) y ácido acético (0,115 ml, 2,01 mmoles) en metanol (4,994 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se diluyó con metanol (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(1-

metilpiperidin-4-il)pirimidin-5-carboxilato de metilo (223 mg, 94%) como un sólido ceroso de color crema. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,77 - 1,88 (2H, m), 1,95 (2H, d), 2,00 - 2,07 (2H, m), 2,22 (3H, s), 2,83 - 2,90 (3H, m), 3,91 (3H, s), 9,19 (2H, s). MS: m/z 236 (MH+).

El 2-piperidin-4-ilpirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió cloruro de hidrógeno (4M en 1,4-dioxano, 3,04 ml, 12,15 mmoles) a una suspensión agitada de 2-(1-(terc-butoxicarbonil)piperidin-4-il)pirimidin-5-carboxilato de metilo (976 mg, 3,04 mmoles) en metanol (15,20 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(piperidin-4-il)pirimidin-5-carboxilato de metilo (600 mg, 89%) como un sólido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,63 - 1,73 (2H, m), 1,86 - 1,89 (2H, m), 2,58 - 2,65 (2H, m), 2,96 - 3,07 (3H, m), 3,91 (3H, s), 9,19 (2H, s), NH no observado. MS: m/z 222 (MH+).

El 2-[1-[(2-metilpropan-2-il)oxicarbonil]piperidin-4-il]pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se agitaron 2-(1-(terc-butoxicarbonil)-1,2,3,6-tetrahidropiridin-4-il)pirimidin-5-carboxilato de metilo (960 mg, 3,01 mmoles) y paladio, 10% sobre carbón (96 mg, 0,09 mmoles) en etanol (10 ml) y acetato de etilo (40,0 ml) en una atmósfera de hidrógeno a presión atmosférica y temperatura ambiente durante 18 h. La mezcla de reacción se filtró a través de celita, lavando con metanol, acetato de etilo y diclorometano, y se concentró a presión reducida para dar 2-(1-(terc-butoxicarbonil)piperidin-4-il)pirimidin-5-carboxilato de metilo (966 mg, 100%) como un aceite amarillo, que cristalizó al dejar reposar. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,42 (9H, s), 1,61 - 1,70 (2H, m), 1,97 (2H, d), 2,91 (2H, s), 3,10 - 3,16 (1H, m), 3,91 (3H, s), 4,03 (2H, d), 9,20 (2H, s). MS: 322 m/z (MH+).

El 2-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió gota a gota (trimetilsilil)diazometano, 2M en hexanos (4,19 ml, 8,38 mmoles), a ácido 2-(1-(terc-butoxicarbonil)-1,2,3,6-tetrahidropiridin-4-il)pirimidin-5-carboxílico (1,28 g, 4,19 mmoles) en tolueno (12 ml) y metanol (3,00 ml) a 25°C durante un periodo de 2 min en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se paralizó con la adición gota a gota de ácio acético hasta que se detuvo el burbujeo, y después la mezcla de reacción se diluyó con EtOAc (100 ml) y agua (100 ml). La capa orgánica se eliminó, y la acuosa se extrajo adicionalmente con EtOAc (2 x 50 ml). Los orgánicos combinados se lavaron con disolución de hidrogenocarbnato de sodio (100 ml), agua (100 ml), salmuera (100 ml), y se secaron sobre MgSO4, se filtraron y se evaporaron para dar 2-(1-(terc-butoxicarbonil)-1,2,3,6-tetrahidropiridin-4-il)pirimidin-5-carboxilato de metilo (1,182 g, 88%) como un sólido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,44 (9H, s), 2,63 - 2,66 (2H, m), 3,56 (2H, t), 3,92 (3H, s), 4,16 (2H, d), 7,38 (1H, s), 9,21 (2H, s). MS: m/z 320 (MH+).

El ácido 2-[1-[(2-metilpropan-2-il)oxicarbonil]-3,6-dihidro-2H-piridin-4-il]pirimidin-5-carboxílico usado como material de partida se preparó según lo siguiente:

Se añadió disolución saturada acuosa de hidrogenocarbonato de sodio (25,00 ml) a 2-cloropirimidin-5-carboxilato de metilo (0,863 g, 5 mmoles), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5,6-dihidropiridin-1(2H)-carboxilato de terc-butilo (1,855 g, 6,00 mmoles), acetato de paladio (II) (0,056 g, 0,25 mmoles) y trifenilfosfina (0,262 g, 1,00 mmoles) en 1,2-dimetoxietano (25,00 ml) a 25°C en nitrógeno. La mezcla resultante se agitó a 80°C durante 4 h. La mezcla de reacción enfriada se recogió en agua (50 ml), se lavó con EtOAc (50 ml), y después la capa acuosa se acidificó hasta pH 1 con HCl 2N. La capa acuosa se extrajo con EtOAc (3 x 25 ml), y los orgánicos combinados se lavaron con salmuera, se secaron sobre MgSO4 y se concentraron a presión reducida para dar ácido 2-(1-(terc-butoxicarbonil)-1,2,3,6-tetrahidropiridin-4-il)pirimidin-5-carboxílico (1,280 g, 84%) como un sólido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,44 (9H, s), 2,65 (2H, q), 3,56 (2H, t), 4,15 (2H, m), 7,36 (1H, s), 9,18 (2H, s), 13,6 (1H, s). MS: m/z 304 (M-H).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 163

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-metil-1,4-diazepan-1-il)pirazin-2-carboxamida

Se añadió 1-metil-1,4-diazepano (0,20 ml, 1,60 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (310 mg, 0,80 mmoles) en DMSO (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto como una película seca naranja. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (296 mg, 79 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,95 - 2,01 (2H, m), 2,32 (3H, s), 2,53 (2H, t), 2,66 (2H, t), 2,84 - 2,92 (4H, m), 3,65 - 3,75 (2H, m), 3,70 (6H, s), 3,81 - 3,86 (2H, m), 6,26 (1H, t), 6,29 (2H, d), 6,45 (1H, s), 7,82 (1H, d), 8,83 (1H, d), 9,65 (1H, s). One NH peak not observed.

MS: m/z 466 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0018μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 164

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-prop-2-enil-1,4-diazepan-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-prop-2-enil-1,4-diazepan-1-il)-benzamida se preparó usando el mismo procedimiento como en el Ejemplo 159, pero

partiendo de 4-(4-alil-1,4-diazepan-1-il)benzoato de etilo (0,288 g, 1 mmol), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1 mmol) y una disolución 2M de trimetilaluminio (1,250 ml, 2,50 mmoles) en tolueno. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar una goma, que solidificó al triturar con DCM/éter para dar el compuesto del título (0,071 g, 14,50 %).

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,87 - 1,93 (2H, m), 2,53 (2H, t), 2,68 (2H, t), 2,86 - 2,91 (4H, m), 3,07 (2H, d), 3,43 (2H, t), 3,48 (1H, t), 3,50 (1H, d), 3,71 (6H, s), 5,11 - 5,13 (1H, m), 5,12 - 5,17 (1H, m), 5,79 - 5,86 (1H, m), 6,28 (1H, t), 6,33 (2H, d), 6,59 (2H, d), 7,75 (2H, d), 9,26 (1H, s). MS: m/z 490 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00078μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 4-(4-alil-1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió 3-bromoprop-1-eno (0,433 ml, 5,00 mmoles) a una disolución agitada de 4-(1,4-diazepan-1-il)benzoato de etilo (1,242 g, 5 mmoles) y DIPEA (2,183 ml, 12,50 mmoles) en diclorometano (20 ml). La mezcla de reacción se agitó en nitrógeno a temperatura ambiente durante 24 h. Ésta se diluyó con diclorometano (20 ml), se lavó con agua (2 x 25 ml) y disolución saturada de cloruro de sodio (20 ml), se secó sobre $MgSO_4$, se filtró y se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de amoníaco 2,5M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-alil-1,4-diazepan-1-il)benzoato de etilo (0,700 g, 48,5 %) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,36 (3H, t), 1,94 - 2,00 (2H, m), 2,57 - 2,60 (2H, m), 2,75 (1H, d), 2,77 - 2,77 (1H, m), 3,10 - 3,12 (2H, m), 3,54 - 3,64 (4H, m), 4,31 (2H, q), 5,11 - 5,15 (1H, m), 5,11 - 5,19 (1H, m), 5,78 - 5,91 (1H, m), 6,62 - 6,66 (2H, m), 7,87 - 7,90 (2H, m). MS: m/z 289 (MH+).

El 4-(1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

4-Fluorobenzoato de etilo (11,01 ml, 75 mmoles) y 1,4-diazepano (30,0 g, 300,00 mmoles) en DMSO (150 ml) calentado hasta 100ºC en nitrógeno. La disolución resultante se agitó a 100ºC durante 24 h. La mezcla de reacción se enfrió y se evaporó hasta sequedad. La mezcla de reacción se paralizó con NaOH 2M (150 ml), se extrajo con EtOAc (3 x 75 ml), la capa orgánica se lavó con salmuera saturada (100 ml), se secó sobre MgSO4, se filtró y se evaporó para dar 4-(1,4-diazepan-1-il)benzoato de etilo (17,43 g, 94 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,27 - 1,31 (3H, m), 1,71 (1H, s), 1,79 - 1,85 (2H, m), 2,74 (1H, d), 2,74 (1H, d), 2,95 (1H, d), 2,96 (1H, d), 3,51 (2H, t), 3,56 (2H, t), 4,21 - 4,27 (2H, m), 6,56 - 6,60 (2H, m), 7,80 - 7,83 (2H, m). MS: m/z 249 (MH+).

Ejemplo 165

4-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]benzamida

La 4-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-benzamida se preparó usando el mismo procedimiento como en el Ejemplo 159, pero partiendo de 4-(4-ciclopropil-1,4-diazepan-1-il)benzoato de etilo (0,288 g, 1 mmol), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,247 g, 1 mmol) y una disolución 2M de trimetilaluminio (1,250 ml, 2,50 mmoles) en tolueno. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar una goma, que solidificó al triturar con DCM/éter para dar el compuesto del título (0,165 g, 33,7 %).

RMN ^{1}H (500,13 MHz, DMSOd6 + CD3COOD @ 373K) δ 0,32-0,36 (2H, m), 0,41-0,47 (2H, m), 1,84 – 1,90 (2H, m), 2,93-2,98 (1H, m), 2,76 (2H, t), 2,87 (4H, s), 2,93 (2H, t), 3,50 –3,58 (4H, m), 3,72 (6H, s), 6,29 (1H, s), 6,30-6,32 (1H, m), 6,39 (2H, d), 6,72 (2H, d), 7,81 (2H, d). MS: m/z 490 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,000064μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 4-(4-ciclopropil-1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Una disolución de 4-(1,4-diazepan-1-il)benzoato de etilo (0,621 g, 2,5 mmoles), (1-etoxiciclopropoxi)trimetilsilano (2,51 ml, 12,50 mmoles) y ácido acético (0,286 ml, 5,00 mmoles) en tetrahidrofurano (50 ml), metanol (5 ml) se trató con cianoborohidruro de sodio (0,393 g, 6,25 mmoles) a 20°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción se enfrió, se filtró y se evaporó hasta sequedad. Se añadieron HCl 1N (40 ml) y agua (60 ml), y la disolución se extrajo con acetato de etilo (3 x 50 ml). La capa acuosa se basificó hasta pH 10 con carbonato de potasio sólido, y se extrajo con acetato de etilo (4 x 50 ml). Los extractos orgánicos se lavaron con NaCl saturado (50 ml), y se secaron sobre $MgSO_4$, se filtraron y se evaporaron hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-ciclopropil-1,4-diazepan-1-il)benzoato de etilo (0,849 g, 118 %) como un aceite incoloro.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 0,33 (1H, t), 0,34 - 0,35 (1H, m), 0,36 - 0,41 (1H, m), 0,37 - 0,40 (1H, m), 1,29 (3H, t), 1,74 - 1,79 (1H, m), 1,84 - 1,90 (2H, m), 2,69 (2H, t), 2,86 (2H, t), 3,47 (2H, t), 3,49 (2H, t), 4,24 (2H, q), 6,58 (1H, d), 6,60 (1H, s), 7,81 - 7,84 (2H, m). MS: m/z 289 (MH+) (ESI+).

Ejemplo 166

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-propan-2-il-1,4-diazepan-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-propan-2-il-1,4-diazepan-1-il)-benzamida se preparó usando el mismo procedimiento como en el Ejemplo 159, pero partiendo de 4-(4-isopropil-1,4-diazepan-1-il)benzoato de etilo (0,212 g, 0,73 mmoles), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,181 g, 0,73 mmoles) y una disolución 2M de trimetilaluminio (0,913 ml, 1,83 mmoles) en tolueno. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar una goma que solidificó al triturar con DCM/éter para dar el compuesto del título (0,154 g, 42,9 %) como un sólido de color crema.

RMN ^{1}H (500,13 MHz, DMSOd6 + CD3COOD a 373K) δ 1,00 (6H, s), 1,85-1,90 (2H, m), 2,64 (2H, t) 2,80-2,85 (2H, m), 2,88 (4H, s), 2,94-3,01 (1H, m), 3,53-3,59 (4H, m), 3,72 (6H, s), 6,29 (1H, s), 6,30-6,32 (1H, m), 6,40 (2H, d), 6,73 (2H, d), 7,81 (2H, d). MS: m/z 492 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0007μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 4-(4-isopropil-1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Una disolución de 4-fluorobenzoato de etilo (0,293 ml, 2 mmoles) y 1-isopropil-1,4-diazepano (0,539 ml, 4,00 mmoles) en dimetilsulfóxido (10 ml), se calentó a 120ºC durante 18 h. La mezcla de reacción se diluyó con agua (75 ml), y se extrajo con acetato de etilo (3 x 25 ml). Los extractos se lavaron con disolución saturada de cloruro de sodio (50 ml), se secó sobre MgSO4, se filtró y se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 4-(4-isopropil-1,4-diazepan-1-il)benzoato de etilo (0,212 g, 36,5 %) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, CDCl3) δ 0,92 (6H, d), 1,28 (3H, t), 1,80 - 1,86 (2H, m), 2,46 (2H, t), 2,69 (2H, t), 2,81 - 2,89 (1H, m), 3,51 (4H, t), 4,24 (2H, q), 6,58 (2H, d), 7,81 (2H, d). MS: m/z 291 (MH+) (ESI+).

Ejemplo 167

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-propan-2-il-1,4-diazepan-1-il)pirazin-2-carboxamida

Se añadió 1-isopropil-1,4-diazepano (228 mg, 1,60 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (310 mg, 0,80 mmoles) en DMSO (4,00 ml) a 25ºC. La disolución resultante se agitó a temperatura ambiente durante 2 horas. La reacción no estaba terminada así que la temperatura se incrementó hasta 60ºC, y la mezcla de reacción se agitó otras 2 h. La reacción todavía estaba sin terminar de forma que la mezcla de reacción se agitó otras 18 h a temperatura ambiente. La mezcla de reacción se diluyó con

MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto como una película seca naranja. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (167 mg, 42%) como un sólido amarillo pálido.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 0,93 (6H, d), 1,83 - 1,89 (2H, m), 2,54 (2H, t), 2,72 (2H, t), 2,82 - 2,92 (5H, m), 3,70 (6H, s), 3,73 - 3,76 (4H, m), 6,26 (1H, d), 6,29 (2H, d), 6,43 (1H, s), 7,81 (1H, d), 8,82 (1H, d), 9,64 (1H, s). No se observó una señal de NH. MS: m/z 494 (MH+). Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00063μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 168

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-propan-2-il-1,4-diazepan-1-il)tiofen-2-carboxamida

Se añadió gota a gota trimetilaluminio (0,751 ml, 1,50 mmoles) a una suspensión agitada de 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (148 mg, 0,60 mmoles) y 5-(4-propan-2-il-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo (178 mg, 0,60 mmoles) en tolueno (3,002 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se añadió a metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o inferior), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar material impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (123 mg, 41%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,95 - 0,96 (6H, m), 1,79 - 1,85 (2H, m), 2,54 - 2,56 (2H, m), 2,72 (2H, m), 2,85 (4H, s), 2,88 (1H,m), 3,42 - 3,48 (4H, m), 3,72 (6H, s), 5,86 (1H, d),

6,33 (1H, s), 6,34 (1H, s), 6,41 (2H, d), 7,78 (1H, d), 10,14 (1H, s), 12,00 (1H, s). MS: m/z 498 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0015μM.

El 5-(4-propan-2-il-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió en porciones triacetoxiborohidruro de sodio (396 mg, 1,87 mmoles) a 5-(1,4-diazepan-1-il)tiofen-2-carboxilato de etilo (190 mg, 0,75 mmoles) y ácido acético (0,086 ml, 1,49 mmoles) en acetona (1,917 ml) a temperatura ambiente. La disolución resultante se agitó a temperatura ambiente durante 18 h en nitrógeno. La mezcla de reacción se concentró y se diluyó con agua (200 ml) y se basificó con NaOH 2M. La capa acuosa se extrajo con éter dietílico (3 x 100 ml) y se lavó secuencialmente con agua (200 ml) y salmuera saturada (200 ml). La capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar producto deseado 5-(4-isopropil-1,4-diazepan-1-il)tiofen-2-carboxilato de etilo (181 mg, 82%). Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 0,99 - 1,01 (6H, m), 1,33 (3H, t), 1,89 - 1,95 (2H, m), 2,59 - 2,62 (2H, m), 2,75 - 2,77 (2H, m), 2,88 - 2,95 (1H, m), 3,48 - 3,52 (4H, m), 4,27 (2H, q), 5,77 - 5,78 (1H, d), 7,54 (1H, d). MS: m/z 297 (MH+).

El 5-(1,4-diazepan-1-il)tiofen-2-carboxilato de etilo usado como material de partida se preparó según lo siguiente:

Se añadió acetato de paladio (II) (52,1 mg, 0,23 mmoles), seguido de terc-butóxido de sodio (624 mg, 6,49 mmoles), a una disolución agitada de 5-bromotiofen-2-carboxilato de etilo (1090 mg, 4,64 mmoles), homopiperazina (511 mg, 5,10 mmoles) y (rac)-(-)-2,2'-bis(difenilfosfino)-1,1'-binaftilo (289 mg, 0,46 mmoles) en tolueno (20 ml) a 25ºC en nitrógeno. La suspensión resultante se agitó a 110ºC durante 3 h. La mezcla de reacción enfriada se diluyó con MeOH, y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones que contienen el producto deseado se evaporaron hasta sequedad para dar producto impuro como un aceite marrón. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7N/MeOH en DCM, y después 0 a 3% de NH3/MeOH en DCM. Las fracciones puras

se evaporaron hasta sequedad para dar 5-(4-etilpiperazin-1-il)tiofen-2-carboxilato de etilo (195 mg, 17%) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,33 (3H, t), 1,89 - 1,95 (2H, m), 2,88 (2H, t), 3,03 - 3,06 (2H, m), 3,49 - 3,54 (2H, m), 3,57 (2H, t), 4,27 (2H, q), 5,80 (1H, d), 7,54 (1H, d) NH no observado. MS: m/z 255 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 169

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-etil-1,4-diazepan-1-il)pirazin-2-carboxamida

Se añadió 1-etil-1,4-diazepano (205 mg, 1,60 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (310 mg, 0,80 mmoles) en DMSO (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 2 h. La reacción no estaba terminada así que la temperatura se incrementó hasta 60°C y la mezcla de reacción se agitó otros 15 min. La mezcla de reacción se diluyó con MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto como una película seca naranja. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (228 mg, 59 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,00 (3H, t), 1,91 - 1,97 (2H, m), 2,50 (2H, q), 2,56 (2H, t), 2,72 (2H, t), 2,84 - 2,91 (4H, m), 3,69 (6H, s), 3,67 - 3,71 (2H, m), 3,79 - 3,82 (2H, m), 6,25 (1H, t), 6,29 (2H, d), 6,45 (1H, s), 7,81 (1H, d), 8,83 (1H, d), 9,68 (1H, s). MS: m/z 480 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0027μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 170

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-etil-1,4-diazepan-1-il)benzamida

La N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-etil-1,4-diazepan-1-il)benzamida se preparó usando el mismo procedimiento como en el Ejemplo 159, pero partiendo de 4-(4-etil-1,4-diazepan-1-il)benzoato de etilo (0,502 g, 1,4 mmoles), 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (0,346 g, 1,40 mmoles) y una disolución 2M de trimetilaluminio (1,750 ml, 3,50 mmoles) en tolueno. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar una goma que solidificó al triturar con DCM/éter para dar el compuesto del título (0,171 g, 25,6 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,00 (3H, t), 1,89 (2H, d), 2,53 (2H, d), 2,73 (4H, s), 2,87 (4H, s), 3,49 - 3,54 (2H, m), 3,54 - 3,58 (2H, m), 3,73 (6H, s), 6,33 (1H, t), 6,42 (3H, d), 6,73 (2H, d), 7,87 (2H, d), 10,17 (1H, s), 12,04 (1H, s). MS: m/z 478 (MH+) (ESI+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00071μM.

El 4-(4-etil-1,4-diazepan-1-il)benzoato de etilo usado como material de partida se preparó según lo siguiente:

Una disolución de 4-(1,4-diazepan-1-il)benzoato de etilo (0,621 g, 2,5 mmoles), acetaldehído (0,701 ml, 12,50 mmoles) y ácido acético (0,286 ml, 5,00 mmoles) en tetrahidrofurano (30 ml), metanol (3 ml) se trató con cianoborohidruro de sodio (0,393 g, 6,25 mmoles) a 20°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción se enfrió, y se añadió una cantidad extra de acetaldehído (2,146 ml, 38 mmoles) y triacetoxiborohidruro de sodio (1,060 g, 5,00 mmoles). La reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se filtró y se evaporó hasta sequedad. El residuo se disolvió en HCl 2N (5 ml) y metanol (20 ml). La disolución de producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar 4-(4-etil-1,4-diazepan-1-il)benzoato de etilo (0,526 g, 76 %)

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,07 (3H, t), 1,36 (3H, t), 1,90 - 2,05 (2H, m), 2,52 - 2,61 (2H, m), 2,70 - 2,77 (2H, m), 3,54 (2H, t), 3,57 (2H, t), 4,29 - 4,34 (2H, m), 6,63 - 6,67 (2H, m), 7,86 - 7,90 (2H, m). MS: m/z 277 (MH+).

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

Ejemplo 171

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-etil-1,4-diazepan-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (1,25 ml, 2,50 mmoles) a una suspensión agitada de 2-(4-etil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (265 mg, 1,00 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (248 mg, 1,00 mmoles) en tolueno (5,01 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se paralizó en metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen producto deseado aún contenían una impureza, de forma que se concentraron hasta sequedad y se purificaron mediante cristalización en MeCN para dar el compuesto del título (104 mg, 22%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,99 (3H, t), 1,82 - 1,87 (2H, m), 2,48 (2H, q, ocultos parcialmente por el pico de DMSO), 2,52 - 2,57 (2H, m, ocultos parcialmente por el pico de DMSO), 2,71 (2H, m), 2,87 (4H, s), 3,72 (6H, s), 3,82 (2H, t), 3,87 (2H, t), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,88 (2H, s), 10,56 (1H, s), 12,13 (1H, s). MS: m/z 480 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0092μM.

El 2-(4-etil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (200 mg, 1,16 mmoles) en diclorometano (4,00 ml) a una disolución agitada de 1-etil-1,4-diazepano (149 mg, 1,16 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,902 ml, 5,22 mmoles) en diclorometano (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(4-etil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (268 mg, 87%) como un aceite crema, que cristalizó al dejar reposar. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,98 (3H, t), 1,81 - 1,87 (2H, m), 2,45- 2,50 (2H, m), 2,55 (2H, m), 2,70 - 2,72 (2H, m), 3,81 (3H, s), 3,82 (2H, q), 3,86 - 3,89 (2H, m), 8,79 (2H, s). MS: m/z 265 (MH+).

El 1-etil-1,4-diazepano usado como material de partida se preparó según lo siguiente:

Se añadió hidruro de litio y aluminio (38,2 ml, 38,19 mmoles) a 1-(1,4-diazepan-1-il)etanona (1,697 g, 11,93 mmoles) en THF (59,7 ml) a 0°C en nitrógeno. La disolución resultante se agitó a temperatura ambiente durante 1 h, y después a 60°C durante 1 h. La mezcla de reacción enfriada se vertió sobre hielo (500 ml), se acidificó con HCl (disolución acuosa 2M) y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 1-etil-1,4-diazepano (0,610 g, 40%) como un líquido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,07 (3H, t), 1,74 - 1,80 (2H, m), 2,58 (2H, q), 2,64 - 2,70 (4H, m), 2,89 - 2,95 (4H, m).

Ejemplo 172

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-5-(4-prop-2-enil-1,4-diazepan-1-il)pirazin-2-carboxamida

Se añadió 1-prop-2-enil-1,4-diazepano (224 mg, 1,60 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (310 mg, 0,80 mmoles) en DMSO (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 3 h. La

mezcla de reacción se diluyó con MeOH (5 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto como un aceite naranja. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (271 mg, 69 %) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,91 - 1,97 (2H, m), 2,57 (2H, t), 2,72 (2H, t), 2,84 - 2,91 (4H, m), 3,06 (2H, d), 3,70 (6H, s), 3,74 - 3,83 (4H, m), 5,07 - 5,13 (2H, m), 5,73 - 5,83 (1H, m), 6,25 (1H, t), 6,29 (2H, d), 6,43 (1H, s), 7,82 (1H, d), 8,83 (1H, d), 9,64 (1H, s). MS: m/z 492 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0034μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 173

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-propan-2-il-1,4-diazepan-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (1,19 ml, 2,38 mmoles) a una suspensión agitada de 2-(4-propan-2-il-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (265 mg, 0,95 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (235 mg, 0,95 mmoles) en tolueno (4,76 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se paralizó en metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (81 mg, 17%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,94 - 0,95 (6H, m), 1,78 (2H, m), 2,51 - 2,54 (2H, m, ocultos parcialmente por el pico de DMSO), 2,67 - 2,74 (3H, m), 2,87 (4H, s), 3,73 (6H, s),

3,82 (4H, t), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,88 (2H, s), 10,55 (1H, s), 12,13 (1H, s). MS: m/z 494 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,018μM.

El 2-(4-propan-2-il-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (209 mg, 1,21 mmol) en diclorometano (4,00 ml) a una disolución agitada de 1-propan-2-il-1,4-diazepano (172 mg, 1,21 mmol) y N-etil-N-propan-2-ilpropan-2-amina (0,523 ml, 3,02 mmoles) en diclorometano (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(4-propan-2-il-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (267 mg, 79 %) como un aceite de color crema, que cristalizó al dejar reposar. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,92 - 0,94 (6H, m), 1,74 - 1,80 (2H, m), 2,71 (2H, t), 2,82 - 2,89 (1H, m), 3,81 (3H, s), 3,80 - 3,85 (4H, m), 8,78 - 8,78 (2H, m), 1 x (2H, m) oscurecido por el pico de DMSO. MS: m/z 279 (MH+).

El 1-propan-2-il-1,4-diazepano usado como material de partida se preparó según lo siguiente:

Se agitaron 4-propan-2-il-1,4-diazepan-1-carboxilato de bencilo (3,00 g, 10,85 mmoles) y paladio, 10% sobre carbón (0,289 g, 2,71 mmol) en etanol (54,3 ml) en una atmósfera de hidrógeno a presión atmosférica y temperatura ambiente durante 18 h. La mezcla de reacción se filtró a través de celita, lavando con etanol, metanol y diclorometano, y el filtrado se concentró a presión reducida para dar 1-propan-2-il-1,4-diazepano (1,54 g, 100%) como un líquido amarillo. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, CDCl3) δ 1,00 - 1,02 (6H, m), 1,69 - 1,74 (2H, m), 1,94 (1H, br s), 2,63 - 2,68 (4H, m), 2,87 - 2,94 (5H, m).

El 4-propan-2-il-1,4-diazepan-1-carboxilato de bencilo usado como material de partida se preparó según lo siguiente:

Se añadió en porciones triacetoxiborohidruro de sodio (5,79 g, 27,32 mmoles) a 1,4-diazepan-1-carboxilato de bencilo (2,56 g, 10,93 mmoles) y ácido acético (1,251 ml, 21,85 mmoles) en acetona (5,00 ml) a temperatura ambiente. La disolución resultante se agitó a temperatura ambiente durante 18 h en nitrógeno. La mezcla de reacción se concentró y se diluyó con agua (200 ml), y se basificó con NaOH 2M. La capa acuosa se extrajo con éter dietílico (3 x 100 ml) y se lavó secuencialmente con agua (200 ml) y salmuera saturada (200 ml). La capa orgánica se secó sobre MgSO4, se filtró y se evaporó para dar el producto deseado (3,00 g, 99%). Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,92 - 0,95 (6H, m), 1,63 - 1,69 (2H, m), 2,60 (2H, t), 2,80 - 2,88 (1H, m), 3,38 - 3,45 (4H, m), 5,09 (2H, s), 7,29 - 7,40 (5H, m), un (2H, m) oscurecido por el pico del disolvente. MS: m/z 277 (MH+).

Ejemplo 174

5-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida

Se añadió 1-ciclopropil-1,4-diazepano, 2HCl (205 mg, 0,96 mmoles) a 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida (310 mg, 0,80 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,48 ml, 2,80 mmoles) en DMSO (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 24 h. La reacción no estaba terminada así que la temperatura se incrementó hasta 80°C y la mezcla de reacción se agitó otras 3 h. La mezcla de reacción se diluyó con MeOH (5 ml). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto bruto como un aceite marrón. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (277 mg, 70%) como un sólido amarillo.

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 0,32 - 0,37 (2H, m), 0,38 - 0,43 (2H, m), 1,75 - 1,80 (1H, m), 1,86 - 1,92 (2H, m), 2,74 (2H, t), 2,83 - 2,92 (6H, m), 3,70 (6H, s), 3,70 - 3,77 (4H, m), 6,26 (1H, t), 6,29 (2H, d), 6,42 (1H, s), 7,82 (1H, d), 8,83 (1H, d), 9,64 (1H, s). MS: m/z 492 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0037μM.

La 5-cloro-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirazin-2-carboxamida se preparó como se muestra en el Ejemplo 105.

Ejemplo 175

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-prop-2-enil-1,4-diazepan-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (1,35 ml, 2,70 mmoles) a una suspensión agitada de 2-(4-prop-2-enil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (300 mg, 1,09 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (268 mg, 1,09 mmoles) en tolueno (5,43 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se paralizó en metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (220 mg, 41%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,82 - 1,88 (2H, m), 2,53 - 2,57 (2H, m, ocultos parcialmente por el pico de DMSO), 2,71 (2H, t), 2,88 (4H, s), 3,08 (2H, d), 3,73 (6H, s), 3,83 (2H, t), 3,86 - 3,88 (2H, m), 5,10 - 5,13 (1H, m), 5,17 (1H, d), 5,77 - 5,87 (1H, m), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,89 (2H, s), 10,56 (1H, s), 12,13 (1H, s). MS: m/z 492 (MH+). Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,007μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(4-prop-2-enil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (200 mg, 1,16 mmoles) en diclorometano (4,00 ml) a una disolución agitada de 1-prop-2-enil-1,4-diazepano (163 mg,

1,16 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,501 ml, 2,90 mmoles) en diclorometano (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeCN (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar el compuesto deseado (304 mg, 95%) como un aceite de color crema que cristalizó al dejar reposar. Éste se usó directamente sin purificación adicional. RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,81 - 1,87 (2H, m), 2,55 (2H, m), 2,70 - 2,72 (2H, m), 3,06 - 3,09 (2H, m), 3,81 (3H, s), 3,80 - 3,89 (4H, m), 5,09 - 5,13 (1H, m), 5,13 - 5,19 (1H, m), 5,76 - 5,86 (1H, m), 8,79 (2H, d). MS: m/z 277 (MH+).

El 1-prop-2-enil-1,4-diazepano usado como material de partida se preparó según lo siguiente:
A una disolución de 1-homopiperazincarboxilato de terc-butilo (9,73 ml, 50 mmoles) en diclorometano (250 ml) se añadió resina de PS-TBD (40g, 100 mmoles) y 3-bromoprop-1-eno (4,33 ml, 50 mmoles) gota a gota a 25°C. La mezcla se agitó durante 2h. La PS-TBD se separó por filtración, y el filtrado se evaporó hasta sequedad, se redisolvió en MeOH/EtOAc (1:9) y después se filtró a través de una columna de sílice corta. El filtrado obtenido se evaporó hasta sequedad, se trató con TFA (20 ml) y después se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (50 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 1-prop-2-enil-1,4-diazepano (4,07 g, 58,0 %) como un aceite amarillo pálido.
RMN ^{1}H (399,902 MHz, CDCl3) δ 1,70 (m, 2H), 1,98 (s, 1H), 2,59 (m, 4H), 2,85 (m, 4H), 3,06 (m, 2H), 5,07 (m, 2H), 5,81 (m, 1H)

Ejemplo 176

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-2-(4-metil-1,4-diazepan-1-il)pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (1,35 ml, 2,70 mmoles) a una suspensión agitada de 2-(4-metil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (270 mg, 1,08 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (267 mg, 1,08 mmoles) en tolueno (5,39 ml) a

25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se paralizó en metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen compuesto deseado puro se evaporaron hasta sequedad para dar el compuesto del título (136 mg, 27%) como un sólido de color crema. Las fracciones que contienen producto impuro se concentraron y se purificaron mediante cristalización en MeCN para dar el compuesto del título (56,0 mg, 11%) como un sólido beige.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,86 - 1,92 (2H, m), 2,27 (3H, s), 2,64 (2H, t), 2,88 (4H, s), 3,73 (6H, s), 3,81 (2H, t), 3,89 (2H, t), 6,33 (1H, t), 6,41 - 6,45 (3H, m), 8,89 (2H, s), 10,57 (1H, s), 12,13 (1H, s). 2H ocultos por el pico de DMSO. MS: m/z 466 (MH+).

Media de n= 1, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0058μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(4-metil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (200 mg, 1,16 mmoles) en diclorometano (4,00 ml) a una disolución agitada de 1-metil-1,4-diazepano (0,144 ml, 1,16 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,902 ml, 5,22 mmoles) en diclorometano (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(4-metil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (274 mg, 94%) como un sólido blanco. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,86 - 1,89 (2H, m), 2,26 (3H, s), 2,49 - 2,54 (2H, m, ocultos parcialmente por el pico de DMSO), 2,62 - 2,64 (2H, m), 3,81 (3H, s), 3,80 - 3,84 (2H, m), 3,89 - 3,91 (2H, m), 8,79 (2H, d). MS: m/z 251 (MH+)

Ejemplo 177

2-(4-ciclopropil-1,4-diazepan-1-il)-N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]pirimidin-5-carboxamida

Se añadió gota a gota trimetilaluminio (1,402 ml, 2,80 mmoles) a una suspensión agitada de 2-(4-ciclopropil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (310 mg, 1,12 mmoles) y 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (277 mg, 1,12 mmoles) en tolueno (5,61 ml) a 25°C. La disolución resultante se agitó a 60°C durante 18 h. La mezcla de reacción enfriada se paralizó en metanol (50 ml) y se trató con HCl (disolución acuosa 2M, hasta pH 7 o menor), y se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar producto impuro. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (8,00 mg, 1%) como un sólido de color crema. Algunas fracciones impuras se combinaron y se concentraron hasta sequedad, y se purificaron mediante cristalización en MeCN para dar el compuesto del título (51 mg, 9%) como un sólido de color crema.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,31 (2H, m), 0,41 - 0,44 (2H, m), 1,84 - 1,89 (3H, m), 2,71 (2H, t), 2,88 (4H, s), 3,73 (6H, s), 3,81 - 3,87 (4H, m), 6,33 (1H, t), 6,42 (2H, d), 6,44 (1H, s), 8,89 (2H, s), 10,55 (1H, s), 12,14 (1H, s), 2H ocultos por el pico de DMSO. MS: m/z 492 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0073μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 2-(4-ciclopropil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió una disolución de 2-cloropirimidin-5-carboxilato de metilo (200 mg, 1,16 mmoles) en diclorometano (4,00 ml) a una disolución agitada de 1-ciclopropil-1,4-diazepano (247 mg, 1,16 mmoles) y N-etil-N-propan-2-ilpropan-2-amina (0,902 ml, 5,22 mmoles) en diclorometano (4,00 ml) a 25°C. La disolución resultante se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad y se redisolvió en MeOH (20 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y se evaporó hasta sequedad para dar 2-(4-ciclopropil-1,4-diazepan-1-il)pirimidin-5-carboxilato de metilo (312 mg, 97%) como un sólido de color crema. Éste se usó directamente sin purificación adicional.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 0,28 - 0,31 (2H, m), 0,40 - 0,45 (2H, m), 1,80 - 1,84 (2H, m), 1,85 - 1,89 (1H, m), 2,71 (2H,m), 2,85 - 2,88 (2H, m), 3,81 (3H, s), 3,82 - 3,88 (4H, m), 8,79 (2H, s). MS: m/z 277 (MH+)

Ejemplo 178

N-[5-[2-[3-(metilcarbamoil)fenil]etil]-2H-pirazol-3-il]-4-(4-metilpiperazin-1-il)benzamida

Se añadió gota a gota una disolución 2M de trimetilaluminio (0,936 ml, 1,87 mmoles) en tolueno a una suspensión agitada de 3-(2-(5-amino-1H-pirazol-3-il)etil)-N-metilbenzamida (0,183 g, 0,75 mmoles) y 4-(4-metilpiperazin-1-il)benzoato de metilo (0,176 g, 0,75 mmoles) en tolueno (5 ml) a temperatura ambiente. La disolución se agitó entonces a 60°C durante 18 h. La mezcla de reacción se enfrió, se vertió en metanol (5 ml) y se acidificó con HCl 2N (15 ml). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones puras se evaporaron hasta sequedad para dar un aceite. El producto bruto se purificó mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes. Las fracciones que contienen el compuesto deseado se evaporaron hasta sequedad para dar el compuesto del título (0,109 g, 32,6 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d6) δ 1,88 (3H, s), 2,23 (3H, s), 2,45 (4H, t), 2,87 - 3,02 (4H, m), 3,40 (4H, t), 6,39 (1H, s), 6,97 (2H, d), 7,37 (1H, s), 7,38 (2H, t), 7,65 - 7,67 (1H, m), 7,75 (1H, s), 7,90 (2H, d), 8,36 (1H, d), 10,36 (1H, s). MS: m/z 447 (MH+).

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0011μM.

La 3-(2-(5-amino-1H-pirazol-3-il)etil)-N-metilbenzamida usada como material de partida se preparó según lo siguiente:

Se añadió LDA 1,8M en THF (30,0 ml, 54,00 mmoles) a tetrahidrofurano (60 ml), y se enfrió hasta -78°C. Se añadió gota a gota acetonitrilo (2,82 ml, 54,00 mmoles) durante 15 min. Se añadió una disolución de 3-(3-(metilcarbamoil)fenil)propanoato de metilo (2,99 g, 13,5 mmoles) en tetrahidrofurano (10 ml). La mezcla resultante se agitó a -78°C durante 10 min. La mezcla de reacción se calentó hasta 5°C y se agitó durante 30 min, se añadieron hidrocloruro de hidrazina (3,70 g, 54,00 mmoles) y etanol (60,0 ml), y la mezcla de reacción se calentó a 80°C durante 18 h. La mezcla de reacción se enfrió y se evaporó hasta sequedad. El residuo se disolvió en metanol (50 ml), y el producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar un aceite. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar 3-(2-(5-amino-1H-pirazol-3-il)etil)-N-metilbenzamida (0,450 g, 13,64 %) como un aceite amarillo.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,73 - 2,79 (4H, m), 2,89 (1H, d), 3,18 (3H, d), 4,09 (1H, d), 5,19 (1H, s), 7,35 (1H, s), 7,35 - 7,37 (1H, m), 7,63 - 7,66 (1H, m), 7,72 (1H, s), 8,38 (1H, d) – 1 protón no observado. MS: m/z 245 (MH+).

El 3-(3-(metilcarbamoil)fenil)propanoato de metilo usado como material de partida se preparó según lo siguiente:

Una disolución de (E)-3-[3-(metilcarbamoil)fenil]prop-2-enoato de metilo (3,77 g, 17,20 mmoles) y paladio al 10% sobre carbón (0,458 g, 0,43 mmoles) en una mezcla de etanol (100 ml) y DMF (10,00 ml) se agitó a temperatura ambiente durante 18 h en un balón de hidrógeno. La mezcla de reacción se filtró a través de celita y se evaporó hasta sequedad para dar 3-(3-(metilcarbamoil)fenil)propanoato de metilo (3,05 g, 80 %) como un sólido blanco. MS: m/z 222 (MH+).

El (E)-3-[3-(metilcarbamoil)fenil]prop-2-enoato de metilo usado como material de partida se preparó según lo siguiente:

Una disolución de 3-formil-N-metilbenzamida (2,9 g, 17,77 mmoles) y 2-trifenilfosforanilidenacetato de metilo (8,91 g, 26,66 mmoles) en diclorometano (85 ml) se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se evaporó hasta sequedad. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 10% de MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar producto impuro. Se repurificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 50 a 100% de EtOAc en hexanos. Las fracciones puras se evaporaron hasta sequedad para dar (E)-3-[3-(metilcarbamoil)fenil]prop-2-enoato de metilo (3,77 g, 97 %).

RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 3,02 - 3,03 (3H, m), 3,81 (3H, s), 6,34 (1H, s), 6,51 (1H, s), 7,42 - 7,48 (2H, m), 7,61 - 7,66 (1H, m), 7,67 (1H, d), 7,74 - 7,76 (1H, m), 7,93 (1H, t).

La 3-formil-N-metilbenzamida usada como material de partida se preparó según lo siguiente:

Se añadió una disolución 2M de metilamina en THF (44 ml, 5 eq, 87,5 mmoles) a 3-formilbenzoato de metilo (2,875 g, 1 eq, 17,5 mmoles) en THF seco (65 ml). La mezcla de reacción se enfrió hasta –50°C en nitrógeno, y se añadió lentamente una disolución 2M de trimetilaluminio en tolueno (22 ml, 2,5 eq, 43,75 mmoles) durante 15 min. La mezcla de reacción se dejó calentar lentamente hasta la temperatura ambiente, y se agitó durante 18 h. La mezcla de reacción se paralizó con un disolución al 20% p/v de tartrato sódico potásico en agua (50 ml). Ésta se extrajo con acetato de etilo (2x100 ml) y se lavó con agua (50 ml), con disolución saturada de cloruro de sodio (50 ml), se secó sobre $MgSO_4$ y se evaporó a presión reducida para dar una goma. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 2,5% de metanol en DCM. Las fracciones puras se combinaron y se evaporaron para dar 3-formil-N-metilbenzamida (1,6502g, 58%) como un sólido blanquecino.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 2,78 - 2,85 (3H, m), 7,70 - 7,75 (1H, t), 8,05 - 8,08 (1H, m), 8,04 - 8,09 (1H, m), 8,37 - 8,39 (1H, d), 8,63 - 8,70 (1H, s), 10,08 (1H, s). MS: m/z 164 (MH+).

Ejemplo 179

N-[5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-il]-4-(4-etilpiperazin-1-il)benzamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,51 ml, 3,02 mmoles) a 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina, HCl (345 mg, 1,21 mmoles) y 4-(4-etilpiperazin-1-il)benzoato de metilo (300 mg, 1,21 mmol) en tolueno (6,0 ml) a 25°C. La disolución resultante se agitó a 60°C durante 19 h en nitrógeno. La reacción no estaba terminada y se añadió más trimetilaluminio (0,50 ml, 3,02 mmoles), y la disolución se agitó a 60°C otras 4 h. La mezcla de reacción se añadió a metanol (100 ml) y se trató con HCl (disolución acuosa 2N, hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. Algo de producto cristalizó de las fracciones puras y se recogió mediante filtración a vacío para dar el compuesto del título (95 mg, 17%) como un sólido blanco. El filtrado se evaporó hasta sequedad para dar una muestra adicional del compuesto del título (115 mg, 20 %) como un sólido blanco. Las fracciones impuras que contienen el producto deseado se repurificaron mediante HPLC preparativa, usando mezclas cada vez menos polares de agua (que contiene 1% de NH3) y MeCN como eluyentes, para dar una tercera muestra del compuesto del título (27 mg, 5 %) como un sólido blanco.

RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,05 (3H, t), 2,38 (2H, q), 3,75 (6H, s), 5,08 (2H, s), 5,67 (1H, s), 6,45 (1H, t), 6,60 (2H, d), 7,01 (2H, d), 7,86 (2H, d). A aproximadamente δ 2,5, pico de 4H oscurecido por DMSO. A aproximadamente δ 3,3, pico de 4H oscurecido por H_2O.

MS: m/z 466 (MH+)

Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,00068 μM.

El hidrocloruro de 5-[(3,5-dimetoxifenil)metoxi]-2H-pirazol-3-amina usado como material de partida se preparó como en el Ejemplo 12.

El 4-(4-etilpiperazin-1-il)benzoato de metilo usado como material de partida se preparó según lo siguiente:

Se añadió 1-etilpiperazina (3,68 ml, 29,0 mmoles) a 4-fluorobenzoato de metilo (1,50 ml, 11,6 mmoles) en dimetilsulfóxido (29,0 ml) a 25°C. La disolución resultante se agitó a 120°C durante 18 h. La mezcla de reacción se concentró y se diluyó con EtOAc (50 ml) y agua (20 ml). Se añadió NaOH (disolución acuosa 2N, 20 ml), y las capas se separaron y se lavaron con EtOAc (40 ml). Las capas orgánicas se combinaron y se lavaron con agua (40 ml) y

salmuera saturada (40 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se evaporó para dar el producto deseado (1,960 g, 68%). Éste se usó sin purificación adicional.
RMN ^{1}H (399,9 MHz, $CDCl_3$) δ 1,06 (3H, t), 2,40 (2H, q), 2,52 (4H, t), 3,29 (4H, t), 3,79 (3H, s), 6,78 - 6,81 (2H, m), 7,83 - 7,86 (2H, m). MS: m/z 249 (MH+)

Ejemplo 180

N-[5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-il]-4-(4-etilpiperazin-1-il)benzamida

Se añadió gota a gota trimetilaluminio (2M en tolueno, 1,51 ml, 3,02 mmoles) a 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina (299 mg, 1,21 mmoles) y 4-(4-etilpiperazin-1-il)benzoato de metilo (300 mg, 1,21 mmoles) en tolueno (6,0 ml) a 25°C. La suspensión resultante se agitó a 60°C durante 24 h en nitrógeno. La mezcla de reacción se añadió a metanol (100 ml) y se trató con HCl (disolución acuosa 2N, hasta que el pH fue 7 o menor). El producto bruto se purificó mediante cromatografía de intercambio iónico, usando una columna SCX. El producto deseado se eluyó de la columna usando NH3 7M/MeOH, y las fracciones se evaporaron hasta sequedad para dar producto impuro. El producto bruto se purificó mediante cromatografía en columna de sílice, eluyendo con un gradiente de 0 a 5% de NH3 7M/MeOH en DCM. Las fracciones puras se evaporaron hasta sequedad para dar el compuesto del título (288 mg, 51 %) como un sólido de color crema.
RMN ^{1}H (399,9 MHz, DMSO-d_6) δ 1,05 (3H, t), 2,38 (2H, q), 2,50 (4H, peak obscured by DMSO), 2,87 (4H, s), 3,26 - 3,29 (4H, m), 3,73 (6H, s), 6,33 (1H, t), 6,42 (2H, d), 6,45 (1H, s), 6,96 (2H, d), 7,90 (2H, d), 10,29 (1H, s), 12,07 (1H, s). MS: m/z 464 (MH+).
Media de n = 2, ensayo de FGFR cinasa – Caliper Echo Dosing, IC_{50} 0,0017μM.

La 5-[2-(3,5-dimetoxifenil)etil]-2H-pirazol-3-amina, usada como material de partida, se preparó como se indica en el Ejemplo 2.

El 4-(4-etilpiperazin-1-il)benzoato de metilo usado como material de partida se preparó como se esquematiza en el Ejemplo 179.

Ensayos enzimáticos

Ensayo de FGFR cinasa - Caliper

Para determinar la inhibición de la actividad de FGFR, se llevaron a cabo ensayos de cinasa usando tecnología de Caliper.

Los ensayos de la actividad de cinasa se llevaron a cabo en placas Greiner de bajo volumen, de 384 pocillos, con un volumen total de reacción de 12 µl por pocillo. La concentración final de FGFR1 cinasa activa en cada pocillo de reacción fue 7,2 nM. El sustrato para cada ensayo fue un péptido habitual con marcador fluorescente (13 aminoácidos de longitud, KKSRGDYMTMQIG con el marcador fluorescente en el primer K).

Los compuestos se diluyeron en serie en DMSO al 5% (v/v), antes de añadirlos a las placas de ensayo. La enzima (a 7,2 nM [final]) y el sustrato (a 3,6 µM [final]) se añadieron por separado a las placas con los compuestos, en tampón de reacción [que comprende: 50 mM de MOPS (Sigma, nº de catálogo M1254) – pH 6,5, 0,004% de Triton (Sigma, nº de catálogo X-100), 2,4 mM de DTT, 12 mM de $MgCl_2$, 408 µM de ATP], dando como resultado una concentración final de DMSO en la mezcla de reacción de 0,8%.

Las placas de ensayo se incubaron a temperatura ambiente durante 1,5h, antes de que la reacción se detuviese por adición de tampón [que comprende: 100 mM de HEPES – pH 7,5, 0,033% de Brij-35 (nº de catalógo de Sigma B4184), 0,22% de reactivo de revestimiento nº 3 de Caliper (nº de catálogo de Caliper Life Sciences 760050), 88 mM de EDTA, 5% de DMSO]. Las placas de ensayo detenidas se leyeron entonces usando el aparato Caliper LabChip® LC3000 (que usa tecnología de microfluidos para medir un desplazamiento en la movilidad entre el péptido marcado fluorescente y la forma fosforilada mediante FGFR1 cinasa de este péptido).

En el ensayo, los compuestos se probaron en un intervalo de concentraciones. Los valores medios de los datos para cada concentración, junto con los pocillos de controles no tratados y los pocillos de controles con 100% de inhibición se usaron para derivar una gráfica de inhibición frente a la concentración. A partir de estos datos, se puede determinar el valor de IC50 o un valor de porcentaje de inhibición a concentración fija.

El porcentaje de inhibición a 1 µM, como se expresa aquí, es un valor calculado basado en el ajuste de curvas que se generó experimentamente. A partir de la gráfica de la curva ajustada, se calculó el efecto del compuesto a una concentración de 1 µM como un

porcentaje de inhibición. En el contexto de este ensayo, la IC_{50} es la concentración de compuesto, que inhibe la actividad de FGFR1 cinasa un 50%.

Resultados de los ensayos de inhibición de FGFR para los Ejemplos

Ejemplo	Clase de actividad
3	A
4	A
5	A
6	A
7	A
8	A
9	A
13	B
14	B
15	A
16	B
17	B
18	B
19	B
20	A

Actividad: A menos de 0,3 μM

B más de 0,3 μM y menos de 1 μM

C más de 1 μM y menos de 30 μM

Por ejemplo, el Ejemplo 14 es 612 nM.

Ensayo de FGFR cinasa – Caliper Echo Dosing

Para determinar la inhibición de la actividad de FGFR, se llevaron a cabo ensayos de cinasa usando la tecnología de Caliper.

Los ensayos de la actividad de cinasa se llevaron a cabo en placas Greiner de bajo volumen, de 384 pocillos, con un volumen total de reacción de 12 μl por pocillo. La

concentración final de FGFR1 cinasa activa en cada pocillo de reacción fue 7,2 nM. El sustrato para cada ensayo fue un péptido habitual con marcador fluorescente (13 aminoácidos de longitud, KKSRGDYMTMQIG con el marcador fluorescente en el primer K).

Los compuestos se dispensaron directamente en placas de ensayo usando una unidad de expulsión de gotitas acústica Labcyte Echo 550. Cada pocillo recibió 120 nl de DMSO que contiene compuesto, de forma que la concentración final de compuesto en el ensayo antes de la adición de la disolución de parada osciló entre 30 μM y 30 pM. Además de los compuestos, cada placa tenía pocillos de control máximos y mínimos; los pocillos máx contenían 120 nl de DMSO, y los pocillos mín contenían 120 nl de estaurosporina 10 mM (LC Laboratories, MA 01801, USA, nº de catálogo S-9300). La enzima (a 7,2 nM [final]) y el sustrato (a 3,6 μM [final]) se añadieron por separado a las placas con los compuestos, en tampón de reacción [que comprende: 50 mM de MOPS (Sigma, nº de catálogo M1254) – pH 6,5, 0,004% de Triton (Sigma, nº de catálogo X-100), 2,4 mM de DTT, 12 mM de $MgCl_2$, 408 μM de ATP], dando como resultado una concentración final de DMSO en la mezcla de reacción de 1%.

Las placas de ensayo se incubaron a temperatura ambiente durante 1,5h, antes de que la reacción se detuviese por adición de tampón [que comprende: 100 mM de HEPES – pH 7,5, 0,033% de Brij-35 (nº de catalógo de Sigma B4184), 0,22% de reactivo de revestimiento nº 3 de Caliper (nº de catálogo de Caliper Life Sciences 760050), 88 mM de EDTA, 5% de DMSO]. Las placas de ensayo detenidas se leyeron entonces usando el aparato Caliper LabChip® LC3000 (que usa tecnología de microfluidos para medir un desplazamiento en la movilidad entre el péptido marcado fluorescente y la forma fosforilada mediante FGFR1 cinasa de este péptido).

En el ensayo, los compuestos se probaron en un intervalo de concentraciones. Los valores medios de los datos para cada concentración, junto con los pocillos de controles no tratados y los pocillos de controles con 100% de inhibición se usaron para derivar una gráfica de inhibición frente a la concentración. A partir de estos datos, se puede determinar el valor de IC50 o un valor de porcentaje de inhibición a concentración fija.

El porcentaje de inhibición a 1 μM, como se expresa aquí, es un valor calculado basado en el ajuste de curvas que se generó experimentamente. A partir de la gráfica de la curva ajustada, se calculó el efecto del compuesto a una concentración de 1 μM como un porcentaje de inhibición. En el contexto de este ensayo, la IC_{50} es la concentración de

compuesto, que inhibe la actividad de FGFR1 cinasa un 50%. Este valor se calculó usando un paquete de programa de ordenador para ajustes de curva estándar Origin™. Cuando los compuestos se ensayaron más de una vez, el valor de IC_{50} se da como una media geométrica.

Ensayo de FGFR cinasa - Elisa

Para determinar la inhibición de la actividad de FGFR, se llevaron a cabo ensayos de cinasa usando la tecnología de ELISA (Ensayo Inmunoabsorbente Ligado a Enzimas).

Los ensayos de la actividad de cinasa se llevaron a cabo en placas de polipropileno de 384 pocillos (Matrix, nº de catálogo 4311. Matrix es parte de Thermo Fisher Scientific, 22 Friars Drive, Hudson, New Hampshire 03051, USA), con un volmen total de 40 µl en cada pocillo. Cada pocillo se revistió con 2 µg de sustrato polyEAY (Sigma, nº de catálogo P3899) a 4°C toda la noche. La placas se lavaron entonces una vez con 100 µl de PBS y una vez con 100 µl de 50mM de HEPES (pH 7,4), antes de añadir los reactivos de ensayo de cinasa. Las reacciones contenían el domino de FGFR cinasa marcado con His_6 (dominio de FGFR cinasa (aminoácidos 458-765, C488A, C584S) fusionado N-terminalmente a un marcador His_6 y un sitio de escisión del TEV codificado por la siguiente secuencia: [MHHHHHHEFKGSTSLYKKAGSSENLYFQGA]. La alanina final representa el comienzo de la secuencia de la proteína del FGFR. La proteína resultante se expresó y purificó basándose en Mohammadi et al, Cell Vol 86, 577-587 (1996). Cada reacción de cinasa contenía 0,1 ng de dominio de FGFR cinasa marcado con His_6, 50 mM de HEPES (pH 7,4), 0,1 mM de Na_3VO_4, 0,1 mM de DTT, 0,05% (v/v) de Triton X100, 20 mM de $MgCl_2$, 160 µM de ATP. Se añadieron a cada una diversas concentraciones de compuestos de ensayo en DMSO al 5% (v/v), para producir una concentración final de DMSO en el ensayo de 1,25% (v/v). Las reacciones de cinasa se incubaron a temperatura ambiente durante 45 minutos, y se detuvieron lavando tres veces la placa con 100 µl de PBS más 0,05% de Tween. Entonces se añadieron a cada pocillo 40 µl de una dilución de uno en 10000 de anticuerpo 4G10-HRP (Upstate Biotechnology, UBI 16-105. Upstate es parte de Millipore Corporation, 290 Concord Road, Billerca MA 01821 USA) preparado en 0,5% (p/v) de BSA/ PBS, y las placas se incubaron a temperatura ambiente durante una hora. Después de esto, las placas se lavaron entonces repetidamente con 100 µl de PBS más 0,05% de Tween, para eliminar todas las trazas de la disolución de anticuerpo. Se añadieron a cada pocillo 40 µl de 3,3',5,5'-tetrametilbencidina 50 µg/ml (Sigma, nº de catálogo T2885), 0,05M de tampón de fosfato-

citrato, que contiene 0,03% de perborato de sodio, y las placas se incubaron a temperatura ambiente durante doce minutos. La reacción coloreada se detuvo mediante adición de 20 µl de H_2SO_4 2M, y las placas se leyeron a 450 nm en un Spectrafluor Plus (Tecan Trading AG, Suiza). En el ensayo, los compuestos se probaron en un intervalo de concentraciones. Los valores medios de los datos para cada concentración, junto con los pocillos de controles no tratados y los pocillos de controles con 100% de inhibición se usaron para derivar una gráfica de inhibición frente a la concentración. A partir de estos datos, se puede determinar el valor de IC50 o un valor de porcentaje de inhibición a concentración fija.

El porcentaje de inhibición a 1 µM, como se expresa aquí, es un valor calculado basado en el ajuste de curvas que se generó experimentamente. A partir de la gráfica de la curva ajustada, se calculó el efecto del compuesto a una concentración de 1 µM como un porcentaje de inhibición. El valor de IC_{50} es la concentración de compuesto de ensayo que inhibe un 50% la actividad de FGFR cinasa.

Resultados de los ensayos de inhibición de FGFR para los Ejemplos

Ejemplo	Clase de actividad
1	A
3	A
4	A
5	A
6	A
7	A
8	A
9	A
10	A
11	A
12	A
13	B
14	B
15	A
16	B

17	B
18	B
19	A
20	A

Actividad: A menos de 0,3 μM

B más de 0,3 μM y menos de 1 μM

C más de 1 μM y menos de 30 μM

Por ejemplo, el Ejemplo 14 es 732 nM.

Ensayos celulares

pErk celular – fosforilación de Erk estimulada por el factored crecimiento

Estos y otros ensayos se usaron para evaluar la capacidad de un compuesto de ensayo para inhibir la señalización celular, estimulada por el facto de crecimiento, en estirpes celulares de mamíferos. Esto se logró midiendo la cantidad de fosforilación de Erk, regulada por tirosina cinasa receptora, en una célula tras el tratamiento con el compuesto.

Se hicieron pasar de forma habitual células NIH 3T3 (ECACC, 93061524) en DMEM (Gibco BRL, 41966) más 10% de suero fetal de ternera (FCS), 1% de L-glutamina (Gibco BRL, 25030) a una confluencia no mayor de 80%. Para llevar a cabo el ensayo, las NIH 3T3 se sembraron a $1x10^4$ células/pocillo en DMEM más 10% de suero fetal de ternera, 1% de L-glutamina en placas de 96 pocillos (Costar, 3904), y se incubaron a 37°C (+5% de CO_2) en una incubadora humidificada. Una vez que las células se adhirieron completamente (típicamente tras 4-5 horas de incubación), se eliminaron los medios de cada pocillo, y las células se lavaron suavemente con 100 μl de medio tibio libre de suero. Entonces se añadieron a cada pocillo 90 μl de DMEM libre de suero, más 1% de L-glutamina, y las placas se devolvieron a una incubadora humidificada, a 37°C (+5% de CO_2). Al siguiente día, las placas se dosificaron con 10 μl de compuesto (diluido a partir de 10 mM de disolución madre en DMSO usando DMEM libre de suero), y las placas se devolvieron a una incubadora humidificada a 37°C (+5% de CO_2), durante una hora. Las células NIH 3T3 se estimularon entonces con una concentración final de 3 ng/ml de bFGF (Sigma, F0291) durante 20 minutos a 37°C. Tras la estimulación, las células se fijaron añadiendo formaldehído (concentración

final 4% v/v) e incubando a temperatura ambiente durante 20 minutos. Entonces se eliminó la disolución fijadora, y los pocillos se lavaron dos veces con 100 µl de disolución salina tamponada con fosfato (PBS/A) antes de permeabilizar las células mediante adición de 50 µl/ pocillo de 0,1% de Triton/ PBS/A durante 10 minutos a temperatura ambiente. La disolución de permeabilización se eliminó entonces, y las células se lavaron dos veces más con 100 µl/pocillo de PBS/A antes de añadir 50 µl/pocillo de anticuerpo anti-fosfo p44/42 (Cell Signalling Technology, 9106), diluido 1/500 con PBS/A más 10% de FCS. El anticuerpo anti-fosfo p44/42 reconoce Erk fosforilada en treonina 202 y tirosina 204. Tras la incubación a temperatura ambiente durante 2 horas, la disolución de anticuerpo se eliminó, y los pocillos se lavaron dos veces con 100 µl/pocillo de PBS/A. Se añadieron 50 µl/pocillo de 1/250 de anticuerpo secundario Alexa fluor 488 anti-ratón de cabra (Molecular Probes, A11001) y de 1/10000 de Hoescht (Molecular Probes, H-3570) diluido con PBS/A más 10% de FCS, y la placa se incubó en la oscuridad a temperatura ambiente durante una hora. Finalmente, las placas se lavaron tres veces con 100 µl/pocillo de PBS/A, dejando el lavado final en los pocillos antes de cerrar herméticamente las placas. Las placas se leyeron a 350 nm y 488 nm usando un aparato Arrayscan (Cellomics). Los valores medios de la intensidad media de la fluorescencia para cada concentración de compuesto de ensayo, pocillos de control no tratados y pocillos de control con 100% de inhibición se usaron para determinar el valor de IC_{50} de los compuestos de ensayo. El valor de IC_{50} es la concentración de compuesto de ensayo que inhibe un 50% la fosforilación de Erk.

Resultados de los ensayos de inhibición de FGFR para los Ejemplos

Ejemplo	Clase de actividad
1	B
2	A
7	C
8	A
9	B
10	A
11	A
18	B

Actividad: A menos de 0,3 μM

B más de 0,3 μM y menos de 1 μM

C más de 1 μM y menos de 30 μM

Por ejemplo, el Ejemplo 18 es 877 nM.

FGFR1 celular – Inhibición a nivel celular de la fosforilación de FGFR1 IIIc expresado transitoriamente (medida usando anticuerpos primarios fosfoespecíficos y secundarios fluorescentes).

Este ensayo se diseñó para detectar inhibidores de la fosforilación de FGFR1, expresado transitoriamente, mediante tinción con anticuerpos de células fijadas detectada usando tecnología ArrayScan. (Para una descripción de la tecnología ArrayScan, véase http://www.cellomics.com/content/menu/Arrayscan/)

Se hicieron pasar de forma habitual células Cos-1 en DMEM (Gibco BRL, 41966) más 3% de suero fetal de ternera (FCS), 1% de L-glutamina (Gibco BRL, 25030) a una confluencia de 80%. Para llevar a cabo el ensayo, las células Cos-1 se recogieron a una confluencia de 90-95% para la transfección celular. Para cada placa de 96 pocillos, se añadieron 24 μl de Lipofectamine 2000 (Invitrogen, nº de catálogo 11668-019) a 809 μl de OptiMEM (Invitrogen, nº de catálogo 11058-021), y se incubó a temperatura ambiente durante 5 minutos. Para cada placa de 96 pocillos, 20 μg de FGFR1 marcado con FLAG en 3' / pcDNA3,1 (clon 15 de nuestro laboratorio, MSD 4793) se diluyeron con OptiMEM hasta un volumen total de 833 μl. Se combinaron volúmenes iguales de ADN y Lipofectamine 2000 (relación ADN:Lípido = 1:1,2), y se incubaron a temperatura ambiente durante 20 minutos. El "marcador FLAG" fue un marcador de purificación/detección que comprende la secuencia de aminoácidos: N-DYKDDDDK-C. El "marcador FLAG" se clonó en el término N de FGFR1. El clon era la isoforma FGFR1 IIIc de tipo natural, de longitud completa.

Las células Cos-1 cosechadas se contaron usando un contador Coulter, y se diluyeron adicionalmente con 1% de FCS/DMEM hasta 2,5 x 10^5 células/ml. Para cada placa de 96 pocillos, se necesitaron 8,33 ml de células. La disolución de transfección complejada se añadió a la disolución celular, y las células se sembraron a 2,5x10^5 células/pocillo en DMEM más 1% de suero fetal de ternera, 1% de L-glutamina en placas de 96 pocillos (Costar, 3904), y se incubaron toda la noche (24 h) a 37ºC (+5% de CO_2) en una incubadora humidificada. Al

siguiente día, a las placas se les añadieron 25 µl de compuesto (diluido a partir de 10 mM de disolución madre en DMSO usando DMEM libre de suero), y las placas se devolvieron a una incubadora humidificada a 37°C (+5% de CO_2), durante una hora. Los medios se eliminaron de los pocillos usando aspiraciones por vacío; las células se fijaron añadiendo 50 µl de metanol al 100% a cada pocillo, y se incubaron a temperatura ambiente durante 20 minutos. Entonces se eliminó la disolución fijadora, y los pocillos se lavaron una vez con 200 µl de disolución salina tamponada con fosfato (PBS/A) antes de permeabilizar las células mediante adición de 50 µl/pocillo de 0,1% de Triton/ PBS/A durante 20 minutos a temperatura ambiente. La disolución de permeabilización se eliminó entonces, y las células se lavaron una vez más con 200 µl/pocillo de PBS/A antes de añadir 40 µl de 1/1000 de disolución de anticuerpo primario (Cell Signalling Technology #CS3476; anti-fosfo FGFR1 de ratón diluido en PBS/A con 10% de FCS + 0,1% de Tween 20) a cada pocillo.

Después de incubar a temperatura ambiente durante 1 hora, la disolución de anticuerpo se eliminó, y los pocillos se lavaron una vez con 200 µl/ pocillo de PBS/A. Después, se añadieron 40 µl de disolución de anticuerpo secundario 1/500 (A11005; anti-ratón de cabra 594) y 1/10000 de Hoechst (diluidos juntos en PBS/A con 10% de FCS + 0,1% de Tween 20), y la placa se incubó en la oscuridad a temperatura ambiente durante una hora. Finalmente, las placas se lavaron una vez con 200 µl / pocillo de PBS/A, dejando el lavado final en los pocillos antes de cerrar herméticamente las placas. Las placas se leyeron en un aparato Arrayscan (Cellomics). Los valores del Canal 2 (594 nm) obtenidos a partir de los pocillos sin dosificar (máx) y con compuesto de referencia (mín) en una placa se usaron para establecer los límites para la inhibición de 0% y 100% por el compuesto. Los datos de los compuestos se normalizaron frente a estos valores para determinar el intervalo de dilución de un compuesto de ensayo que da una inhibición del 50% de FGFR1 fosforilado.

FGFR1 celular (ECHO) - Inhibición celular de la fosforilación de FGFR1 IIIc expresado transitoriamente vía uso de tecnología ECHO (medida usando anticuerpos primarios fosfoespecíficos y secundarios fluorescentes).

Este ensayo se diseñó para detectar inhibidores de la fosforilación de FGFR1 expresado transitoriamente, mediante tinción con anticuerpos de células fijadas detectada usando tecnología ArrayScan.

Se hicieron pasar de forma habitual células Cos-1 en DMEM (Gibco BRL, 41966) más 3% de suero fetal de ternera (FCS), 1% de L-glutamina (Gibco BRL, 25030) a una confluencia de 80%. Para llevar a cabo el ensayo, las células Cos-1 se recogieron a una confluencia de 90-95% para la transfección celular. Para cada placa de 96 pocillos, se añadieron 24 µl de Lipofectamine 2000 a 809 µl de OptiMEM, y se incubó a temperatura ambiente durante 5 minutos. Para cada placa de 96 pocillos, 20 µg de FGFR1 marcado con FLAG en 3'/ pcDNA3,1 (clon 15 de nuestro laboratorio, MSD 4793) se diluyeron con OptiMEM hasta un volumen total de 833 µl. Se combinaron volúmenes iguales de ADN y Lipofectamine 2000 (relación ADN:Lípido = 1:1,2), y se incubaron a temperatura ambiente durante 20 minutos.

Las células Cos-1 cosechadas se contaron usando un contador Coulter, y se diluyeron adicionalmente con 1% de FCS/DMEM hasta 2,5 x 10^5 células/ml. Para cada placa de 96 pocillos, se necesitaron 8,33 ml de células. La disolución de transfección complejada se añadió a la disolución celular, y las células se sembraron a 2,5x10^5 células/pocillo en DMEM más 1% de suero fetal de ternera, 1% de L-glutamina en placas de 96 pocillos (Costar, 3904), y se incubaron toda la noche (24 h) a 37ºC (+5% de CO_2) en una incubadora humidificada.

Al siguiente día, se disolvieron compuestos procedentes de muestras de peso seco en 100 de DMSO %, para dar una concentración de 10mM. Se añadieron 40 µl del compuesto a los pocillos de cada cuadrante a lo largo de la placa Labcyte de 384 pocillos (nº de catálogo de Labcyte P-05525) (incluyedo un control positivo (100% de DMSO), un control negativo (10 µM) y un compuesto de referencia (250 nM)). La placa Labcyte de 384 pocillos se transfirió entonces a la Hydra para diluir los compuestos 1:100 en los pocillos que quedan del cuadrante. Se aspiraron 70 µl de medio a partir de la placa de ensayo, usando el Quadra antes de que la placa se transfiriese al ECHO 550. La placa Labcyte de 384 pocillos con el compuesto también se transfirió al ECHO 550. La transferencia de compuestos a la placa de ensayo en el ECHO 550 se realizó a intervalos de concentración 1) 10 µM, 2) 3 µM, 3) 1 µM, 4) 0,3 µM, 5) 0,1 µM, 6) 0,01.

Las placas se golpearon suavemente para mezclar el compuesto con el medio celular, y se dejaron incubar a 37ºC con 5% de CO_2 durante 1 hora.

El medio se eliminó de los pocillos usando aspiración por vacío; las células se fijaron añadiendo 50 µl de metanol al 100% a cada pocillo, y se incubaron a temperatura ambiente

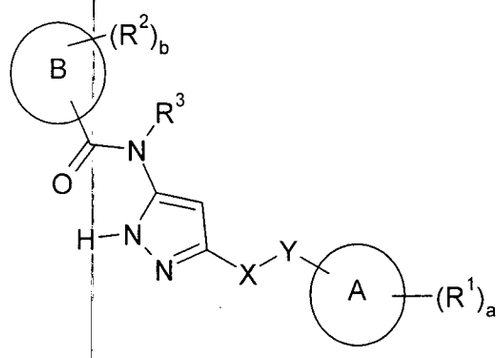
durante 20 minutos. Entonces se eliminó la disolución fijadora, y los pocillos se lavaron una vez con 200 µl de disolución salina tamponada con fosfato (PBS/A) antes de permeabilizar las células mediante adición de 50 µl/pocillo de 0,1% de Triton/ PBS/A durante 20 minutos a temperatura ambiente. La disolución de permeabilización se eliminó entonces, y las células se lavaron una vez más con 200 µl/pocillo de PBS/A antes de añadir 40 µl de 1/1000 de disolución de anticuerpo primario (Cell Signalling Technology #CS3476; anti-fosfo FGFR1 de ratón diluido en PBS/A con 10% de FCS + 0,1% de Tween 20) a cada pocillo.

Después de incubar a temperatura ambiente durante 1 hora, la disolución de anticuerpo se eliminó, y los pocillos se lavaron una vez con 200 µl/ pocillo de PBS/A. Después, se añadieron 40 µl de 1/500 de disolución de anticuerpo secundario (A11005; anti-ratón de cabra 594) y 1/10000 de Hoechst (diluidos juntos en PBS/A con 10% de FCS + 0,1% de Tween 20), y la placa se incubó en la oscuridad a temperatura ambiente durante una hora. Finalmente, las placas se lavaron una vez con 200 µl / pocillo de PBS/A, dejando el lavado final en los pocillos antes de cerrar herméticamente las placas. Las placas se leyeron en un aparato Arrayscan (Cellomics). Los valores del Canal 2 (594 nm) obtenidos a partir de los pocillos sin dosificar (máx) y con compuesto de referencia (mín) en una placa se usaron para establecer los límites para la inhibición de 0% y 100% por el compuesto.

Los datos de los compuestos se normalizaron frente a estos valores para determinar el intervalo de dilución de un compuesto de ensayo que da una inhibición del 50% de FGFR1 fosforilado.

REIVINDICACIONES

1. Un compuesto de fórmula **(I)**:



(I)

o una sal farmacéuticamente acceptable del mismo

en la que

el anillo **A** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

el anillo **B** representa un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre;

cada $\mathbf{R^1}$ representa independientemente

un halógeno,

un grupo hidroxilo,

un grupo ciano,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^4R^5$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo cicloalquilo C_{3-5} opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquiltio C_1-C_3, $-NR^6R^7$ (cada uno de los cuales puede estar

opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^8R^9$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo fenilo opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{10}R^{11}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{12}R^{13}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo $-NR^{16}R^{17}$,

un grupo $-OCOR^{18}$,

un grupo $-CO_2R^{19}$,

un grupo $-CONR^{20}R^{21}$,

un grupo $-NR^{22}COR^{23}$,

un grupo $-NR^{24}CO_2R^{25}$,

un grupo $-OSO_2R^{26}$,

o dos grupos R^1 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{27}R^{28}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

cada **R^2** representa independientemente

un grupo hidroxilo,

un halógeno,

un grupo ciano,

un grupo $-CO_2R^{29}$,

un grupo $-CONR^{30}R^{31}$,

un grupo $-NR^{32}COR^{33}$,

un grupo $-NR^{34}CO_2R^{35}$,

un grupo $-NR^{36}R^{37}$,

un grupo $-SO_2R^{38}$,

un grupo $-SO_2NR^{39}R^{40}$,

un grupo $-NR^{41}SO_2R^{42}$,

un grupo alquilo C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{43}R^{44}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo y un grupo heterociclilo de 4 a 7 miembros

opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, cicloalquilo C_3-C_6, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, ciano, hidroxilo, trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{45}R^{46}$, $-CO_2R^{47}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), ciano, halógeno e hidroxilo,

un grupo cicloalquilo C_3-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{48}R^{49}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{50}R^{51}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alquenilo C_2-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{52}R^{53}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo, y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido

con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{54}R^{55}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo heterociclilo de 4 a 7 miembros opcionalmente condensado a un grupo carbociclilo o heterociclilo de 4 a 7 miembros y opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, alquil C_1-C_6-carbonilo, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, ciano, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, oxo, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

un grupo alcoxi C_1-C_6 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_6, cicloalquilo C_3-C_6, $-NR^{62}R^{63}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_6, alquil C_1-C_6-tio, $-NR^{64}R^{65}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o dos grupos R^2 adyacentes, junto con los átomos a los que están unidos, forman un anillo carbociclilo o heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{66}R^{67}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

R^3 representa hidrógeno,

un grupo alquilo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, alquil C_1-C_3-tio, $-NR^{68}R^{69}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo;

a es 0, 1, 2, 3 ó 4;

b es 0, 1, 2, 3 ó 4;

R^4 y **R^5** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^4 y R^5, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^6 y **R^7** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^6 y R^7, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^8 y **R^9** representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^8 y R^9, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{10} y R^{11} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{10} y R^{11}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{12} y R^{13} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{12} y R^{13}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{14} y R^{15} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{14} y R^{15}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{16} y R^{17} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{16} y R^{17}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{18} representa alquilo C_1-C_4, o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{19} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{20} y R^{21} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{20} y R^{21}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{22} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de

halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{23}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{24}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{25}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{26}}$ representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{27}}$ y $\mathbf{R^{28}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{27} y R^{28}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

$\mathbf{R^{29}}$ representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{30}}$ y $\mathbf{R^{31}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{30} y R^{31}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{32} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{33} representa hidrógeno, alquilo C_1-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{34} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{35} representa hidrógeno, alquilo C_1-C_4, alquenilo C_2-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

R^{36} y R^{37} representan cada uno independientemente hidrógeno, alquilo C_1-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6 o un grupo aromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo anular seleccionado de nitrógeno, oxígeno y azufre, o R^{36} y R^{37}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo y un grupo carbociclilo o heterociclilo de 4 a 7 miembros que puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo, trifluorometilo);

R^{38} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno,

alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{39}}$ y $\mathbf{R^{40}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{39} y R^{40}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{41}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquil C_1-C_3-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{42}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6 (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, alquiltio C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo);

$\mathbf{R^{43}}$ y $\mathbf{R^{44}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{43} y R^{44}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

$\mathbf{R^{45}}$ y $\mathbf{R^{46}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloaquilo C_3-C_6, o R^{45} y R^{46}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

$\mathbf{R^{47}}$ representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6;

$\mathbf{R^{48}}$ y $\mathbf{R^{49}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{48} y R^{49}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

$\mathbf{R^{50}}$ y $\mathbf{R^{51}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{50} y R^{51}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

$\mathbf{R^{52}}$ y $\mathbf{R^{53}}$ representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{52} y R^{53}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{54} y R^{55} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{54} y R^{55}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{56} y R^{57} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{56} y R^{57}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{58} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{59} y R^{60} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{59} y R^{60}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{61} representa alquilo C_1-C_4 o cicloalquilo C_3-C_6;

R^{62} y R^{63} representan cada uno independientemente hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, o R^{62} y R^{63}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{64} y R^{65} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{64} y R^{65}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{66} y R^{67} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{66} y R^{67}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros;

R^{68} y R^{69} representan cada uno independientemente hidrógeno, alquilo C_1-C_6 o cicloalquilo C_3-C_6, o R^{68} y R^{69}, junto con el átomo de nitrógeno al que están unidos, forman un heterociclilo saturado de 4 a 6 miembros; y en la que

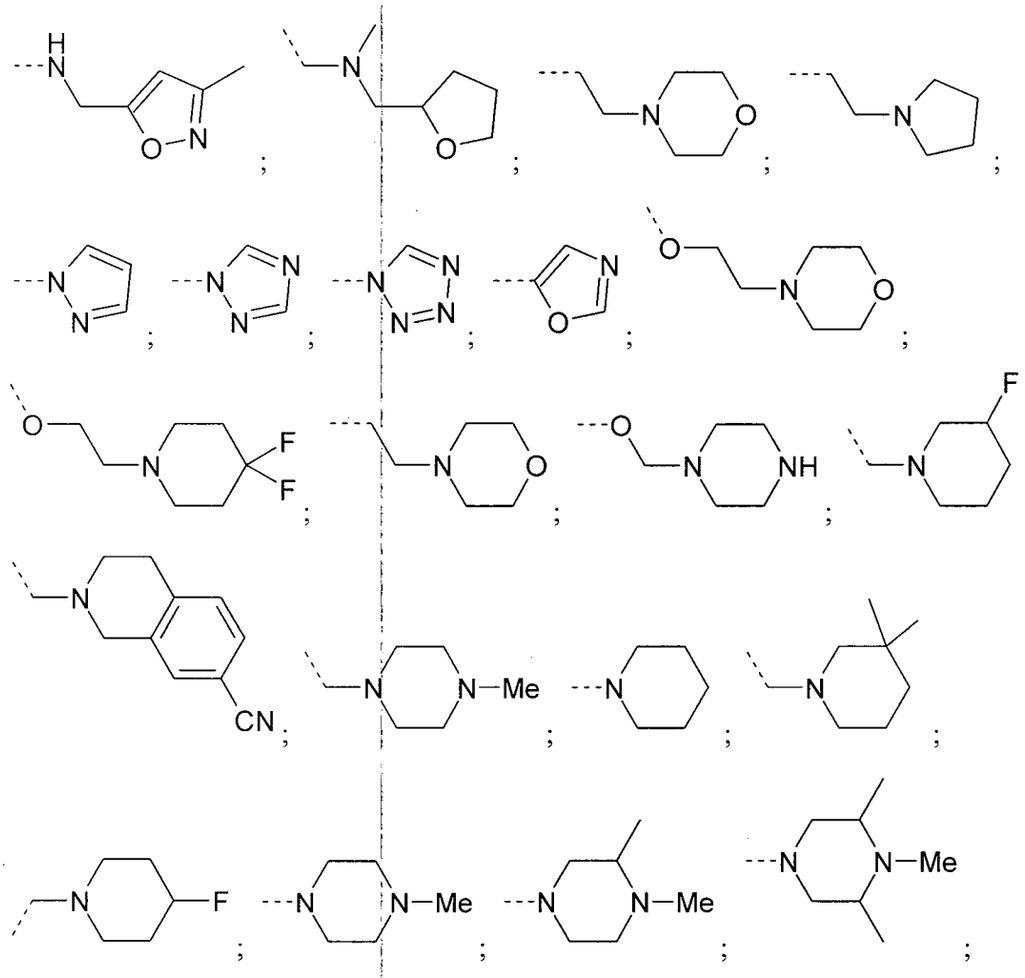
cuando **Y** representa CH_2, **X** representa CH_2, O, NR^{70} o $S(O)_X$, en el que R^{70} representa hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, y **x** es 0, 1 ó 2; o

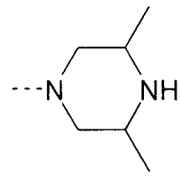
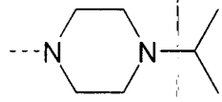
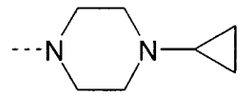
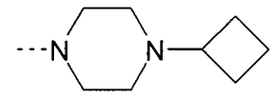
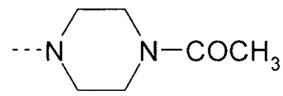
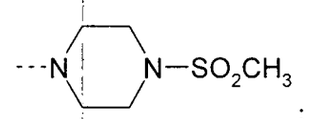
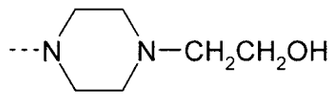
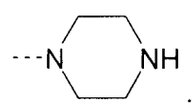
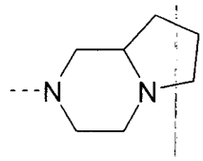
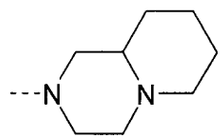
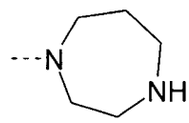
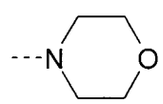
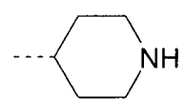
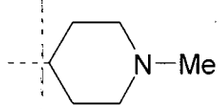
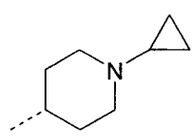
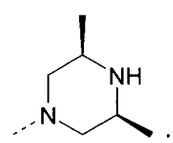
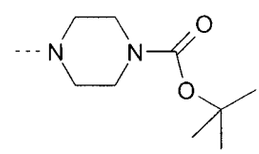
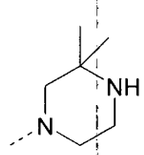
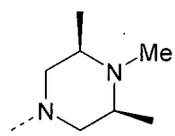
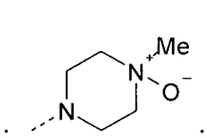
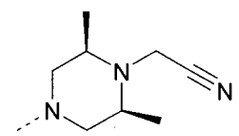
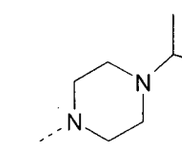
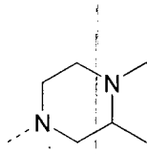
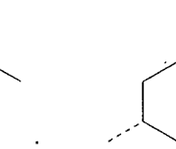
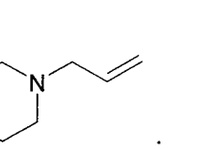
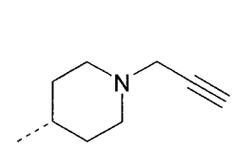
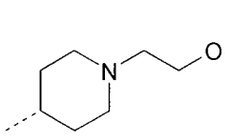
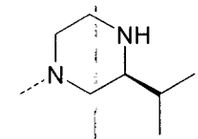
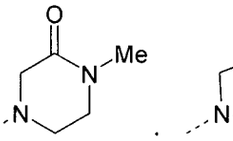
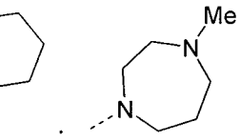
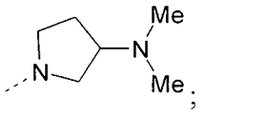
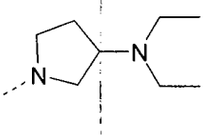
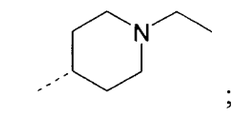
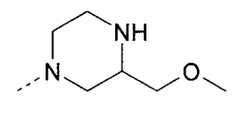
cuando **X** representa CH_2, **Y** representa CH_2, O, NR^{71} o $S(O)_y$, en el que R^{71} respresenta hidrógeno, alquilo C_1-C_4 o cicloalquilo C_3-C_6, e **y** es 0, 1 ó 2.

2. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que R^3 es hidrógeno.

3. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1 ó 2, en el que X representa CH_2 o O; e Y representa CH_2.

4. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según cualquiera de las reivindicaciones 1 a 3, en el que cada R^2 representa independientemente un grupo -Cl; -F; -I; -OH; -CN; $-CH_3$; $-CH_2OH$; $-CH_2N(CH_3)_2$; $-CH_2CH(CH_3)NH_2$; $-OCH_3$; $-OCH_2CH_2OH$; $-OCH_2CH_2OCH_2CH_3$; $-SO_2CH_3$; $-N(CH_3)_2$; -NHPh; $-NHCH_2C{\equiv}CH$; $-NHCH_2CH_3$; $-NHCH_2CH_2N(CH_3)_2$; $-NHCO_2CH_2CH{=}CH_2$; $-NHCOCH_3$; -NHCOH; -NHCOPh; $-CONH_2$; $-NHSO_2Me$; $-SO_2N(CH_3)_2$; $-CO_2H$; $-CO_2CH_3$; $-CO_2CH_2CH_3$;




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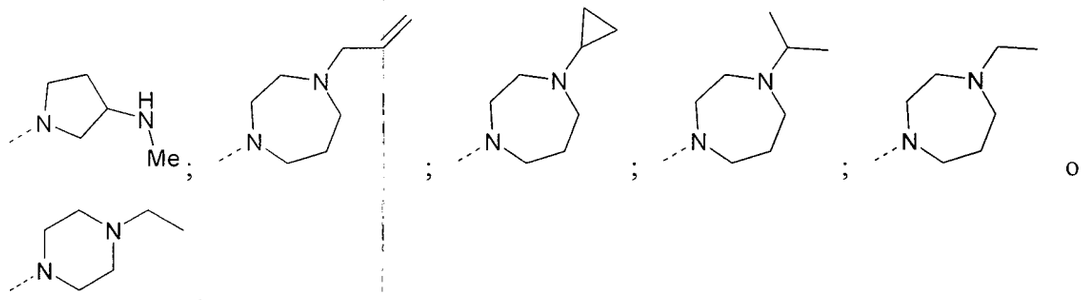
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5. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según cualquiera de las reivindicaciones 1 a 4, en el que cada R^1 representa independientemente un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o un grupo $-CONR^{20}R^{21}$.

6. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según cualquiera de las reivindicaciones 1 a 5, en el que el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo.

7. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según cualquiera de las reivindicaciones 1 a 6, en el que el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo.

8. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo;

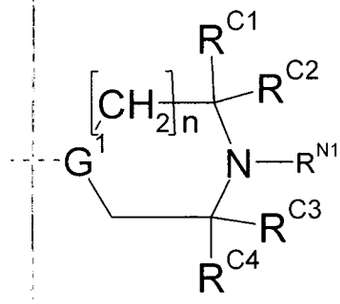
el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo, tienilo o tiazolilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de ciano, halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquiltio C_1-C_3, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

9. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

el anillo A representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

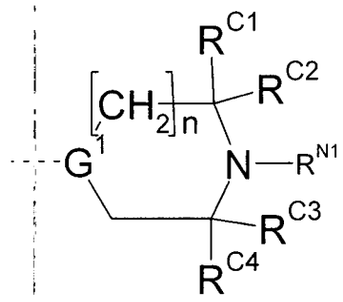
el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo

C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

10. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

el anillo A representa un anillo furilo, fenilo o piridilo;

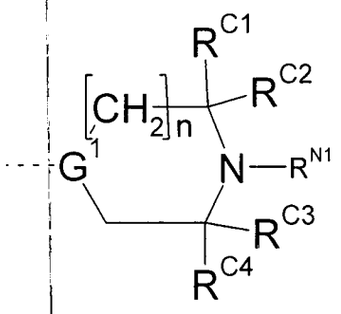
el anillo B representa un anillo fenilo, pirazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar

opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;
X representa CH_2 o O;
Y representa CH_2;
a es 0, 1 ó 2; y
b es 1.

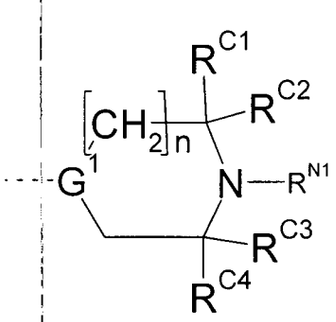
11. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

el anillo A representa un anillo fenilo;
el anillo B representa un anillo fenilo, pirazinilo, piridilo, pirimidinilo o tienilo;
cada R^1 representa independientemente

un grupo alcoxi C_1-C_3 opcionalmente sustituido con uno o más sustituyentes seleccionados de alcoxi C_1-C_3, cicloalquilo C_3-, $-NR^{14}R^{15}$, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_3, alcoxi C_1-C_3, amino ($-NH_2$), mono- y di-alquil C_1-C_3-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo, o

un grupo $-CONR^{20}R^{21}$;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno, halógeno e hidroxilo, o

R^{C1} y R^{C2} y/o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico o heterocíclico de 3 a 6 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, o

R^{C1} y R^{C3}, junto con los átomos a los que están unidos y el átomo de nitrógeno al que está unido el grupo R^{N1}, forman un anillo carbocíclico o heterocíclico de 5 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo, y

R^{N1} se selecciona de alquilo C_1-C_4, alquenilo C_2-C_4, alquinilo C_2-C_4, cicloalquilo C_3-C_6, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), hidrógeno y un grupo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{59}R^{60}$, $-SO_2R^{61}$ (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno e hidroxilo,

o R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros opcionalmente sustituido con uno o más sustituyentes seleccionados de alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, cicloalquilo C_3-C_5, alquil C_1-C_3-tio, $-NR^{56}R^{57}$, SO_2R^{58} (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil C_1-C_2-tio, amino ($-NH_2$), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo), halógeno, hidroxilo;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

b es 1.

12. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

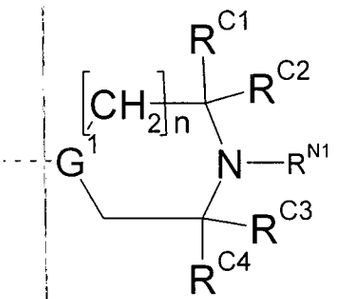
el anillo A representa un anillo fenilo;

el anillo B representa un anillo furilo, fenilo, pirazinilo, piridazinilo, piridilo, pirimidinilo o tienilo;

cada R^1 representa independientemente

un grupo alcoxi C_1-C_3;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo carbocíclico de 3 a 5 miembros,

y

R^{N1} se selecciona de alquilo C_1-C_2, alquenilo C_2-C_3, alquinilo C_2-C_3, cicloalquilo C_3-C_5, (cada uno de los cuales puede estar opcionalmente sustituido con uno o más sustituyentes seleccionados de halógeno, alquilo C_1-C_2, alcoxi C_1-C_2, alquil

C_1-C_2-tio, amino (-NH_2), mono- y di-alquil C_1-C_2-amino, hidroxilo y trifluorometilo) e hidrógeno, o

R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 4 a 7 miembros;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2;

a es 0, 1 ó 2; y

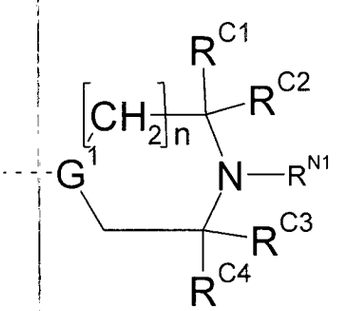
b es 1.

13. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

$A(R^1)_a$ representa 3,5-dimetoxifenilo;

el anillo B representa un anillo fenilo, pirazinilo, pirimidinilo o tienilo;

R^2 representa



en la que

G^1 es C o N,

n es 1 ó 2,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o

R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo,

y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo, propenilo, propinilo, propilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros;

R^3 representa hidrógeno;

X representa CH_2 o O;

Y representa CH_2; y

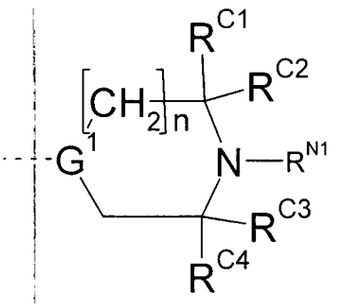
b es 1.

14. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según la reivindicación 1, en el que:

$A(R^1)_a$ representa 3,5-dimetoxifenilo;

el anillo B representa un anillo fenilo, pirazinilo, pirimidinilo o tienilo;

R^2 representa



en la que

G^1 es C o N,

n es 1,

R^{C1}, R^{C2}, R^{C3} y R^{C4} se seleccionan cada uno independientemente de hidrógeno, metilo, etilo, hidroximetilo, hidroxietilo, metoximetilo, metoxietilo, 2,2,2-trifluoroetilo, o R^{C3} y R^{C4}, junto con el átomo al que están unidos, forman un anillo ciclopropilo,

y

R^{N1} se selecciona de hidrógeno, metilo, etilo, metoxietilo, etoxietilo, hidroxietilo, propenilo, propinilo, i-propilo, $-CH(CH_3)CH_2OH$, ciclopropilo, ciclobutilo, ciclopentilo, o R^{N1} y R^{C4}, junto con los átomos a los que están unidos, forman un anillo heterociclilo de 5 ó 6 miembros;

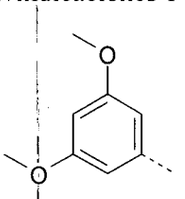
R^3 representa hidrógeno;

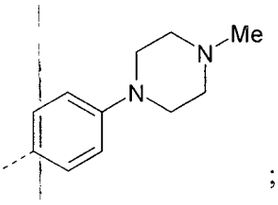
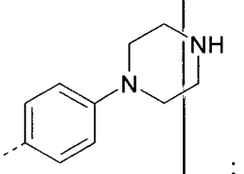
X representa CH_2 o O;

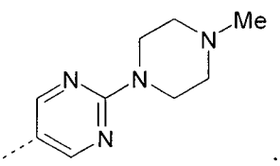
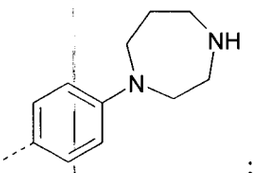
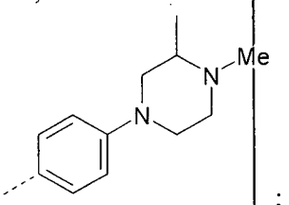
Y representa CH_2; y

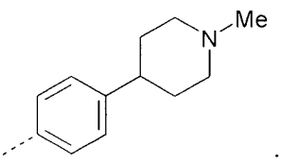
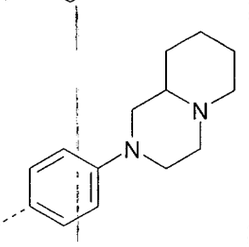
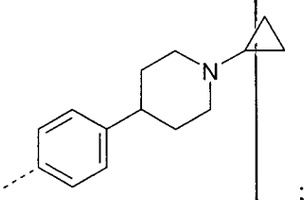
b es 1.

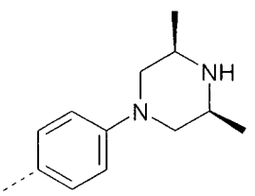
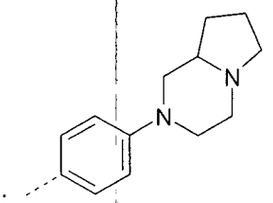
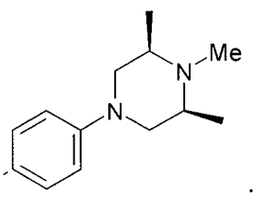
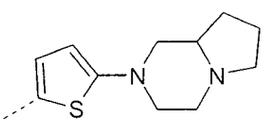
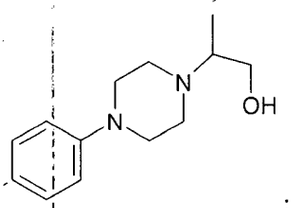
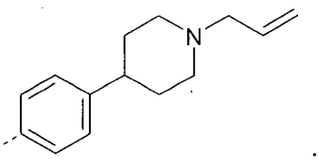
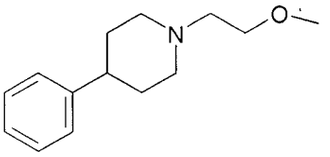
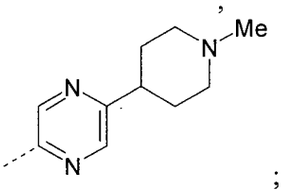
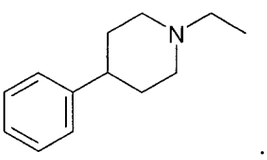
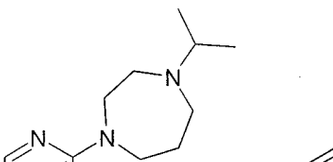
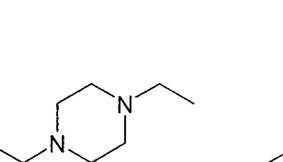
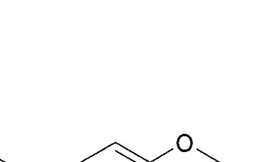
15. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 3, en el que:

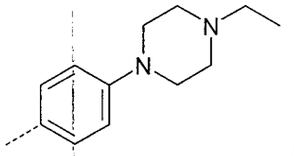
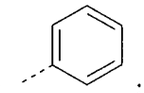
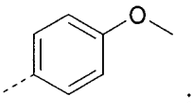
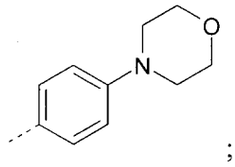
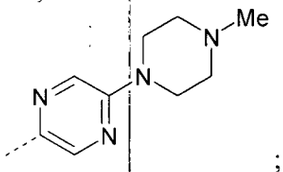
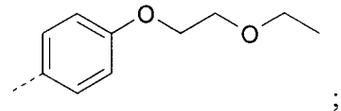
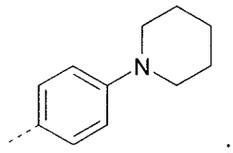
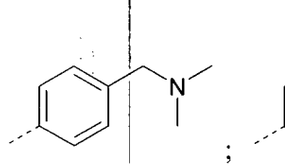
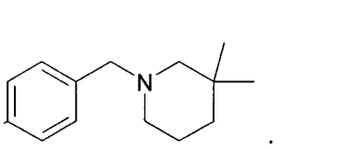
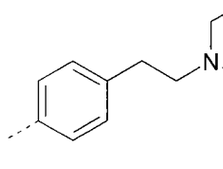
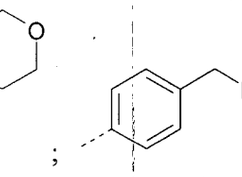
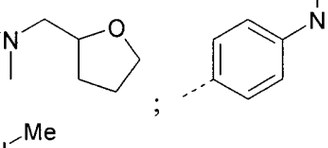
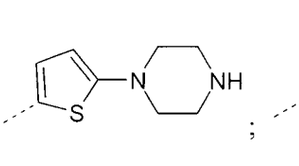
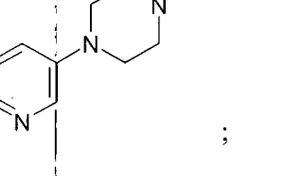
-A-$(R^1)_a$ representa un grupo  ; y

-B-$(R^2)_b$ representa un grupo  ;  ;

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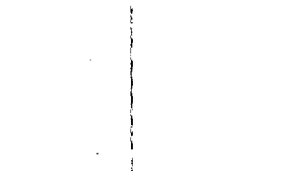
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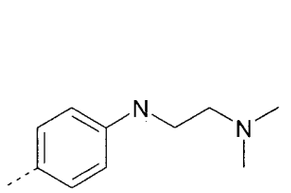
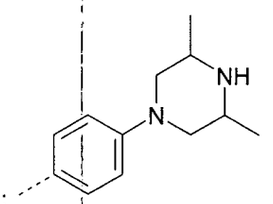
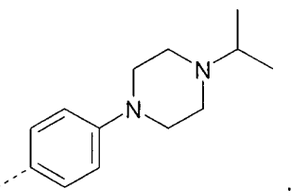
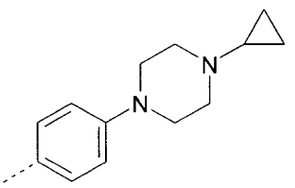
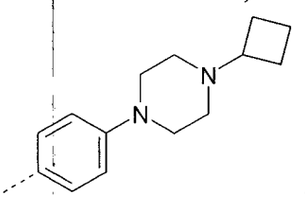
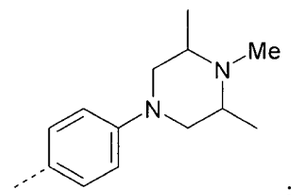
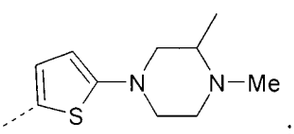
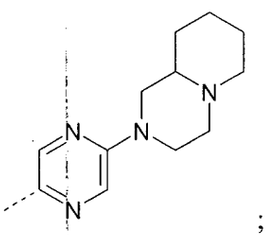
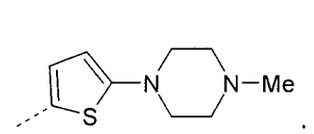
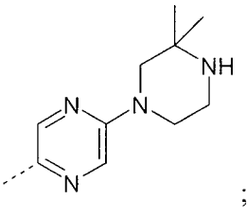
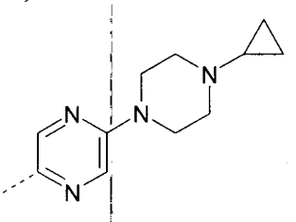
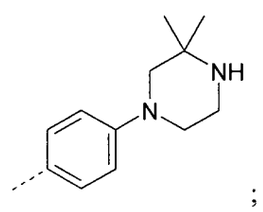
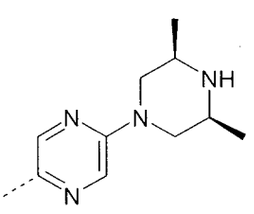
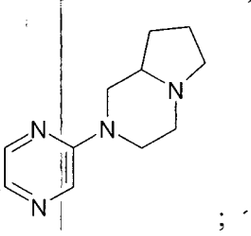
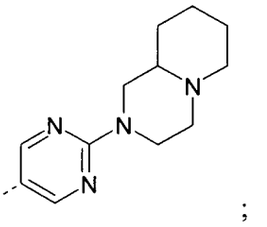
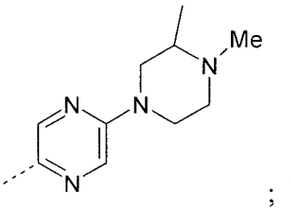
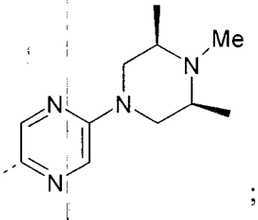
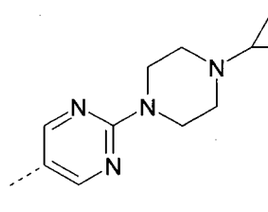
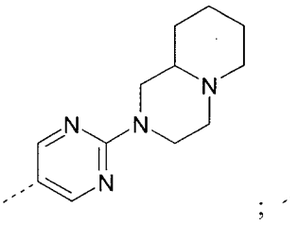
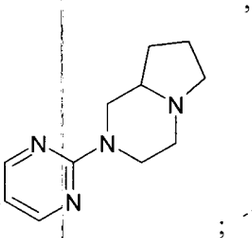
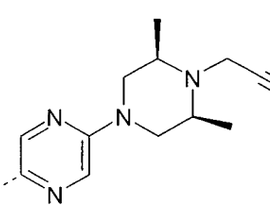
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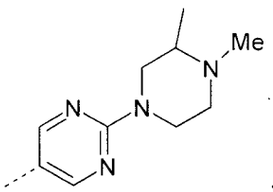
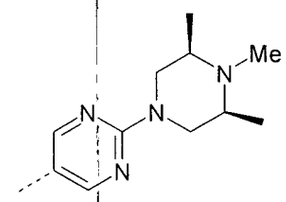
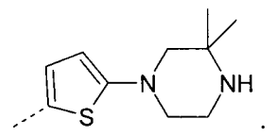
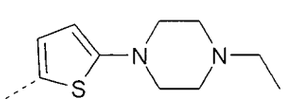
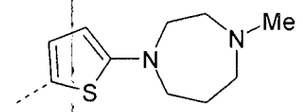
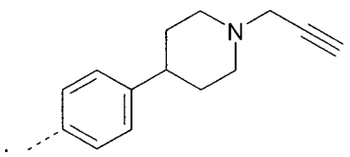
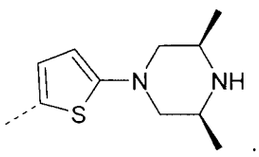
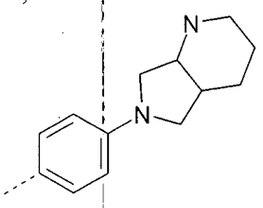
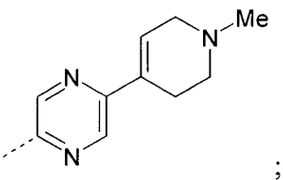
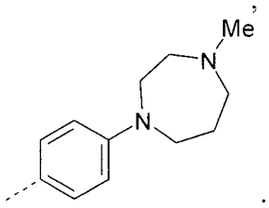
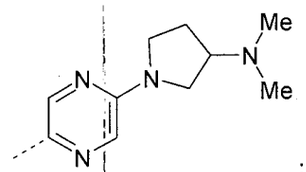
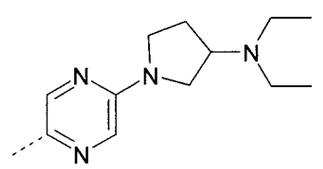
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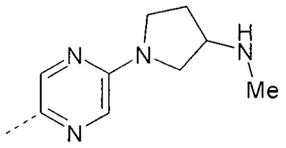
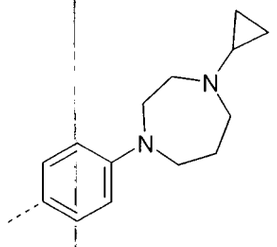
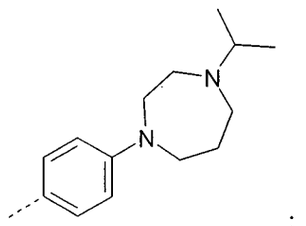
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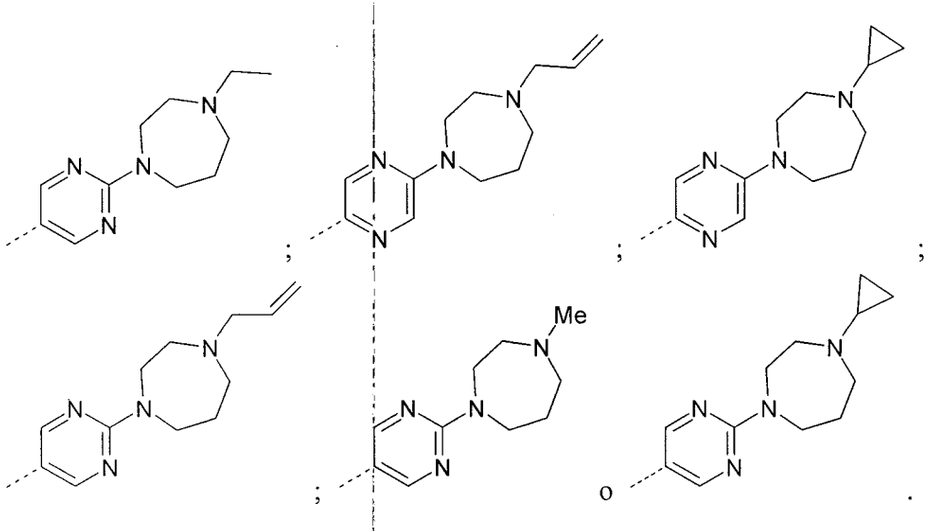
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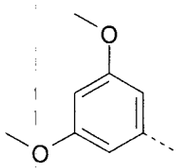
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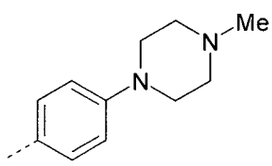
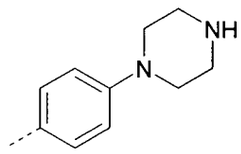
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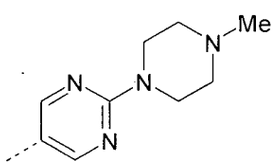
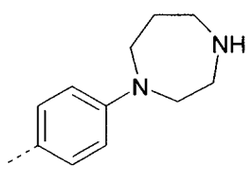
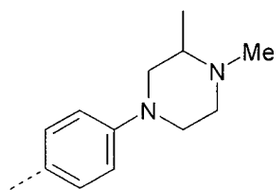
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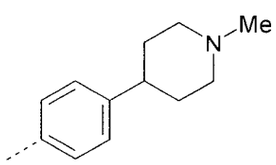
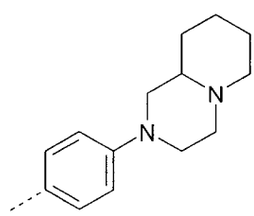
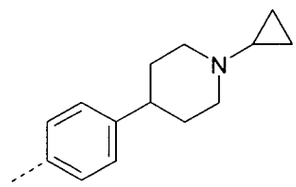


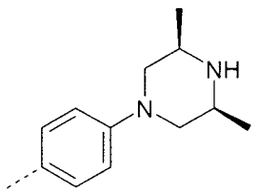
16. Un compuesto de fórmula **(I),** o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 3, en el que:

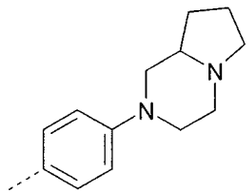
-A-$(R^1)_a$ representa un grupo  ; y

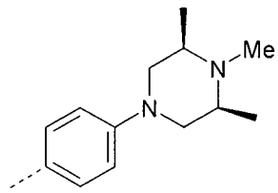
-B-$(R^2)_b$ representa un grupo  ;  ;

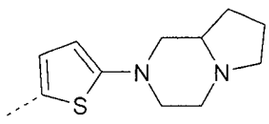
 ;  ;  ;

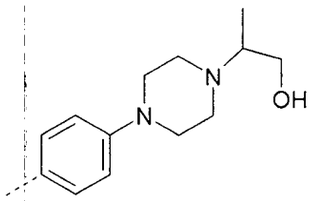
 ;  ;  ;

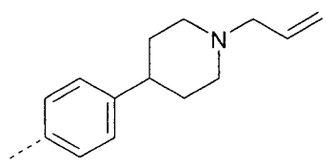


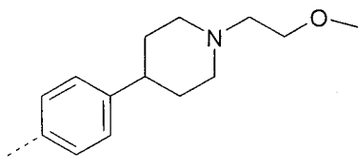
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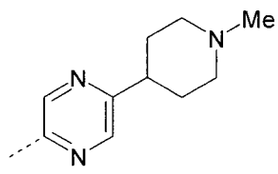
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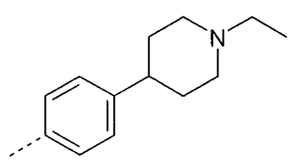
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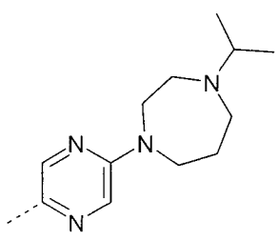
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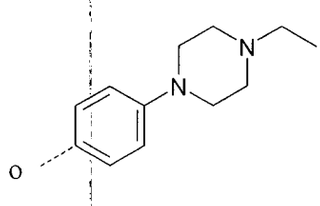
;


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.

17. Un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, para uso en terapia.

18. Un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, para uso en un método de tratamiento del cuerpo humano o animal mediante terapia.

19. El uso de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable, según una cualquiera de las reivindicaciones 1 a 16, en la fabricación de un medicamento para uso en terapia.

20. Un método para tratar cáncer, que comprende administrar a un paciente que lo necesite una cantidad terapéuticamente eficaz de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16.

21. Un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, para uso como un medicamento.

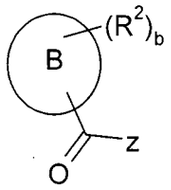
22. El uso de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, en la fabricación de un medicamento para uso en la producción de un efecto inhibidor de FGFR en un animal de sangre caliente.

23. El uso de un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, en la fabricación de un medicamento para uso en la producción de un efecto anticancerígeno en un animal de sangre caliente.

24. Una composición farmacéutica que comprende un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según cualquiera de las reivindicaciones 1 a 16, en asociación con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

25. Un procedimiento para la preparación de una composición farmacéutica de la invención, que comprende mezclar un compuesto de fórmula **(I)**, o una sal farmacéuticamente aceptable del mismo, según una cualquiera de las reivindicaciones 1 a 16, con un adyuvante, diluyente o vehículo farmacéuticamente aceptable.

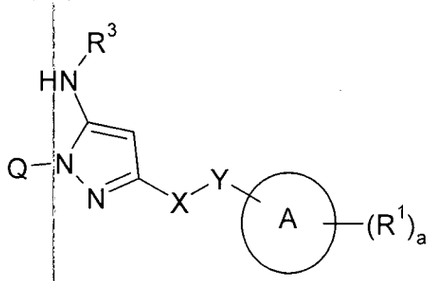
26. Un procedimiento para la preparación de un compuesto de fórmula **(I)** según la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que comprende hacer reaccionar un compuesto de fórmula **(II)**



(II)

en la que Z representa un grupo saliente, y B, R^2 y b son como se definen en la reivindicación 1 para un compuesto de fórmula **(I),**

con un compuesto de fórmula **(III)**



(III)

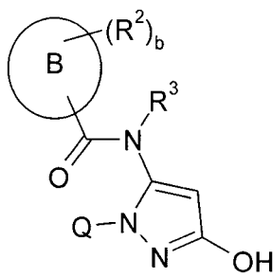
en la que Q es hidrógeno o un grupo protector, y A, R^1, R^3, X, Y y a son como se definen en la reivindicación 1 para un compuesto de fórmula **(I)**

para dar un compuesto de fórmula **(I),**

y opcionalmente llevar a cabo una o más de las siguientes:

- convertir el compuesto obtenido en un compuesto adicional de la invención
- formar una sal farmacéuticamente aceptable del compuesto.

27. Un procedimiento para la preparación de un compuesto de fórmula **(I)** según la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, que comprende hacer reaccionar un compuesto de fórmula **(IV)**

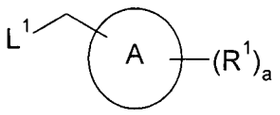


(IV)

en la que Q es hidrógeno o un grupo protector; y

B, R^2, R^3 y b son como se definen en la reivindicación 1 para un compuesto de fórmula **(I),**

con un compuesto de fórmula **(V)**



(V)

en la que L^1 representa OH o un grupo saliente; y A, R^1 y a son como se definen en la reivindicación 1 para un compuesto de fórmula **(I)**

para dar un compuesto de formula **(I)**

y opcionalmente llevar a cabo una o más de las siguientes:

- convertir el compuesto obtenido en un compuesto adicional de la invención
- formar una sal farmacéuticamente aceptable del compuesto.

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/GB2007/004917

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

INV. C07D231/40 C07D401/06 C07D401/12 C07D401/14 C07D403/12
C07D405/06 C07D409/12 C07D413/12 C07D471/04 C07D487/04
A61K31/415 A61P35/00

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CPI

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)
A61K C07D

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
A	US 2005/209297 A1 (M. A. SANNER ET AL.) 22 de septiembre de 2005 (2005-09-22) reivindicaciones 1-20	1-27
A	WO 2005/051919 A (PFIZER PRODUCTS INC.) 9 de junio de 2005 (2005-06-09) reivindicaciones 1-10	1-27
A	WO 2005/048948 A (AMBIT BIOSCIENCES CORPORATION) 2 de junio de 2005 (2005-06-02) reivindicaciones 1-75	1-27
A	WO 2005/105780 A (VERTEX PHARMACEUTICALS INCORPORATED) 10 de noviembre de 2005 (2005-11-10) reivindicaciones 1-27	1-27

-/--

☒ En la continuación del recuadro C se relacionan otros documentos.

☒ Los documentos de familias de patentes se indican en el anexo.

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante

"E" documento anterior aunque publicado en la fecha de presentación internacional o en fecha posterior

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada)

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad, que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, resultando dicha combinación evidente para un experto en la materia

"&" documento que forma parte de la misma familia de patentes

Fecha en que se ha concluido la búsqueda internacional	Fecha de expedición del Informe de Búsqueda Internacional
11 de julio de 2008	01/08/2008

Nombre y dirección postal de la Administración encargada de la Búsqueda Internacional	Funcionario autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31 40) 340-2040, Tx. 31 651 epo nl Fax. (+31 40) 340-3016	Herz, Claus

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/GB2007/004917

C (Continuación). DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
A	C.N. CAVASOTTO ET AL.: "In silico identification of novel EGFR inhibitors with antiproliferative activity against cancer cells" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 18 de enero de 2006 (2006-01-18) páginas 1969-1974, XP002487848 * Compuesto 41 * tabla 1 -----	1-27

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de la familia de patentes

Solicitud internacional N°
PCT/GB2007/004917

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
US 2005209297 A1	22-09-2005	NINGUNO	
WO 2005051919 A	09-06-2005	BR PI0416989 A	06-02-2007
		CA 2547283 A1	09-06-2005
		EP 1689721 A1	16-08-2006
		JP 2007512315 T	17-05-2007
		US 2007276010 A1	29-11-2007
WO 2005048948 A	02-06-2005	AU 2004291147 A1	02-06-2005
		CA 2545711 A1	02-06-2005
		EP 1684762 A2	02-08-2006
		JP 2007512255 T	17-05-2007
		US 2005261315 A1	24-11-2005
		WO 2005048953 A2	02-06-2005
WO 2005105780 A	10-11-2005	JP 2007535551 T	06-12-2007
		US 2006019956 A1	26-01-2006

RWS Group Ltd de Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, Inglaterra, por la presente declara que a su mejor saber y entender lo que sigue, documento preparado por uno de sus traductores competentes y que tiene conocimiento de las lenguas inglesa y española, es una traducción verdadera y exacta del documento en lengua inglesa que acompaña esta traducción.

RWS Group Ltd, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, hereby declares that, to the best of its knowledge and belief, the following document, prepared by one of its translators competent in the art and conversant with the English and Spanish languages, is a true and correct translation of the accompanying document in the English language.

Firmada en el día 19 de mayo de 2009

Signed this 19th day of May 2009

C. E. SITCH

Managing Director - UK Translation Division

Para RWS Group Ltd

For and on behalf of RWS Group Ltd

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/075068 A3

(51) International Patent Classification:
C07D 231/40 (2006.01) *C07D 409/12* (2006.01)
C07D 401/06 (2006.01) *C07D 413/12* (2006.01)
C07D 401/12 (2006.01) *C07D 471/04* (2006.01)
C07D 401/14 (2006.01) *C07D 487/04* (2006.01)
C07D 403/12 (2006.01) *A61K 31/415* (2006.01)
C07D 405/06 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/GB2007/004917

(22) International Filing Date:
20 December 2007 (20.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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60/985,542 5 November 2007 (05.11.2007) US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-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)*: **FOOTE, Kevin, Michael** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **THEOCLITOU, Maria-Elena** [GR/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **THOMAS, Andrew, Peter** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **BUTTAR, David** [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).

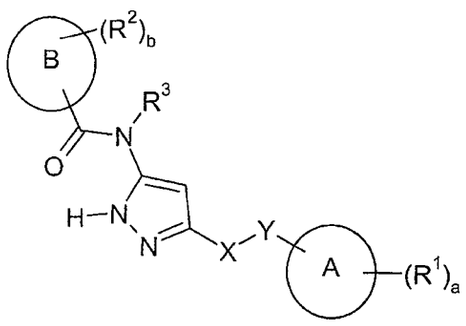
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

(88) Date of publication of the international search report:
2 October 2008

(54) Title: ACYLAMINOPYRAZOLES AS FGFR INHIBITORS



(I)

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

WO 2008/075068 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/004917

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/40 C07D401/06 C07D401/12 C07D401/14 C07D403/12
C07D405/06 C07D409/12 C07D413/12 C07D471/04 C07D487/04
A61K31/415 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)
A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/209297 A1 (M. A. SANNER ET AL.) 22 September 2005 (2005-09-22) claims 1-20	1-27
A	WO 2005/051919 A (PFIZER PRODUCTS INC.) 9 June 2005 (2005-06-09) claims 1-10	1-27
A	WO 2005/048948 A (AMBIT BIOSCIENCES CORPORATION) 2 June 2005 (2005-06-02) claims 1-75	1-27
A	WO 2005/105780 A (VERTEX PHARMACEUTICALS INCORPORATED) 10 November 2005 (2005-11-10) claims 1-27	1-27

-/--

[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
11 July 2008	01/08/2008

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	Herz, Claus

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/004917

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C. N. CAVASOTTO ET AL.: "In silico identification of novel EGFR inhibitors with antiproliferative activity against cancer cells". BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 18 January 2006 (2006-01-18), pages 1969-1974, XP002487848 * Compound 41 * table 1 -----	1-27

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/004917

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	9 62879
	Solicitud internacional	PCT/GB2007/004917
	Fecha inicio fase nacional	21/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8675

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 31 JUL. 2009
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	Actuación	430
	Oficio No.	8676

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

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